Rickham's Neonatal Surgery

Paul D. Losty
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ISBN 978-1-4471-4720-6 ISBN 978-1-4471-4721-3 (eBook)
https://doi.org/10.1007/978-1-4471-4721-3

Library of Congress Control Number: 2017964011

Printed on acid-free paper

This Springer imprint is published by the registered company Springer-Verlag London Ltd. part of Springer Nature
The registered company address is: The Campus, 4 Crinan Street, London, N1 9XW, United Kingdom

Peter Paul Rickham (1917–2003)

This textbook is dedicated to Peter Paul Rickham, pioneering surgeon, who co-founded the world's First neonatal surgical unit at Alder Hey Children's Hospital Liverpool, United Kingdom.

Foreword

Peter Paul Rickham graduated in medicine from Queens' College, Cambridge, and St Bartholomew's Hospital, London, in 1941. He trained in paediatric surgery at the Hospital for Sick Children, Great Ormond Street, London, under Sir Denis Browne and under Isabella Forshall at Alder Hey Children's Hospital, Liverpool, where he was appointed consultant paediatric surgeon in 1953.

At Alder Hey, Rickham established the hospital as a regional centre for neonatal surgery, he instituted a neonatal transport system for the safe transfer of surgical neonates from a wide area around Liverpool to Alder Hey and he inaugurated the world's first neonatal surgical intensive care unit which was the prototype emulated at centres throughout the world. As a result of the developments, neonatal surgical mortality decreased from 78% to 26% over a period of only 3 years. The subject of his MD thesis was "The Metabolic Response of the Newborn to Surgery".

Rickham remained in Liverpool until 1971 when he was then appointed Professor of Paediatric Surgery at the University Children's Hospital, Zurich, Switzerland, where he remained until retirement in 1983. At Alder Hey he trained numerous surgeons throughout the world particularly from the United States, Japan, Europe, Asia and South Africa.

He was the recipient of many awards and distinctions including the Denis Browne Gold Medal of the British Association of Paediatric Surgeons of which he was founder member and later President, the Legion d'Honneur, France, the Commander Cross, Germany, Ladd Medal Surgical Section of the American Academy of Pediatrics and two Hunterian Professorships from the Royal College of Surgeons of England.

The first edition of *Neonatal Surgery* co-edited with J. Herbert Johnston was published in 1969. It was the first textbook devoted entirely to neonatal surgery based on the accumulating experience of newborn surgery carried out at Alder Hey Children's Hospital from 1953 to 1968. It was, in its time, the "bible" of neonatal surgery and I read it from cover to cover before, during and after my time as a Smith and Nephew Fellow studying under Peter Paul Rickham in 1970. Two subsequent editions of *Neonatal Surgery* were later published in 1978 and 1990. The scope of these publications was expanded, and new contributions from a range of experts of international repute were included.

It is pleasing now to witness a major new international textbook launched from Alder Hey titled *Rickham's Neonatal Surgery* edited by Paul Losty

(Liverpool, UK), Alan Flake (Philadelphia, USA), Risto Rintala (Helsinki, Finland), Naomi Iwai (Kyoto, Japan) and John Hutson (Melbourne, Australia). This new textbook has a truly international list of distinguished contributors covering the full range of neonatal surgical conditions and related topics. Among many key themes comprehensively included in the new book attention also focuses on advances in fetal surgery, minimal invasive surgery, long-term outcomes and evidence-based surgery.

The textbook is a fitting tribute to the life and work of Peter Paul Rickham who was my mentor and good friend.

London, UK Lewis Spitz

Editors' Preface: Rickham's Neonatal Surgery

In 1969, Peter Paul Rickham and Herbert Johnston published the first edition of Neonatal Surgery from Alder Hey Children's Hospital Liverpool which for many paediatric surgeons was considered to be one of the leading textbooks in the world dedicated to newborn surgery. The huge success of the first edition was followed with further editions of this landmark textbook published in 1978 and 1990. Peter Paul Rickham is credited with establishment of the world's first neonatal surgical unit at Alder Hey in 1953 co-founded together with Isabella Forshall. Indeed, it is perhaps then no great surprise that several generations of young paediatric surgeons travelled to Liverpool to work with Rickham and the team of surgical staff based at Alder Hey. Peter Rickham was fortunate to also have Jackson Rees a pioneer in neonatal anaesthesia as a consultant colleague during that era. The "impossible became possible". Many young surgeons who visited Alder Hey later advanced to become world leaders in paediatric surgery across four continents.

This new textbook "Rickham's Neonatal Surgery" is dedicated to Peter Paul Rickham including past and present staff at Alder Hey. The team of editors have assembled leading experts with co-authors to provide state-of-the-art chapters covering the speciality field of neonatal surgery and its related disciplines including fetal medicine, fetal surgery, radiology, newborn anaesthesia, intensive care, neonatal medicine, medical genetics, pathology, cardiac surgery and urology. Contributions from the basic sciences and laboratory research are highlighted in the textbook reflecting steady progress in our current working knowledge and understanding of many neonatal surgical disorders. Evidence-based studies and "best practice" provide the reader wide-ranging information including the latest developments in many chapters. As huge advances have been made in neonatal surgery with improved survival particularly in the past decade(s), ethical issues, long-term outcomes and quality of life are also emphasised by the individual contributors. We hope the textbook will be an authoritative reference for surgical residents in training, consultant surgeons, general surgeons with an interest in paediatric surgery, neonatologists, paediatricians, intensive care specialists and nursing staff. The editors are greatly indebted to the many authors from across the world for their excellent contributions and for some their lifelong professional associations having trained or worked as surgeons at Alder Hey.

Special thanks must go to Barbara Lopez Lucio who worked tirelessly with all authors, editor-in-chief and editorial team to make the project possible. We greatly value and appreciate the skills of the artist(s) and illustrators

for their high-quality work. Finally, enormous gratitude is owed to Julia Megginson, Wyndham Hacket Pain and Melissa Morton at Springer, London, UK, for the final production of the textbook.

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Part I

General

Medical Law as Applied to Neonatal Surgery

1

Robert Wheeler

Abstract

Medical law as applied to neonatal surgery, when considered in terms of the number of requests for legal or ethical opinions, is mainly concerned with the withdrawal or withholding of treatment. However, this must be placed into the context of the chronological opportunities for law to intervene in clinical care. For that reason alone, this chapter commences with the unborn child, passing through the stage of birth, initial decisions on viability (and acquiring a legal parent); before progressing to the 'baby cases', and subsequent guidance when considering the withdrawal of care in neonatal surgery.

Keywords

Ethics • Medical law • Neonatal surgery • Paediatric surgery

Medical law as applied to neonatal surgery, when considered in terms of the number of requests for legal or ethical opinions, is mainly concerned with the withdrawal or withholding of treatment. However, this must be placed into the context of the chronological opportunities for law to intervene in clinical care. For that reason alone, this chapter commences with the unborn child, passing through the stage of birth, initial decisions on viability (and acquiring a legal parent); before progressing to the 'baby cases', and subsequent guidance when considering the withdrawal of care in neonatal surgery.

Contained within a book emerging from one of the founding centres of neonatal surgery in the British Isles, it is unsurprising that this chapter rests squarely on the common law in England and Wales. However the judges creating that law constantly survey the decisions of their colleagues in North America, Canada and Australasia which in turn influences the English decisions. Since the commencement of the Human Rights Act 1998, our courts are also constrained by the European Convention of Human

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_1

Rights, so that the law pertaining to neonatal surgery described in this book is derived from broad international experience.

1.1 Wrongful Birth

International experience is nowhere better reflected than in wrongful birth. This is a topic which mainly relates to foetal medicine, rather than to neonatal surgery. Applicable only to the precursor of the newborn child, it is included for completeness. But many of us provide antenatal counselling to prospective parents, and it is instructive to reflect on the consequences that could, in principle, flow from this.

Parents of children born with an affliction that could and should have been detected in utero have been suing their clinicians for some years. An early case [1] in the New York Court of Appeals found that parents could claim the costs of institutional care of their child who was born with Down's syndrome, following their doctor's failure to recommend amniocentesis to the 37 year old mother. Courts immediately found such cases difficult due to conflicts of interest. There was public policy to consider; of favouring life over abortion; to be weighed against a woman's prerogative of control over her own body. What emerged was a rule accepted in at least 30 US states that valid claims for wrongful birth will succeed [2].

In the United Kingdom, the action is also allowed, with evidence that many are settled without recourse to the courts [3]. Nevertheless, litigation over failure to diagnose a wide field of diseases that are identifiable antenatally, including congenital rubella syndrome, Duchenne muscular dystrophy and Down's syndrome have been reported.

In addition, in a Scottish case [4], a father was been awarded damages for the shock and distress he has suffered as a result of the birth of an affected child. This was unusual, since such damages have usually been limited to the mother, and evidence of psychiatric harm has previously been required. Neither of these applied in McLelland.

1.2 Proposed Guidelines for Instituting Intensive Care at Birth

In a report [5] commissioned by the Nuffield Council on Bioethics, guidelines were proposed for deciding as to whether babies of certain gestational age should have limitations placed on their resuscitation and intensive care. These proposals were based solely on judgement of the best interests of a premature child, irrespective of the wider issue of whether clinical resources were available to support this aspect of neonatal medicine. The working party concluded that below 22 weeks of gestation, no baby should be resuscitated, unless this was taking place within all the safeguards of a clinical research study. For babies between 22 weeks and 22 weeks 6 days of gestation, "…standard practice should be not to resuscitate a baby, (and that) … resuscitation would normally *not* be considered or proposed". In this group, parents' views might lead to a reversal of this approach, after a thorough discussion of the risks and prognosis with an experienced clinician. In babies between 23 weeks 0 days and 23 weeks 6 days, precedence should be given to the views of the babies parents, but there is no clinical obligation to embark on treatment that is 'wholly contrary' to clinical judgment.

This brief description does not do justice to a 250 page report of great quality. However, it is cited as an illustration of the national efforts being made to define some limits to treatment at the commencement of extra-uterine life, based on a balance between the importance of preserving life, whilst at the same time acting a in a child's best interest.

1.3 Parental Responsibility

Parental responsibility is conferred by statute [6] and is defined as 'all the rights, duties, powers, responsibilities and authority which by law, a parent of a child has in relation to the child …. ' Included is the right to provide consent for

treatment where necessary. The child's mother (the woman who gave birth to the baby, rather than the person who provided the egg from which he was conceived, if different) automatically gains parental responsibility. The child's father gains parental responsibility automatically if married at the time of the birth registration. Since 2003, unmarried fathers also get parental responsibility automatically, when they register the birth.

If the father subsequently marries the mother, he acquires parental responsibility, an acquisition described as 'legitimation' [7].

Alternatively, parental responsibility can be acquired by the unmarried father either with the agreement of the child's mother, or by application to a court.

Parental responsibility is passed to adoptive parents on legal adoption. It may be shared with guardians appointed by parents; with local authorities; and is linked to various legal orders [8].

The person with parental responsibility who provides consent for a child's surgery must act in the child's best interests in so doing. These are usually self evident, and the agreement between parents and surgeon is reached after full disclosure of the relevant information.

1.4 The 'Baby Cases'

Medical law is a relatively modern discipline. In some respects, it has been built upon cases considering whether a child with congenital malformations should be treated, or allowed to die without operation. It should be remembered that these 'withdrawal' cases only get to court if there is dissent; between surgeons, physicians, nurses or parents. Provided all agree that withdrawal (or continuation of treatment) is in a baby's best interest, the effects of their joint decision attract no public attention. It is only where one or other group powerfully disagree over the management plan that litigation occurs, and it is helpful to begin with the English cases, in chronological order.

1.4.1 Baby Alexandra, and the Question of Life's Sanctity

In a case known as Re B,[1] the parents of a newborn with Down's syndrome and duodenal atresia wished to allow their child to die, rather than undergo surgery. Her doctors disagreed, and the local authority was given care and control of the baby. The court authorised surgery, but when the child was transferred for operation, the surgeons were unwilling to operate, in view of the parents' objections. The local authority returned to court, but the judge, after hearing the parents' views, withdrew authorisation for the surgery.

The case was then considered by the Court of Appeal, which was told that other surgeons would be prepared to operate. This court found that the judge had placed too much emphasis on the wishes of the parents, and that it was the *best interests* of the child that should prevail. To determine these best interests, the appeal court created a test: Was Alexandra's life "…. demonstrably going to be so awful that in effect she should be condemned to die, or whether the life of this child is still so imponderable that it would be wrong for her to be condemned to die?"

Concluding that the surgery would give her the chance to live the normal life expectancy of a child with Down's syndrome, the court allowed the appeal, and Alexandra's surgery was performed. However, in his leading judgment, Templeman LJ acknowledged that "… there may be cases … of severe proved damage where the future is so certain and where the life of the child is so bound to be full of pain and suffering that the court might be driven to a different conclusion". The court thus established two cornerstones of modern jurisprudence. That there was no absolute parental right to control the fate of a child in these circumstances; and that there was no absolute right to life for a child.

Thus the foundations were laid for the *quality of life* to be used as a yardstick of the success of

[1] Re B (A Minor) (Wardship: Medical Treatment) (1982) FLR 117.

therapy, rather than merely the preservation of life, irrespective of its quality.

Furthermore, the case provided an early example of a balancing exercise that must be employed when determining the best interests of children. Such an exercise is as applicable to surgical decision-making as it is to judicial deliberation.

1.4.2 Dr. Arthur

No account of neonatal law can ignore the case of Dr. Leonard Arthur [9], who was charged (initially) with the murder of a child with Down's syndrome.

It must be understood that this famous case is a legal anomaly. It is a solitary criminal case nestling amongst a group of private civil medical law cases, and the outcome was unexpected.

Dr. Arthur's patient was a baby boy with uncomplicated Down's syndrome who had been rejected by his mother. On the basis that neither parent wished the child to survive, Dr. Arthur prescribed 'nursing care only', together with dihydrocodeine as required, 5 mg four hourly. The child died 2 days after birth; the cause of death being attributed to bronchopneumonia resulting from Down's syndrome.

The prosecution alleged that Dr. Arthur decided to cause the death of the child. The jury disagreed, and acquitted him after 2 h deliberation. A successful conviction had been anticipated. The case caused a furore, commentators roundly criticising [10] the judge's presentation of the legal issues to the jury. In particular, the judge failed to apprise the jury of Dr. Arthur's homicidal intent.

It could be inferred from the facts of the case that Dr. Arthur administered dihydrocodeine in order to end his patient's life. This element of intention to kill is crucial in obtaining a conviction for murder. How Dr. Arthur escaped this remains a matter of speculation amongst lawyers, who almost invariably point out [11] that the case holds no value as a precedent for future decisions.

Dr. Arthur was represented at trial by George Carman QC, the foremost defence counsel of his generation. Controversially, he advised his client *not* to give live evidence at the trial. Carman's biographer [12] reveals that in the barrister's view, "if Leonard Arthur had been asked 'When you decided on the way to treat this baby, what did you intend to happen?', Arthur would have replied 'I intended it to die'. End of story".

The case was therefore highlighted as an anomalous criminal judgement, but together with a reported case a few weeks preceding it [13], (that no action being taken against a doctor who had allegedly refused to sustain a baby with spina bifida), it brought non-treatment of newborns to the public attention. It also caused consternation amongst doctors, (some of whom) failing to appreciate the distinction that was being made between withholding treatment from a dying patient, as opposed to depriving hydration and nutrition from a child who was otherwise healthy. This error was encapsulated in a statement from the President of the Royal College of Physicians: "… I say that with a child suffering from Down's and with a parental wish that it should not survive, it is ethical to terminate life … [14]".

In reality, Dr. Arthur's mistake, in retrospect, was to conflate 'futility' with an obligation to accede to the parents' wishes that their child should not be treated. One of the legal mistakes was to allow the jury to believe that the doctor's duty to a child with Down's syndrome could be different from, and lower than, that owed to a child without the syndrome. That was and is quite wrong. The doctor's obligation is to do what is reasonable in all the circumstances of his or her patient.

1.4.3 Re C, and the Emergence of the Best Interests of the Child

Baby C was born prematurely in 1988 with hydrocephalus; at birth, her doctors considered her to be terminally ill, due to associated cerebral structural damage. However, a shunt was inserted at 2 weeks to prevent enlargement of her head. The question arose as to whether and how she should be treated in the event of shunt blockage,

or infection. It was the disparity of the advice between the local authority's social and legal services that lead to a review of the case in the Court of Appeal [15]. The child's social worker concluded that the doctors should treat C in a way "appropriate to a non-handicapped child". The legal department concluded differently, that C should "… receive treatment as is appropriate to her condition". The leading judge in the Court of Appeal was firmly in agreement with the latter view:

"You do not treat a blind child as if she were sighted, or one with a diseased heart as if she was wholly fit" [16].

The Court of Appeal was careful to issue directions that were not explicit, authorising the hospital "… to treat the minor to allow her life to come to an end peacefully and with dignity".

Re C is the case that Lord Templeman had anticipated during his judgement in Baby Alexandra. Baby C was dying, untreatable, with a quality of life far removed from that which a child with Down's syndrome could reasonably expect. Baby C's physical limitations could be predicted to lead to the demonstrably awful and intolerable life of suffering that Alexandra would hope to avoid.

The decision confirmed that there is no absolute right to life; and the full judgement provides powerful reassurance [17] that English law refuses to countenance killing patients.

1.4.4 Re J, and 'Substituted Judgements'

In the case of a 27 week premature baby [18] with severe brain damage, the question for the court was how the child should be managed in the event of a further collapse. J was born at 1.1 kg, and required ventilation for 4 weeks. Oxygen-dependent for a further 6 weeks, he was discharged home at 3 months of age, but had a cyanotic collapse at home a few days later. This acute illness, which necessitated 3 more weeks of ventilation, caused parenchymal brain damage; the prognosis was of severe spastic quadriplegia.

In an initial approach to the court, following the diagnosis of the brain damage, an order was made that it would not be in J's best interests to reintubate him "unless to do so seemed appropriate given the prevailing situation. If he developed a chest infection treatment with antibiotics and maintenance of hydration was recommended, but not prolonged ventilation" [19].

Representing the public interest, the Official Solicitor appealed this decision, on the grounds that a court was never justified in withholding consent to life-saving treatment to a child, irrespective of the quality of life which it would afterwards experience. The Court of Appeal held that a medical course of action which failed to prevent death could still be in a child's best interests. Furthermore, that there was no absolute rule that, (except when a child was already dying), neither the court nor any responsible parent could approve the withholding of life-saving treatment on the basis of the quality of the child's life". This judgement, and those that preceded it, established a precedent in English law for the withdrawal of treatment on the basis of a poor quality of life.

The court in Re J also reviewed the 'demonstrably so awful' test that had emerged in baby Alexandra's case. There was concern that this test allowed courts to determine the patient's quality of life by their own standards, whilst having no understanding of the situation from the patient's own perspective. Thus, the restrictions that severely disabled people face in their daily activities might not be as incompatible with a rewarding and fulfilling life as many judges might assume.

From this idea flowed the proposal that the anticipated quality of life that the child might have to endure should be judged *from the viewpoint of the child*; as to whether it would be intolerable *for him*.

This is described as the 'substituted judgement' test. The Court thus emphasised that any assessment of the forthcoming quality of life should be made from the assumed view of the child patient, rather than that of the adult decision-maker.

This was a radical view from a legal system based upon judges arriving at their own view of a

child's best interests, and drew wide criticism [20]. Not least, because it involves the creation of a legal fiction: Baby J had no capacity to create a 'viewpoint', so there was no way in which his supposed views could be predicted. Any assumed view would thus be entirely a creature of the judge's imagination. Nevertheless, the substituted judgement was an important milestone in the jurisprudence of withdrawal, and its effects remain visible today.

1.4.5 Re C, and the Reassertion of Parental Rights?

This case from 1996 concerns a baby with biliary atresia [21]. C underwent a Kasai procedure at three and a half weeks, but biliary drainage was not achieved. His parents were influenced by the pain and distress their son experienced in preparation for, and subsequent to, the surgery and resolved that if the Kasai was unsuccessful, they did not wish him to undergo a liver transplant. The clinicians looking after C provided a unanimous prognosis that without transplant, he would die; and thus it was in his best interests to receive a new liver when one became available.

After the failure of the portoenterostomy was recognised, C's parents left the jurisdiction, taking jobs in a distant Commonwealth country. The clinicians, via the local authority, applied to the courts seeking three decisions; (i) whether it was in C's best interests to undergo liver transplantation; (ii) permission to perform transplantation notwithstanding his mothers refusal to consent; (iii) for the child to be returned to England for this purpose. When C was 17 months old, the High Court granted all three requests, ordering his return to this country within 21 days.

C's parents appealed, and the Court of Appeal handed down the judgement 5 weeks later.

This court distinguished C from previous cases, which it asserted had been decided largely upon the *medical* best interests of the children concerned. Butler-Sloss LJ, a judge in the appeal, considered that insufficient emphasis had been given to "the enormous significance of the close attachment between the mother and baby [and whether it was]. .in the best interests of C … to direct the mother to take on this total commitment where she [did] not agree with the course proposed".

The court thus expanded the concept of 'best interests' to incorporate non-medical considerations, such as how a decision might have impact upon the relationship between a child and his parents; and arguably, on the interests of the mother.

The ruling was mainly criticised on this basis; that there was a failure sufficiently to differentiate the interests of the child and his mother … which arguably, could be in conflict. For instance, cases may occur when parents wish to move to a distant country only for reasons of employment … irrespective of the harm to their child, now unable to get access to necessary therapy. Commentators [22] suggest that the emphasis this case gives to (enhanced) parental rights is reminiscent of the situation in England in the nineteenth century. Nevertheless, the case does emphasise the need to consider the wider aspects of a child's best interests when deciding cases of treatment withdrawal.

1.4.6 Re A; Conjoined Twins, and the Impact on the Influence of Parents

In a case [23] from September 2000, the Court of Appeal was faced with the onerous task of balancing the opposing interests of two babies. Born conjoined, these ischiopagus twins shared a common aorta. The court heard that Mary, the weaker child, would die during the proposed separation from Jodie, who was given a good prognosis if separated. The court was also told that if separation was not performed, death of both twins would be inevitable in a matter of months, due to heart failure.

The reason for the approach to court was that the parents of the twins, who were Maltese, were devout Roman Catholics; they were unwilling to provide consent to allow one twin to be sacrificed in order that the other might live.

In this unusual situation, the court had to decide the correct principle to apply when there

was an overt conflict between the rights of the two girls; and between their rights, and those of their parents. Furthermore, the criminal law problem; that Mary's inevitable death would raise the inescapable inference that the surgeons had intended her death.

In respect of the conflicting rights between the babies, the majority of the judges held that their interests should be balanced, and the least detrimental alternative should be chosen. Since surgery would offer Jodie the chance of a relatively normal life, whilst not affecting Mary's fate, the court sanctioned the operation.

Considering the conflict between the interests of the girls and their parents, the court reiterated the principle that the parents' views were not determinative. In doing so, the court rejected the approach in Re C, above. In finding that the parents' religious views were not of decisive importance when considering the jeopardy a child's life, the court reaffirmed the general principle that it is the *child's* welfare that is of paramount importance. Crucially, what the Court of Appeal *did not do* was reject the wider principle in Re C; that evaluation of the child's best interests should not be confined to medical best interests.

In terms of the criminal law, the difficulty of the situation before the court was reflected in the variety of the solutions found to assert that separation, resulting in Mary's death, would be lawful. The judges were searching for a defence to what would otherwise be murder. One judge construed this as a form of self-defence; seeing "… no difference between … resort to legitimate self defence and removing the threat of fatal harm to [Jodie] presented by Mary's draining her life blood".

The court, agonising, concluded that the surgery could lawfully be performed.

In Bainham's words [24], the case:

> "[Is] one rather stark demonstration of the lack of a shared morality about these life and death decisions. For the Roman Catholic parents it was morally wrong to kill Mary. For others it was morally wrong not to bring about her death since there was a moral duty to save Jodie".

This series of cases provides the common law background for our current handling of withdrawal of care in neonatal surgical cases. These, together with statutory and professional influences have provided the principles by which we are guided in clinical practice.

1.5 Statutory Guidance

The Children Act 1989 is the cornerstone of modern children's legislation in England and Wales, and was intent on placing the child's interests, rather than those of the parents, at the centre of decision making. At the opening line of the Children Act 1989 [25] is the *paramountcy* principle:

"When a court determines any question with respect to:

(a) the upbringing of a child … the child's welfare shall be the court's paramount importance"

The Act provides, in addition, for a welfare 'checklist', by which a court must evaluate the effect of any proposed decision that will affect the child. These include:

(a) the ascertainable wishes and feelings of the child concerned (considered in the light of his age and understanding);
(b) his physical, emotional and educational needs;
(c) the likely effect on him of any change in his circumstances;
(d) his age, sex, background and any characteristics of his which the court considers relevant;
(e) any harm which he has suffered, or is at risk of suffering;
(f) how capable each of his parents, and any other person in relation to whom the court considers the question is relevant, is of meeting his needs;
(g) the range of powers available to the court under this Act in the proceedings in question.

It can immediately be seen that not every heading on the checklist is applicable to surgical

babies. But some headings from this checklist form an aide memoire for reminding us all of the matters that we should be considering when we decide whether the clinical management we propose is in the child's best interest; reminiscent of the expansion from solely medical best interests that the court in *Re C* alluded to. It should be emphasised that although the welfare checklist is applicable to withdrawal of treatment (as a "decision that will affect the child"), in the vast majority of cases, the checklist will be employed in lesser decisions.

As an example, faced with the decision as to whether stoma formation is the correct approach in a baby with NEC, the main consideration will undoubtedly be on 'surgical' grounds of safety and efficacy. However, if the result of that initial determination still leaves you in equipoise, the ability of the nurses (or the parents) to manage the stoma; the cultural implications of exteriorised bowel; and the potential problem this may cause with bonding with his parents may also require some thought. In considering these influences, you have adhered to the principles behind the creation of the welfare checklist.

1.6 Practical Application

As neonatal surgeons, we are sometimes faced with a neonate who has lost all the small bowel. It may be instructive to consider how we deal with the next steps, upon this discovery.

It is self evident that it is far better to anticipate such findings, and discuss the ramifications of total gut loss before you start the surgery on their child. Nevertheless, once the diagnosis is made at operation, it is likely that you will need to return to the parents, further to discuss the clinical situation, before making a final decision on treatment. The correct surgical decision will depend on the circumstances, but options such as central venous catheter insertion and long term parental nutrition, or prompt withdrawal of treatment are likely to be discussed.

In reality, if the clinicians (surgeons, neonatologists and nurses) and the parents are all in complete agreement as to the correct next step, the opportunity to embark upon a discussion of ethical or legal principles does not arise. However, any decision to withdraw treatment should be made only after consideration of the relevant guidelines from the Royal College of Paediatrics & Child Health [26].

These are currently undergoing revision, but provide various categories of clinical situations where it may be legal and ethical to consider withholding or withdrawing life sustaining treatment. Included in theses categories is the "No Chance" situation, where treatment will only delay death, and will not alleviate suffering; and the "No purpose" situation, where the degree of mental or physical impairment would be so great that it would be unreasonable to expect the patient to bear it.

Originally designed to assist clinicians' categorise and thus better understand the wide variety of case they face, these guidelines now begin to feel outdated, hence their revision.

It is to be expected that any unanimous decision will coincide with the best interests of the child, her welfare being paramount, and this will be enacted.

It is only when there is disagreement, with any one of these four parties failing to support the clinical decision, that further exploration of ethics and law may have to begin. In some circumstances, the disagreement is based upon an incorrect belief; and a full discussion between clinical staff and the parents may resolve this.

If the disagreement is based on fundamental differences over the child's prognosis, or over which treatment most closely corresponds with the patient's best interests, it is prudent to obtain an early second clinical opinion. This may be from within the unit, or from an adjacent hospital. If the second opinion does not resolve the disagreement, an opinion from the local clinical ethics committee (CEC) may be helpful, if only to clarify precisely the grounds of conflict.

A member of the CEC may be able to identify options that the clinicians, or parents, regard as sufficiently common ground to allow resolution of the conflict. Even if this is not achieved, a formal review by the CEC will be construed as an important and necessary step, should review by a

court later become necessary. Further consideration by experts within speciality organisations or Royal Colleges may also aid resolution. However, experience indicates that in situations where the CEC review fails to resolve the disagreement, the intervention of a court is likely to become necessary.

This is surprisingly easy to arrange, using the Trust solicitor as a starting point, to clarify the question(s) that the court is asked to decide. Referral to a court should not be seen as a failure. The court is simply another form of second opinion, and its decision will usually be welcomed by those on both sides of the disagreement, since this will bring certainty to the next clinical step, both for clinicians and parents. It should be noted that courts in England and Wales will not usually insist that any identified clinician follows a particular course of treatment. The court merely identifies the child's best interests, and clarifies what further steps would be lawful. If the judgement prescribes treatment that doctors are unwilling to provide on clinical grounds, their obligation will be to refer the patient to a centre that may be prepared to embark on the proposed treatment, and maintain the patient's condition until a transfer can be achieved.

It should be noted that referral to the medical defence organisations is not advocated in this process, since these bodies exist to promote the interests of the doctors, rather than those of the patients. It is submitted that the mechanism described will cater thoroughly for the needs of the neonatal surgical patient; if you feel that recourse to your defence body is prudent, that is clearly a matter for you.

In summary, the common law has provided us with clear guidance in resolving some of the dilemmas in caring for neonatal surgical patients, and this is strongly reinforced by statutory guidance, identifying the child's best interests as paramount.

It will rarely be possible (or proper) to solve dilemmas of treatment limitation without first establishing a broad consensus of opinion that includes those of the baby's parents. In the absence of such unanimity, recourse to the courts for a 'second opinion' will usually be of great assistance, and should be viewed as a positive step.

Conclude … the courts may have an increasing role in resolving these uncertainties.

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Embryology of Surgical Birth Defects

2

Dietrich Kluth and Roman Metzger

Abstract

Today, the embryology of numerous congenital anomalies in humans is still a matter of speculation. This is due to a number of reasons which include:

- Misconceptions and/or outdated theories concerning normal and abnormal embryology.
- A shortage of study material (both normal and abnormal embryos).
- A shortage of explanatory images of embryos and developing embryonic organs.
- Difficulties in the interpretation of serial sections.

In recent years, a number of animal models have been established which helped to overcome the shortage of both, normal and abnormal embryos. However, a general agreement on when, why and how abnormal development takes place, still does not exist. As a result, many typical malformations are still not explained satisfactorily and pediatric surgeons of all specialties are still confused when they are confronted with the background of normal and abnormal embryologic development.

Keywords

Human birth defects • Animal models • Teratology • Human embryology

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_2

2.1 General Remarks on Embryology and The Embryology of Malformations

Today, the embryology of numerous congenital anomalies in humans is still a matter of speculation. This is due to a number of reasons which include:

- Misconceptions and/or outdated theories concerning normal and abnormal embryology.
- A shortage of study material (both normal and abnormal embryos).
- A shortage of explanatory images of embryos and developing embryonic organs.
- Difficulties in the interpretation of serial sections.

In recent years, a number of animal models had been established which helped to overcome the shortage of both, normal and abnormal embryos. However, a general agreement on when, why and how abnormal development takes place, still does not exist. As a result, many typical malformations are still not explained satisfactorily and pediatric surgeons of all specialties are still confused when they are confronted with the background of normal and abnormal embryologic development.

Our understanding of the normal and abnormal development of embryos is still influenced by two theories:

- The 'biogenetic law' after HAECKEL [1].
- The theory of 'Hemmungsmissbildungen' [2].

According to Haeckel's 'biogenetic law', a human embryo recapitulates in its individual development (ontogeny) the morphology observed in all life-forms (phylogeny). This means that during its development an advanced species (a human embryo) seems to pass through stages represented by adult organisms of more primitive species [3]. This theory has been used to 'bridge' gaps in the understanding of normal embryonic development and still has an impact on the nomenclature of embryonic organs. This explains why human embryos have 'cloacas' like adult birds and 'branchial' clefts like adult fish.

The term 'Hemmungsmißbildung' stands for the theory that malformations actually represent 'frozen' stages of normal embryonic development. This theory too has been used to 'bridge' gaps in the understanding of normal embryonic development in a manner which could best describe as 'reversed embryology'. As a result, our knowledge of normal embryology stems more from pathological-anatomic interpretations of observed malformations than from proper embryological studies. The theory of the 'rotation of the gut' as a step in normal development is a perfect example for this misconception [4]. Others are: 'failed fusion of the urethral folds' [5], 'failed closure of the pleuro-peritoneal canals' (congenital diaphragmatic hernia [6],) or 'persistent cloaca' [7].

Today, a growing number of animal models exists which allows embryological studies in various embryological fields. This includes studies in normal as well as in abnormal embryos. Especially for the studies of esophageal and anorectal malformations, a number of animal models had been established.

Advanced technology in a number of fields gives much better insights into human development. This includes ultra sonography of fetuses as well as magnetic resonance imaging (MRI). For detailed embryological studies, scanning electron microscopy is still a very useful tool. STEDING published a scanning electron microscopic atlas of human embryos which provides detailed insights into normal human embryology [8]. Scanning electron microscopy is the perfect tool to document embryonic structures:

- Serial sectioning of embryos and time-consuming three-dimensional reconstructions are not necessary.
- The embryo can be studied in all three dimensions 'on-line'.
- The images and photographs are of superior quality (Fig. 2.1).

Although a number of specific tasks demand the serial section of embryos, the difficulties in the interpretation must not be underestimated. Three dimensional (3D) reconstructions, although feasi-

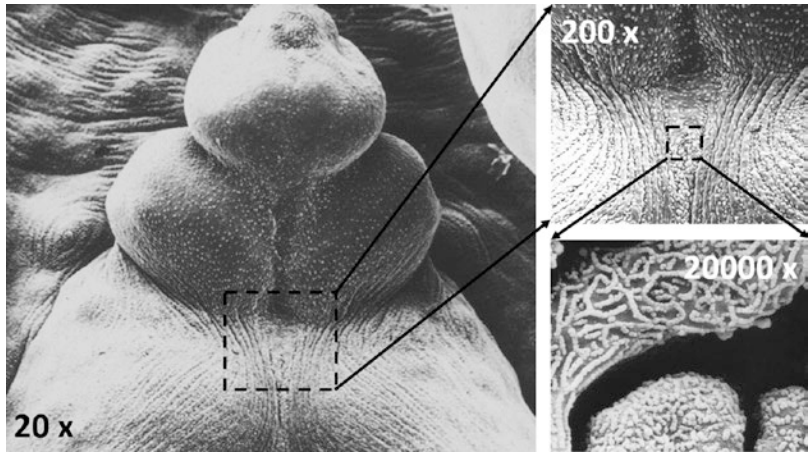


Fig. 2.1 Scanning electron microscopy (SEM) enables a wide range of magnification and a superior quality of photographs: Perineal region of a female rat, ED 20. The highest magnification shows detailed structures on the cell surface. SEM Picture © D. Kluth

ble, are tainted with a loss of information, not only caused by the sectioning itself but also by the use of 3D image software.

2.2 Animal Models Used for Applied Embyology

Over the last two decades a number of animal models had been developed with the potential to gain a better understanding of the morphology of not only of malformed but also of normal embryos. These annual models can be grouped in 5 subgroups:

(a) Embryos of different species for the study of normal embryology.
(b) Surgical models.
(c) Chemical models.
(d) Genetic models.
(e) 'Spontaneous' malformations of unclear cause.

Human embryos are rare. Human embryos displaying typical anomalies are extremely rare. Therefore, it makes sense to study specific developmental processes in embryos of animals with human like abnormalities. However, in all cases of animal models, the detailed study of normal embryos of the same species is mandatory.

We used scanning electron microscopy (SEM) in chicken, rat and murine embryos in order to study certain embryological processes of the normal embryology of the foregut, the hindgut, the midgut, the testicular descent and the development of the external genitalia. The advantage of chicken embryos is the high availability at low costs. They are easily accessible in the eggshell and further breeding is possible when the eggs are treated accordingly. Embryos of rats and mice can be obtained in comparable large numbers; however, local regulations may limit the usage of mammalian embryos.

- The chicken embryo was used to study fore gut development. The aim was to clarify weather lateral ridges occur in the developing foregut or not and, when present, if they fuse to form the trachea-esophageal septum [9, 10].
- Rat embryos were used to study i.e. developmental processes during testicular descent [11], to clarify if 'rotation' takes place during gut development [12, 13] (Fig. 2.2a), to assess the question if 'cloacas' actually exist in rat embryos and how the differentiation of the developing hindgut takes place [12, 13] (Fig. 2.2b).
- Mouse embryos where studied in the SD-mouse model (Fig. 2.3). Here, normal and abnormal hindgut development was studied [14].

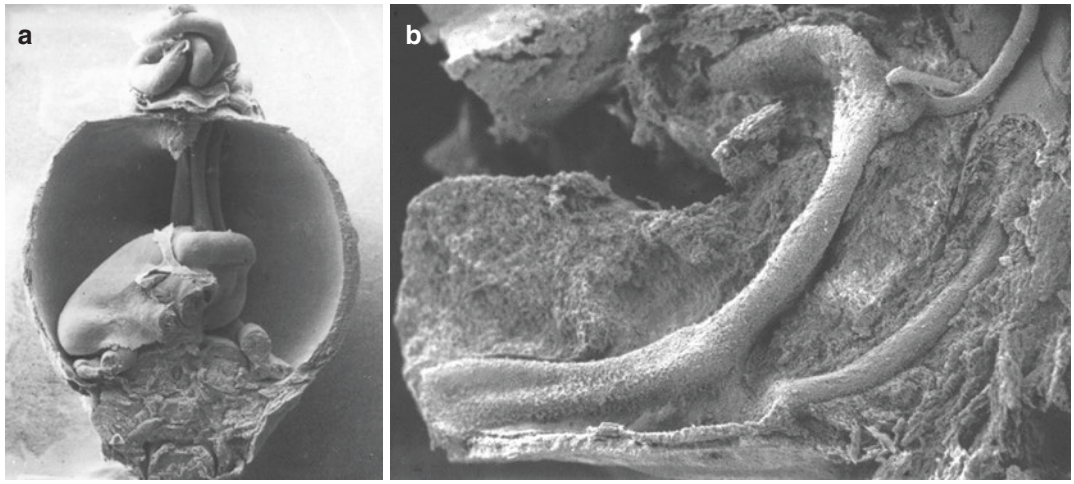
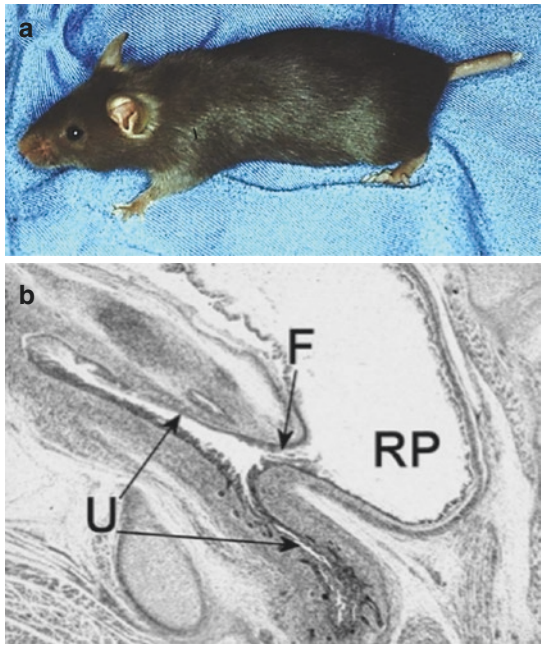


Fig. 2.2 Animal models: Rat embryos were used to study midgut development (**a**) and hindgut development (**b**). SEM Pictures © Dietrich Kluth



c

Anorectal malformations in Sd-mice

	Sd/Sd (n=25)	Sd/+ (n=20)
malformed	24	10
extreme malform.	7	0
recto-ves.fistula	10	1
cloaca	7	4
recto-urethral fistula	0	5
normal	0	8
not documented	1	2

Fig. 2.3 Animal models: SD-mice were used to study ano-rectal malformations. (**a**) Notice the short tail in a heterocygotic SD mouse. (**b**) Histology of the pelvic organs in a newborn heterozygous SD-mouse. The features of an anorectal malformation with recto-urethral fistula (F) and a blind ending rectal pouch (RP) are detectable. *U* urethra. (**c**) The spectrum of malformations seen in SD-Mice. Picture © Dietrich Kluth

In the past, the chicken was an important surgical model to study embryological processes. As mentioned above, the easy access to the embryo, its broad availability and its cheapness makes it an ideal model for experimental studies. It has been widely used by embryologist especially in the field of epithelial/mesenchymal interactions [15–17]. Pediatric surgeons have used this model to study morphological processes involved in intestinal atresia formation [18, 19], gastroschisis [20] and Hirschsprung's disease [21]. The Czech embryologist LAMEZ [22] used chicken embryos in order to induce tracheal agenesis with tracheo-esophageal fistula (Fig. 2.4).

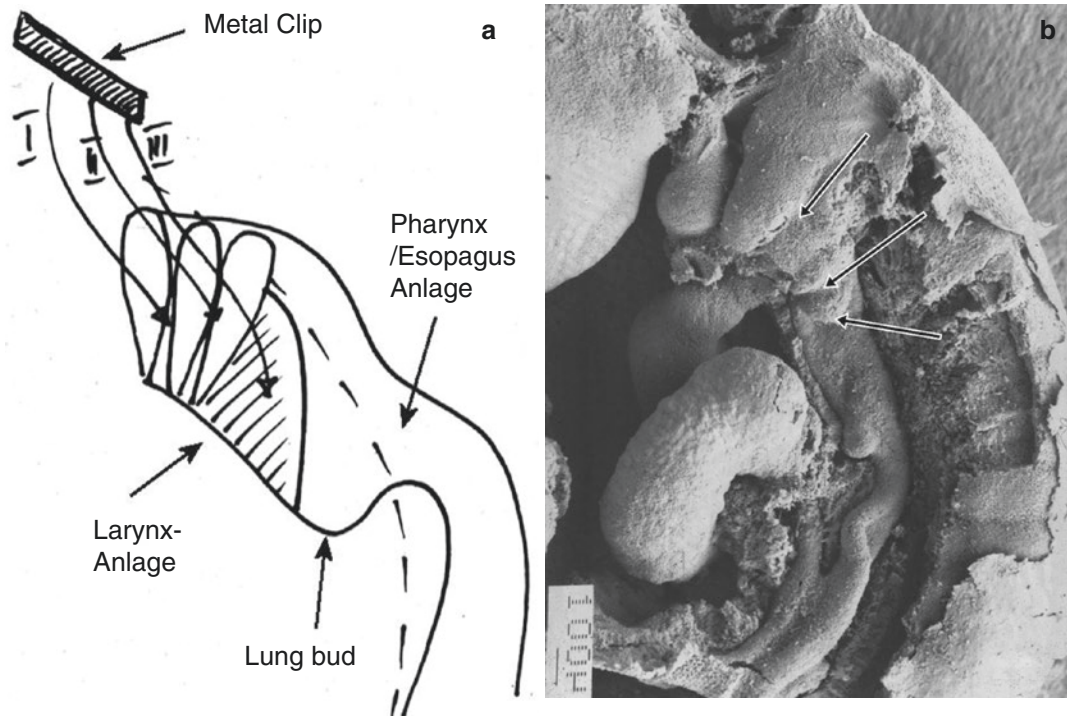


Fig. 2.4 Animal models: Experimental embryology in chicken embryos. Metal clips were used to induce tracheal atresia 18. (**a**) Schematic drawing of the technique, (**b**) arrows indicate the area were the clips were positioned (SEM picture of a chicken embryo). SEM Picture and schematic drawing © Dietrich Kluth

Apart from these purely embryonic models, a large number of fetal models had been developed in the last 30 years. Although they were mainly created to study the feasibility of fetal interventions [23], they also added to our current knowledge of normal and abnormal fetal development and fetal organ systems.

It is well known that a number of chemicals (drugs, chemical fertilizers) can alter normal development of humans and animals alike. Some of these had been used to induce malformations similar to those found in humans. Most important are today:

(a) Adriamycin [24–26]
(b) Etretinate [27, 28]
(c) All-trans retinoic acid (ATRA) [29–31]
(d) Ethylenethiourea [32, 33]
(e) Nitrofen [34–38]
(f) Suramin and Trypan [39, 40]

Models (a-d) have been used to study atresia formation in the esophagus, the midgut and the anorectum. Model (e) was developed to study malformations of the diaphragm, the lungs, the heart and kidneys (hydronephrosis). Model (f) was used in chicken embryos to study the formation of cloacal extrophies.

We used the nitrofen model to study the morphology of diaphragmatic hernia formation in rat embryos (Fig. 2.5).

Many aspects make genetic models the ideal model for the studies of abnormal development. In the past a number of genetic models had been used for embryological studies of malformations. While older models were mostly the product of spontaneous mutations, newer models are, in most instances, the result of genetic manipulations mainly in mice (transgenic mice). The following models had been used by pediatric surgeons:

(a) Models of spontaneous origin: The SD-mouse model [41, 42]. In the SD-mouse model ano-rectal malformations are combined with anomalies of the kidneys, the spine and the external genitalia (Fig. 2.3).

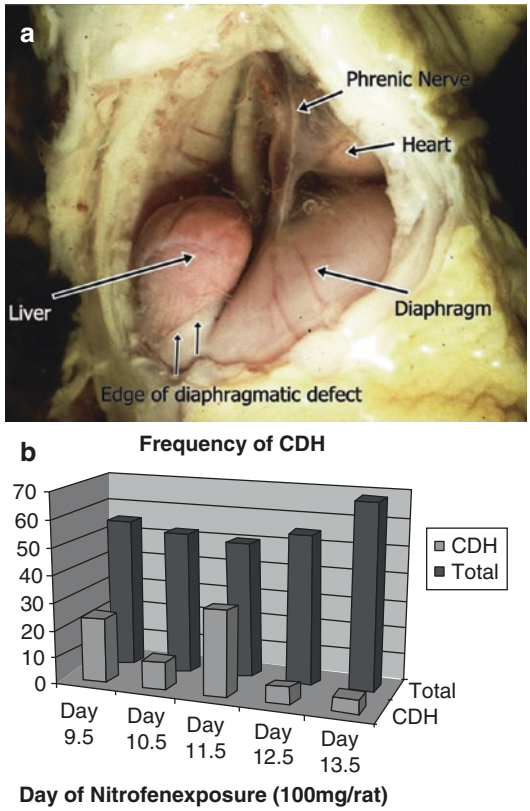


Fig. 2.5 Animal models: The nitrofen model of diaphragmatic hernia. (**a**) Newborn rat with diaphragmatic hernia after nitrofen exposure at day 11.5. (**b**) Results of nitrofen exposure on days 9.5, 10.5, 11.5, 12.5 and 13.5. Most hernias were seen after nitrofen exposure on day 11.5. Picture © Dietrich Kluth

(b) Inheritance models: the pig model of anal atresia [43, 44]. In pigs, ano-rectal malformations are seen quite frequently. One out of 300 newborn piglets present with ano-rectal malformations without evidence of genetical alterations.
(c) 'Knock-out' models.
(d) Viral models.

The number of transgenic animal models is currently growing fast. For pediatric surgeons those models are of major importance, which result in abnormalities of the fore- and hindgut. Here, interference with the Sonic hedgehog (Shh) pathway has proven to be very effective [45–47]. There are two ways to interfere with that pathway:

- Targeted deletion of Sonic hedgehog [45, 46].
- Deletion of one of the three transcription factors Glil, Gli2 and Gli3 [46, 47].

It has been demonstrated, that targeted deletion of Sonic hedgehog resulted in homozygous Shh null mutant mice in the formation of foregut malformations like esophageal atresia/stenosis, tracheo-esophageal fistulas, and tracheal/lung anomalies [48]. In the hindgut, the deletion of Sonic hedgehog caused the formation of 'cloacas' [46], while Gli2 mutant mice presented with the 'classic' form of anorectal malformations and Gli3 mutants showed minor forms like anal stenosis [46, 47]. Interestingly, the morphology of Gli2 mutant mice embryos resembles that of heterocygous SD-mice embryos while Shh null mutant mice embryos had morphological similarities with homocygous SD-mice embryos. It is interesting to note that after administration of adriamycin abnormal pattern of Shh distribution could be demonstrated in the developing foregut [48].

Recently, BOTHAM et al. studied developmental disorders of the duodenum in mutations of the fibroblast growth factor receptor 2 gene (*Fgfr2IIIb*) [49]. They noted an increased apoptotic activity in the duodenal epithelium of *Fgfr2IIIb −/−* embryos at day 10.5, followed by a disappearance of the endoderm at day 11.5. Interestingly, the duodenal mesoderm also disappeared within 2 days and an atresia was formed. Similar processes had been observed in newborn piglets whose esophageal epithelium was removed via endoscopy [50, 51]. This procedure resulted in esophageal atresias in these piglets.

In humans, viral infections are known to cause malformations. Animal models that use viral infections important for pediatric surgeons are very rare. One exception is the murine model of extra hepatic biliary atresia (EHBA) [52]. In this model, newborn Balb/c mice are infected with rhesus rotavirus group A45. As a result, the full spectrum of EHBA develops as it is seen in newborn with this disease. However, this model is not a model to mimic failed embryology. But it highlights the possibility that malformations are not caused by embryonic disorders but caused by fetal or even postnatal catastrophes.

In chicken embryos, a number of spontaneous malformations can be observed. It is not quite clear which processes cause them. One reason may be a prolonged storage (more than 3 days) in fridges below 8° C before breeding is started [53].

Spontaneous malformations of the head anlage (i.e. double anlage of the head), the anlage of the heart as well as abnormalities of the embryonic position (hererotaxia) are frequently seen [53].

This part on embryology and animal models highlights not only the importance to study embryos with experimental malformations but also the study of normal animal embryos. Today, much information in current textbooks on human embryology stems actually from studies done in animals of varies species. Many of these are outdated. The wide use of transgenic mice in order to mimic congenital malformations makes morphological studies of the organ systems in normal mice mandatory. Otherwise the interpretation of the effects by deletion of genetic information can be very difficult or even misleading.

2.3 Scanning Electron Microscopic Atlas of Normal and Abnormal Development in Embryos

In this section we want to present examples of normal and abnormal development as we have seen them in our studies in our labs over the past 30 years using scanning electron microscopy (SEM). We use the form of an embryological atlas following the old motto 'A picture says more than a thousand words'. We focus on the following developmental processes:

- Normal and abnormal foregut development (chicken embryos).
- Normal and abnormal development of the diaphragm (rat embryos).
- Development of the midgut (rat embryos).
- Normal and abnormal development of the hindgut (mice and rats).
- The development of the external genitalia and the urethra (rat embryos).
- Testicular descent (rat embryos).

2.3.1 Normal Foregut Development

Traditionally, foregut malformations like esophageal atresias and trachea-esophageal fistulas are explained by a faulty formation of the so-called 'tracheo-esophageal septum'. It is believed that normal septation takes place in two steps:

1. Lateral endodermal ridges appear in the primitive foregut which fuse and form the trachea-esophageal septum.
2. This solid endodermal septum is partly removed by apoptosis and substituted by mesenchymal cells.

This theory had been described in detail by ROSENTHAL [54] and SMITH [55]. However, neither ZAW TUN [56] nor O'RAHILLY and MÜLLER [57] were able to confirm these sequences of embryological events. According to them, the term 'separation' is a misnomer as the formation of the trachea is simply the result of the down growth of the respiratory diverticulum [58].

Using SEM, we studied the normal development of the foregut in chicken embryos [9, 19, 59].

The first goal of these studies was to see if lateral endodermal ridges appear inside the foregut and if they fuse (Fig. 2.6). However, in our studies we were unable to identify ridges in the lateral foregut wall. Furthermore, signs of fusions of lateral foregut components were also not seen. As no signs of fusion can be demonstrated in the foregut, theories dealing with improper formations of the trachea-esophageal septum are obsolete [56].

The second goal was to visualize the early formation of the lung bud (Fig. 2.7). In our series of embryos we could demonstrate that after the formation of the early lung anlage two lung buds appear, which are the forerunners of the bronchi. The anlage of the trachea itself is seen later as the floor of a 'common foregut' chamber [10]. Thus, not the trachea but the bronchi are the first organs of the respiratory tree that develop. This speaks against the idea of a simple down growth of the tracheal anlage as assumed by ZAW TUN and O'RAHILLY and MÜLLER [56, 57].

The third goal was to identify possible mechanisms of differentiation of the foregut into larynx, pharynx, trachea and esophagus. In our embryos, we could identify typical markers in the foregut (Fig. 2.8). In the dorsal aspect of the foregut a fold appears which

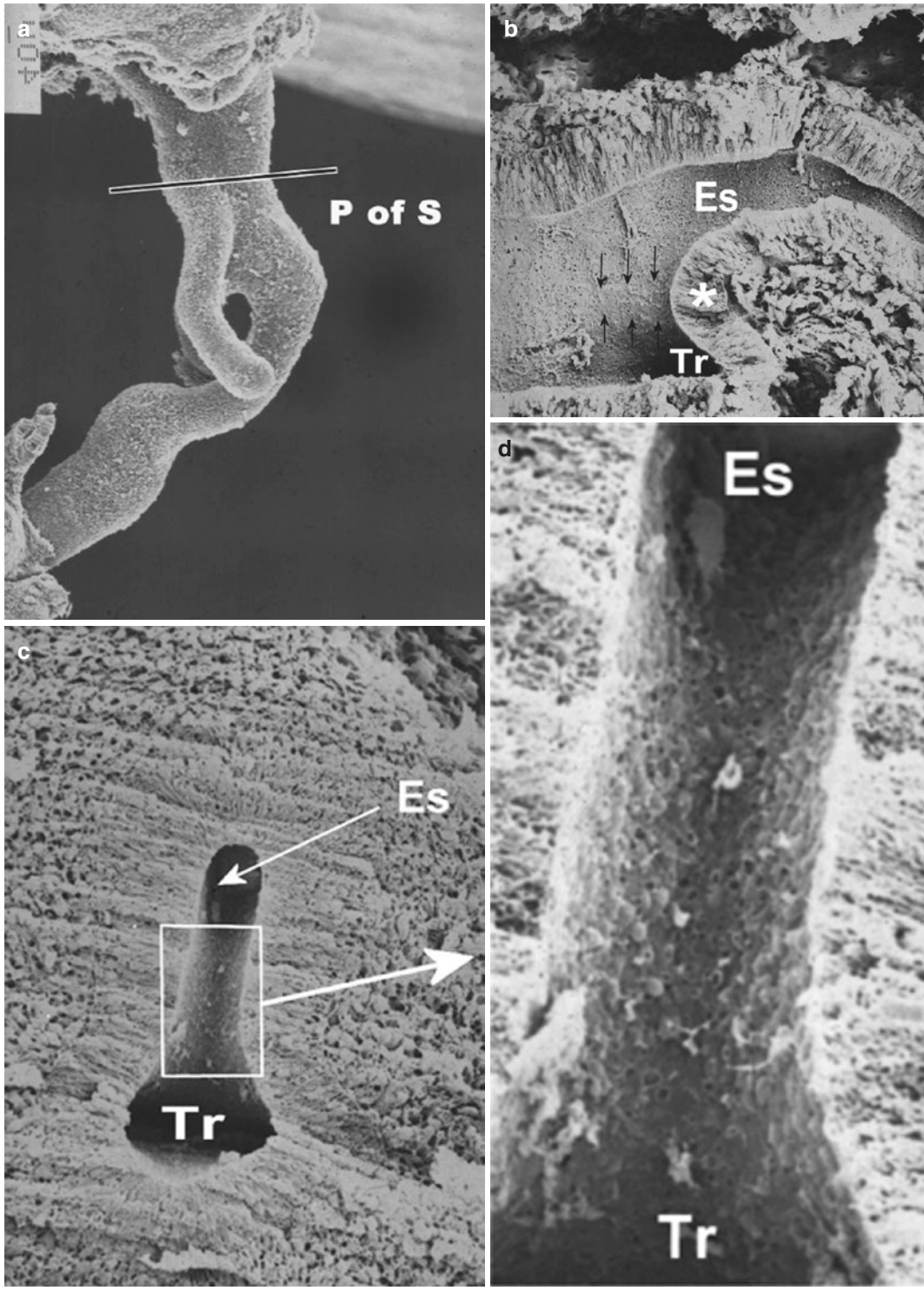


Fig. 2.6 Embryology of the esophagus: SEM studies in chicken embryos. (**a**) Foregut of a chicken embryo of stage20/21, 3.5 days old. (**b**) The foregut is opened from lateral. The inner surface of the foregut is seen. Notice the absence of lateral folds (*arrows*). *ES* esophagus, *TR* trachea, *Asterisk* (*) tip of the trachea-esophageal fold. (**c**) View into the foregut from cranial. The tip of the trachea-esophageal fold can be seen. Notice the absence of fusion (higher magnification in D). *ES* esophagus, *TR* trachea. SEM Pictures © Dietrich Kluth

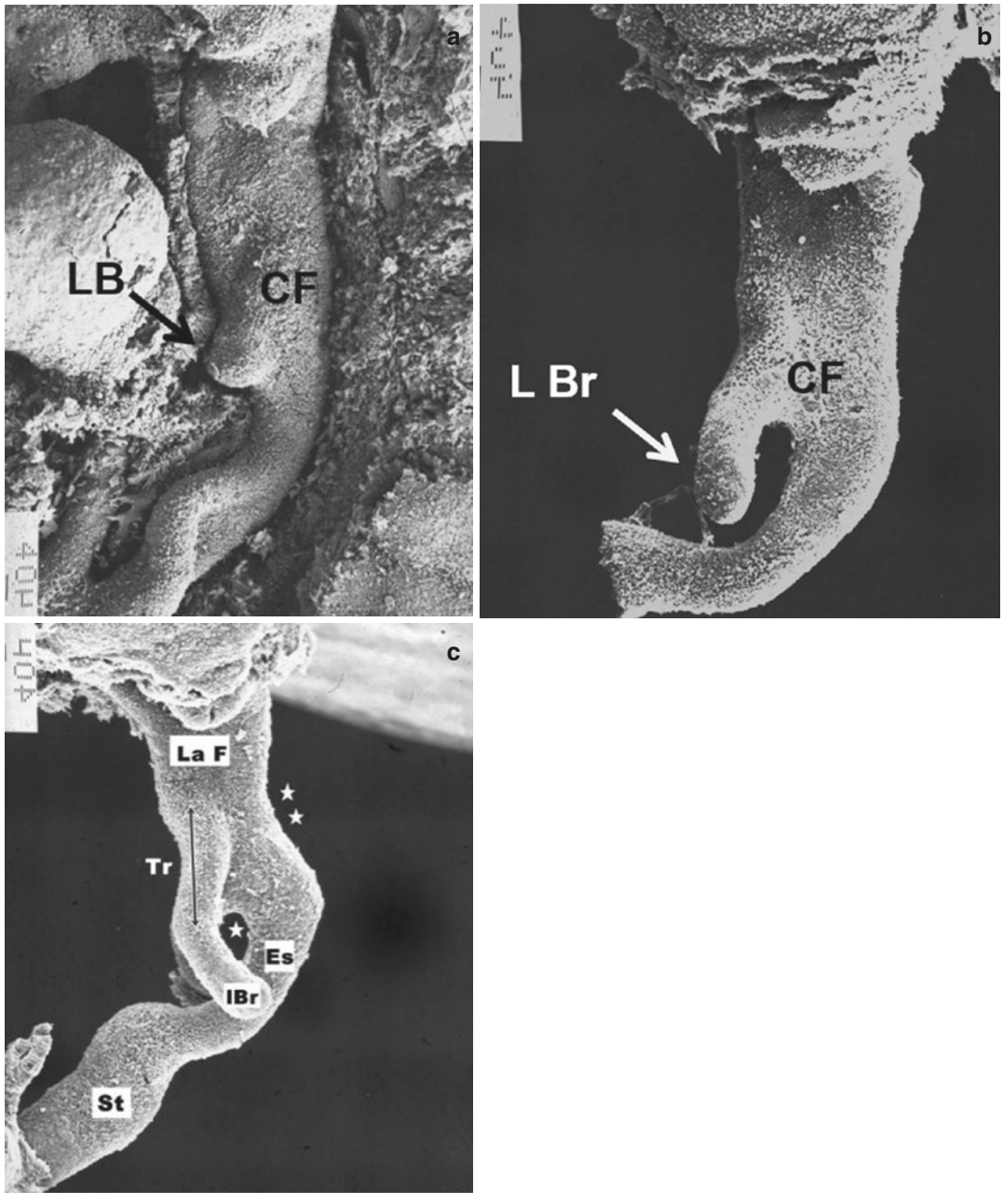


Fig. 2.7 Embryology of the esophagus: Formation of the respiratory tract. (**a**) Lung buds are the forerunners of the bronchi (LB). *CF* common space of foregut. (**b**) The bronchi start to develop (L Br). A trachea is not visible yet. *CF* common space of foregut. (**c**) The trachea (Tr) is still part of the common foregut. *LaF* larynxanlage, *ES* esophagus, *L Br* bronchi, *St* stomach, *Double Asterisk* fold which marks the border between pharynx and esophagus. SEM Pictures © Dietrich Kluth

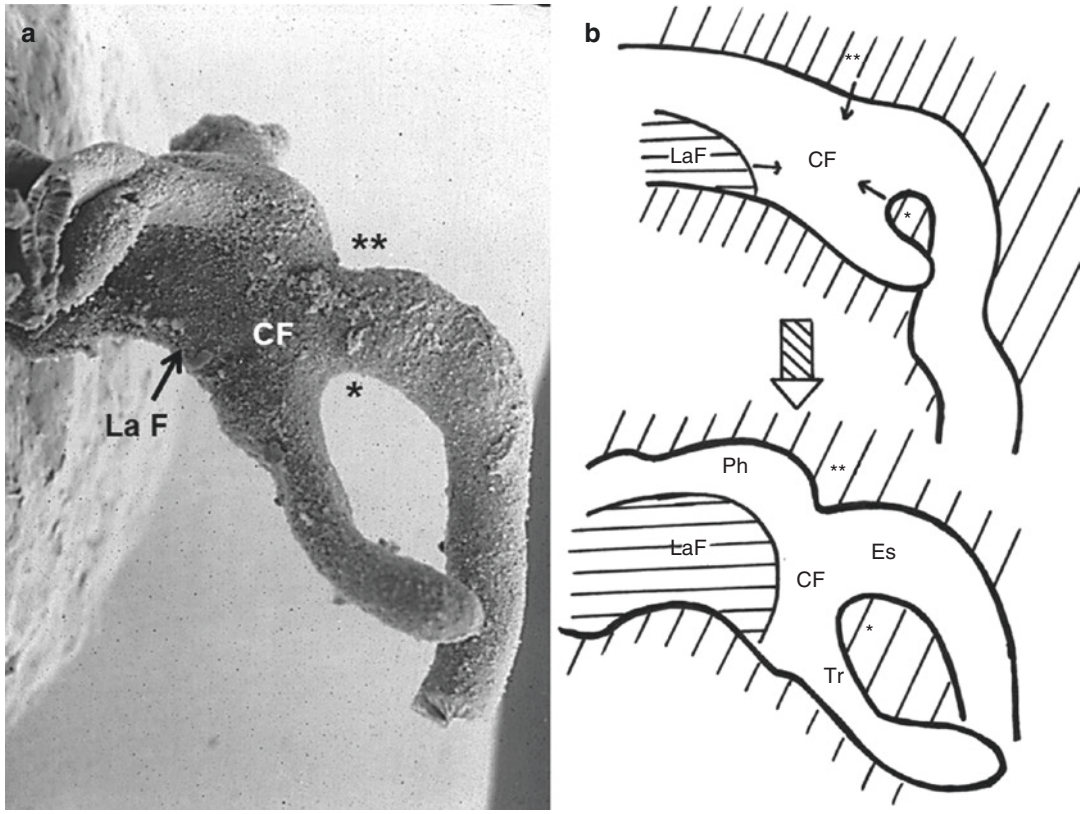


Fig. 2.8 Embryology of the esophagus: The common space of the foregut is reduced in size by a system of folds. (**a**) The trachea is still part of the common space (CF). *LaF* Larynxanlage. (**b**) The size of the common foregut (CF) is reduced by the growth of folds, which are formed by the larynx fold (LaF) from cranial, the trachea-esophageal fold (*asterisk*) from caudal, and the fold between phayrynx and esophagus (*double asterisk*) from dorsal. SEM Picture and schematic drawing © Dietrich Kluth

marks the borderline between pharynx and esophagus. Cranially the larynx develops and caudally, a fold appears between the developing trachea and the esophagus. In the next developmental steps these folds approach each other but do not fuse. As a result, the area of the common foregut is reduced in size and later forms the pharyngo-tracheal canal [5].

2.3.2 The Formation of Esophageal Atresia

Although a number of models for abnormal foregut development exist, a clear morphological description of the embryological events that finally lead to esophageal atresias, are still missing. Based on our observations, the development of the malformation can be explained by disorders either of the formation of the folds or of their developmental movements [9, 10, 59]:

- Atresia of the esophagus with fistula (Fig. 2.9c1):
- The dorsal fold of the foregut bends too far ventrally. As a result the descent of the larynx is blocked. Therefore the common tracheo-esophageal space remains partly undivided and lies in a ventral position. Due to this ventral position the common space differentiates into trachea.
- Atresia of the trachea with fistula (Fig. 2.9c2):

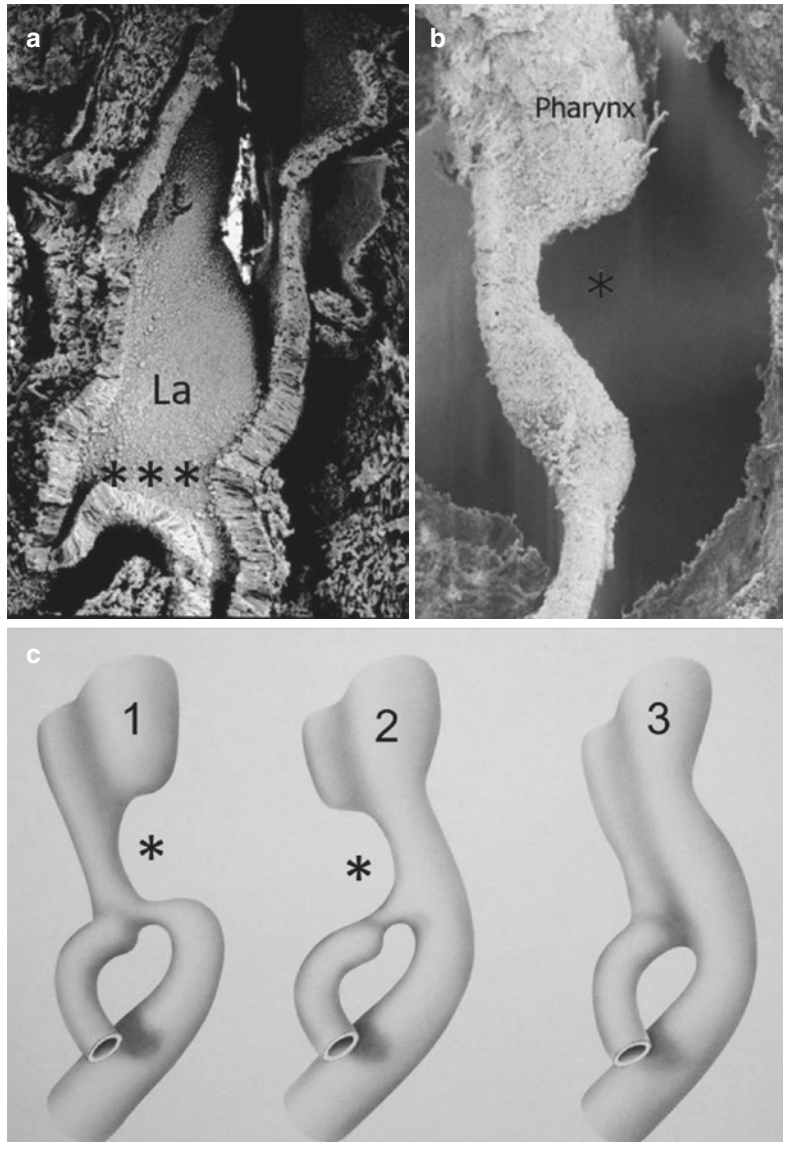


Fig. 2.9 Embryology of the esophagus: Hypothetical formation of foregut malformations. (**a**) Normal foregut of a chicken embryo, view from lateral into the foregut. Notice the reduced size of the common foregut space (*Triple Asterisk*) due to the development of the folds. *La* Larynx. (**b**) Chicken embryo with a spontaneous foregut malformation. The Pharynx ends blindly. Part of the trachea is in normal position and of tracheal size. The dorsal part of the common foregut space is missing (*Asterisk*). (**c**) Hypothetical explanation of foregut maldevelopment. (C1) The dorsal fold (*Asterisk*) between pharynx and larynx grows too deep into the common foregut space. Consequently the rest of the common space develops into trachea and an esophageal atresia with lower fistula develops. (C2) The common foregut space is reduced in size from ventral (*Asterisk*). Consequently the rest of the common space develops into esophagus and a tracheal atresia with fistula occurs (very rare). (C3) Impaired development of the dorsal fold and the tracheo-esophageal fold leads to an undivided common foregut space and a laryngo-tracheo-esophageal cleft. SEM Pictures and schematic drawing © Dietrich Kluth

- The foregut is deformed on its ventral side. The developmental movements of the folds are disturbed and the tracheo-esophageal space is dislocated in a dorsal direction, where it differentiates into esophagus.
- Laryngo-tracheo-esophageal clefts (Fig. 2.9c3): Faulty growth of the folds results in the persistence of the primitive tracheo-esophageal space.

In our collection of chicken embryos we came across an embryo with abnormal foregut features (Fig. 2.9b). When compared to normal embryos of the same age group (Fig. 2.9a), the following statements can be made: (a) obviously, the pharynx ends blindly. (b) The dorsal part of the common foregut space is missing. (c) the ventral part of the common space has the size of a trachea. (d) This foregut looks like the hypothetical form C1 in Fig. 2.9.

2.3.3 Normal Diaphragmatic Development

The traditional theories of diaphragmatic development have been summarized by KLUTH et al. [60]. Using SEM, we have recently restudied the diaphragmatic development. For practical reasons, it is essential to note that the early diaphragm consists of two parts:

- The septum transversum which, in young embryos, is identical to the floor of the pericardium.
- The structures that surround the pleural cavity. They are:
  - The Post Hepatic Mesenchymal Plate (PHMP) [38], which covers the dorsal aspect of the liver and is in continuity to the septum transversum ventrally and cranially.
  - The pleoro-peritoneal fold (PPF) which separates the pleura from the peritoneal cavity. This fold connects ventrally to the septum transversum and the PHMP and dorsally to the mesonephric ridge [61]. This PPF is a structure that is identical to the pleuro-peritoneal membrane of the old literature [60].
  - The dorsal mediastinum which contains the esophagus, the trachea and the Aorta.

According to our SEM studies, the PHMP plays the most important role in normal diaphragmatic development. In Figs. 2.10 and 2.11 the closure process of the pleuro-peritoneal openings (PPO) is depicted. At embryonic day (ED) 13,

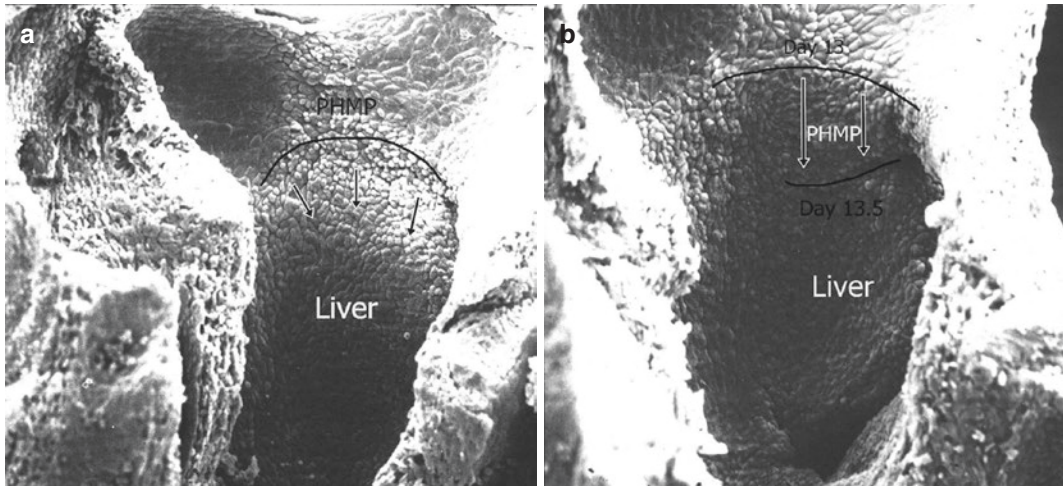


Fig. 2.10 Normal development of the diaphragm: Caudal growth of the posthepatic mesenchymal plate (PHMP) [38]. (**a**) Rat embryo, ED 13. View at the dorsal part of the diaphragm. The dorsal diaphragm is short. The black line in marks the caudal border of the PHMP. Arrows indicate the direction of future PHMP growth. Note the large area of liver still uncovered by the PHMP. (**b**) Rat embryo 13.5 days. Note the caudal growth of the PHMP within 12 h (second dark line). The uncovered liver is markedly smaller. SEM Pictures © Dietrich Kluth

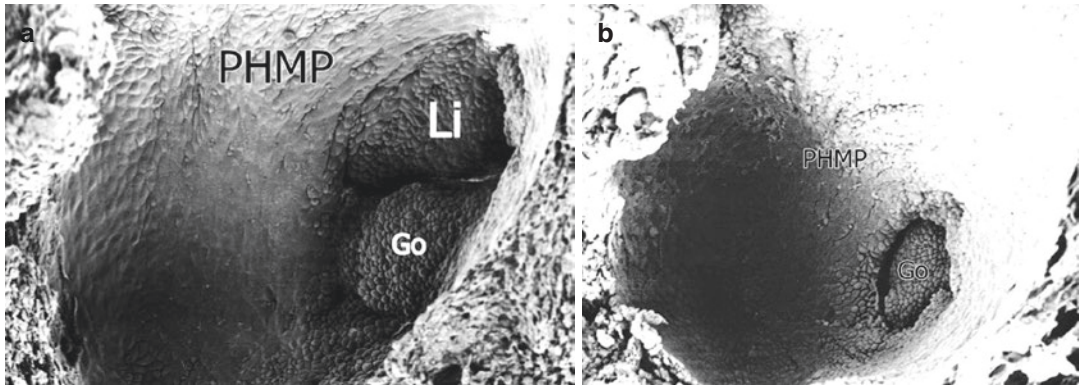


Fig. 2.11 Normal development of the diaphragm: Closure of the pleuroperitoneal openings (PPO). Rat ED 15 (**a**) and ED 16 (**b**). Most of the liver (Li) is covered by the posthepatic mesenchymal plate (PHMP). At ED 16 the only intra-abdominal organ seen is the tip of the gonads (Go). SEM Pictures © Dietrich Kluth

the formation of the PHMP and its lower border can be seen (Fig. 2.10a). The PHMP then expands dorso-laterally at embryonic day 13.5 (Fig. 2.10b), establishing a new lower border.

In Fig. 2.11 the final closure of the PPO is shown. In this process the PHMP starts to cover the last free areas of the liver (Fig. 2.11b). In this process, the PPF plays only a minor role.

In the literature, the nomenclature of the various parts of the diaphragm is confusing. We use the term PPF for a structure which was formally known as pleuro-peritoneal membrane [60, 61]. The term PPF is used differently by GREER and co-workers [62]. Their PPF is very similar to the PHMP as described by IRITANI and us but seems to include the ventral part of our PPF.

2.3.4 Abnormal Diaphragmatic Development

In the past, several theories were proposed to explain the appearance of postero-lateral diaphragmatic defects:

- Defects caused by improper development of the pleuro-peritoneal membrane [63, 64]
- Failure of muscularization of the lumbocostal trigone and pleuro-peritoneal canal, resulting in a 'weak' part of the diaphragm [64, 65]
- Pushing of intestine through postero-lateral part (foramen of Bochdalek) of the diaphragm [66]
- Premature return of the intestines into the abdominal cavity with the canal still open [64, 65]
- Abnormal persistence of lung in the pleuro-peritoneal canal, preventing proper closure of the canal [67]
- Abnormal development of the early lung and posthepatic mesenchyme, causing non-closure of pleuro-peritoneal canals [38]

Of these theories, failure of the pleuro-peritoneal -membrane to meet the transverse septum is the most popular hypothesis to explain diaphragmatic herniation. However, using SEM techniques [60, 61] we could not demonstrate the importance of the pleuro-peritoneal membrane for the closure of the so-called pleuro-peritoneal canals (Fig. 2.11).

It is still speculated, that delayed or inhibited closure of the diaphragm will result in a diaphragmatic defect that would allow herniation of gut into the fetal thoracic cavity. In a series of normal staged embryos, we measured the width of the pleuro-peritoneal openings and the transverse diameter of gut loops [68]. On the basis of these measurements we estimated that a single embryonic gut loop requires at least an opening of 450 μm size to herniate into the fetal pleural cavity. However, in none of our embryos the observed pleuro-peritoneal openings were of appropriate dimensions. This means that delayed or inhibited closure of the pleuro-peritoneal canal cannot result in a diaphragmatic defect of suffi-

cient size. Herniation of gut through these openings is therefore impossible. Thus the proposed theory about the pathogenetic mechanisms of congenital diaphragmatic hernia (CDH) development lacks any embryological evidence. Furthermore the proposed timing of this process is highly questionable [66].

2.3.5 Animal Model

Recently, an animal model for diaphragmatic hernia has been developed [34–38] using nitrofen as noxious substance. In these experiments CDHs were produced in a reasonably high percentage of newborns [36]. We collected a number of affected embryos of different age groups and studied these using SEM [68, 69]. Our results (Figs. 2.12 and 2.13) are as follows:

- Timing of diaphragmatic defect appearance. IRITANI [38] was the first to notice that nitrofen-induced diaphragmatic hernias in mice are not caused by an improper closure of the pleuro-peritoneal openings but rather the result of a defective development of the post-hepatic mesenchymal plate (PHMP). In our study in rats, clear evidence of disturbed

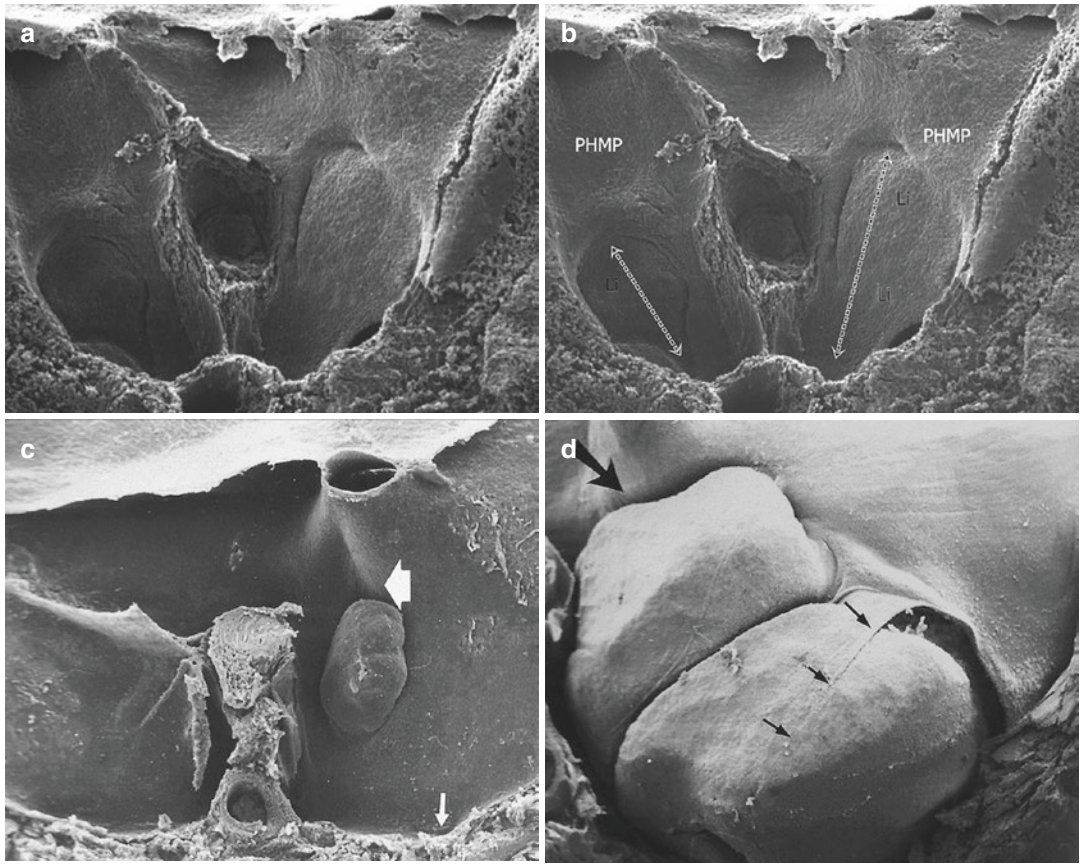


Fig. 2.12 Dorsal diaphragms after nitrofen exposure at rat ED 11.5. (**a**, **b**) Rat embryo at ED 14. The abnormal anlage of the right diaphragm is easy to see. Dotted arrows mark the diameter of the uncovered liver (Li). On the left, the development of the posthepatic mesenchymal plate (PHMP) is normal. On the right, the PHMP stopped to grow to caudal. (**c**) Rat ED 17. A small hernia (liver) can be seen. Note the position close to the vena cava (*large arrow*). The small arrow points to the closed pleuroperitoneal openings (PPO). (**d**) Rat ED 18. The hernia is big. Two lobes of liver project into the thorax. The big arrow points to the vena cava. *Small arrows* mark the border of the PPO, which is open due to the ingrowth of the liver. Note that the size of the diaphragmatic defect is much larger than the PPO itself. SEM Pictures © Dietrich Kluth

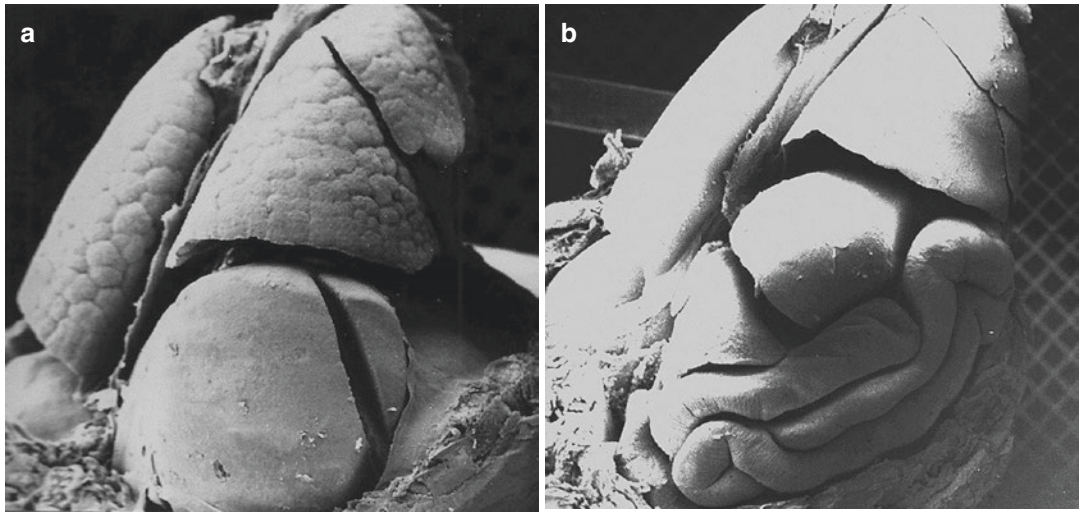


Fig. 2.13 Huge diaphragmatic hernias after nitrofen exposure. (**a**) Rat ED 20. In none of our embryos, gut could be found in this age group. (**b**) Rat ED 21. In this age group and older animals, gut can be found inside the thoracic cavity. SEM Pictures © Dietrich Kluth

development of the diaphragmatic anlage was seen on ED 13 on the left and ED 14 on the right diaphragm anlage (Fig. 2.12) [68, 70]. In all embryos affected, the PHMP was too short. This age group is equivalent to 4–5 week old human embryos [68, 69].

- Location of diaphragmatic defect. In our SEM study, the observed defects were localized in the area of the PHMP (Fig. 2.12). We identified two distinct types of defects: (1) large 'dorsal' defects and (2) small 'central' defects [68, 69]. Large defects extended into the region of the pleuro-peritoneal openings. In these cases, the closure of the pleuro-peritoneal openings was usually impaired by the massive ingrowth of liver (Figs. 2.12 and 2.13). If the defects were small, they were consistently isolated from the pleuro-peritoneal openings which closed normally at the 16th or 17th day of gestation. Thus, in our embryos with CDH, the region of the diaphragmatic defect was a distinct entity and was separated from that part of the diaphragm where the pleuro-peritoneal 'canals' are localized. We conclude therefore that the pleuro-peritoneal openings are not the precursors of the diaphragmatic defect.
- Why lungs are hypoplastic? Soon after the onset of the defect in the 14-day-old embryo, liver grows through the diaphragmatic defect into the thoracic cavity (Fig. 2.12). This indicates that from this time on the available thoracic space is reduced for the lung and further lung growth is hampered. In the following stages, up to two- thirds of the thoracic cavity can be occupied by liver (Fig. 2.13a). Herniated gut was found in our embryos and fetuses only in late stages of development (21 days and newborns) (Fig. 2.13b). In all of these, the lungs were already hypoplastic, when the bowel entered the thoracic cavity [68, 69].

Based on these observations, we conclude that the early ingrowth of the liver through the diaphragmatic defect is the crucial step in the pathogenesis of lung hypoplasia in CDH. This indicates that growth impairment is not the result of lung compression in the fetus but rather the result of growth competition in the embryo: the liver that grows faster than the lung reduces the available thoracic space. If the remaining space is too small, pulmonary hypoplasia will result.

2.3.6 Normal Hindgut Development

As in the foregut, a process of septation has been postulated for the proper subdivision of the 'cloaca' into the dorsal anorectum and the ventral sinus urogenitalis. Disorders in this process of differentiation are thought to be the cause of cloacal anomalies such as persistent cloaca and anorectal malformations [7].

However, for many years, this process of septation has been under dispute. Some authors [71, 72] believe that the descent of a single fold separates the urogenital part from the rectal part by ingrowth of mesenchyme. Others [73] think that lateral ridges appear in the lumen of the cloaca, which progressively fuse along the midline and thus form the septum. Van de PUTTE [74] denied the existence of any process of septation.

In the recent years we studied the cloacal development in rats and SD-mice embryos using SEM techniques [13, 14, 75].

The first goal of these studies was to see if lateral ridges appear inside the 'cloaca' and if these actually fuse to form an endodermal septum (Fig. 2.14). As in the foregut of chick embryos, we were unable to see lateral ridges (Fig. 2.14c)

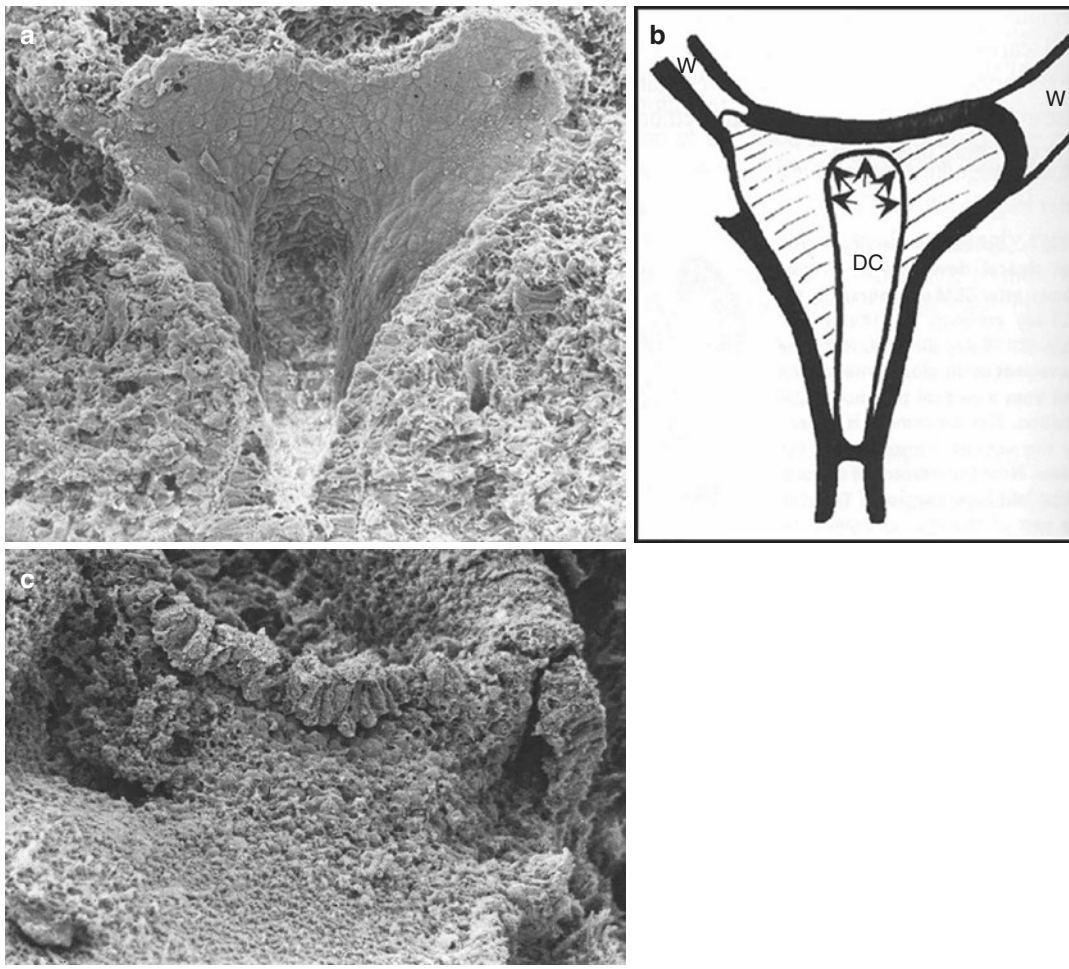


Fig. 2.14 Normal development of the hindgut. Rat ED 14. (**a**) The ventral part of the cloaca is removed. As in the foregut, signs of fusion are lacking. (**b**) Schematic drawing of the situation in A. (**c**) After removal of the lateral wall of the cloaca, internal ridges which could form an uro-rectal septum, are not detectable. SEM Pictures and schematic drawing © Dietrich Kluth

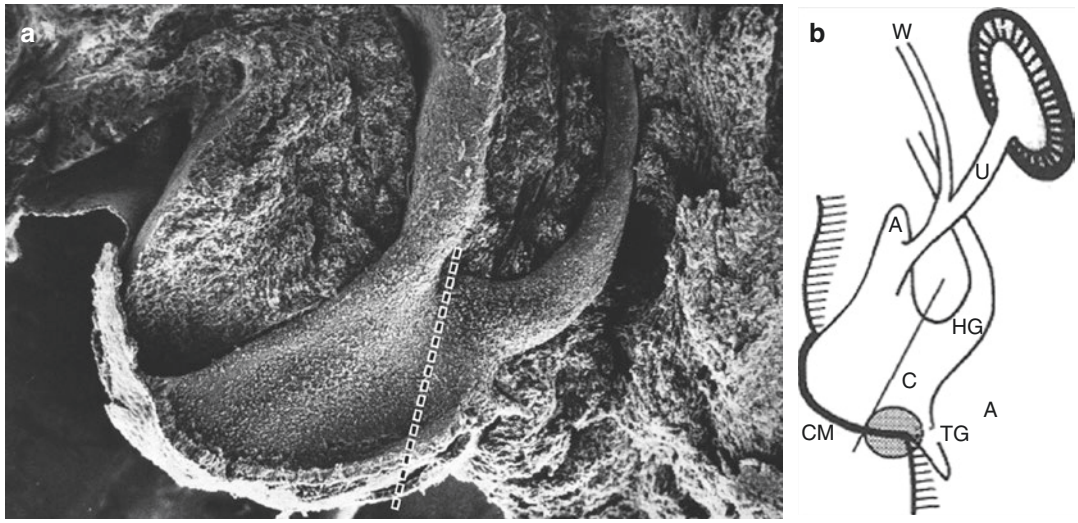


Fig. 2.15 Normal development of the hindgut. (**a**, **b**) The 'cloaca' (C) in a rat embryo ED 14.5 has the following features: Proximal urethra (PU), distal urethra (DU), rectum (HG), tail gut (TG), cloacal membrane (CM). The line marks the border between rectum and urethra. The schematic drawing shows the situation in a rat embryo ED 14. Note that the 'cloaca' is not equally divided by the line. The gray area in the schematic drawing marks the area of the future anus. It lies in the dorsal part of the cloacal membrane close to the tail fold. SEM Pictures and schematic drawing © Dietrich Kluth

projecting into the cloacal lumen. Signs of median fusion of lateral cloacal parts were also lacking (Fig. 2.14a,b). However, in contrast to Van de PUTTE [74] our SEM studies indicate that down growth of the tip of the uro-rectal fold takes place (Fig. 2.15a,b), although it is probably not responsible for the formation of cloacal malformations.

Our findings on normal embryology of the hindgut were:

- The 'cloaca' is not subdivided into two equal parts (Fig. 2.15a, b). The much larger ventral part gives rise to the future distal urethra.
- The dorsal 'cloaca' contains the future ano-rectal region. The future anal opening is situated in the dorsal part of the 'cloacal' membrane, close to the tail fold (Fig. 2.15b).

2.3.7 Abnormal Hindgut Development

As already mentioned, a number of animal models exist which allow embryological studies of abnormal hindgut development. In our studies we used embryos obtained from SD-mice. The SD-mouse is a spontaneous mutation of the house mouse, characterized by a short tail (Fig. 2.3). Homozygous or heterozygous offspring of these mice show skeletal, urogenital and ano-rectal malformations [42]. Therefore, these animals are ideal for detailed studies of ano-rectal malformations.

In all affected embryos we made the following observations (Fig. 2.16):

- Compared to normal embryos (Fig. 2.16a, b) we found abnormally shaped cloacas. The dorsal part was always missing (Fig. 2.16c, d).
- The cloacal membrane was always too short (Fig. 2.16c, d). In all cases the dorsal part of the cloacal membrane was absent.
- The proximal hindgut joined the cloaca at an abnormal position (Fig. 2.16c, d).

In Fig. 2.17 the developmental processes are summarized in a sketch.

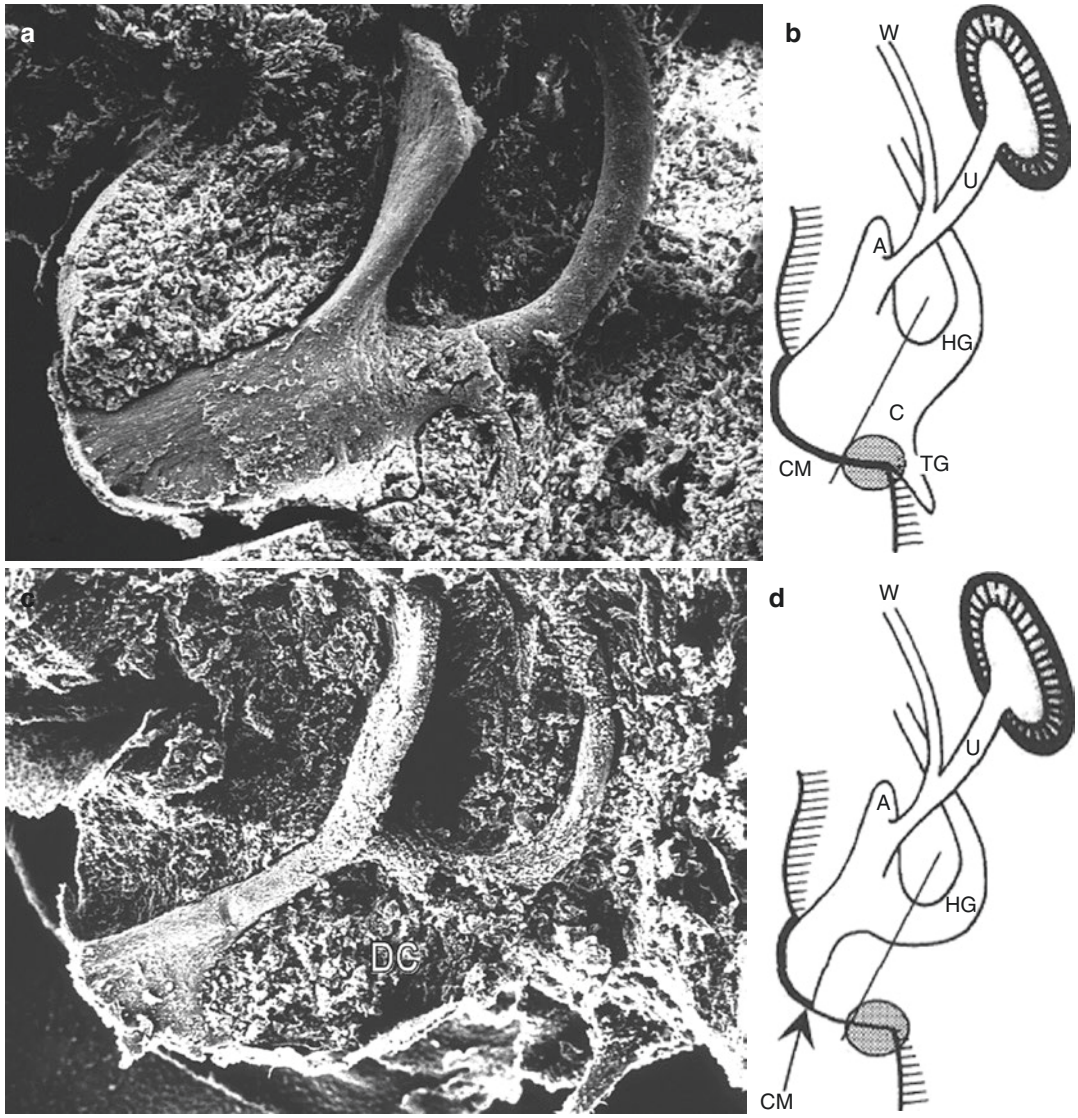


Fig. 2.16 Normal (**a**) and abnormal hindgut (**c**) in heterozygous SD-mouse embryos. Note that in the abnormal hindgut, the dorsal cloaca (DC), which contains the area of the future anus, is completely missing. As a result, the rectum keeps in contact with the urethra too high (so-called fistula). The cloacal membrane (CM) is too short. In B and D the findings are summarized in schematic drawings. *A* future bladder, *U* ureter, *W* WOLFF duct, *HG* rectum (hindgut), *C* 'cloaca', *TG* tail gut. SEM Pictures and schematic drawing © Dietrich Kluth

2.3.8 Normal Development of the External Genitalia

Many investigators [75–77] believe that the urethra develops by fusion of the paired urethral folds which takes place following the disintegration (rupture) of the ventral part of the cloacal membrane, the so-called 'urogenital membrane'. Impairment of this process of fusion is thought to result in the different forms of hypospadias [78, 79]. In order to get more information about this process, we studied the formation of the external genitalia in staged rat embryos and fetuses [80, 81].

This study was carried out in normal rat embryos and fetuses between embryonic day 17.5 (Fig. 2.18) and embryonic day 20.

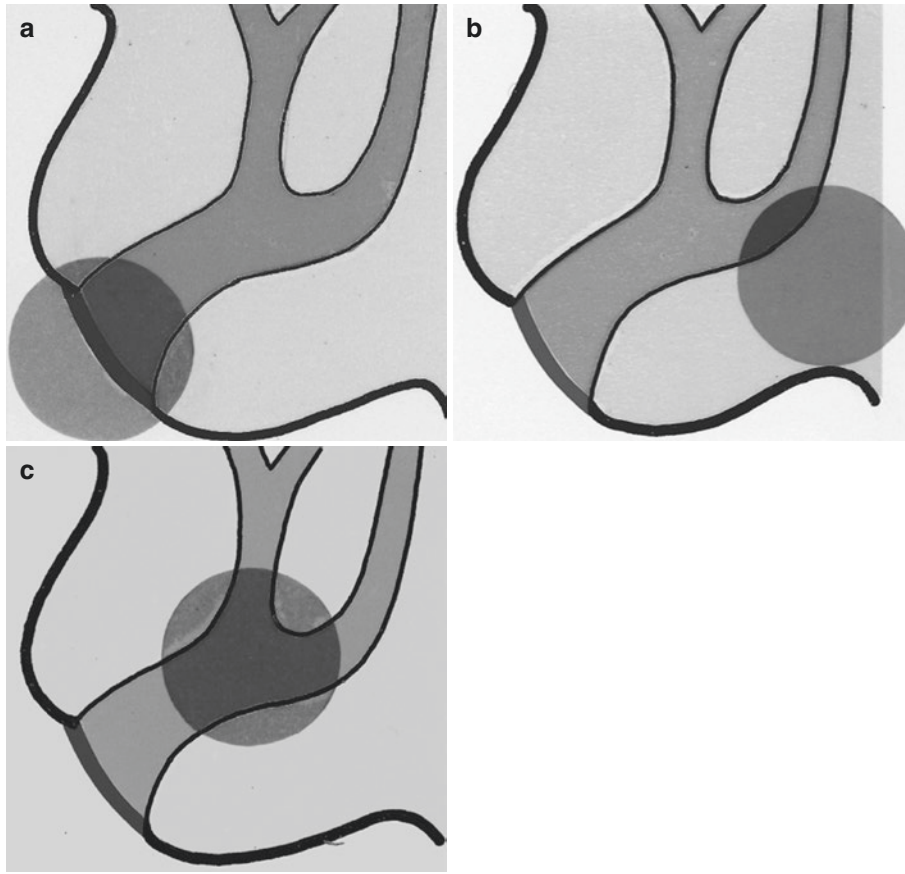


Fig. 2.17 Hypothetical line of events in anorectal malformations: (**a**) In young embryos, the cloacal membrane is too short. (**b**) As a result, the dorsal part of the 'cloaca' is missing, which normally contains the area of the future anal canal. (**c**) The rectum remains attached to the future urethra. Schematic drawing © Dietrich Kluth

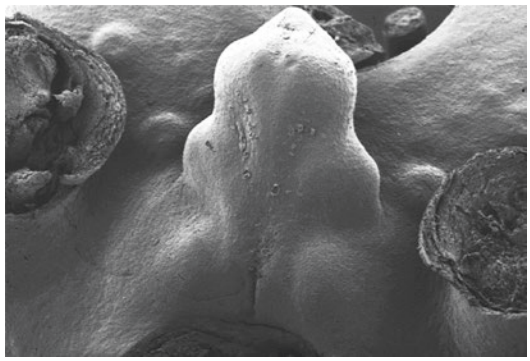


Fig. 2.18 Normal genital development. It is a common assumption that the 'cloacal membrane' ruptures not only in the dorsal (anal) part but also in the ventral (urethral) part [5]. However, the SEM picture of the phallus of a normal rat embryo (ED 17,5) shows only partial rupture of the "cloacal membrane" in its dorsal (anal) region. In this age group the sex of the embryo can't be estimated by the appearance of the outer genitals. SEM Picture © Dietrich Kluth

- Rupture of the cloacal membrane (Fig. 2.19). At embryonic day 17.5 the dorsal disintegration of the cloacal membrane can be seen (Fig. 2.19a, b). The ventral (urethral) part of the cloacal membrane remains intact. In Fig. 2.19c this process of disintegration is seen in more detail. The ectodermal part of the cloacal membrane shows clear signs of disintegration. The tip of the uro-rectal fold is seen which later forms the perineum. Ventral to the tip of the uro-rectal fold an opening is seen which is in connection to the distal urethra. Dorsally the anal opening is seen. At this time point, the external genitals allow no differentiation between the sexes.
- Further development of the external genitalia. A rupture of the ventral part of the cloacal membrane can't be seen in older embryos and fetuses. In males, the transient urethral open-

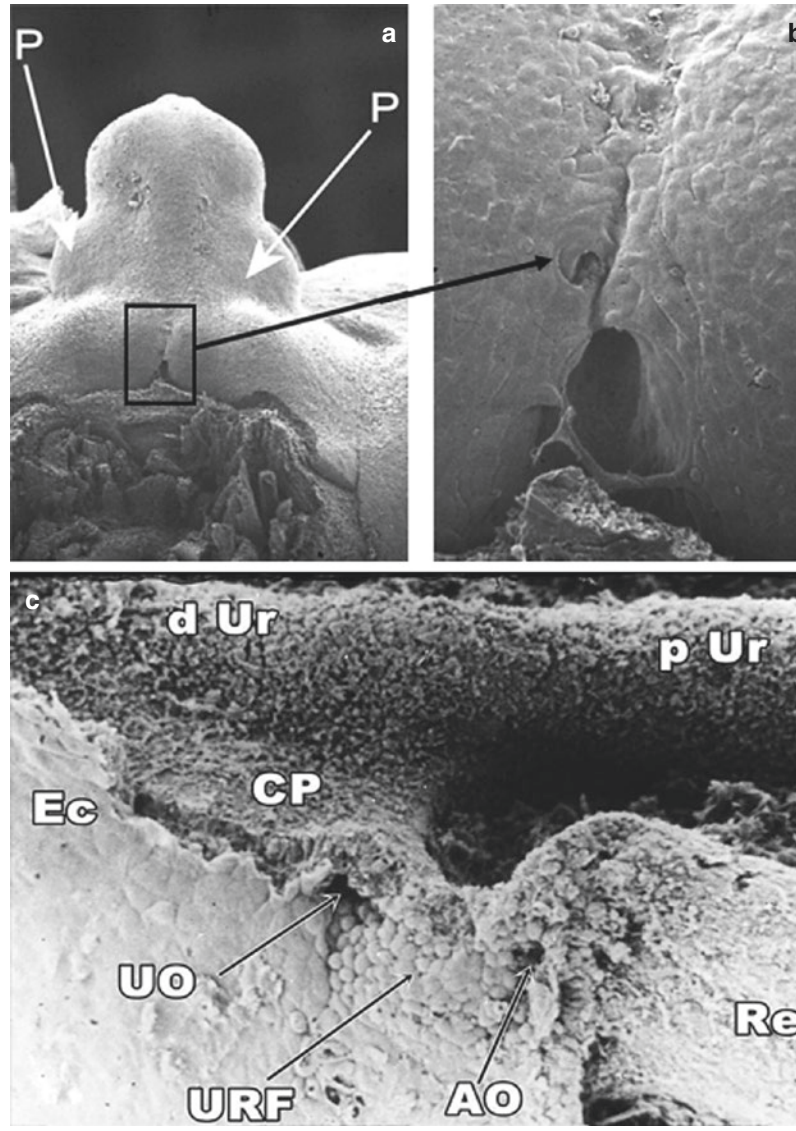


Fig. 2.19 Rupture of the dorsal cloacal membrane in a rat embryo (ED 17.5). (**a**, **b**) The rupture of the membrane is clearly seen. (**c**) In high magnification the situation is visible in detail. Half of the genitals is removed by micro preparations. The Tip of the urorectal fold can be seen (URF). Ventrally the opening of the urethra is seen (UO). The rectum (Re) opens dorsally (AO). Fusion of the URF with the cloacal membrane, as assumed by some researchers, does not take place. *EC* ectoderm, *CP* cloacal plate, *d Ur* distal urethra, *p Ur* proximal urethra. SEM Pictures © Dietrich Kluth

ing disappears. Later a 'raphe' is seen in this position (Fig. 2.20a). In females, this 'raphe' is missing (Fig. 2.20b).

- Special dissections of a rat embryo at embryonic day 18.5 allow the following statements (Fig. 2.21a–c): The urethra is composed of two parts, the proximal and the distal part. The epithelium of the distal part reaches to the tip of the phallus. It is interesting to see that the urethra is connected to the perineal region by a short canal, the so-called 'cloacal canal'. In our opinion this is the future female urethra.

Summarizing our results we found:

- In rats, the urethra is always present as a hollow organ during urethral embryogenesis and that it is always in contact with the tip of the genitals.
- Initially a double urethral anlage exists. The differentiation in female and male urethra happens in rats more than 18.5 days old.
- We had no evidence for the disintegration of the urogenital cloacal membrane, and a fusion of lateral portions within the perineum.

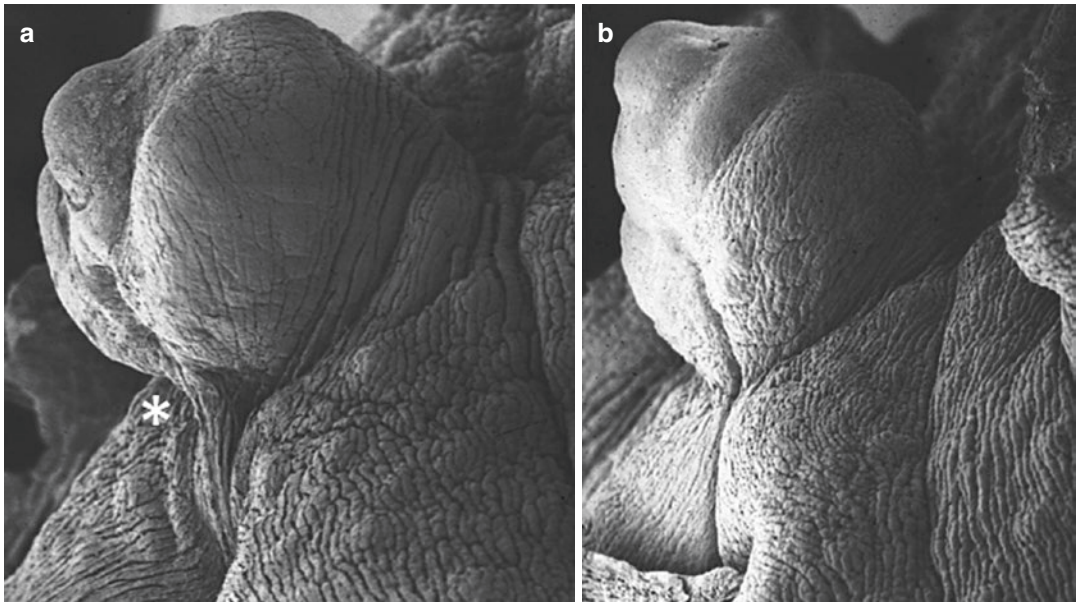


Fig. 2.20 Rat fetuses ED 20, (**a**) male rat, (**b**) female rat. The sex is discernable by external inspection of the genitals. Note the 'raphe' (*Asterisk*) in A, which is typical for the male phallus. This raphe is not the result of fusion, as generally believed. In female rats this 'raphe' is missing. SEM Pictures © Dietrich Kluth

2.3.9 Abnormal Development of the External Genitalia (Hypospadia Formation [80, 81]

In our opinion, more than one embryological mechanism is at play in the formation of the hypospadia complex. The moderate degrees, such as the penile and glandular forms, represent a developmental arrest of the genitalia. They take their origin from a situation comparable to the 20 days old embryo. Consequently the penis, not the urethra, is the primary organ of the malformation. Perineal and scrotal hypospadias are different from the type discussed previously. Pronounced signs of feminization in these forms suggest that we are dealing with a female type urethra. Origin of this malformation complex is an undifferentiated stage as may be seen in the 18.5 days old rat embryo.

2.3.10 Normal Midgut Development

2.3.10.1 Traditional Theories

Traditionally, the midgut development is described as a process of 'rotation'. In this process the following parts are involved: The distal part of the duodenum, the small bowel and most parts of the big bowel. The process of rotation takes place in two phases [82, 83]:

- In the first phase, the midgut loop develops inside the umbilicus (so-called 'physiological herniation of the midgut'). Here, a 90° anti-clockwise rotation around the axis of the mesentery is thought to take place.
- After the 'return' of the midgut into the abdominal cavity, another anti-clockwise 'rotation' of 180° is thought to take place inside the abdominal cavity (second phase). As a result, the region of the cecum moves to the right, thus overcrossing the mesenteric root, while the flexura duodeno-jejunalis is pushed to the left beneath the root of the mesentery [82, 83]. These two phases sum up 270°. In contrast to this description, GROB [84] subdivides this intra-abdominal process of rotation into two steps of 90° each.

2.3.10.2 Own Observations

We studied midgut development in rat embryos using SEM (Figs. 2.22, 2.23, and 2.24) [12, 85,

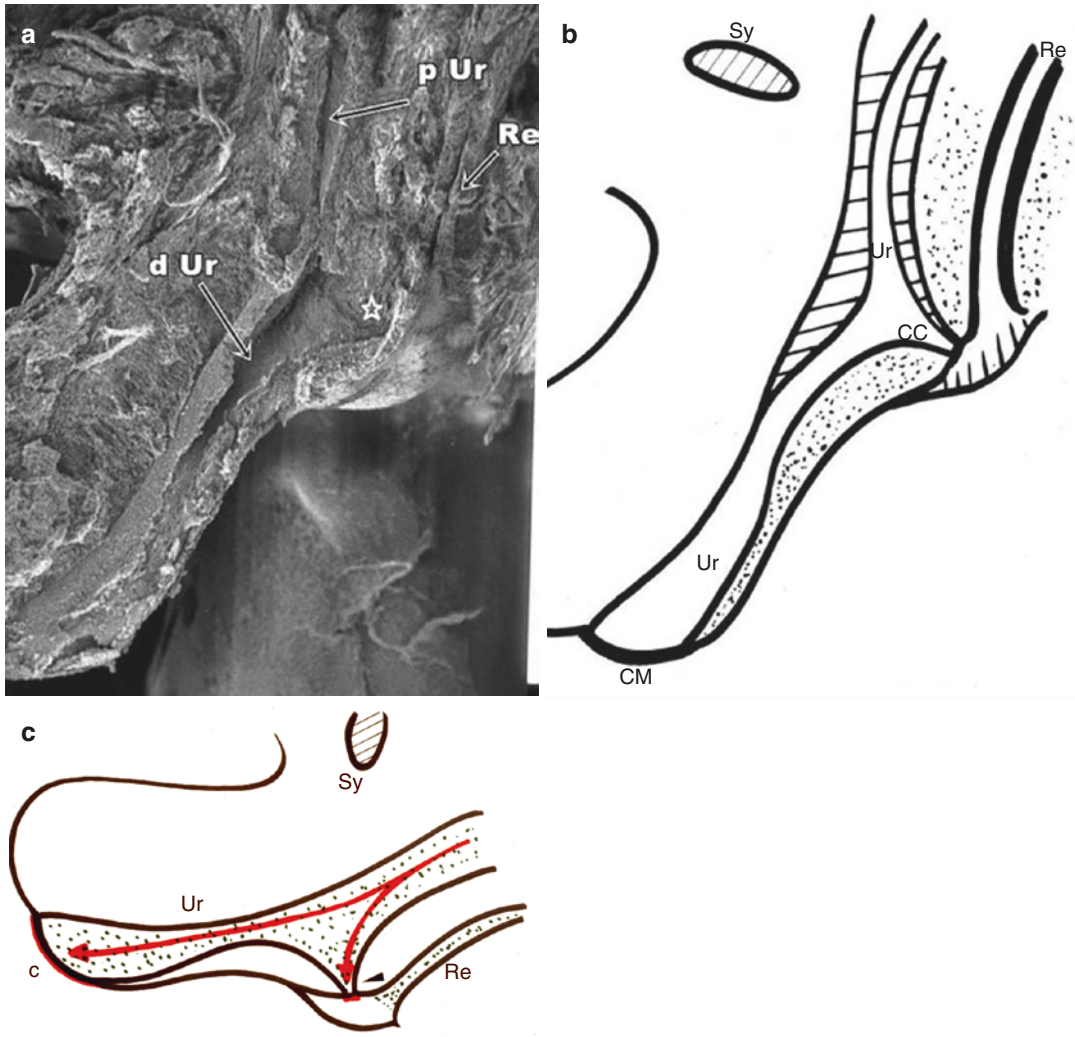


Fig. 2.21 Phallus of a rat ED 18.5. (**a**) The sex is not discernable by external inspection. The lateral portion of the phallus and the lateral wall of the urethra are removed. *p Ur* proximal urethra, *d UR* distal urethra, *Re* rectum. (**b**) The sketch describes the situation in A: *p Ur* proximal urethra, *d UR* distal urethra, *CC* urethral opening in females. Note that the urethra in this stage is not sexually determined. The female urethra is short and ends at the CC opening. (**c**) The male urethra is formed by the distal urethra, which extends to the tip of the pallus. *Sy* symphysis, *Ur* urethra, *C* cloacal membrane, *Re* rectum. SEM Pictures and schematic drawings © Dietrich Kluth

86]. Starting at embryonic day 13, the following parts of the midgut loop can be seen (Fig. 2.22a):

- A central part with the duodenum and the distal colon close to the root of the mesentery.
- A ventral part inside the extra embryonic coelom of the umbilicus (so-called 'physiological herniation'). Here the cecum and the distal small bowel can be identified.
- A middle part which connects the central part with the ventral part inside the umbilicus. Here the umbilical vessel, the small bowel on the right and the proximal part of the colon on the left can be seen (Figs. 2.22b, and Fig. 2.23d).

In the further development (ED 14—16) growth activities are seen in the area of the duodenum and inside the extraembryonic coelom.

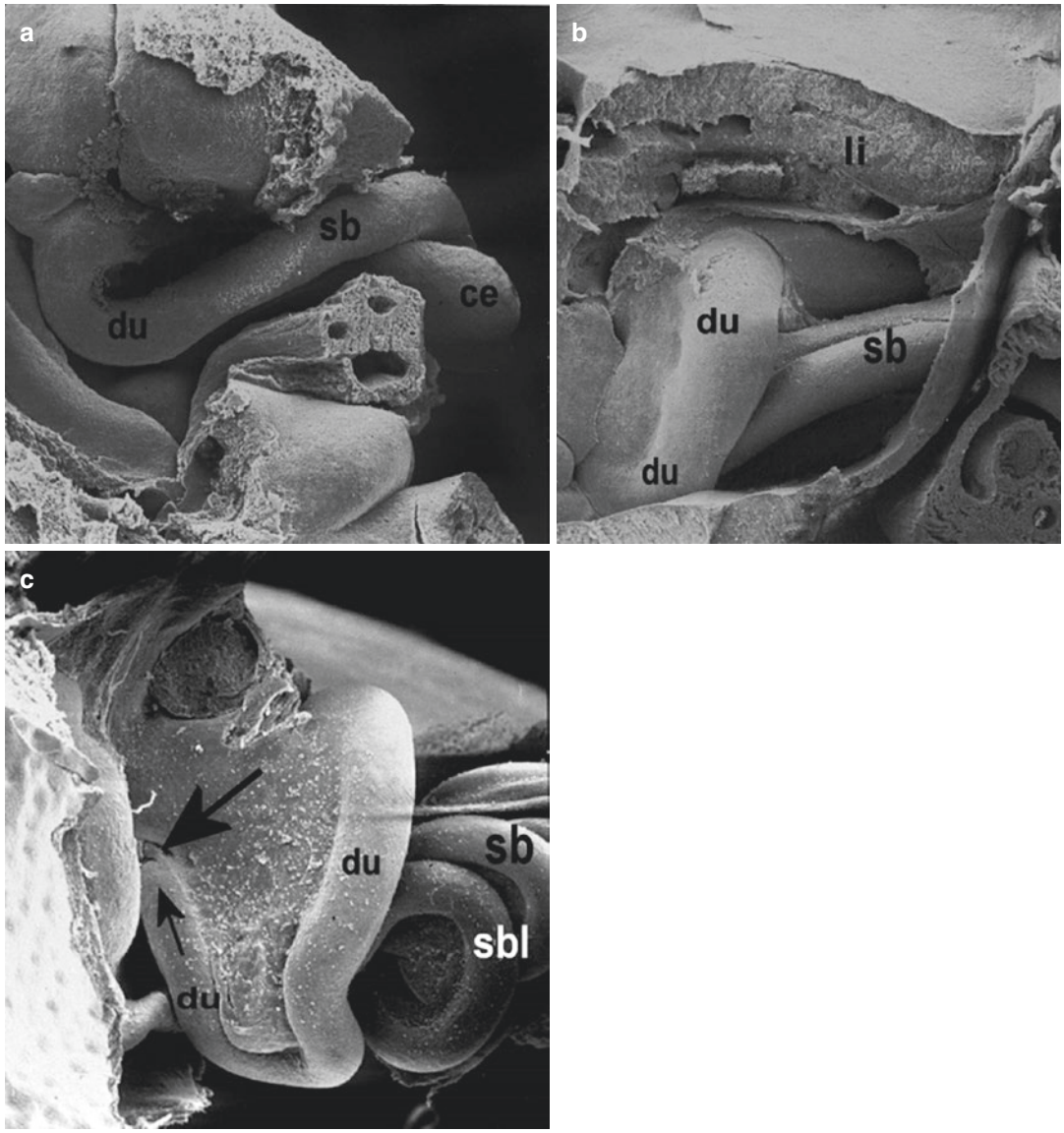


Fig. 2.22 Normal development of the midgut. (**a**) Rat embryo ED 13. The early midgut consists of three parts: A central part with the primitive duodenal loop (du), an extraembryonal part in the extraembryonic sac of the umbilicus (ce) and a straight part in between (sb). (**b**, **c**) The development of the central part, the duodenal loop (du), is seen. Note that the duodeno-jejunal junction is pushed beneath the root of the mesentery (*arrows* in **c**). This is caused by longitudinal growth of the duodenum. *sb* small bowel loops, *li* liver. SEM Pictures © Dietrich Kluth

In Fig. 2.22 the steps important for the duodenal developmental are shown. In Fig. 2.22b (rat embryonic day 15) the duodeno-jejunal loop has been formed due to longitudinal growth of the duodenum. Further growth pushes this loop beneath the root of the mesentery (Fig. 2.22c).

In Fig. 2.23, the development of the intraumbilical loops is shown. These loops are the result of longitudinal lengthening of the small gut. Note the absence of any signs of rotation around the axis of the mesentery in Fig. 2.23d in a phase of active loop development inside the extra embryonic coelom.

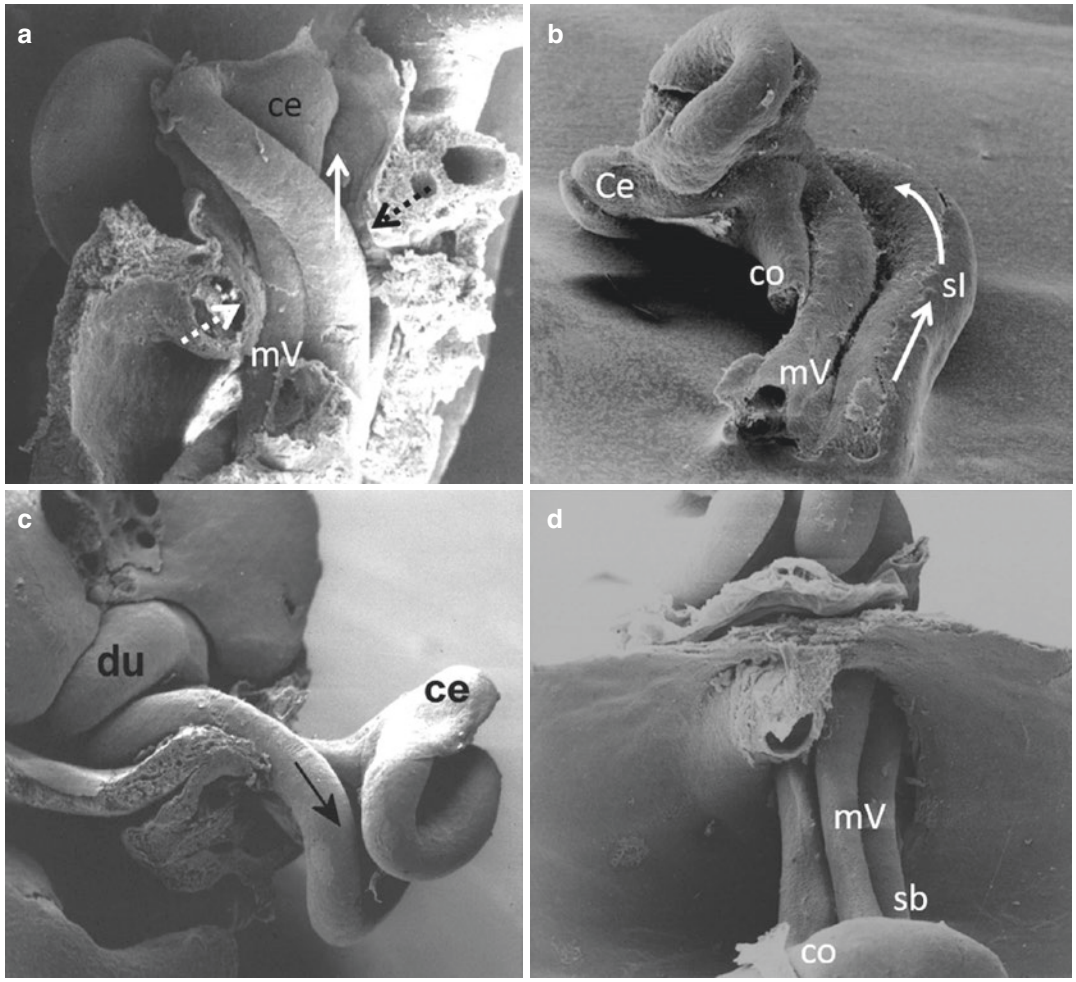


Fig. 2.23 Normal development of the midgut. (**a**) Rat ED 13. The cecum and the most distal part of the small gut are seen in the extraembryonic sac of the umbilicus. *Dotted arrows* indicate the border between extraembryonic and intraembryonic coelom. (**b**, **c**) Rapid lengthening of the small bowel leads to the formation of loops inside the extarembryonic sac of the umbilicus. Arrows indicate the direction of growth. (**d**) Note that during this process rotation around the axis of the mesentery does not take place. *ce* cecum, *sb* small bowel, *co* colon, *mV* mesenteric vessel. SEM Pictures © Dietrich Kluth

In Fig. 2.24, the 'return' of the midgut into the abdominal cavity is shown. The cecum is seen inside the abdominal cavity in a ventral position close to the abdominal wall (embryonic day 17). The colon is entirely to the left in this phase of development. It's a small bowel loop which is still extra embryonic inside the umbilicus. In this phase of small bowel 'return', the bowel loops have already developed locally inside the abdominal cavity (Fig. 2.22c).

We conclude from our observations that the midgut can be subdivided in three parts, of whom the central and the ventral part are of mayor importance. Localized longitudinal growth in the area of the duodenum leads to the formation of the duodeno-jejunal loop and its final position beneath the root of the mesentery. At the same time, localized growth of the small bowel has led to the formation of bowel loops inside the umbilicus and, later, inside the abdominal cavity. The

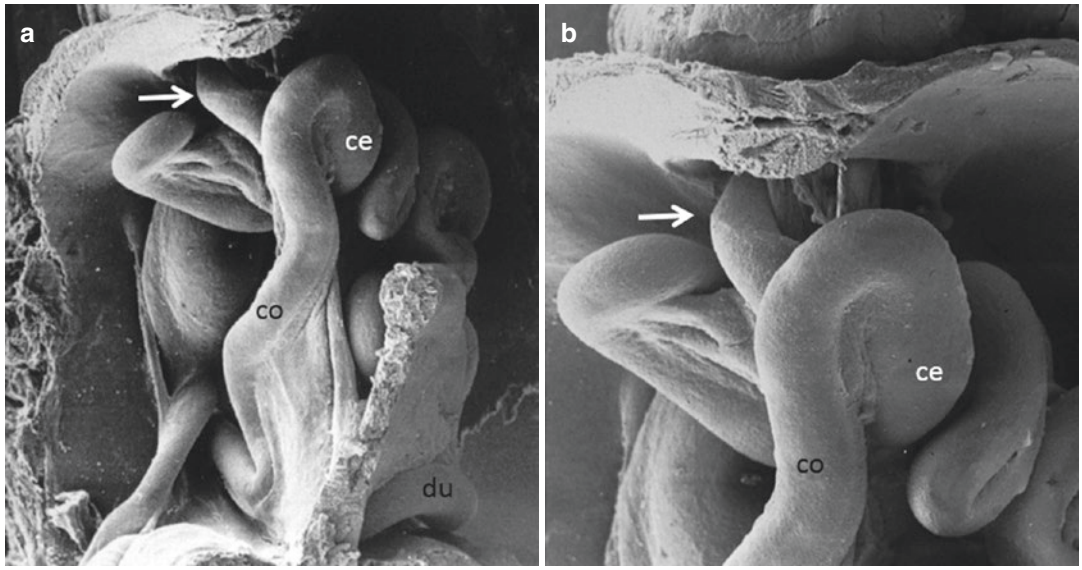


Fig. 2.24 Normal development of the midgut. Rat ED 17. (**a**) The Cecum (ce) is found in the abdominal cavity. A small bowel loop is still outside in the umbilical sac (*arrow*). *Co* colon, *du* duodenum. (**b**) Higher magnification of the area of the ventral body wall. *Ce* Cecum, *co* colon. SEM Pictures © Dietrich Kluth

growth activity of the large bowel is minimal, compared to that of the small bowel. Neither in the phase of loop formation inside the extra embryonic coelom of the umbilicus, nor in the phase following the 'return' of the gut into the abdominal cavity, rotation of the gut around the axis of the mesentery can be observed. All processes in midgut development are the result of longitudinal lengthening of gut.

2.3.11 Normal Testicular Descent

Since JOHN HUNTER in 1762, many researchers studied the embryology of testicular descent. In many of these studies, the importance of the gubernaculum during this process has been highlighted. However, a clear illustration of this rather simple process is still lacking [87].

Today, most researchers in the field [88–90] see two developmental phases during testicular descent:

- The intra-abdominal descent: In this phase, the testis, which initially lies in close contact to the kidney, moves into the inguinal area.
- The inguinal descent: In this phase the testis moves into the area of the scrotum.

We [11, 91] studied the morphology of testicular descent in rat embryos between embryonic day 15 and 20 using SEM in order to illustrate in detail the various steps of the testicular development. While in rat embryos at embryonic day 15, male and female gonads look still identical (Fig. 2.25a) they become clearly distinguishable in rats of embryonic day 16 (Fig. 2.25b). The male gonad is getting thicker and slightly shorter than the female gonad, but both gonads are initially in close approximation to the kidneys.

Starting at embryonic day 16.5, the testis moves away from the lower pole of the kidney. On ED 19 the testis is located between the lower kidney pole and the roof of the bladder (Fig. 2.26a) and moves towards the bladder neck at ED 21 (Fig. 2.26b). This brings the intra-abdominal descent to an end and the inguinal descent starts.

At the end of the intra-abdominal descent (ED 22), the bulb of the gubernaculum is still visible. (Fig. 2.27a). A little later, around birth (embryonic day 22), the bulb disappears partially and the pro-

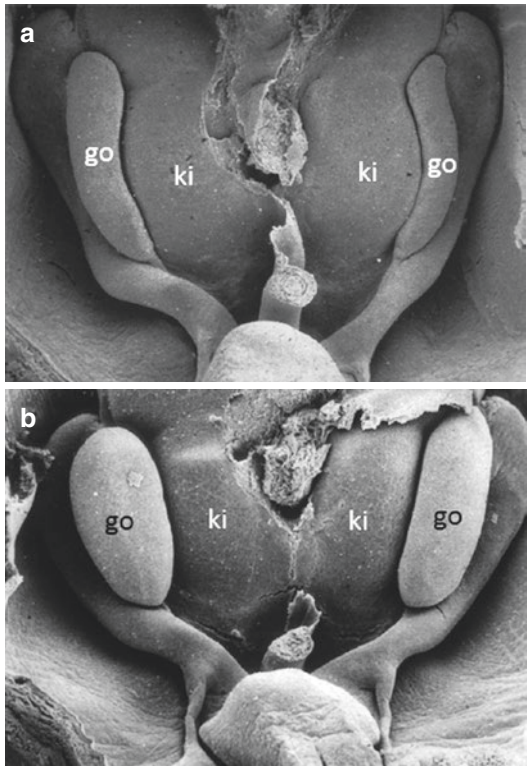


Fig. 2.25 Descensus of the testis. Rat ED 15, female rat in (**a**), male rat in (**b**). Notice the difference in the size of the male and female gonads (go). Both gonads lie in close approximation to the kidneys (ki). SEM Pictures © Dietrich Kluth

cessus vaginalis peritonei (PVP) develops (compare with Fig. 2.27b). Notice the rest of the bulb at the lower pole of the PVP. In this phase, the corda of the gubernaculum is still visible and attached to the caudal part of the epididymis, which has entered the PVP. At birth and later, the testis finally enters the PVP (Fig. 2.27c).

2.3.12 The Role of the Gubernaculum

In our series, we studied the formation and the fate of the gubernaculum (Fig. 2.28). In rat embryos at embryonic day 16 the gubernaculum consists of two parts, the gubernacular bulb and the corda of the gubernaculum (Fig. 2.28a). The corda is rather attached to the lower anlage of the epididymis (Fig. 2.28a, c) than to the testis, as it is often described in the literature. Furthermore, it is often assumed, that the testis is pulled downwards by corda and bulbus. While this—in initial stages—seems to be morphologically possible, we identified later stages, where testis and gubernaculum were positioned in such a way that pulling of the testis by the gubernaculum seems to be impossible (Fig. 2.28c, e).

Thus in our findings we cannot support the opinions about the role of the gubernaculum

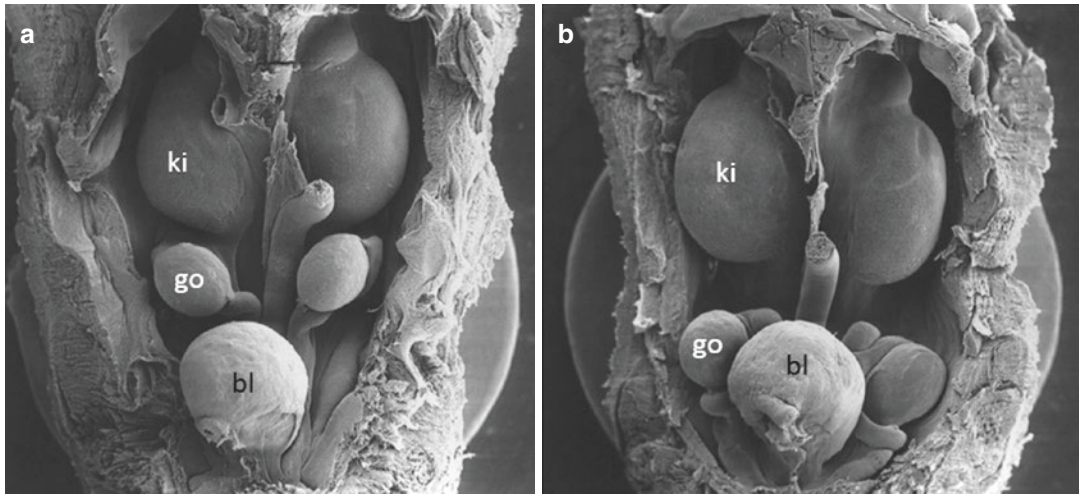


Fig. 2.26 Testicular descent: Intraabdominal descent (first phase). (**a**) Male rat, ED 19. The gonads (go) have lost contact to the lower pole of the kidneys (ki) and lie in the middle portion between kidney and bladder (bl). (**b**) Male rat, ED 21. The gonads are now close to the bladder in the inguinal area. This movement relative to the urinary bladder can't be attributed to the relatively ascent of the kidneys. SEM Pictures © Dietrich Kluth

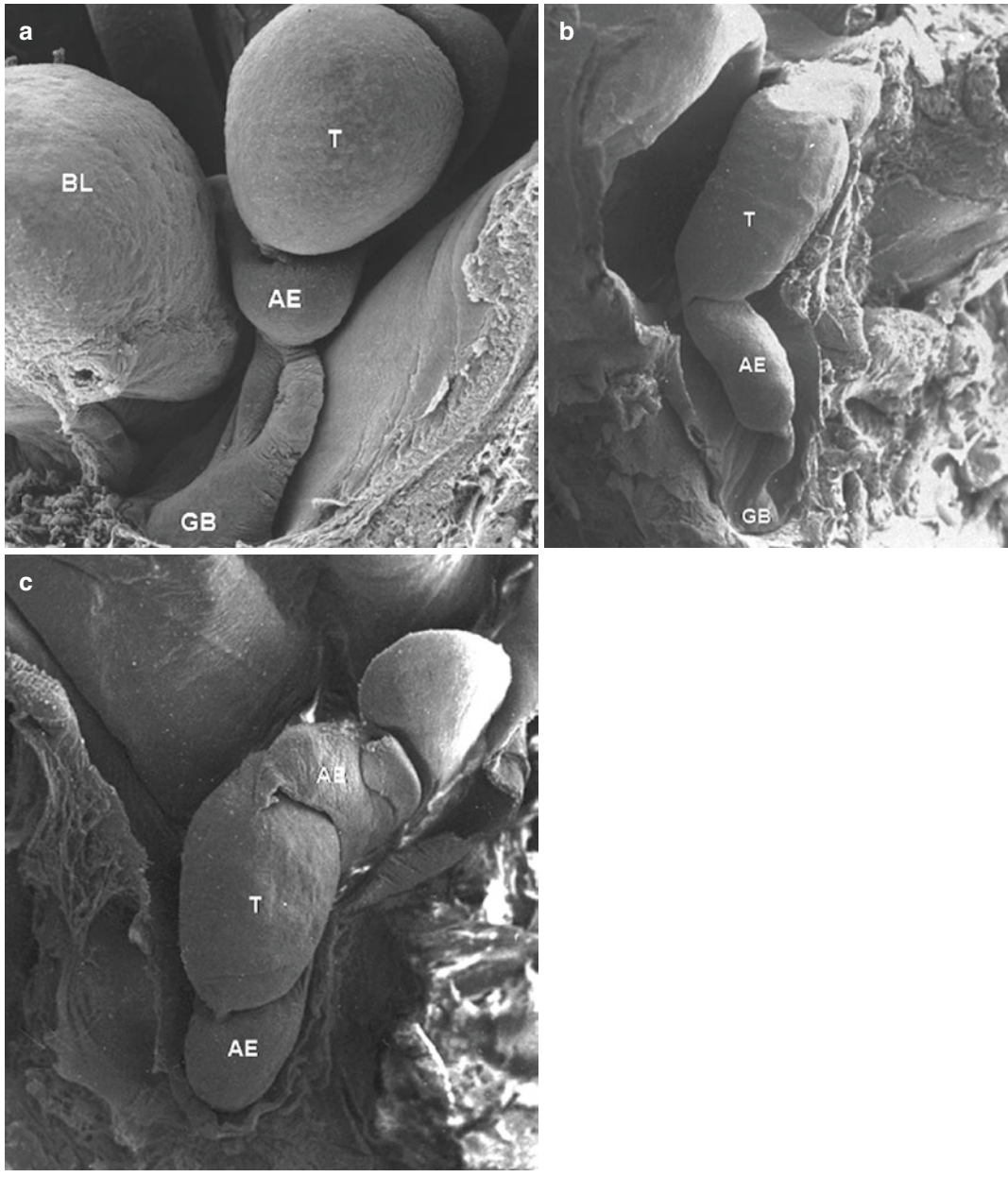


Fig. 2.27 Testicular descent: Inguinal descent (second phase). (**a**) male rat ED 21. The testis (T) has reached a position close to the inguinal region. The bulbic gubernaculum (GB) is still present. *BL* bladder, *AE* epididymis. (**b**) Male newborn rat, D 0. The bulbic part of the gubernaculum (GB) disappeared and the processus vaginalis peritonei is formed (PVP). The border between peritoneal cavity and PVP is marked by *arrows*. The epididymis has entered the PVP. The corda of the gubernaculum is still visible. (**c**) Male newborn D 1-5. Not only the epididymis but also half of the gonads (T) has entered the PVP. The gubernaculum has completely disappeared. *Arrows mark* the border between the peritoneal cavity and the PVP. *AE* epididymis. SEM Pictures © Dietrich Kluth

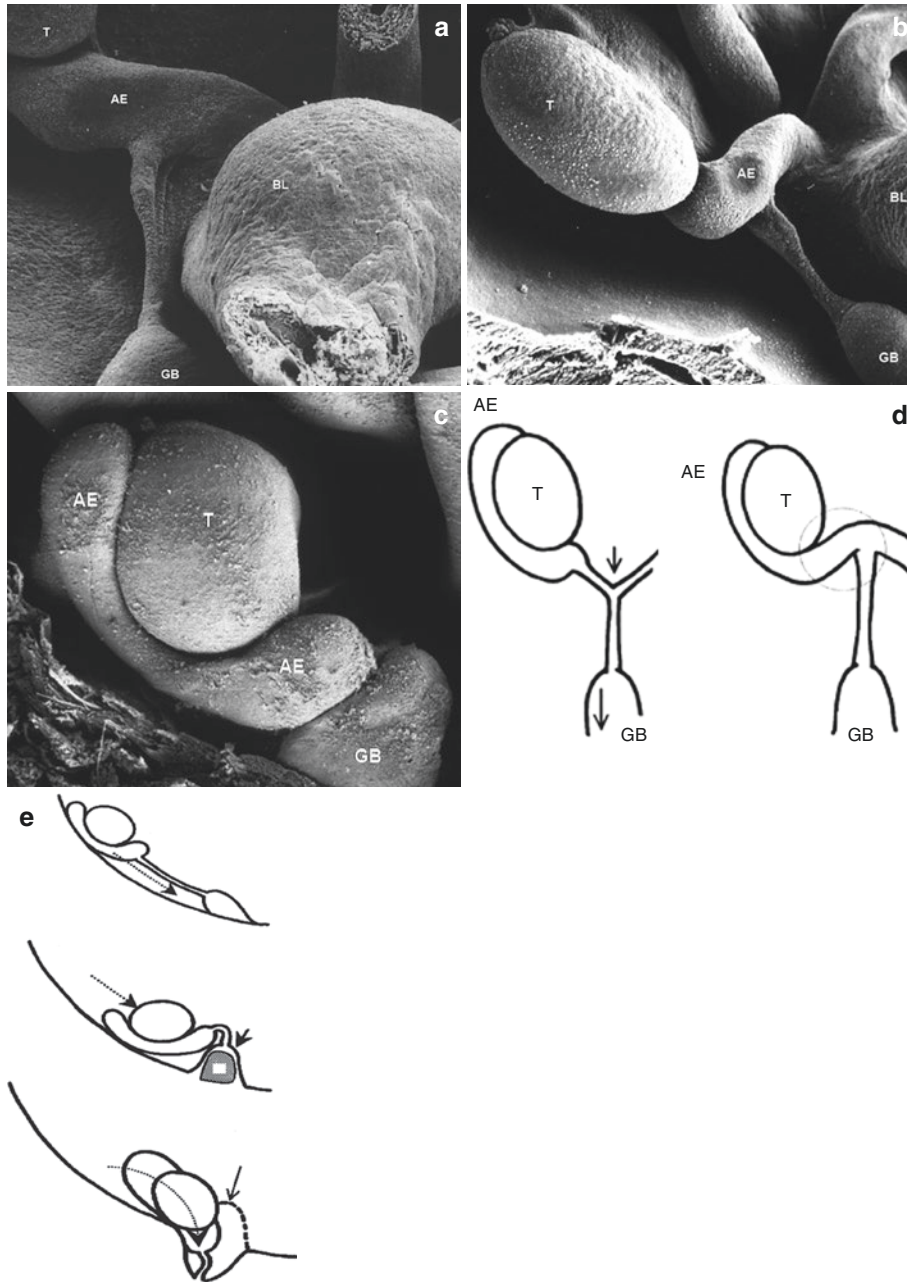


Fig. 2.28 Testicular descent: In this series of SEM pictures, the morphology of the gubernaculum is shown (rat ED 19). (**a**, **b**) Here the gubernaculum consist of two parts, the corda of the gubernaculum (*arrows* in **a** and **b**) and the bulbus of the gubernaculum (GB). The corda inserts rather into the caudal anlage of epididymis (AE)/ mesonephric ridge than into the testis (T), as often assumed. *BL* bladder. (**c**) While in A and B tension caused by the gubernaculum seems to be theoretically possible, C demonstrates that the testis (T) is rather blocked by the bulb of the gubernaculum (GB) than pulled. Rat ED 21, *AE* epididymis. (**d**) Many researchers believe that tension caused by the corda is at play during testicular descent. However, the morphology of the insertion zone of the corda into the anlage of the epididymis shown in A and B speaks against this assumption. Sketch on the left shows expected morphology (traction!) vs. observed morphology on the right. *AE* epididymis, *T* testis, *GB* bulbus of the gubernaculum. (**e**) The sketch summarizes our morphological data on the developmental sequence of the testicular descent. SEM Pictures and schematic drawing © Dietrich Kluth

during the testicular descent. Its main role seems to be its transformation into the PVP. We believe that intra-abdominal pressure probably plays an active role at least in the phase of the inguinal phase of testicular descent.

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Research in Pediatric Surgery

3

Christopher G. Turner and Dario O. Fauza

Abstract

Pediatric surgeons have the privilege to care for patients at every stage of human development, from the fetus to the fully developed young adult. As such, we must cultivate and advance an all-encompassing knowledge base ranging from obstetrics to pediatrics to adult medicine and surgery. This unique, sweeping perspective on human disease requires an equally broad approach to research, which in our field is as vast and varied as it is stimulating.

Keywords

Surgery research • Newborn surgery • Animal models • Regenerative medicine • Innovation

3.1 Introduction

Pediatric surgeons have the privilege to care for patients at every stage of human development, from the fetus to the fully developed young adult. As such, we must cultivate and advance an all-encompassing knowledge base ranging from obstetrics to pediatrics to adult medicine and surgery. This unique, sweeping perspective on human disease requires an equally broad approach to research, which in our field is as vast and varied as it is stimulating.

Yet, despite the appeal of research in such a diversified and vibrant spectrum, the relative proportion of pediatric surgeons performing research appears to have been dwindling in recent years. While different factors can be debated as implicated in this scenario, perhaps one should be emphasized, namely the increasingly restricted exposure to research during training. The greater significance of this trend lies in the fact that, unlike most other components of this conjuncture, it has career-long consequences, rendering the unexposed trainees essentially unable to develop as independent investigators once they become practicing pediatric surgeons, notwithstanding the eventual will to do so. Regrettably,

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_3

fewer and fewer countries and institutions can afford the time and resources necessary for surgical trainees to develop a strong research background.

While the recent emphasis on a multidisciplinary approach to research has allowed for many developments that would not have been possible in isolation, we must aspire to a central role within research groups related to our specialty. Clinical expertise is often a pre-requisite for one to provide consequential guidance to the powerful scientific methodology currently available and the perspective offered by the pediatric surgeon cannot be replaced. By the same token, only we can protect and expand the role of research in the education of our future peers. This chapter is aimed at tendering some support, however limited, to this need.

It would be beyond the scope of any book chapter to present a comprehensive, exhaustive review of all the possible developments applicable to research in Pediatric Surgery. Here, we present a summarized overview of different aspects involving both laboratory- and clinical-based research that should be of interest to both trainees and practicing colleagues, through select examples representative of the far reach of our field. Our focus will be on translational research, as this is typically the chief dominion of the pediatric surgeon, as opposed to that of the basic scientist.

3.2 Animal Models

Although much can be learned from *in vitro* analyses of intracellular processes and defined cellular manipulations, especially in light of recent developments in cellular reprogramming, the complexity of organ systems or whole organisms cannot yet be substituted. Both developmental and interventional research pursuits still depend heavily on animal models, which remain the workhorses at most pediatric surgical laboratories.

There is now an overwhelming variety of animal models for research, spanning widely across taxonomic groups [1]. A few basic considerations should guide animal selection for a given experiment. One is of course the degree of correspondence to the human disease or biological process of interest. The options here are perhaps surprisingly broad, depending on the subject, not infrequently including significantly less prescient species, such as in the zebra fish model of lymphatic malformation, in addition to more predictable mammals. At the same time, species-specific variations in physiology and anatomy can render certain higher species essentially irrelevant to a given human disease process. For example, a swine model of naturally occurring congenital diaphragmatic hernia (CDH) (*Sus scrofa*) does not include pulmonary hypoplasia, virtually ubiquitous to CDH in human infants.

Another consideration is the availability of genetic tools conducive to in depth molecular and pathway-specific analyses of mechanisms behind the phenomena being studied. Mice (*Mus musculus*) constitute the prime representative of that set of considerations, not the least due to the plethora of knockout and knock-in murine models, though the thornier rat knockouts have also become options in the last several years. The International Mouse Phenotyping Consortium is striving to create viable strains of identical genetic background mice in which only one of the approximately 20,000 genes in the mouse genome can be selectively deactivated for systematic phenotypic screens, further expanding the scope of the murine genetic manipulation platform [2]. The more recent development of the first cloned rat also paves the way for the establishment of overexpression rat models based on targeted insertions [3].

Yet another consideration of special appeal to pediatric surgery is tolerance to fetal manipulation/intervention. While this can be accomplished in a number of species, sheep (*Ovis aries*) deserves special attention due to their inordinately high tolerance to such manipulations, the size of their fetuses and newborns, and the easily manageable gestational times. The ovine model can also be an asset to an additional aspect to be taken into consideration when selecting an animal model, namely is fast growth rate combined to the fact that their sizes are comparable to that of humans, from infancy to adulthood.

Meaningful growth is often a pre-requisite to pediatric surgical research, for example in projects involving different forms of structural repair.

Expectedly, as always, logistical and financial constraints come into play as well. The following is a brief review of select animal models of interest to certain specific groups of pediatric surgical diseases, as representative illustrations of the breadth of animal research in our field. Other lists equally focused on our specialty, though based on somewhat different criteria, should also be of particular interest to the reader [4].

3.2.1 Abdominal Wall Defects

Not infrequently, a given structural congenital anomaly can be modeled in animals by either of five methods: surgery; genetic manipulation; drugs/chemicals; other environmental manipulations; or it may be naturally occurring. Selecting which one best correlates with the clinical disease is not always straightforward, especially when the etiology of the human condition is unknown. Animal models of gastroschisis and omphalocele illustrate that scenario.

There is an inbred mouse strain, namely HLG/Zte, in which gastroschisis occurs spontaneously. The typical prevalence of 3% can be increased with irradiation during pre-implantation development [5]. Studies with these animals have identified a region of the mouse chromosome 7 as a responsible locus [6]. Further similar studies may shed more light on genes eventually involved in the development of abdominal wall defects.

Abdominal wall defects can also be induced experimentally with a variety of teratogens. However, these agents typically lead to inconsistent results, as well as multiple associated anomalies. Aminpyrine causes omphalocele when given to pregnant mice at midgestation [7]. This can be augmented by supplementation with barbital [8]. In rats, omphaloceles have been induced with maternal exposure to DA-125 (anthracycline antineoplastic agent) [9], beta-aminoprpioitrile [10], or flubendazole [11]. Additional teratogenic agents have been explored in assorted species, including doxorubicin hydrochloride [12], ethanol [13, 14], nitrous oxide [15], ethylene glycol [16], scopolamine hydrobromide [17], acetazolamide [18], and cyclooxygenase inhibitors [19]. The rate of gastroschisis in this studies, however, is somewhat limited, ranging from 3.7 to 19.8%. In guinea pigs, a daily period of maternal hyperthermia can result in abdominal wall defects, among other abnormalities [20].

Various species have been used in surgical models of gastroschisis, the most prominent of which are sheep, rabbit, and the chicken embryo. Haller et al. first described a sheep model of gastroschisis by operating on fetal lambs at midgestation and excising a full thickness disk of abdominal wall lateral to the umbilical cord [21]. The exposed intestine in surviving fetuses was edematous and matted, similar to the findings in humans. Langer and colleagues later modified this model by placing a silastic ring in the abdominal wall defect [22–24]. Though this design was associated with a relatively high rate of spontaneous abortion, it demonstrated that intestinal damage correlates with the time of exposure to the amniotic fluid. Less costly rabbit models of gastroschisis have also been described [25, 26]. Improvements in experimental fetal surgery have improved the success rate of this model to the range of 80–90% [27, 28]. An interesting modification of the leporine model has been described so as to remove the effect of amniotic fluid exposure on the intestinal damage during fetal development [29]. The least costly models for gastroschisis involve chicken embryos. The chicken embryo is enveloped in amniotic fluid and a number of membranes. After confirming fertility of an egg, a 1 cm defect is created in the shell. Using the allantoic vessels and the umbilical cord as landmarks, the physiologic umbilical hernia sac can be incised in order to create a gastroshisis [30]. Using this model, the effects of amniotic fluid exchange as a means to reduce the severity of intestinal damage have been studied [31–33].

3.2.2 Biliary Atresia

Multiple theories have been proposed to account for the varied spectrum of pathology in biliary

atresia, ranging from putative congenital malformations of the bile ducts to the presence of a causative infectious agent. Reflecting this diversity, several types of models have been described.

Lampreys provide an arguable natural model for biliary atresia. Adult lampreys are the only vertebrates with an absence of a bile duct system in their livers. This occurs through programmed degeneration of the biliary tract during normal morphogenesis [34]. As the biliary tract regresses, the adult lamprey develops progressive cholestasis and bile pigment accumulation. The spectrum of pathology resembles the human form of the biliary atresia with the accumulation of luminal debris, basement membrane thickening, disorganization of hepatic architecture, extra-hepatic bile duct atresia, and shrinkage or loss of the gall bladder [35]. These animals live for several years after biliary tract regression allowing for studies on compensatory response to cholestasis as well as changes in the evolution of biliary atresia at the molecular level [36].

Bile duct injury has been induced with several agents in an attempt to mimic histological features of biliary atresia. After having identified low levels of L-proline in the serum of patients with biliary atresia, Vacanti and Folkman were able to induce bile duct enlargement with a continuous intraperitoneal infusion of L-proline [37]. 1,4-phenylenediisothiocyanate (PDT), an antihelminthic agent, can be employed to induce bile duct inflammation [38, 39]. The bile duct pathology is related to the timing of exposure to this agent. When gavaged in the postnatal period, PDT causes bile duct enlargement. When gavaged to pregnant rats, PDT causes fibrosis in the bile ducts. However, with a combination of gavage to the pregnant rats and during the postnatal period, the bile ducts exhibit wall thickening with stenosis and atresia. Further study of this temporal relationship may aid in the understanding of bile duct development. Another agent, phorbol myristate acetate (PMA), has been infused directly into the gallbladders of adult rats with a subcutaneous pump [40]. After a 28-day infusion, portal fibrosis and neo-cholangiogenesis were observed. PMA is a nonspecific activator of inflammation and may lead to insights on the role of inflammation in the development of biliary atresia.

Surgical models involving ligation of the fetal bile duct have been described in sheep [41]. Although the distal bile duct can become atretic, similarly to what is found in the human form of biliary atresia, the same does not apply to the impact on the liver, which does not correlate with what is found in the human disease. More recently, it has been shown, also in the ovine model, that occlusion of the fetal bile duct and the consequent hyperarterialization of the liver actually/instead significantly affects hepatic hematopoiesis, leading to a new perspective into the mechanisms that govern hematopoiesis in general, illustrating the potentially far reaching impact of fetal surgical models [42].

3.2.3 Congenital Diaphragmatic Hernia

Multiple animal models of congenital diaphragmatic hernia (CDH) have been described, however only few bear relevance to the human disease.

A model of familial CDH has been described in pigs which were originally bred to produce anorectal malformations, with a prevalence of approximately 10% [43]. Animals show herniated intra-abdominal organs within the thoracic cavity, but not the pulmonary hypoplasia characteristic of CDH. Several genetically manipulated mice models have also demonstrated CDH in combination with other associated malformations. If both murine retinoic acid receptors are deleted, mice have a high incidence of cranial, vertebral, limb, cardiac, foregut and pulmonary malformations, in addition to occasional CDH [44, 45]. Mutations in the homeobox *Hlx* gene result in CDH with large lungs and small livers [46]. Homozygous inactivation of *WT-1* causes CDH and major defects in the urogenital system [47]. Knockout mice homozygous for *Slit3* deficiency exhibit CDH in a ventral midline location with herniation of the liver and gallbladder, along with renal and ureteral agenesis [48].

The first surgical model of CDH was described by De Lorimier using third trimester fetal lambs [49]. Through a maternal hysterotomy and a fetal thoracotomy, a large defect was created in the left dome of the diaphragm. This model resulted in hypoplastic lungs, however with essentially normal pressure-volume curves. Further studies using an inflatable balloon in the fetal chest produced significantly reduced tidal volume and pulmonary compliance compared with control animals [50, 51]. Deflation of the balloon *in utero* improved these pathophysiologic effects and improved newborn survival [50]. In another variation of fetal manipulation, the diaphragmatic defect was created in the second trimester rather than the third, in order to more closely mimic the human disease [52]. In these animals, the lungs were hypoplastic, had abnormal airway branching, and a smaller and more muscularized pulmonary arterial tree when compared with controls [53, 54]. The fetal surgical model of CDH has also been described and further explored in rabbits [55–57]. As these surgical models are created during fetal life, they hold limited significance to the embryogenesis of CDH.

Experimental CDH can also be produced in other animal species through different interventions, other than surgical creation of the defect, including: exposure to diet deficient in either vitamin A [58, 59], zinc [60], or cadmium [61]; administration of either thalidomide [62], anti-rat rabbit serum [63], 2,4-diclorophenil-p-nitrofenilic ether (nitrofen, a herbicide) [64–66], or polibromate biphenils [67, 68]; and genetic manipulations, such as FOG-2, COUP-TFII, and GATA-4 mutations [69–71]. However, with the possible exception to the nitrofen model, there's been no conclusive relationship between these experimental models and clinical/epidemiological data in humans. The nitrofen model has been increasingly accepted as the most relevant to clinical CDH due to the fact that, in that model, the pulmonary hypoplasia precedes the diaphragmatic defect and is independent from the latter. This is in accordance with today's favored notion that the primary defect is not in the diaphragm, but rather in the developing lung buds, with the diaphragmatic defect being actually secondary to a primary pulmonary hypoplasia. Such pulmonary hypoplasia, in turn, could be made worse by the herniated content into the chest.

Laboratory developments in CDH include a peculiar facet which further epitomizes the impact that fetal intervention models can have in our understanding of not only a given disease, but also of germane biological processes. In the sixties, Carmel and colleagues used a healthy leporine model to demonstrate that fetal tracheal occlusion induced lung growth [72]. In the seventies, Alcorn et al. suggested, in a healthy ovine model, that fetal tracheal occlusion and drainage led to hyperplasia and hypoplasia of the lungs, respectively [73]. It was not until the early nineties, however, that Wilson et al. showed, also in sheep, that fetal tracheal occlusion could actually be a means to reverse the pulmonary hypoplasia associated with both CDH and fetal nephrectomy [74–76]. Wilson's sentinel studies on therapeutic fetal tracheal occlusion have triggered one of the most fertile experimental and clinical development sprees of recent memory in our specialty, with ramifications that have crossed the boundaries of our field.

3.2.4 Hirschsprung's Disease

A number of animal species have naturally occurring aganglionic megacolon, including mice, rats and horses [77–79]. In 1966, Lane described two strains of mice with autosomal recessive aganglionosis [79]. The lethal spotting (ls) mice have approximately 2 mm of aganglionosis while piebald lethal (s^l) mice have approximately 10 mm of aganglionosis. Lane and Liu also described megacolon associated with a dominant spotting gene (Dom) in mice, characterized by distal colonic aganglionosis and a long hypoganglionic transition zone [78]. Ikadai and Agematsu described an autosomal recessive total colonic aganglionosis in a strain of rats [77]. These animals have a high mortality rate and are only able to survive for 3–4 weeks after birth, eventually succumbing to severe bowel obstruction and enterocolitis. Histological studies using acetyl cholinesterase whole-mounts in all these rodent

models are virtually identical to the human histopathology [80].

Various genes have been actively disrupted in mice, producing phenotypes similar to human Hirschsprung's Disease (HD). The Ret gene encodes a receptor tyrosine kinase, which has four ligands: glial cell line derived growth factor (GDNF), neurturin (NTN), artemin (ATM) and persephin (PSP) [81]. The complete receptor complex includes the Ret receptor tyrosine kinase and a glycosylphosphatidylinositol-anchored binding component (gfrα1, gfrα2, gfrα3 or gfrα4). This receptor has been suggested to function as an adhesion molecule, which is required for neural crest migration and could also play a role in either differentiation or survival of the neural crest cells which have stopped migrating [82, 83]. Ret (−/−) transgenic mice have a homozygous, targeted mutation of the tyrosine kinase receptor resulting in a loss of its function. These mice exhibit total intestinal aganglionosis and renal agenesis [84]. The Ret gene has been demonstrated to be a major gene causing HD in humans. Mutations of Ret account for 50% of familial and 15–20% of sporadic cases of HD [85–88]. GDNF, one of the Ret receptor ligands, stimulates the proliferation and survival of neural crest derived precursor cells in the embryonic gut [89, 90]. Mice homozygous for null mutation in Ret, GDNF and gfrα1 have almost identical phenotypes characterized by failure of enteric nervous system development distal to the esophagus and absent kidneys [84, 91–95]. Although a causative role for GDNF mutations in some patients with HD has been suggested, the occurrence of such cases is uncommon. It is more likely that the GDNF mutations are involved via its interaction with the Ret receptor [96, 97]. No gfrα1 mutations have been identified in patients with HD [98].

Endothelins are intercellular local messengers that comprise four members to date: ET-1, ET-2, ET-3 and VIP. They transduce a signal via two cell surface transmembrane receptors: ENDR-A and ENDR-B [81]. Both ET-3 and ENDR-B genes have been disrupted and have been identified as the cause for the natural mutants lethal spotting mice and piebald lethal mice, respectively [99, 100]. Moreover, a transgenic mouse ENDR-B knockout has a phenotype identical to the piebald lethal mouse [101]. As the connection between mutations in the Ret receptor and familial HD was established, ET-3 and ENDR-B mutations were also implicated in the disease [99, 100, 102]. However, these mutations have been demonstrated in less than 10% of the cases of HD in humans [103]. Endothelins are initially produced as an inactive proendothelin that has to be activated by a specific enzyme, the endothelin-converting enzyme (ECE). Two ECE genes have been described, ECE-1 and ECE-2 [81]. ECE-1 knockout mice show craniofacial and cardiac abnormalities in addition to colonic aganglionosis [104]. A heterozygous ECE-1 mutation has been identified in a patient with HD who also had craniofacial and cardiac defects [105].

Sox10 is a member of the SRY-related family of transcription factors that is expressed by enteric nervous system precursors before and throughout colonization of the gut mesenchyme [81]. Disruption of the Sox10 gene has been demonstrated to be the cause of the Dom mouse natural mutant [106, 107]. Interestingly, both homozygous and heterozygous animals produce a lethal HD-like phenotype [108]. Mutations in Sox10 have been identified in Waardenburg syndrome associated with HD [109].

Phox2B is a transcription factor that is essential for the development of the neural crest derivates as it regulates the Ret expression in enteric nervous system precursors [110, 111]. Targeted Phox2B gene disruption leads to a complete absence of enteric nervous system in the mice, a phenotype that is very similar to that of the Ret knockout mouse [110]. Garcia-Barcelo et al. reported that Phox2B deficiency might predispose to HD in humans [112].

Pax3 is a member of the paired-box containing family of nuclear transcription factors that is expressed in neural cell precursors giving rise to enteric ganglia and synergizes with Sox10 to activate an enhancer in the Ret gene [113]. In the mouse, Pax3 mutations result in a phenotype characterized by deficient enteric ganglia in the heterozygous state. Homozygous deficient embryos die during mid-gestation

with neural tube defects, cardiac defects and absence of enteric ganglia [113]. So far, no Pax3 mutations have been identified in patients with HD, though.

Most surgical models of HD have involved chick embryos because they are easily accessible and the development of their enteric nervous system has been well studied. In that species, aganglionosis can be caused by surgical ablation of the premigratory neural crest [114]. This model is useful for the investigation of possible treatment strategies. It has been used to recolonize aganglionic bowel with neural crest cells by transplanting tissue obtained from the dorsal neural tube [115–117]. It has also been employed to show that neurons from more proximal regions of bowel are capable of recolonizing distal bowel and forming enteric ganglia [115, 118].

Sato and colleagues described a chemical model of HD [119]. They created segmental aganglionosis by applying benzalkonium chloride topically to the colon and rectum in rats. This model has been reproduced in mice and guinea pigs [120, 121]. It has also been used in the distal esophagus as a model of achalasia [122]. Benzalkonium chloride causes cell damage and death by producing an irreversible depolarization of the cell membrane. Due to the high cell membrane negative charge of neurons, they are more intensely affected then other cells. As a result, benzalkonium chloride induces a selective neuronal ablation in the intestinal wall eliminating almost all myenteric neurons and glia in treated segments [121]. Although the aganglionic bowel does not show hypertrophic nerve bundles and the chemical does not affect the number of submucosal neurons, the treated part does become narrowed and the rectoanal reflex is abolished [119]. Compared to the other models of HD, this technique is inexpensive, easy to perform and the animals can survive longer. It has been used to study functional and structural changes in the bowel resulting from loss of these neural elements. It could also be used to study the chronic changes caused by the aganglionic segment, as well as the long-term effects of different surgical treatments [123–128].

3.2.5 Necrotizing Enterocolitis

To date, no true animal model for necrotizing enterocolitis (NEC) has been described. Nevertheless, as multiple factors have been implicated in the pathogenesis of NEC, several animal models exist that may provide useful platforms for the study of different aspects relevant to the pathophysiology of this disease.

The ischemia/reperfusion model involves direct occlusion of mesenteric vessels or the superior mesenteric artery for varied periods of time followed by reperfusion. It has been performed in different species. In one study in neonatal piglets, the mesenteric vessels were tied off at different points near the distal ileum for 48 h [129]. There was a higher chance of intestinal injury when the occlusion was closer to the ileocecal junction. The degree of injury was greatest in low birth weight piglets as measured by ulceration, vascular engorgement, pneumatosis intestinalis, full-thickness necrosis, and ulceration with perforation. In normal birth weight piglets no injury was observed. This model allows for the investigation of eventual differences in the intestinal response to injury dependent on developmental stages. In mice, the time for the development of ischemic injury following vascular occlusion is substantially less than in low birth weight piglets. For example, occlusion of the superior mesenteric artery for 20 min in adult mice can result in the development of ischemic intestinal lesions in 50% of the animals by 48 h [130].

Studies in human infants with NEC have shown that, within the intestinal lumen, the pH was generally less than 5.0, the protein content less than 5 g/dL, and sufficient carbohydrate and bacteria were available to produce organic acids by fermentation [131]. Based on these data, investigators have created a rabbit model of NEC using a bovine casein formulation acidified with propionic acid [131, 132]. In weanling rabbits, either saline or a solution of 10 mg/mL casein and 50 mg/mL calcium gluconate acidified to a pH of 4.0 was instilled into isolated intestinal loops triggering increased intestinal blood flow, mucosal permeability and histamine release. After 3 h,

the villa were blunted, the lymphatic vessels dilated and edema was observed [133]. After 16 hours, several rabbits had hemorrhagic necrosis and died. Advantages of this model include its simplicity and reproducibility as well as the fact that assorted animals at varied stages of development can be evaluated as to their response.

3.2.6 Short Bowel Syndrome

Perhaps not surprisingly, many models of short bowel syndrome (SBS) have been described. For example, intestinal resection and subsequent gut adaptation have been characterized in the pig [134, 135], dog [136–138], rat [139, 140], and mouse [141]. Warner and colleagues have shown that the murine model can be particularly useful for the study of various genes germane to intestinal adaptation [141]. In this model, a proximal resection is preferred, as adaptive changes are most pronounced in the distal intestine. Large animal models such as the pig are more useful for the development of new surgical bowel lengthening techniques [142–144].

3.2.7 Parenteral Nutrition

Now exceedingly rare due to animal welfare regulations, canine models were instrumental to one of the most relevant achievements not only in pediatric surgery, but in all of medicine and surgery, namely the ability to sustain life exclusively by parenteral nutrition, chiefly through the work of Dudrick and colleagues [145]. In their original study, the aim was to support growth and development in beagle puppies for 10 weeks [146]. Small lipoid pigment deposits and hemosiderin pigment were present in the liver, so dosages of fat and iron were reduced. These results lead to a subsequent study in which 6 beagle puppies were fed entirely by central venous infusion for 72 to 256 days and compared with their littermates [147]. These puppies exceeded their orally fed control littermates in weight gain and matched them in skeletal growth, development, and activity for the study period. The longest-term animals, fed for 235 and 256 days, more than tripled their body weight and developed comparably to their control littermates. These studies first demonstrated that it was both possible and practical to feed animals entirely by vein for prolonged periods of time without excessive risks or compromise of growth and development. Soon thereafter, Dudrick and colleagues administered total parenteral nutrition to six severely malnourished adult patients with chronic, severe gastrointestinal disease for up to 48 days [148]. Positive nitrogen balance was achieved in all of them, along with weight gain, normalized wound healing, and increased activity. All patients were eventually discharged from the hospital. The first neonatal administration occurred in that same year, in an infant with near-total small bowel atresia who underwent a massive intestinal resection [149].

3.2.8 Vacter and Other Models

As previously stated, this was not to be an all-inclusive list, but rather one illustrative of the different development avenues offered by a variety of animal platforms. Other models applicable to the pediatric surgical diseases discussed above, as well as models of interest to other pathological processes, will be discussed in their respective chapters. A special note must be mentioned on the remarkable variety of models of the VACTER (vertebral, anorectal, cardiac, trachea-esophageal, and renal) association, both as far as mechanism of action, as well as variability within the broad spectrum of this "syndrome" [4, 150–159].

3.3 Cell-Based Research

Cell-based therapies remain largely experimental, yet cell-based research has undergone dramatic growth and diversification over the last few decades. Certainly, in light of recent advances in stem cell biology, tissue engineering, gene manipulations, and other so-called regenerative medicine strategies, it is reasonable to speculate that these therapies may become alternatives, if not preferred treatment modalities, for a number

of structural congenital anomalies and other diseases within the realm of pediatric surgery in the not so distant future [160, 161]. The following is a much summarized outline of a few aspects of this burgeoning field that are of particular consequence to our specialty.

Prenatal stem cell and gene therapies have tremendous potential to treat a range of disorders that can be diagnosed or predicted before birth, stemming from the unique environment present during fetal developmental, which can facilitate and enhance cellular engraftment. A notable example is *in utero* hematopoietic stem cell transplantation (IUHSCT). While few disorders have a compelling rationale for IUHSCT based on the prevention of irreversible damage to the fetus before birth, such as for example glycogen storage diseases with neurologic involvement, this methodology can be a powerful means to induce tolerance to transplantation later in life. Flake and colleagues have developed germane work in this area aimed at maximizing chimerism through a variety of strategies so as to achieve complete or near complete replacement of host hematopoiesis by donor cells without toxicity or graft versus host disease in rodent models [162–164]. Consistent results in preclinical large animal models are now being pursued by that group and others [165].

Fetal tissue engineering is another notable development. It constitutes a novel therapeutic concept in perinatal surgery, involving the procurement of fetal cells, which are then used to engineer tissue *in vitro* in parallel to the remainder of gestation, so that an infant, or a fetus, with a prenatally diagnosed birth defect could benefit from having autologous, expanded tissue readily available for surgical implantation in the perinatal period. The fetus is a prime tissue engineering subject, both as a donor and as a host. The many exclusive characteristics of fetal cells, in conjunction with the developmental and long-term impacts of engineered graft implantation into a fetus or a newborn, add new dimensions to tissue engineering generally. Also, the fact that certain congenital anomalies present as perinatal surgical emergencies further justifies the fetal tissue engineering principle. Our group and others have been developing this notion in a variety of animal models of structural congenital anomalies, typically employing the amniotic fluid as a preferred source of fetal cells [166–180]. Preclinical studies have been reported and the first clinical trials are expected for the near future [181–183]. Another facet of fetal cell-based treatments of structural anomalies being developed experimentally is the use of fetal neural stem cells for the repair of spinal cord damage in the setting of neural tube defects, such as spina bifida [184]. Additionally, select fetal cells have also been proven valuable experimentally in studies on wound healing modulation [185].

Tissue engineering techniques have already been used to repair congenital anomalies postnatally in children. Shin'oka and colleagues have accumulated considerable clinical experience with the use of engineered conduits as vascular replacements in low-pressure systems, in children with varying forms of complex congenital cardiovascular anomalies [186–190]. Further clinical experience with tissue engineering in pediatric surgery beyond the more prevalent anecdotal reports is expected in the coming years.

More recently, transamniotic stem cell therapy (TRASCET) has emerged experimentally as a novel therapeutic strategy for the treatment of different birth defects. It is based on the principle of harnessing/enhancing the normal biological role of mesenchymal stem cells that are naturally occurring in the amniotic fluid for therapeutic benefit. Specifically, we have recently shown that amniotic fluid-derived mesenchymal stem cells (afMSCs) play a central role in fetal wound healing, widely known to be enhanced when compared with postnatal repair of tissue damage [185]. This germane finding was not only the first demonstration of a biological role for any amniotic cell, it has also provided validation for the use of afMSCs in regenerative strategies, in that these cells already play a regenerative role in nature. More recently, we have also shown, in different animal models, that the simple intra-amniotic delivery of afMSCs in large numbers can either elicit the repair, or significantly mitigate the effects associated with major congenital anomalies, putatively by boosting the activity

that these cells normally have. For example, concentrated amounts of these cells injected into the amniotic cavity can induce partial or complete coverage of experimental spina bifida by promoting the local formation of a host-derived primitive skin, thus protecting the spinal cord from damage [191, 192]. Placenta-derived MSCs also seem to be a suitable option for TRASCET, at least in experimental spina bifida [193]. In another example, TRASCET has been shown to significantly alleviate the bowel damage associated with gastroschisis [194]. Many other applications of this practical therapeutic concept, involving a variety of congenital anomalies, are currently being investigated.

3.4 Clinical Research

Clinical research has evolved appreciably, particularly over the last two decades. It has essentially become a science deserving of a whole book, rather than a segment of a book chapter. The several aspects that make up clinical research need careful planning and execution if a study is to be any relevant. More specifically, conceiving the research question(s); establishing the appropriate study/trial format; defining randomization criteria when suitable; choosing and recruiting the research subjects; estimating sample size and power; assessing control/independent variables and/or causal interference; designing questionnaires and interviews; organizing and managing databases; analyzing data; implementing quality control; and addressing ethical issues are just some of the components that need to be tackled before one can embark on a meaningful project. By the same token, as the clinical research endeavor becomes more refined, it expectedly subdivides, perhaps more notably between clinical trials and outcomes research.

As critical as it is to any medical/surgical field, the overall adequacy of clinical research design and reporting in our specialty has been rather inconsistent over time [195]. Fortunately, however, pediatric surgeons have grown increasingly more discerning of late, progressively driving our scientific journals and professional societies to implement enhanced and more standardized peer-review guidelines which ultimately should be of great benefit to the field as a whole [195–199].

3.5 Final Considerations

The history of our young specialty is already rich in original translational initiatives which have shaped clinical practice both within and across the boundaries of our field. Among the many of these, perhaps one should stand out as an inspiration to all of us. A pediatric surgeon, Dr. M. Judah Folkman, was the first to propose and coin the term "antiangiogenesis" as a potential therapeutic approach to cancer and other conditions in his landmark paper of 1971 [200]. With this seminal insight, he established a new perspective on cancer biology by expanding the focus beyond the tumor cells to their microenvironment. The concept that proliferating endothelial cells may be better therapeutic targets than the neoplastic cells themselves represented a momentous shift of focus and triggered an enormous research enterprise. Folkman's direct and rational approach to angiogenesis redefined cancer biology, as well as multiple other processes in health, embryonic development, and other diseases [201]. It has been predicted that angiogenesis-related therapies can eventually benefit half a billion people worldwide [202].

As Dr. Folkman used to say, "science goes where you imagine it". Let us hope that more and more of our colleagues can be drawn by that inspirational vision and manage to incorporate either of the many forms of pediatric surgical research into their daily activities and ambitions.

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4 Antenatal Diagnosis: Current Status for Paediatric Surgeons

Ryan Hodges, Luc De Catte, Roland Devlieger, Liesbeth Lewi, Tim Van Mieghem, and Jan Deprest

Abstract

In this chapter we review antenatal diagnosis and obstetric management of fetal conditions that are relevant to paediatric surgeons. We restrict our discussion to fetal conditions that have been shown to, or have the potential to, benefit from in utero surgical therapy.

Keywords

Prenatal diagnosis • Fetal medicine • Fetal surgery

4.1 Introducing the Fetal Patient

The ascendancy of antenatal imaging and genetic biotechnology has transformed fetal medicine in the modern era. In current clinical practice, women are offered a raft of early pregnancy screening options for aneuploidy, placental disorders and increasingly earlier diagnosis of fetal abnormalities. The introduction of first trimester ultrasound for nuchal translucency measurement as part of Down syndrome screening also potentiates early diagnosis of several major structural malformations [1–6]. For pregnancies categorized as higher risk based on this early screening or on past or familial history, invasive genetic diagnostic testing can be pursued and further highly specialized diagnostic fetal ultrasound and echocardiography can be offered from 16 weeks gestation [7–9]. Furthermore, fetal magnetic resonance offers additional imaging capabilities to further define anatomical defects detected on ultrasound screening. Most recently, the stage is now set for non-invasive prenatal diagnosis, whereby free fetal DNA is extracted from maternal plasma during pregnancy, to radically change our approach to antenatal diagnosis as high resolution genome wide evaluation becomes available [10]. Multidisciplinary counselling, therefore, must assume even greater

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_4

clinical importance if we are to effectively assist pregnant women to navigate through the increasingly complex information and myriad of choices that come with improved antenatal diagnosis.

In this regard, for some very selected abnormalities, fetal surgical intervention may prove beneficial. It is indeed possible that early antenatal diagnosis will allow timely *in utero* surgical correction of an anatomic defect or reverse a pathophysiologic process, which may then permanently alter the trajectory of growth and development in a positive way. For this to be successful, however, strict criteria have been proposed as a means of justifying the implicit risks to the mother and fetus by surgically invading the amniotic cavity during pregnancy (Table 4.1, [11]). Of paramount importance in this selection is accurate antenatal diagnosis with a clearly defined antenatal and postnatal course. In recent years, we have made some headway in defining these parameters for certain pathologies. Furthermore, detailed sonographic diagnostic criteria, often complemented by fetal MRI, have developed novel predictive indices to better delineate the likely *in utero* progression of disease, health at birth and even in the neonatal period. This has allowed patient selection for fetal intervention to be refined [12]. In addition, the literature has transcended from heterogeneous, small observational studies of fetal surgical interventions to successful multicentre randomised trials for instance on twin-twin transfusion syndrome [13], myelomeningocoele [14], congenital diaphragmatic hernia [15, 16] and lower urinary tract obstruction [17]. Notwithstanding the maternal burden, we are now in a better position to provide counselling to parents to determine whether fetal surgery is likely to rescue abnormal fetal development or not. There remains more to be done. It should be remembered the inspiration and translation of fetal surgery has all come from the careful antenatal examination and meticulous description of the fetal patient.

Table 4.1 Criteria for fetal patient selection

1. Accurate diagnosis, staging where relevant, with exclusion of associated anomalies
2. Well documented natural history and prognosis of the disease
3. No effective postnatal therapy
4. *In utero* surgery shown to be feasible and effective in animal models
5. All interventions performed in dedicated multidisciplinary fetal treatment centres with strict protocols, local Ethics Committee approval and informed consent of mother or parents.

Adapted from Harrison, M.R. and N.S. Adzick, The fetus as a patient. Surgical considerations. Ann Surg, 1991. 213(4):279–91; discussion 277–8; used with permission

Herein lies the focus of this chapter, where we review antenatal diagnosis and obstetric management of fetal conditions that are relevant to paediatric surgeons. We restrict our discussion to fetal conditions that have been shown to, or have the potential to, benefit from *in utero* surgical therapy.

4.2 Lower Urinary Tract Obstruction

4.2.1 Definition and Epidemiology

Lower urinary tract obstruction (LUTO) refers to a heterogeneous, pathological group of disorders that directly affect the urethra. The presence of posterior urethral valves (PUV) is most common, whereby a Mullerian or cloacal embryological membranous remnant is responsible for the obstruction. Obstruction can also be caused by urethral atresia, urethral stenosis, ectopic insertion of a ureter, perivesical tumours and prune belly syndrome [18]. The incidence of LUTO is reported at 2.2 cases in 10,000 births, with PUV occurring in 1 in 7031 births [19]. Most cases are in males (PUV are exclusively male), whereby in females urethral atresia is more common and consideration should be given to rarer cloacal plate pathologies such as megacystis-microcolon-hypoperistalsis-syndrome (MMHS).

4.2.2 Genetics

Most cases are sporadic; in some, cases have been associated with polymorphisms of genes expressed during development of the urinary tract [20]. Recurrence risk is low. MHHS syn-

drome is an exception, which has an autosomal recessive inheritance pattern. Chromosomal abnormalities, in particular trisomies 13, 18 and 21 have been reported in 12% of cases [21]. Genetic testing is therefore mandatory.

4.2.3 Pathophysiology and Natural History

LUTO results in bladder distension with compensatory smooth muscle hypertrophy of the bladder wall. With increasing pressure and distension, the bladder wall eventually loses its natural elasticity and poor tone and function develops. Increasing backpressure from vesico-ureteric reflux drives bilateral hydronephrosis above, with enlarging pyelectasis and calyectasis then responsible for progressive compression of the vulnerable developing renal parenchyma. This pressure-induced mechanism of injury may act in concert with premature activation of the renin-angiotensin system causing vasoconstriction and further hypoxic injury [22]. Fibrosis to the renal medulla and renal cortex results in renal dysplasia and eventually renal insufficiency. Some have suggested dysplasia may even result from other abnormal embryological communication unrelated to the obstruction [23]. Regardless, urine production fails and oligohydramnios ensues. This results in the development of pulmonary hypoplasia [24]. Oligohydramnios inhibits lung expansion up to 20%, primarily a result of altered fetal posture and narrowing of the fetal thorax, with reduced fetal respiration [24]. Respiration is considered an important factor in stimulating lung growth. Decreased airway branching may occur and alveoli numbers are reduced and may be structurally immature with reduced collagen and elastin [25]. Depending on gestational age and severity, respiratory embarrassment at birth is the norm, yet the condition can also be lethal.

Prognosis is dependent on the degree of renal insufficiency and the presence and degree of pulmonary hypoplasia. Mortality for antenatally diagnosed cases is 45%, but rises to 95% for those with persistent oligohydramnios [26]. For survivors at birth, one third will develop renal failure necessitating dialysis and is the leading cause of childhood renal transplantation [27]. Voiding problems happen as well.

4.2.4 Antenatal Diagnosis

The sensitivity of ultrasound for detecting LUTO is 95% with 80% specificity [27]. The diagnosis is usually made at the 18–20 week ultrasound, although in some may be evident at the 11–13 week ultrasound and confirmed, if persistent, at 16 weeks [28]. The classical sonographic feature is the "key hole" sign (Fig. 4.1), whereby the dilated proximal urethra above the obstruction extends into the dilated and thick walled bladder (greater than 2 mm is considered pathologic) [22]. The dilated bladder, or *megacystis,* may occupy much of the abdomen, and even spontaneously rupture and produce urinary ascites. Ureterectasis, caliectasis and hydronephrosis are all evident sonographically (Fig. 4.2). Bilateral renal dysplasia appears as increased echogenicity of the renal parenchyma and subcortical cysts are indicative of particularly poor prognosis [26]. Similarly, the presence of oligohydramnios signifies major obstruction, and if present prior to 24 weeks is associated with a

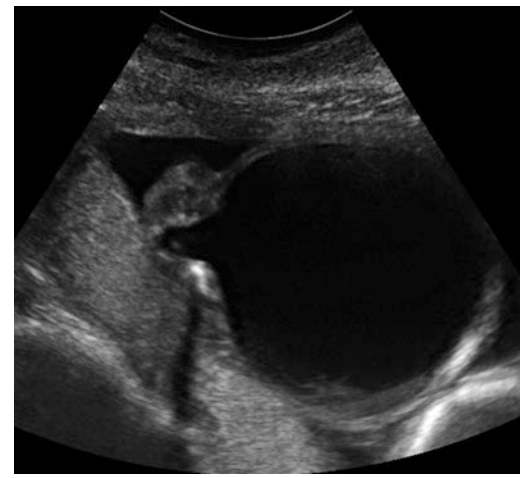

Fig. 4.1 Lower urinary tract obstruction: key hole sign. The fetal abdomen is distended by an anechogenic cystic structure, extending into the proximal urethra. Image: courtesy and copyright UZ Leuven

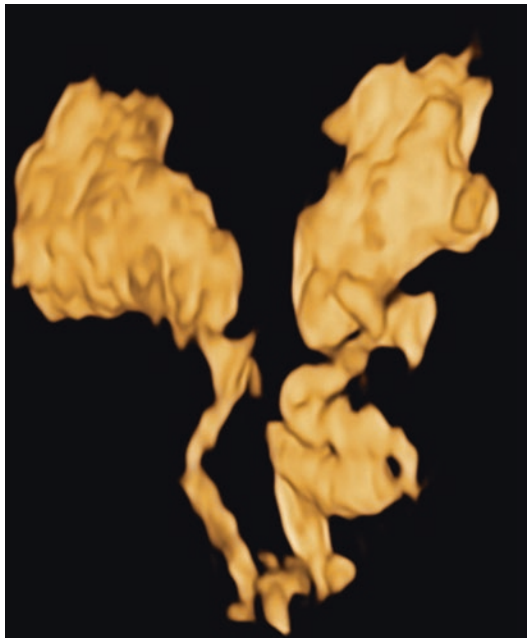

Fig. 4.2 Lower urinary tract obstruction later in gestation with bilateral ureterectasis and hydronephrosis and caliectasis, clearly displayed by 3Dinverted rendering. This modality extracts the fluid filled higher urinary tract, dilated into its intrarenal portions. Image: courtesy and copyright UZ Leuven

higher prevalence of renal dysplasia and pulmonary hypoplasia [21]. Oligohydramnios with an absence of caliectasis may suggest such severely damaged dysplastic kidneys that they are no longer capable of producing demonstrable urine [22]. Where possible, the bladder should be observed during voiding for the presence of vesicoureteric reflux. Fetal sex should also be determined. Of note, Potter's facies and club feet can be seen in chronic cases. A thorough search for features of trisomy 13, 18 and 21 must also be undertaken and a detailed examination for the presence of other abnormalities.

The limitation of ultrasound is in accurately defining the specific aetiology of the LUTO as well as to predict renal function. Amnioinfusion may be required to explore structural integrity. Fetal MRI may offer additional information, particularly when oligohydramnios prevents adequate resolution. Fetal MRI has been shown to modify the diagnosis of LUTO in 5 of 16 cases in the third trimester [29] and to better define subcortical cysts, potentially aiding prenatal counselling.

4.2.5 Antenatal Prediction of Prognosis

Much effort has been expended to define antenatal determinants of fetal and postnatal renal (and therefore respiratory) function, with a view to identify candidates for *in utero* intervention. Unfortunately, in the present day, the waters remain somewhat muddied. Momentum developed in the late 1980s following experimental animal studies that demonstrated rescuing renal function by decompressing the obstructed bladder *in utero* [30, 31]. The rationale for this approach is that renal development is complete at birth, rendering postnatal surgical strategies largely ineffective. This raised the possibility that relieving the obstruction *in utero*, particularly during the peak of nephrogenesis (20–30 weeks gestation), may be beneficial [22]. Several observational series have since highlighted the importance of appropriate patient selection, whereby the risks of surgical invasion (most commonly preterm prelabour rupture of membranes, premature birth and chorioamnionitis) are applied only to a fetus that has potentially salvageable renal function. To predict this, there is now a large body of work examining the performance of urinary and serum electrolytes to quantify fetal renal function (Table 4.2) [18]. It has become apparent that serial measurements of urinary electrolytes (via vesicocentesis) are more representative of fetal renal function, as urinary stasis may confound the initial measurement [32]. However, in a 2007 systematic review, Morris and colleagues [33] argued that no particular fetal urinary analyte could accurately predict poor postnatal renal function. Profiling fetal serum obtained by cordocentesis for beta 2 microglobulin may improve this

Table 4.2 Fetal urine prognostic tresholds based on different series

Electrolytes	Good prognosis	Poor prognosis
Sodium	<90 mmol/L	>100 mmol/L
Chloride	<90 mmol/L	>100 mmol/L
Osmolality	<180 mOsm/L	>200 mOsm/L
Total protein	<20 mg/dL	>40 mg/dL
Beta 2 microglobulin	<6 mg/L	>10 mg/L

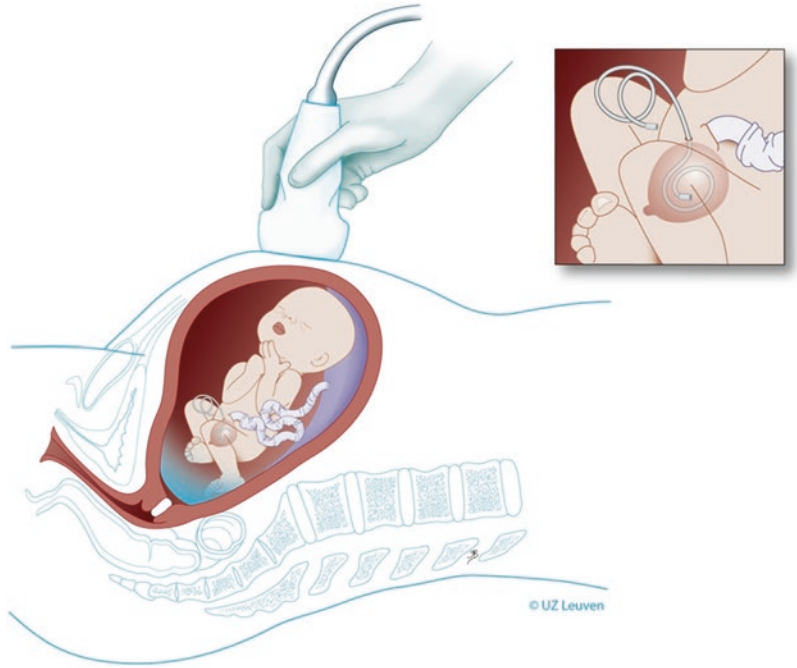

Fig. 4.3 Schematic drawing of vesico-amniotic shunt in place. *Insert*: double pigtail shunt connects the bladder to the amniotic cavity (reproduced with permission from the UZ Leuven, Belgium)

assessment. It is not possible to measure directly fetal urea and creatinine due to their small molecular size and placental filtration between fetal and maternal circulations, however beta 2 microglobulin has a larger molecular size and appears to reflect fetal glomerular filtration rate more reliably [34, 35]. Furthermore, repeated measurements are possible even after the placement of a shunt, which is not possible for urinary electrolytes [36]. Some groups have even suggested renal biopsy [37]. Our group uses a combined algorithm of sonographic features (kidney echogenicity and presence of cortical cysts, amniotic fluid volume), urinary electrolytes and serum beta 2 microglobulin. We simultaneously perform amniocentesis for karyotype, vesicocentesis for urinary electrolytes and cordocentesis for beta 2 microglobulin to help select potential candidates for a vesicoamniotic shunt (Fig. 4.3) and inform our prenatal counselling. In some cases of severe oligohydramnios, an amnioinfusion is required to complete this diagnostic work up. Candidates for prenatal intervention are generally considered if they are male fetuses with "good" prognostic features and worsening oligohydramnios. Regrettably, there are probably some fetuses with a favourable renal function profile but with normal amniotic fluid that, although currently not considered for shunting, do deteriorate later, sometimes even in infancy. Predicting this group remains problematic. Furthermore, shunting in utero intervention in female fetuses is usually not successful owing to the complexity of LUTO in this group [18]. Overall, several observational studies in males with LUTO have now suggested shunting seems to prevent neonatal death from lethal pulmonary hypoplasia, but the effect on improving renal function in survivors is less clear [21, 32, 38]. The most recent systematic review was in 2010 by Morris and colleagues [39], who examined 20 studies including 369 fetuses with LUTO. At that time there were no randomised trials and several studies were of poor methodological quality in accounting for bias and in reporting the techniques used. In their meta-analysis of 12 studies, they found that antenatal bladder drainage improved perinatal survival compared with no treatment (OR 3.86, 95% CI 2.00–7.45) and appeared most beneficial in a subgroup of fetuses with a poor predicted prognosis (OR 12.85, 95% CI 1.25–153.03). However, when examining survival with normal renal function in seven studies,

a key component in prenatal counselling with parents, the analysis favoured no intervention. This may suggest that the reduced number of survivors with normal renal function following antenatal intervention compared to those without fetal treatment, may represent a group of fetuses with severe renal disease who would have died *in utero* from pulmonary hypoplasia if they had not received intervention. This may also suggest, as discussed above, that additional mechanisms are responsible for renal parenchymal damage other than an entirely pressure-mediated process from obstruction. When the authors examined a subgroup of fetuses with LUTO and good predicted renal function from urinalysis, there was a trend to favour intervention but this did not reach statistical significance. No fetuses with poor predicted prognosis survived. Caution must be applied in interpreting this data however, particularly subgroup analysis, given the observational nature of this research. With regard to longer term follow up, Biard and colleagues [40] recently reported long-term follow up of 20 male fetuses with LUTO and oligohydramnios who were shunted antenatally. Renal function was acceptable in 45% of cases, with 22% having renal impairment and 33% with end-stage renal disease necessitating transplantation. Of note is that the self-perceived qualtiy of life of survivors fell in the normal range. Hence, despite several decades of research, a robust prospective randomised trial was still in the making.

The Birmingham group in 2007 designed the PLUTO trial [17], whereby fetuses with LUTO were randomized to either vesicoamniotic shunt placement or observation when the treating clinician was uncertain of the need for a shunt. Key to this study design was the demonstration of clinical equipoise, which was attempted by surveying paediatric nephrologists, paediatric urologists and maternal fetal medicine subspecialists [41]. After demonstrating clinical equipoise, the PLUTO trial study design did not stipulate an algorithm to formally evaluate fetal renal function prior to randomisation and instead relied on the clinician's uncertainty as to whether the fetus would benefit from a vesicoamniotic shunt placement or not. Disappointingly, the trial was stopped early in 2012 due to poor recruitment and many questions remain unresolved [42]. They concluded that survival seemed to be higher after shunting, but the size and direction of the effect remain uncertain, such that benefit could not be conclusively proven. Also, the chance of newborn babies surviving with normal renal function seems very low irrespective of whether or not vesicoamniotic shunting is done. A further advance may yet come from fetal cystoscopy (Fig. 4.4). Cystoscopy potentially offers an attractive combination of improved diagnosis, and thereby improved patient selection, and potentially even definitive treatment. Fetoscopic antegrade catheterization and hydro- or laser ablation of urethral valves has now been described, but technical challenges of instrument size and manoeuvrability limits percutaneous access to the bladder neck. Nevertheless, Ruano and colleagues have recently reported the largest prospective series of 23 fetuses with LUTO managed with the option of fetal cystoscopy [43]. The procedure, which can be done as early as 16 weeks of gestation, allows a more robust diagnosis, and in case of urethral valves, definitive treatment by laser fulguration may be attempted. A recent systematic review of four fetal cystoscopy studies [44] demonstrated that the initial diagnosis of posterior urethral valves changed in 32% (6/19) typically towards urethral atresia. In terms of postnatal survival, cystoscopic ablation of the valves was superior to expectant management yet comparable to shunting. The latter procedure is neither without any risk for collateral damage to pelvic floor structures.

4.2.6 Obstetric Management

Patients should be referred to a fetal medicine referral centre for diagnosis and multidisciplinary counselling with maternal fetal medicine specialists, paediatric urologists, paediatric nephrologists and neonatologists all considered essential. In most cases, delivery at a tertiary centre is appropriate. A detailed sonographic assessment should be undertaken as described above, and given the presence of chromosomal abnormalities in 12% of cases [21], fetal karyotype should be offered. As described earlier, for mild cases where fetuses have normal amniotic fluid and no evidence of

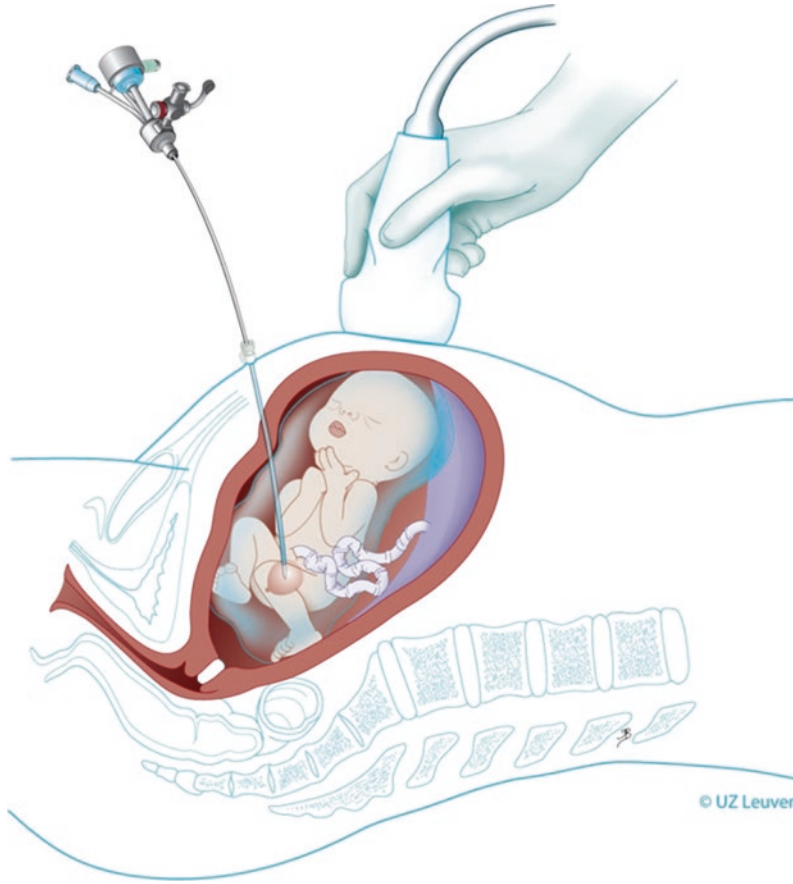

Fig. 4.4 Schematic drawing of fetal cystoscopy. *Insert*: Through a 7 Fr cannula a semi-flexible endoscope has been inserted into the bladder to visualize the bladder outlet (reproduced with permission from the UZ Leuven, Belgium)

renal dysplasia on ultrasound, they should be observed closely for evidence of reducing amniotic fluid or signs of renal dysplasia. If renal function remains stable, there should be no respiratory problems at birth, and thus timing and mode of birth should be guided by usual obstetric considerations. Post-natal surgical evaluation and correction is then undertaken. Should there be sonographic signs of failing renal function, then management is guided by gestational age. If the pregnancy is more than 32 weeks, elective delivery (covered by glucocorticoids for fetal lung maturity when appropriate) is advised to pursue postnatal repair [22]. When less than 32 weeks gestation, we would offer investigational fetal MRI to aid in the examination for signs of renal dysplasia and recommend formal evaluation of fetal renal function by both urinary electrolytes and serum beta 2 microglobulin. In the good prognosis group, we will offer parents the option of vesicoamniotic shunting and/or fetal cystoscopy after through counselling of the limitations discussed earlier and close ongoing surveillance. In the poor prognosis group, or in those who present early with severe chronic obstruction, oligo- or anhydramnios and renal dysplasia evident on ultrasound, we would counsel the parents regarding termination of pregnancy or expectant care. Expectant care should be clearly defined by obstetric and neonatal physicians, including advising no intervention for fetal heart rate abnormalities in labour, providing intermittent auscultation of the fetal heart rate at maternal request only, no indication for cardiotocograph monitoring in labour and no active resuscitation at birth. Parents should be well counselled regarding comfort care of the neonate after birth, post mortem and diagnostic investigations and support services for the family should be initiated. The place of active management is as described above.

4.3 Sacrococcygeal Teratoma

4.3.1 Definition and Epidemiology

Sacrococcygeal teratomas (SCT) are tumours derived from the totipotent Hensen node of the primitive streak, thereby retaining a full differentiation repertoire down ectodermal, endodermal or mesodermal cell pathways [45]. It is the most common tumour in the fetus with an incidence of one in 40,000 births with more females than males affected (4:1) [46], although malignant change is more common in males. The American Academy of Pediatrics Surgical Section classification system is shown in Table 4.3, [47] which describes SCTs according to their relationship with the sacral region. Note that this classification is a surgical description and does not reflect prognosis.

4.3.2 Genetics

Considered sporadic. Rare autosomal dominant inheritance in some families has been reported [26]. Rarely associated with aneuploidy.

4.3.3 Pathophysiology and Natural History

Given SCT's are of totipotent origin, cells can differentiate into embryonic (mature and immature teratomas) or extraembryonic (choriocarcinoma and yolk sac teratoma) tumours. Most commonly, gastrointestinal, respiratory and nervous tissue material is present [26]. SCT's show a paraxial or midline distribution usually from the brain to the sacral region, thereby reflecting aberrant migration of the primordial germ cells. Other less common sites are the anterior mediastinum, pineal area, retroperitoneal area, neck, stomach, and vagina [18]. SCT's are the most common presentation at birth. They represent an extragonadal form that arise in the presacral area, which, as demonstrated by the classification presented in Table 4.3, can extend into the pelvic and abdominal cavity or develop more exteriorly. They are heralded for imposing vascularity and the propensity for rapid growth *in utero*, which can risk fetal survival through the development of high output cardiac failure and/or fetal anaemia, non-immune hydrops, destructive processes to adjacent viscera or obstetric complications. The condition can also cause maternal problems (Ballentyne Syndrome). Most SCT's are benign, however can recur following surgical resection and do have malignant potential in around 10% of neonates born with SCT, particularly in more immature and in type IV tumours [22].

Table 4.3 Type of tumour as per the American Academy of Pediatrics, Surgical Section (AAPS)

Tumour type	Description
Type 1	Predominantly external, with minimal intra-pelvic extension
Type 2	Mainly external, with significant intra-pelvic extension
Type 3	Visible external, but predominantly internal
Type 4	Internal, although external parts may be visible

From Altman, R.P., J.G. Randolph, and J.R. Lilly, Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey-1973. Journal of pediatric surgery, 1974. 9(3):389–98; used with permission

4.3.4 Antenatal Diagnosis

SCT is usually diagnosed at the 18–20 week ultrasound, although occasionally reported at the 12-week ultrasound [6]. Alternatively, patients may present later with the clinical sequelae of polyhydramnios, such as large for dates, uterine irritability, preterm labour or preterm prelabour rupture of membranes. Sonography reveals a mixed solid and cystic mass, often with calcification, arising from the distal spine and sacral region (Fig. 4.5). A SCT is considered destructive to the spine, whereas as a myelomeningocoele will widen the spine and is likely to have additional cerebral signs [26]. A thorough description of the external and internal pelvic components of the tumour is necessary. The latter may benefit from fetal MRI to more accurately delineate the degree of pelvic extension and distortion of local

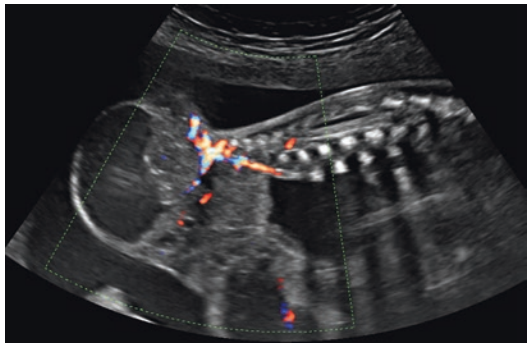

Fig. 4.5 Sacrococcygeal teratoma. Sagittal section on the midline with the lumbosacral vertebrae visible. A tumor orginates at its distal end, and with Doppler ultrasound the feeding vessels from the presacral area. The echogenicity of the tumor varies, with cysts as well as within the solid parts. Image: courtesy of and copyright UZ Leuven

anatomy, where acoustic shadowing from pelvic bones on 2D ultrasound may be bothersome [48]. Bladder elevation, ureteral dilatation and hydronephrosis with the potential for renal dysplasia from compression forces may occur. Similarly, gastrointestinal dilatation may result from obstruction. Rectovaginal fistula and imperforate anus may also develop from direct tumour spread. Danzer and colleagues (2006) [48] evaluated their experience with additional fetal MRI compared with sonography alone. In their series of 24 patients, MRI was superior to sonography for assessing colon displacement (n = 11), urinary tract dilatation (n = 9), hip dislocation (n = 4), intraspinal extension (n = 2), and vaginal dilation (n = 1). In fetuses with sacrococcygeal teratoma types II and III, MRI was again superior to sonography in demonstrating the cephalic extent of the tumor. In two referred cases, MRI led to a changed diagnosis (healthy, $n = 1$; myelomeningocele, $n = 1$). They concluded additional anatomic resolution from MRI resulted in more accurate antenatal counselling and preoperative planning for surgical resection.

SCT's are renowned for their impressive vascularity, often jeopardising fetal cardiac integrity. This can be simply visualised with 2D colour Doppler or more recently has been evaluated with 3D power Doppler, allowing calculation of the vascular volume of the tumour relative to the heart [49]. Cardiac failure and non-immune hydrops may develop, usually from high output cardiac failure following rapid growth of the tumour with extensive arteriovenous shunting. Furthermore, if the tumour outgrows its blood supply and becomes necrotic it can rupture, resulting in haemorrhage and fetal anaemia [22]. Fetal anaemia can be observed by an increase in the middle cerebral artery Doppler peak systolic velocity [50]. High output failure can be diagnosed sonographically and with fetal echocardiography, demonstrating increased inferior vena cava diameter (reflecting increased venous return), dilated ventricles, increased cardiac output and descending aortic flow velocity, and absent or reversed end diastolic flow of the umbilical artery from vascular "steal" from the umbilical artery to the placenta [22, 26, 51]. Olutoye and colleagues (2004) [52] suggested reversal of end diastolic flow may indicate "backwash" of flow into the low resistance vascular bed of the tumor. Polyhydramnios, placentomegaly, hepatomegaly, increased skin thickness and fluid within fetal compartments may then be recognised consistent with hydrops. Fetal hydrops is considered a pre-terminal sign. Fetal growth restriction may also be apparent. A thorough examination for additional abnormalities should be undertaken, although most are usually the direct result of tumour extension.

4.3.5 Antenatal Prediction of Prognosis

Overall, fetal SCT confers a reasonable prognosis, however a particular subset of fetuses is at great risk. The mortality rate for those who present for the first time as neonates is around 5%, considerably better when compared to those who present antenally who have 50% mortality [53]. Similarly, those who present earlier in gestation have a higher mortality rate of up to 90% less than 30 weeks, compared to 15% in later pregnancy [26, 54]. Accordingly, reliable antenatal prediction of disease progression and survival is imperative to counsel parents. A rapidly growing tumour places enormous burden on the fetal heart and the presence of hydrops should confer grave

concerns for the survival of the fetus. Flake and colleagues (1986) [53] described the presence of hydrops and polyhydramnios being associated with a mortality of seven out of seven fetuses and in a series by Bond and colleagues (1990) [54], they reported ten out of ten hydropic fetuses and nine out of nine fetuses with placentomegaly died. There have been some occasional cases of survival with early delivery and post-natal resection reported since then [55, 56] (Robertson 1995, Nakayama 1991), however this appears uncommon. Some fetal deaths may also occur in fetuses without demonstrable hydrops [57], although abnormalities of absent or reversed end diastolic flow of umbilical artery Doppler may herald impending fetal loss [52].

It would seem reasonable that tumour size would be predictive of the risk of cardiac failure and thus, mortality. Wilson and colleagues (2009) [58] reported tumour growth rates approaching 150 cm^3 per week as a predictor of increased perinatal mortality. However, Westerburg and colleagues (2000) [59] did not confirm that tumor size to be predictive of demise, but instead found the most vascular tumours, regardless of size, had the worst prognosis. In 2006, Benachi and colleagues [60] devised a combined classification system based on tumour diameter, vascularity and rate of growth determined by ultrasound (Table 4.4). This was from a series of 44 fetuses with SCT mostly diagnosed on second trimester ultrasound. The fetal and neonatal loss rates were similar (12% and 13% respectively) and half were born preterm. Group one and three did very well, delivering at term with all fetuses surviving. Group two had the worse prognosis, delivering at 31 weeks on average with a 52% perinatal mortality rate; about half dying *in utero* and half dying in the neonatal period. Surprisingly in this series, most who died were not hydropic. It is worth mentioning that in survivors, morbidities included intraventricular hemorrhage, pulmonary hypertension (and other steal syndromes), acute renal failure and three infants had a rectal perforation or sepsis requiring colostomy. For smaller tumours, a good prognosis is generally expected, presumably due to less circulatory demand. Makin and colleagues [61] reported in 2006 on 29 cases of SCT diagnosed antenatally. The long-term outcome for fetuses not requiring intervention (n = 17) was excellent, with constipation in one child the only reported outcome at 39 months. Of note in this series, six of the seven cases of hydrops resulted in fetal or neonatal demise.

Most recently, Rodriquez and colleagues (2011) [62] have proposed tumour volume to fetal weight ratio (TFR) as an early prognostic classification for fetal SCT. In a retrospective series of ten cases, a TFR greater than 0.12 measured at less than 24 weeks gestation either by ultrasound or fetal MR, was predictive of poor outcomes with a sensitivity of 100% and a sensitivity of 83%. A TFR less than 0.12 predicted an uncomplicated course with 100% survival. All hydropic fetuses

Table 4.4 Proposed classification based on prenatal tumor development, according to Benachi et al. [60]

	Number	Mean gestational age at diagnosis	Prenatal interventions in this case series	Mean gestational age at birth
Group 1: small tumors (<10 cm) with a poor vascularity and slow growth	n = 13	24.0±1.6	no fetal intervention.	38.0 ± 0.47
Group 2: large (>10 cm) and fast growth (>8 mm/week) and high vascularity OR high output cardiac failure (cardiomegaly and increased diameter of inferior vena cava)	N = 21	23.2±0.9	One embolization and one cyst puncture for obstetrical reason	31.0 ± 1.03
Group 3: large (>10 cm) tumors, but predominantly cystic, poorly vascularized or slowly growing tumors	N = 10	22±1.2	None apart from cyst puncture for obstetrical reasons	37 ± 0.3

and all fetuses that died had a TFR greater than 0.12, with just 20% of fetuses having an uncomplicated outcome above this threshold.

4.3.6 Obstetric Management

All patients with suspected SCT should be referred to a tertiary fetal medicine centre for evaluation and multidisciplinary counselling. Maternal fetal medicine specialists, neonatologists and paediatric surgeons are essential members of this team. A detailed sonogram, echocardiogram and fetal MRI are recommended to confirm the diagnosis and exclude additional abnormalities. If SCT is confirmed, a detailed evaluation of the extent of internal pelvic extension, additional visceral involvement and fetal haemodynamic state is required. Classification according to Benachi [60] and the TFR discussed above [62] could be considered. Karyotype is generally not required, unless additional abnormalities are present. Termination of pregnancy should be discussed with parents, particular for a large or rapidly growing SCT, the presence of dysplastic renal involvement and if cardiovascular compromise is evident on ultrasound. The presence of hydrops should be conveyed as a particularly ominous prognostic feature. If termination of pregnancy delivery is planned, it is important that the delivery team consider possible labour dystocia. An intact fetus is preferable for thorough post mortem pathological examination.

For ongoing pregnancies, close surveillance is mandatory. Serial sonography is recommended every 1–2 weeks to identify progression of disease. It must be remembered that SCT's can grow very rapidly and the fetal cardiovascular system may come quickly into jeopardy. Sonographic and echocardiographic signs of hydrops should be pursued, including measurements of a high output circulation such as the inferior vena caval diameter (>1 cm), descending aorta flow velocity (>120 cm/s) and the umbilical artery Doppler waveform [22]. The middle cerebral artery Doppler peak systolic velocity should be examined for signs of anaemia [50]. The renal and gastrointestinal tract should be examined for signs of obstruction. Amniotic fluid volume should be measured for polyhydramnios, and if present, a cervical length measurement to predict preterm labour is advised. Obstetric complications may evolve with advancing pregnancy. In a series by Hedrick and colleagues in 2004 [57], in 26 women with fetal SCT who did not undertake termination of pregnancy, 81% experienced obstetric complications. These included polyhydramnios in seven women, oligohydramnios if four women, preterm labour in 13 women, pre-eclampsia in four women and gestational diabetes, HELLP syndrome and hyperemesis each occurring in one woman. Maternal mirror syndrome has also been reported in cases of SCT with hydrops.

Antenatal fetal intervention for SCT may be an option for selected cases. Dr. Flake and colleagues discuss fetal surgical resection for SCT in detail in Chap. 10. For our purposes in this Chapter, we will briefly discuss additional interventions in the antenatal period, and how this is informed by antenatal diagnosis. In general terms, antenatal intervention is reserved for fetuses at high risk that are still remote from term. Drainage of polyhydramnios is a simple and safe procedure that may help resolve uterine irritability and maternal discomfort. Similarly, if fetal anaemia is detected by increased peak systolic velocity of the middle cerebral artery Doppler signal, intrauterine blood transfusion is a feasible option [63]. In cases of renal tract obstruction from pelvic extension of the SCT, a vesicoamniotic shunt may protect the renal parenchyma from injury in much the same way as fetuses with LUTO [60, 61, 64]. Clinical experience, however, is scarce to formally evaluate these strategies. Open resection with cardiac monitoring, thermocoagulation and radiofrequency ablation of the tumour is discussed elsewhere in this book.

Timing of birth is usually dictated by either fetal or maternal complications. The presence of fetal haemodynamic compromise mandates immediate delivery. For small tumours in healthy fetuses, vaginal delivery may be possible. Delivery in a tertiary centre is essential. Cyst aspiration and decompression does not seem beneficial to aid vaginal delivery [26]. There have, however, been reports of fetal death after

tumour rupture, avulsion and asphyxia following complications of vaginal birth [22]. Close surveillance in labour with continuous cardiotocography monitoring and the presence of senior obstetric and neonatal staff are necessary. For tumours more than 4.5 cm, or in cases of fetal haemodynamic compromise, caesarean section is advised to prevent labour dystocia and reduce the chance of tumour rupture and fatal haemorrhage [26]. This approach requires meticulous planning with obstetric, anaesthetic, neonatal, haematologic and paediatric surgical teams. The caesarean should take place in an elective setting with fetal lung maturity assisted by glucocorticoids when less than 37 weeks gestation [65]. Depending on tumour size, consideration should be given to maternal general anaesthesia to aid uterine relaxation for careful manipulation and delivery of the fetus. The uterine incision should be generous to facilitate an atraumatic delivery of the fetus, particularly in cases with a large mass. A classical (vertical) uterine incision may be advisable to increase the surgical field of exposure, especially in more preterm gestations where a lower uterine segment may not be sufficiently formed and where delivery is anticipated to be difficult. Intraoperative cyst aspiration of 2 L in one case has also been reported to aid delivery [66]. Uterine bleeding from extension of the incision during delivery of the fetus or from atony must be anticipated in advance and oxytocics be used readily, if not prophylactically. Neonatal intensivists and haematologists should be prepared for resuscitation of the neonate and extreme care must be taken when handling the tumour, especially if a "stalk" is present with a risk of torsion [26]. Even superficial bleeding can result in life threatening haemorrhage [26]. Tumour rupture and neonatal death have been reported even from handling during caesarean delivery [67]. In the absence of haemorrhage at birth, surgical excision can generally be delayed to allow stabilisation of neonatal circulation and further imaging to be undertaken in the neonatal intensive care to inform definitive surgical plans. When there is hemodynamic instability, immediate neonatal surgery, even restricted to debulking, may be required to arrest the steal effect. In that case an adjacent operation suite must be available.

4.4 Fetal Congenital Thoracic Malformations

4.4.1 Definition and Epidemiology

Fetal congenital thoracic malformations (CTMs) constitute a heterogeneous group of pathologies involving the airways and/or lung parenchyma. Fur our purposes in this chapter, we will focus our attention on congenital cystic adenomatoid malformation (CCAM), and the related pathology, bronchopulmonary sequestration (BPS). CCAM's are defined as benign, multicystic, dysplastic lung tumours with an overgrowth and proliferation of terminal bronchioles that receive their blood supply from pulmonary vessels. BPS on the other hand, refers to a distinct mass of non-functioning lung tissue that is not in communication with the normal lung architecture and receives its blood supply from an anomalous systemic vessel. Both lesions may also coexist together referred to as a hybrid CCAM-BPS [22, 68].

The European Surveillance of Congenital Anomalies (EUROCAT) population-based registry [69], in 2008 reported on 222 fetuses with CTMs, with an incidence of 4.44/10,000 (i.e. including live births, fetal deaths and terminations of pregnancy). Of these 222 cases, 52 had CCAM alone with an incidence of 1.04/10,000. With regard to live births, the incidence was 3.52 and 0.94 per 10,000 live births in 2008 for all CTMs and CCAMs respectively in EUROCAT countries. The reported annual incidence of BPS ranges between 0.15 and 6.45% of all CTMs [68].

4.4.2 Genetics

Sporadic inheritance. When isolated, not associated with aneuploidy.

4.4.3 Pathophysiology and Natural History

CCAM's (Fig. 4.6) may be the result of failed maturational processes during the psuedoglandular stage of lung development [70], represent-

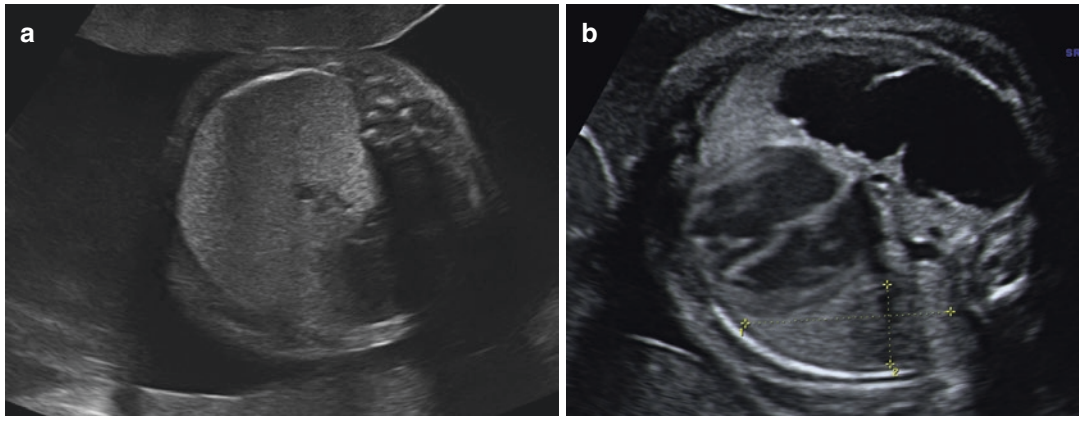

Fig. 4.6 Congenital Cystic Adenomatoid Malformation. *Left*: microcystic type, with uniform more echogenic lung tissue; *right*: macrocystic type, next to remnant lung tissue measured with the calipers. Images courtesy and copyright UZ Leuven

ing focal dysplastic regions [71] or related to airway obstruction [72]. Importantly, to help differentiate them from BPS, they derive their vasculature directly from pulmonary vessels. CCAM's are almost always unilobular, with bilateral tumours occurring in less than 2% of cases. About one in four are associated with additional fetal abnormalities, such as pectus excavatum, renal agenesis, congenital diaphragmatic hernia, bowel atresia and non-immune hydrops [26]. The natural history and progression is rather variable but overall prognosis is good. Small lesions are largely asymptomatic, while larger lesions can result in mediastinal shift, compression of systemic venous return, resulting in hydrops and risking fetal death. Pulmonary hypoplasia may also be evident, but difficult to predict. The haemodynamic state may in turn be worsened by a leakage of proteins into the amniotic fluid and thereby reducing systemic oncotic pressure [73]. Polyhydramnios may occur due to mechanical compression of the fetal oesophagus inhibiting swallowing, and occurs in 70% of cases [74]. The risk of preterm prelabour rupture of membranes and/or preterm birth naturally follows. However, in some fetuses, the CCAM may reduce in size and resolution of the lesion may occur. This has been observed in between 5 and 10% of cases [74]. CCAM's tend to plateau in their rate of growth around 26 weeks gestation, and furthermore, resolution via involution may eventually occur if the tumour outgrows its vascular supply.

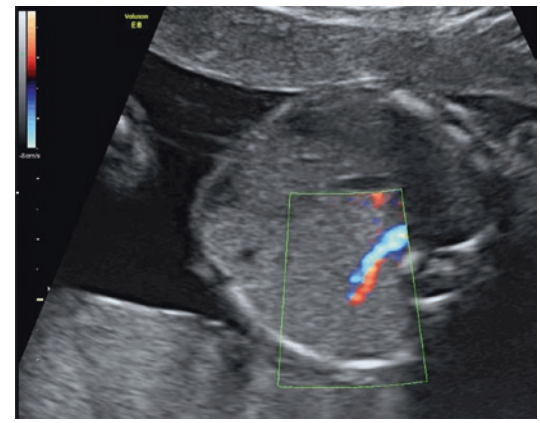

Fig. 4.7 Bronchopulmonary sequestration: hyperechogenic pathologic lugn tissue, feeding vessel being demonstrated by Doppler ultrasound. Images courtesy and copyright UZ Leuven

BPS is generally thought to represent ectopic pulmonary buds, which can be either intralobular or extralobular (Fig. 4.7). This difference is explained embryologically. Intralobular sequestration develops early, before the development of the pleura, and the ectopic buds become incorporated within the adjacent lung, almost exclusively in the lower lobe (98%). Extralobular sequestration develops later and is less common (25%), whereby the pulmonary bud is separated from the adjacent lung and has its own pleural covering. This is more likely to be associated with additional abnormalities than intralobular sequestration (50% versus 10%), particularly congenital heart disease, and is most common on the left

side of the thorax (90%) [26]. In both cases, the ectopic bud is thought to develop caudal to the lung and migrates in a caudal direction along with the oesophagus [22]. Up to 10% of extralobular sequestrations may lie inferior to the diaphragm [26]. Around 75% of antenatally diagnosed BPS may resolve, most likely from outgrowing their blood supply or infarction mediated by vascular torsion of their pedicle. However, in some fetuses, there exists a considerably poorer outlook. Torsion of the extralobular pedicle may then obstruct venous and lymphatic drainage and result in ipsilateral hydrothorax, which may then place the mediastinum under tension. Without intervention, hydrops and fetal death are likely. If there is an abdominal extralobular BPS, hydrops is less likely, however polyhydramnios may occur from impaired swallowing due to gastro-oesophageal compression. Similarly, for intralobular BPS, hydrops may be the result of high output circulation from a "left to left" ateriovenous shunting between the anomalous arterial supply and pulmonary veins [22].

4.4.4 Antenatal Diagnosis

In the antenatal period, there has been a shift in recent years away from pathological diagnosis to descriptive appearances based on imaging. The original histological classification system for CCAM was by Stocker and colleagues in 1977 [70], which they more recently updated in 2002 [75] (Fig. 4.6). In their most recent classification, five types of lesions are suggested that attempt to present a spectrum of abnormalities across consecutive airway types (Table 4.5). In other words, lesions are described as moving down the bronchial tree from bronchial, bronchiolar, alveolar and to peripheral. However, this system has not been embraced universally. Applying a histopathological classification system to a condition that is increasingly recognized and diagnosed antenatally, may not be useful in predicting prognosis and guiding clinical management decisions. Furthermore, it appears likely that types 0, 3 and 4 represent different pathogenetic processes. More recently, the Children's Hospital of Philadelphia published a simplified classification

Table 4.5 Comparison of two proposed classifications of CCAMs

Congenital pulmonary airway malformation: a new name for and an expanded classification of congenital cystic adenomatoid malformation of the lung. [75] (Stocker classification)	New concepts in the pathology of congenital lung malformations (Langston 2003) [72]
Type 0 CCAM—Acinar atresia	**Bronchogenic cyst**
Type 1 CCAM—Cysts up to 10 cm. The cysts are lined by pseudostratified ciliated cells that are often interspersed with rows of mucous cells	**Bronchial atresia** • Isolated • With systemic arterial/venous connection (intralobar sequestration) • With connection to GI tract • Systemic arterial connection to normal lung
Type 2 CCAM—Sponge-like multiple small cysts (<2 cm) and solid pale tumour-like tissue. The cysts resemble dilated bronchioles separated by normal alveoli. Striated muscle seen in 5%	**CCAM, large cyst type (Stocker type 1)** • Isolated • With systemic arterial/venous connection (hybrid/intralobar sequestration)
Type 3 CCAM—Solid. Excess of bronchiolar structures separated by small air spaces with cuboidal lining (foetal lung)	**CCAM, small cyst type (Stocker Type 2)** • Isolated • With systemic arterial/venous connection (hybrid/intralobar sequestration
Type 4 CCAM—Cysts up to 10 cm. The cysts are lined by flattened epithelium resting upon loose mesenchymal tissue	**Extralobar sequestration** • Without connection to GI tract • With connection to GI tract
	Pulmonary hyperplasia and related lesions • Laryngeal atresia • Solid or adenomatoid CCAM (Stocker Type3) • Polyalveolar lobe
	Congenital lobar over-inflation
	Other cystic lesions Lymphatic cysts, Enteric cysts, Mesothelial Cysts, Simple parenchymal cysts, Regressed type 1 pleuropulmonary blastoma

of microcystic (solid sonographic appearance) and macrocystic (single or multiple cysts >5 mm) types. It is likely this can be more useful clinically [76]. Sonographic examples of this classification of CCAM are shown in Fig. 4.6. It is important to visualise the vascular supply by colour Doppler to help differentiate with BPS, whereby an anomalous systemic vessel commonly arising from the descending aorta will be seen feeding a solid echogenic mass (Fig. 4.7). In both cases of CTM, sonographic features of hydrops, mediastinal shift and the presence of additional fetal abnormalities should be sought. Polyhydramnios is commonly encountered, in which case a cervical length measurement may be informative. Fetal MRI may have additional value is cases where the diagnosis is uncertain, in particular with CCAM versus congenital diaphragmatic hernia, or when they coexist [77].

4.4.5 Antenatal Prediction of Prognosis

A significant proportion of lung lesions may regress; nevertheless cautious frequent observation is required to identify a large or enlarging CCAM that imposes pulmonary compression and risks the development of hydrops. The presence of fetal hydrops alerts a poor prognosis and its detection is essential to guide counselling and management. This is demonstrated by a large series reported by Adzick and colleagues [74] in 1998 of 134 fetuses diagnosed antenatally with CCAM. In 25 fetuses with a large CCAM causing hydrops, there was a 100% mortality rate. This is in stark contrast to non-hydropic fetuses, who experienced 100% postnatal survival. In 2002 Crombleholme and colleagues [78] developed a prognostic measure for the development of hydrops. They defined the ratio of the mass area to head circumference as the CCAM volume ratio (CVR). This is sonographically measured (in milliliters) by using the formula for an ellipse: CCAM volume/Head Circumference = (length × height × width × 0.52)/HC (Fig. 4.6). It is gestational age independent. They found when the CVR is higher than 1.6, there was an 80% risk for fetal hydrops. Sonographic follow-up frequency based on the CVR has been also proposed, with weekly follow-up for CVR less than 1.2, twice a week for CVR 1.2–1.6, or even more for CVR greater than 1.6, but this protocol remains to be validated in larger studies.

4.4.6 Obstetric Management

All cases of a suspected CTM should be referred to a tertiary fetal medicine referral centre for diagnostic work up, counselling and management. The multidisciplinary team should comprise maternal fetal medicine specialists, paediatric surgeons and neonatologists. A detailed ultrasound and echocardiographic examination should be performed to define the CTM, its vascular supply, the presence of mediastinal shift or signs of hydrops. The potential for coexisting abnormalities should be excluded, in particular cardiac abnormalities such as truncus arteriosus and Tetralogy of Fallot [22]. Amniocentesis for karyotype is not necessary when isolated. We suggest performing a CVR for cases of CCAM and followed serially as described above. Fetal MRI may be required when the diagnosis is uncertain, in hybrid CCAM-BPS cases or in the presence of CDH. To our knowledge there are no series demonstrating predictive value of lung size in terms of pulmonary hypoplasia, which overall is uncommon. Termination of pregnancy is an option when there are additional severe abnormalities or in the presence of hydrops.

Alternatively, for hydropic fetuses with macrocystic CCAM (unilocular or multilocular), fetal intervention should be discussed with parents as an option to try to reverse hydrops, potentially protect residual fetal lung parenchyma. Expectant management offers a nearly hopeless prognosis and risks maternal complications. The rationale for intervention is to decompress a dominant cyst or resect or involute a larger solid mass to resolve mediastinal compression, restore fetal haemodynamic equilibrium and thus improve cardiac function. Minimally invasive intrauterine puncture or shunting of macrocystic masses (Fig. 4.8) is the treatment of choice when possible, now that its efficacy has been demonstrated.

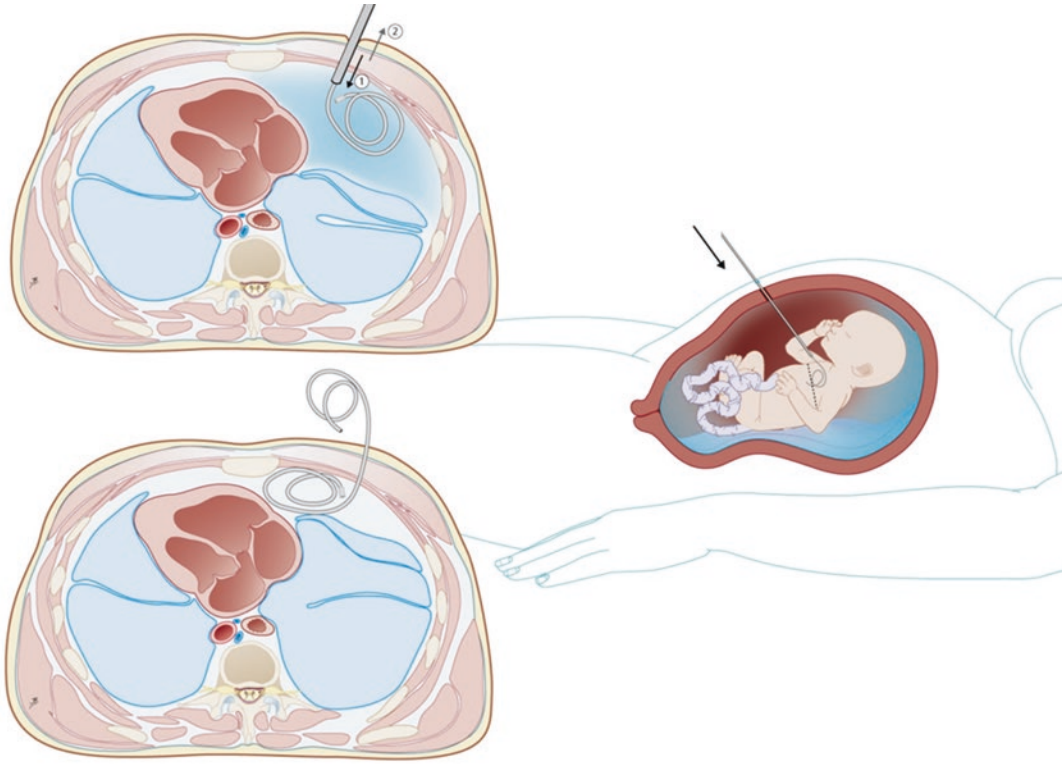

Fig. 4.8 Schematic drawing of thoracic shunt being deployed in the chest. First the pig tail loops in the effusion are deployed, and thereafter the tail is deployed in the amniotic cavity. Drawing Myrthe Boymans; copyright UZ Leuven

Despite an evidence gap of randomised trials, the systematic review by Knox and colleagues [79] showed *in utero* therapy was associated with significantly improved survival in hydropic fetuses (OR 19.28, 95% CI 3.67–101.27), particularly at preterm gestations. With regard to thoracoamniotic shunting in particular, Wilson and colleagues (2006) [80] described 23 cases from CHOP at a mean gestational age of 21–22 weeks. The mean CVR in this group was 2.4, which reduced considerably to 0.7 after shunting. The survival was 74%, with one fetal and five neonatal deaths. In a review by Witlox and colleagues [81] in 2011, summarizing 68 shunted cases including 44 hydropic and 24 non-hydropic fetuses, whereby a large cyst was causing major mediastinal shift. For hydropic fetuses, 89% (39/44) were live born, nine infants died in the neonatal period, giving an overall perinatal survival of 68% (30/44). For non-hydropic fetuses (n = 24), all were live-born, three died in the neonatal period due to pulmonary hypoplasia, giving an overall perinatal survival of 87.5%. Thoracic deformation has been reported but seems rare [82]. Shunting is typically performed until 32 weeks gestation, although more recently has been reported for hydropic fetuses up until 37 weeks [81]. The risk of intervention at later gestations, mostly preterm prelabour rupture of membranes, is less troublesome when compared to the considerable neonatal risks of delivering a preterm hydropic infant. The potential to mitigate hydrops *in utero* and thereby gain further lung maturation before birth would seem likely to translate into improved respiratory function during transition to air breathing and even during postnatal surgery. This approach requires validation.

Not all hydropic fetuses will have a dominant or large cyst(s) amenable to drainage, in particular fetuses with microcystic CCAM. However, most interestingly, several authors have now observed

resolution of hydrops following glucocorticoid therapy [83, 84]. This has occurred at standard dosages given for fetal lung maturation. Curran and colleagues (2010) [85] recently updated Tsao's initial series from 2003 and reported 13 fetuses with microcystic CCAM and hydrops or a CVR>1.6 receiving glucocorticoids. Hydrops resolved in 78% of cases and survival was 85%. It is hypothesised that glucocorticoids may accelerate maturation or involution of the tumour. The same group has now embarked on a randomized controlled trial (clinical-trials.gov NCT00670956) to investigate this more specifically, however in the meantime, glucocorticoids seem a reasonable first-line therapy or medical adjunct for these hydropic fetuses. Their role in non-hydropic fetuses has not been examined. Other fetuses may have solid lesions not suitable for drainage. These are best treated by open fetal surgery and lobectomy, as reviewed by Flake et al. in this book. In the largest fetal surgery series available today, survival rate was 50% [76].

Hydropic fetuses with BPS theoretically may benefit from minimally invasive techniques as well, although this is less defined. In particular occlusion to the anomalous systemic feeding vessel using thermocoagulation by laser or electrosurgery, or sclerosing agents have been reported in a very small number of high-risk fetuses with good outcomes [81, 86–89].

In non-hydropic fetuses, mode of delivery is determined by usual obstetric factors, with spontaneous vaginal delivery at term in a tertiary centre generally favoured.

4.5 Fetal Hydrothorax/Pleural Effusion

4.5.1 Definition and Epidemiology

Pleural effusion can be defined as primary or secondary. Primary pleural effusion is more correctly termed *hydrothorax* antenatally and is due to lymphatic or "chylous" leak with resultant fluid accumulation in the thorax. This may be unilateral or bilateral. After birth, *chylothorax* becomes the more common terminology. In the more common secondary pleural effusion, the effusion harbingers underlying pathology often part of widespread fluid accumulation from immune or non-immune hydrops. The overall incidence is around 1 in 15,000 pregnancies [26].

4.5.2 Genetics

Chromosomal abnormalities can be present. In the most recent series, Ruano and colleagues (2011) [90] reported 23 of 56 (41%) fetuses with pleural effusion had underlying chromosomal abnormalities. Turner's syndrome (45 XO) was the most common in 15 of 56 fetuses (65%) followed by Down syndrome in five fetuses (22%). However, Yinon and colleagues (2010) reported a much smaller association with anuploidy, with four from 88 fetuses being abnormal [91]. A number of genetic syndromes have also been reported, such as Caffey's cortical hyperostosis (autosomal dominant) and Opitz-Frias hypertelorism hypospadius syndrome (autosomal recessive) [26]. Males appear twice as likely to be affected than females.

4.5.3 Pathophysiology and Natural History

Small effusions may remain stable or even regress. Aubard and colleagues [92] observed spontaneous resolution in 22% of 204 cases of primary fetal hydrothorax (Fig. 4.9). However, large (or enlarging) effusions have the potential to cause mediastinal shift, compromised venous return and lung compression, risking pulmonary hypoplasia, hydrops fetalis and intrauterine death (Fig. 4.9). Bigras and colleagues [93] demonstrated by echocardiography a cardiac tamponade effect from rising intrathoracic pressure, whereby ventricular dimensions decreased and the inferior vena cava dimensions consequently increased, reflecting impaired ability of the heart to accommodate venous drainage. Oesophageal compression and impaired fetal swallowing will result in polyhydramnios, which in turn increases the likelihood of preterm prelabour rupture of membranes and preterm birth. When bilateral, pulmonary

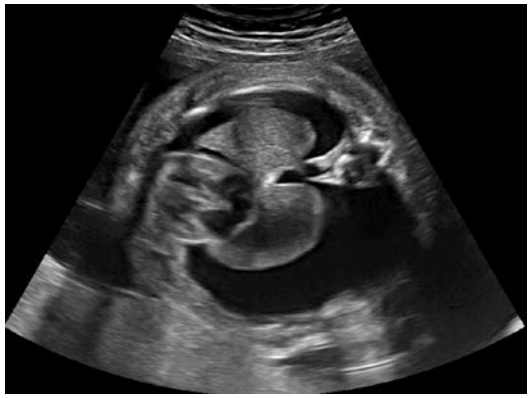

Fig. 4.9 Bilateral hydrothorax. Image: courtesy UZ Leuven

lymphangiectasia should be expected and the prognosis is poor even despite fetal treatment, because abnormal lymphatics preclude normal gas exchange in the lung [18]. Furthermore, lung development appears most sensitive to compression effects during the cannalicular phase of lung development; this corresponds to an increased risk of pulmonary hypoplasia between 16 and 24 weeks gestation [94].

Ruano (2011) [90] attempted to define the natural history of fetal pleural effusions without antenatal intervention. In their observational study on 56 fetuses, they divided their cohort into three groups: Group 1 included 14 (25%) fetuses with isolated pleural effusion without other structural abnormalities; Group 2 included 19 fetuses (34%) with a pleural effusion and additional anomalies but normal karyotype; Group 3 included 23 fetuses (41%) with a pleural effusion and an abnormal karyotype. The overall perinatal mortality was 42/56 (75.0%), with fetal death observed in 38 (68%) and neonatal death in 6 (10.7%) cases. Group I demonstrated a significantly higher rate of neonatal survival (64%), less fetal death (29%) and less neonatal death (7.1%) when compared to Group II (0, 78.9 and 21.1%, respectively) and Group III (13.0, 82.6 and 4.3%, respectively).

4.5.4 Antenatal Diagnosis

Pleural effusions may be evident on ultrasound from as early as the first trimester, however these are more commonly associated with aneuploidy. Most cases are diagnosed in the third trimester. Effusions are seen as anechoic regions surrounding and usually compressing the lung, which can be unilateral or bilateral. A classic "bat wing" appearance may become evident. The diaphragm may appear flattened or everted. The mediastinum can come under tension with shifting to the contralateral hemithorax. In this case, ventricular diameters decrease, inferior vena cava diameters widen and pulmonary artery Doppler peak velocities increase [93]. An effusion ratio has been reported, which is a ratio of the cross-sectional area of the effusion to that of the thorax [94]. Furthermore, the severity of left ventricular compression correlates with the effusion ratio [93].

Once an effusion is identified, differentiating between primary and secondary causes is important. Primary pleural effusion is a diagnosis of exclusion. Additional structural abnormalities are found in over a third of cases [90] and a detailed fetal echocardiography is mandatory. A large effusion with mediastinal shift may make visualisation of cardiac anatomy difficult, however this may improve after drainage. Concomitant pulmonary pathologies such as CDH, CCAM and BPS are secondary causes that should be especially sought. Signs of hydrops should be looked for in other fetal compartments and the amniotic fluid index measured for polyhydramnios. Sonographic features of congenital infection, aneuploidy and anaemia should be examined. In practice however, a fetal thoracocentesis (pleural aspiration) is required to confirm the diagnosis. This can be performed in a single pass following amniocentesis for karyotype. A pleural fluid that is predominantly lymphocytic (>80%) is considered pathognomic for chylothorax or primary pleural effusion [22, 94].

4.5.5 Antenatal Prediction of Prognosis

The presence of hydrops has consistently shown to predict poor prognosis [90, 92, 94].

In the presence of fetal hydrops, the estimated survival rate falls steeply from 80% to 30%. Fetuses with a secondary pleural effusion fare considerably worse than those with a primary hydrothorax. In Ruano and colleagues' recent series [90], mortality for hydropic fetuses in Group 1 was 50% versus 100% mortality for hydropic fetuses in Group 2. Other predictors have been suggested, but do not appear consistently across studies: bilateral effusions [90], effusion ratio [95] and gestation at diagnosis [96]. Furthermore, prognosis after thoracoamniotic shunting is often related to the resolution of hydrops [97].

Most recently, fetal total lung volumes as assessed by three-dimensional ultrasonography were used to predict perinatal outcomes in cases of primary pleural effusion. In a cohort of 19 fetuses, the observed to expected total lung volumes were significantly correlated with perinatal outcomes such as respiratory morbidity and perinatal death, and to bilateral effusions and hydrops [98]. The place for this measurement in clinical management will need to be examined in larger studies.

4.5.6 Obstetric Management

A referral to a dedicated fetal medicine tertiary centre is required. The diagnostic work up is similar to that of hydrops. A detailed sonogram and echocardiogram for structural abnormalities and signs of aneuploidy and infection is performed. The middle cerebral artery peak systolic velocity is examined for anaemia. Maternal blood is analysed for serological evidence of infection (toxoplasmosis, rubella, cytomegalovirus, herpes, parvovirus B19, varicella, syphilis), red cell group and antibodies for immune hydrops, haemoglobin electrophoresis, and Kleihauer–Betke test of fetomaternal haemorrhage. Parents should be counselled for amniocentesis for genetic testing and congenital infectious screen (culture and PCR) [94]. Thoracocentesis should be considered at the same time, especially in cases of presumed primary hydrothorax. If a large effusion is evident, then delivery should occur at a tertiary centre. Multidisciplinary counseling with maternal fetal medicine specialists, neonatologists, paediatric surgeons and geneticists are appropriate.

Small effusions nevertheless require close follow up every 1–2 weeks to watch for volume expansion, mediastinal shift, hydrops, polyhydramnios and cervical shortening. A small stable effusion can be managed conservatively with good outcome (survival between 75–100%) [92, 99]. The same cannot be said, however, for fetuses that become hydropic. Survival rates are universally poor without intervention. Hydrops therefore represents the principal indication for fetal intervention. The systematic review of Knox [79] mentioned earlier concluded that in the presence of hydrops therapy seems warranted. Survival rates improve to 45–66% [79, 94, 97]. One may start with thoracocentesis however the effusion may be expected to reaccumulate over several days. Thoracoamniotic shunting can be performed using a double-pigtail catheter (Fig. 4.10). Alternatively, serial thoracenteses can be performed [100]. There is no evidence of a difference in outcome between the two approaches [101]. The complication rate of shunting is about 15% for iatrogenic rupture of membranes [102] and 5–10% for direct fetal loss. Shunt dislodgment has been reported, however posterior insertion may prevent the fetus from dislodging it. Preterm birth is common, with a mean gestational age at birth of 34–35 weeks. At birth the shunt is usually left, however needs obviously to be clamped.

Larger effusions risk pulmonary hypoplasia and respiratory distress at birth and ventilatory support may be needed. There is some discussion in the literature about thoracocentesis immediately prior to delivery to improve the transition to air breathing and facilitate resuscitation measures at birth. Others advocate thoracocentesis after birth, as they believe fluid reaccumulation can be rapid and render the fetus hypovolaemic and compromise resuscitation efforts at birth. Thoracocentesis can instead be performed once circulatory access has been established and fluid therapy initiated [22, 103].

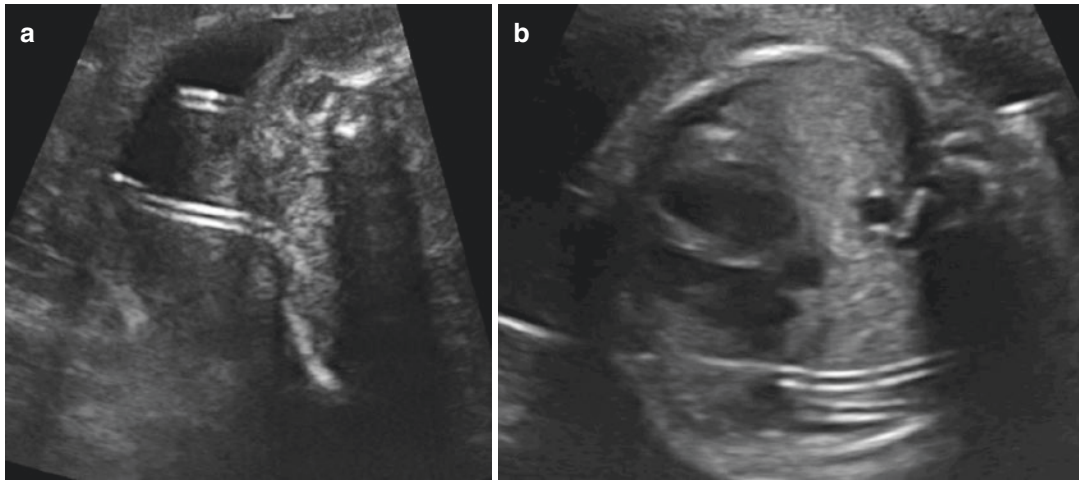

Fig. 4.10 ultrasound images after thoraco-amniotic shunt placement. (**a**) On the left the free part in the amniotic cavity is seen, and (**b**) on the right the intra-thoracic part. Image: courtesy UZ Leuven

4.6 Congenital Diaphragmatic Hernia

4.6.1 Definition and Epidemiology

The prevalence of congenital diaphragmatic hernia (CDH) ranges between 1 and 4 per 10,000 births, qualifying it as a rare disease. The exact etiology of the condition remains unknown. The vast majority of cases are left sided (LCDH), 13% are right sided (RCDH), and bilateral lesions, complete agenesis and other rarities comprise less than 2%. CDH can occur in association with other anomalies (in which case the mortality is over 85%) (Table 4.6), or as an *isolated* condition [104, 105].

Table 4.6 Non-limitative list of anomalies often associated to CDH, in descending order [104, 105]

Identified genetic defects and syndromes
Trisomy 13, 18, 21, XO, Partial Trisomy 5, 20, Tetraploidy 21, Tetrasomy 12p Syndromes: Fryns, Fraser, Stickler, Pierre Robin, Goldenhar, Beckwidth Wiedeman, Apert, Klippel-Fiel, Rubenstein Taybi, Brachman de Lange, Coffin-Siris, Pentalogy of Cantrell VACTERL or CHARGE association
Structural defects (descending order of occurrence)
Cardiovascular, Gastrointestinal, Urogenital, Musculoskeletal, Respiratory, Central Nervous System, Craniofacial

4.6.2 Genetics

CDH most likely is caused by disruption of common developmental pathways, by several genes spread across the genome [106]. We recently reviewed the genetic factors underlying CDH, including evidence from genetic & teratogenic animal models of CDH and differential expression analysis [107]. Though all these fetuses with isolated CDH are routinely karyotyped, identification of (novel) submicroscopic imbalances and novel genes and/or therapeutic targets, requires the use of high resolution diagnostic methods. Several large centers do so, both from a clinical perspective as well as for research. We custom designed a high resolution array for comparative genomic hybdrization (CGH) [108]. The next step will be to use exome sequencing techniques in selected familial cases. Given the high probability of a mutation(s) segregating with the CDH phenotype, this approach will likely reveal the underlying gene(s) involved in the pathogenesis of CDH for each family studied. Advanced genetic testing in large populations with (apparently) isolated CDH, will lead to a better understanding of the genetics of this condition [109].

4.6.3 Pathophysiology and Natural History

Isolated CDH refers to the surgically correctable defect in the diaphragm, but the key problem is its consequence for lung development. Already from

the first trimester the abdominal content herniates into the thorax, interfering with lung development. This causes hypoplasia of both lungs, i.e. fewer airway branches and abnormal pulmonary vessels, as well as a lesser lung compliance. At birth this causes ventilatory insufficiency and pulmonary hypertension, which can be lethal before the defect can be surgically repaired. The condition remains lethal in up to 30%, despite prenatal referral to a high volume center offering standardized neonatal care [110–112]. Survivors may have several morbidities, such as bronchopulmonary dysplasia and persistent pulmonary hypertension, gastro-esophageal reflux and other feeding problems, less frequently they have thoracic deformations after successful repair or other issues. Eventually most lead a life very close to normal provided when managed in a multidisciplinary follow up program [113, 114].

4.6.4 Antenatal Diagnosis

As ultrasound screening programmes have become widely implemented, one would expect the diagnosis is made before birth. In reality around two out of three cases are picked up before birth [115, 116]. The most striking signs become obvious on a cross section of the thorax, with compression and in left sided cases obvious displacement of the heart, by abdominal organs. In left CDH the stomach is often more posterior, viscera as well as spleen may be herniated (Fig. 4.11). An important feature is the presence of liver into the thorax. Right CDH is more difficult to recognize, because only the liver may be herniated, and echogenicity of the liver may be confused with that of the lung. Assessment of liver position is done by Doppler interrogation of

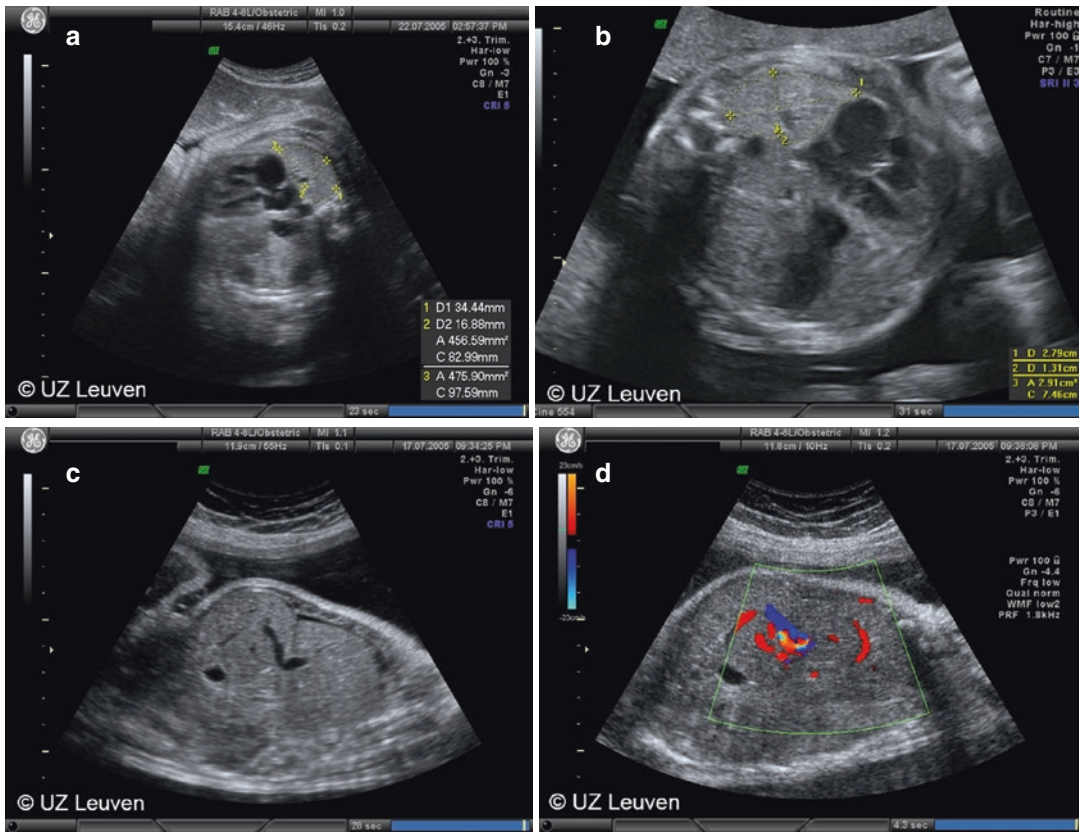

Fig. 4.11 Fetus with left CDH before and after fetal therapy. (**a**) lung measurement at the four chamber view with the so-called "longest axis method" as well as "tracing method". These dimensions will be used to calculate the Lung to Head Ratio. (**b**) measurement of the lung 1 day after balloon insertion, with changed echogenicity and dimensions. (**c**) Herniation of the liver. (**d**) visualization of the major vessels help in its identification. Copyright UZ Leuven; (From Deprest et al., Treatment of Congenital Diaphragmatic Hernia. In: Fetal MRI. Prayer D (Ed). Springer Verlag, Heidelberg 2011, 528 pp.)

the umbilical vein and liver vessels, as well as the position of the gall bladder (Fig. 4.11). Indirect signs of CDH are polyhydramnios and a smaller abdominal circumference. Differential diagnosis includes essentially other pulmonary pathology with cystic features, such as cystic adenomatoid malformation, bronchogenic cysts, rarely enteric or neuroenteric cysts, mediastianal teratoma and thymic cysts, or bronchopulmonary sequestration or bronchial atresia.

Prenatal diagnosis of CDH should prompt referral to a tertiary centre experienced in assessing this anomaly and managing CDH in the perinatal period. A comprehensive diagnostic and prognostic work up comprises advanced imaging, genetic testing and multidisciplinary counselling, so that parents can take a well informed decision. In view of the options, an individualized prediction of outcome is crucial.

4.6.5 Antenatal Prediction of Prognosis

Most frequent quoted predictors of outcome are the presence of associated anomalies, and for isolated cases, lung size, position of the liver and the stomach, and to a lesser extent assessment of lung vasculature. Herein we will focus on the best validated predictors; however research on improved prediction is actively ongoing.

The Lung-to-Head Ratio (LHR) consists of measurement of the lung contralateral to the defect, at the level of the four chamber view. It is divided by the head circumference as measured in the standard biparietal view [117] (Fig. 4.11). The most accurate method for measuring is by tracing the lung contours [118, 119]. The LHR is a function of gestational age, because the lung grows four times more than the head over the entire gestation. To overcome this problem, we proposed to express the LHR of the index case as a function of what is expected in a gestational aged control (observed [O]/expected [E] LHR). The expected value can be calculated using formulas specific for the side of the lesion [120], which are also available on line (www.totaltrial.eu). The prognostic value of the O/E LHR was validated in 354 fetuses with unilateral isolated CDH, that were evaluated between 18 and 38 weeks gestation; later meta-analyses have confirmed this [121]. The O/E LHR is predicting mortality as well as early neonatal morbidity (Fig. 4.12) [122, 123].

Lung size can also be estimated by volumetric techniques, either using 3D ultrasound or fetal Magnetic Resonance Imaging (MRI). Because the ipsilateral lung is not always visible on 3D

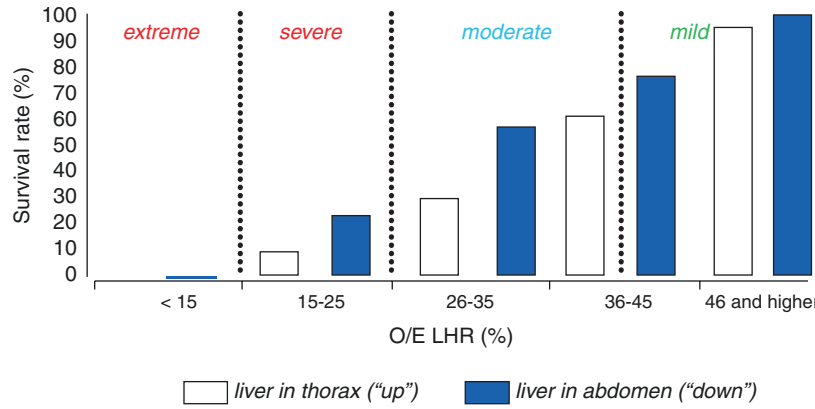

Fig. 4.12 Survival rates of fetuses with isolated left-sided congenital diaphragmatic hernia, depending on measurement of the observed/expected lung:head ratio (O/E LHR) and position of the liver position as in the antenatal congenital diaphragmatic hernia registry. From: Jan A. Deprest et al., Antenatal prediction of lung volume and in-utero treatment by fetal endoscopic tracheal occlusion in severe isolated congenital diaphragmatic hernia, Seminars in Fetal & Neonatal Medicine (2009), doi:https://doi.org/10.1016/j.siny.2008.08.010 (Deprest, Flemmer et al. 2009); with permission of authors and publisher

US, we do prefer MRI [124] (Fig. 4.13). Again measured fetal lung volume must be expressed as a function of what one expects for a gestational age- or weight-matched control [125, 126]. A recent meta-analysis has shown its predictive value [127]. Though we feel fetal MRI will become the method of choice, there is currently no proof for superiority over ultrasound yet [128].

The presence of liver herniation is also predictive, but whether it can be used as a sole feature remains a matter of debate [127, 129]. Liver herniation is easily visualized by ultrasound, using

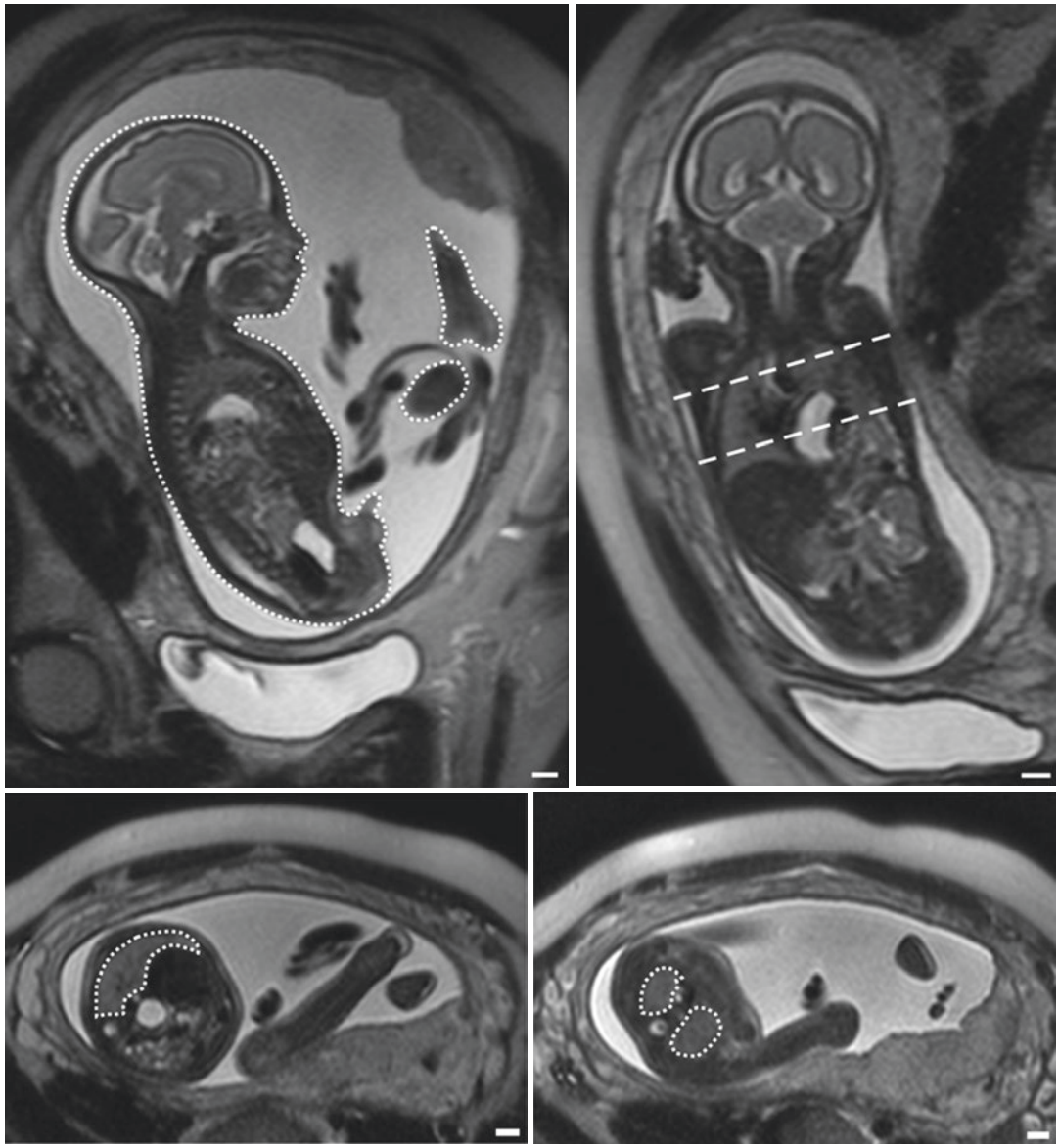

Fig. 4.13 T2 weighted images of fetus with left sided CDH at 26 weeks without liver herniation. Top left, sagittal section with tracing of the body contours. *Top right*: coronal view of the fetus demonstrating the level at which the two axial images are made (*bottom*). Lung tracing (*dotted line*) on the two axial views. *Scale*: white bar in right lower corner is 1 cm (From Deprest et al., Treatment of Congenital Diaphragmatic Hernia. In: Fetal MRI. Prayer D (Ed). Springer Verlag, Heidelberg 2011, 528 pp.)

the umbilical vein as a landmark. We and others have proposed to use MRI to quantify the degree of liver herniation more accurately, but we refer to the literature for further details [130] (Fig. 4.14). Position of the stomach is in Japan accepted as a predictor of outcome, based on its position as up or down [131, 132] or more specifically on its location in the thoracic cavity [133]. Several classification systems have been devised for standardized determinations of the stomach position such as by Kitano et al. [133], and more recently by Cordier et al., yet the latter on ultrasound [134]. Another less studied factor is pulmonary vascular assessment, for which again we refer to the literature (reviewed in [130]). Eventually more accurate prediction can be expected by combining techniques [135, 136], especially when they assess different aspects of the disease, such as parenchymal lung measurement and evaluation of the pulmonary vascularization.

4.6.6 Antenatal Management

CDH has been the sentinel condition proposed for fetal surgery. We refer to a recent review for the history of fetal surgery for this condition [137, 138]. Initially in utero anatomical two step repair was proposed. Since this includes reduction of the liver which causes umbilical vein kinking, the majority of cases are not amenable for fetal surgery. Now prenatal intervention consists of percutaneous Fetoscopic Endoluminal Tracheal Occlusion (FETO) (Fig. 4.15). Tracheal occlusion prevents egress of lung fluid, increasing airway pressure, causing proliferation, increased alveolar airspace and maturation of pulmonary vasculature (reviewed in [139]). The current timing of insertion and removal of the balloon is based on observations in sheep experiments, with a recent trend for later insertion to reduce the impact of preterm delivery, mainly due to ruptured membranes. Sustained TO, though inducing lung growth, reduces

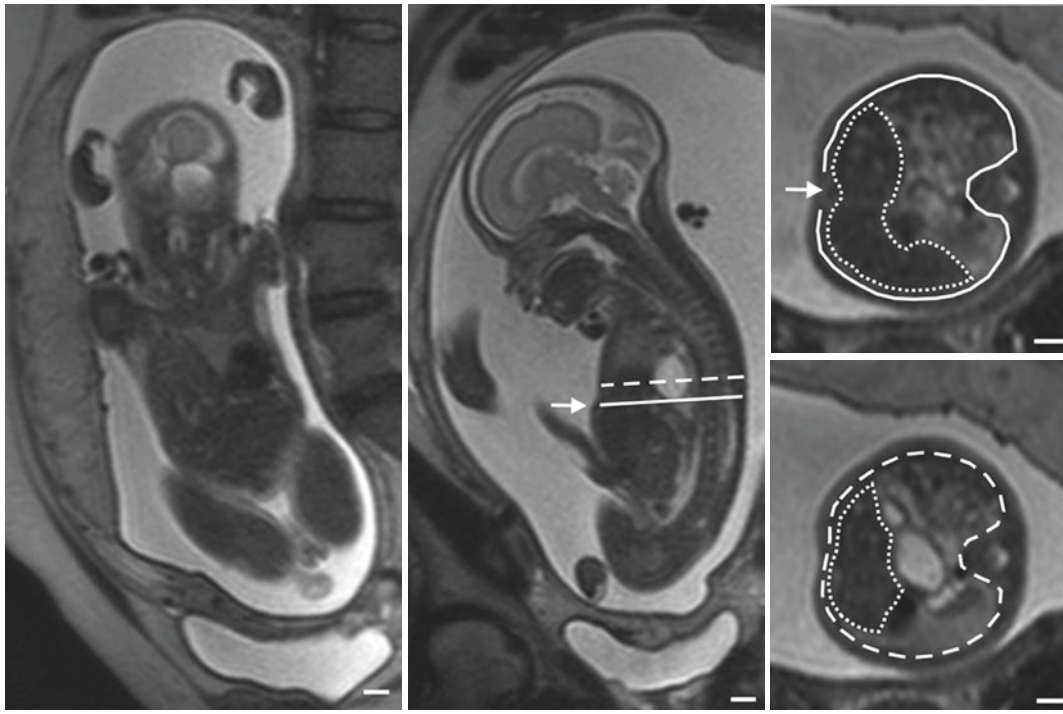

Fig. 4.14 T2 weighted images of fetus with left sided CDH at 26 weeks with liver herniation, as best shown on coronal view (*left image*). Sagittal view (*middle*) demonstrating the reference line (*full line*) at the level of the xyphoid process (*white arrow*) and above (*dashed line*), which correspond to the axial images on the right. Liver tracing (*dotted line*) and contours of the thoracic cavity (*full* and *dashed lines*) shown on both axial views. *Scale*: white bar in right lower corner is 1 cm (From Deprest et al., Treatment of Congenital Diaphragmatic Hernia. In: Fetal MRI. Prayer D (Ed). Springer Verlag, Heidelberg 2011, 528 pp.)

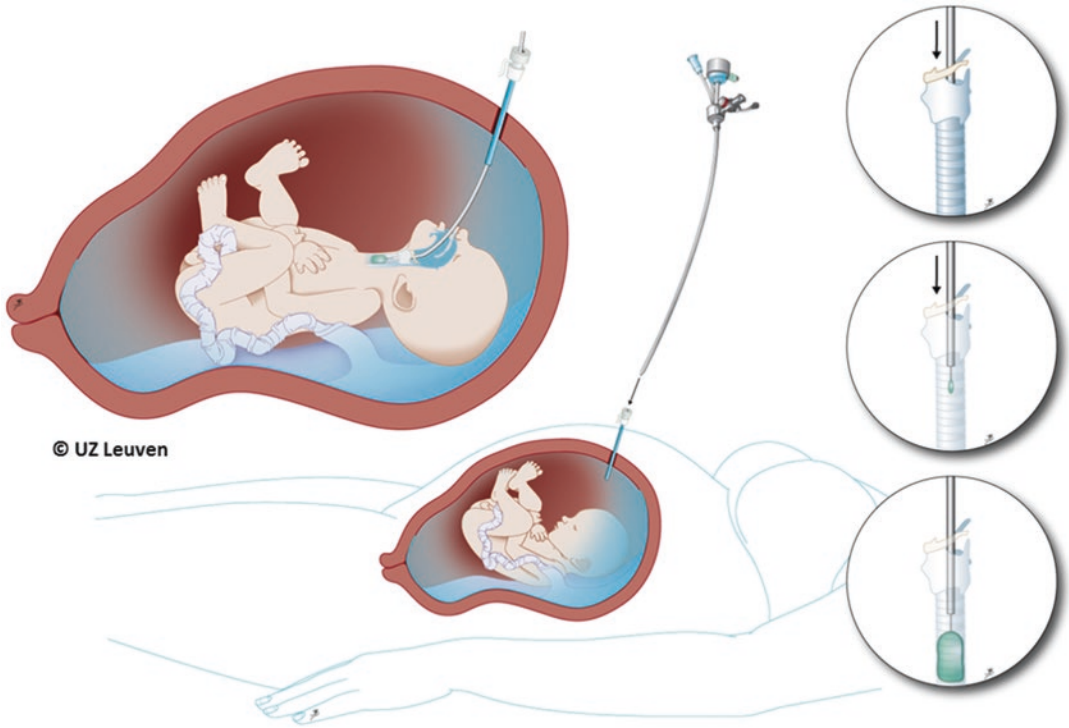

Fig. 4.15 Schematic drawing of percutaneous fetoscopic endoluminal tracheal occlusion. Drawing Myrthe Boymans; copyright UZ Leuven.

the number of type II pneumocytes hence surfactant expression. This can be improved by in utero release ("plug-unplug sequence") [140]. Perinatal steroid administration has also been shown to beneficial [141]. Ideal balanced lung growth and maturation is however obtained experimentally by 47 resp. 1 h cycles of occlusion and release, but this is yet clinically impossible [142].

Several occlusion methods have been described, but an endovascular balloon is what currently is used [143]. This technique is amenable for a percutaneous approach under local anesthesia [144]. Also purpose designed instruments were developed with support of the European Commission (reviewed in [145]). Over time, invasiveness was reduced by moving away from general over locoregional to local anesthesia, with fetal analgesia and immobilization [146]. The FETO task force proposes for severe cases insertion of the balloon at around 28 weeks, and reversal of occlusion at 34 weeks. In utero reversal is achieved either by fetoscopy (50%) or ultrasound guided puncture (19%). Prenatal (>24 h) removal of the balloon has been shown to increase survival and decrease morbidity [147]. Removal at birth can be done on placental circulation or less ideally after birth. Peri- or postnatal retrieval should not be underestimated and problems with this have been the cause of neonatal death [146, 148, 149].

We have reported outcomes of 210 interventions, in fetuses with liver herniation and an O/E LHR <27–28%. Compared to historical controls from the antenatal CDH registry, FETO increased survival in severe cases with left-sided CDH from 24.1 to 49.1%, and in right-sided from 0 to 35.3% ($p < 0.001$) [122]. The strongest predictors of survival were observed/expected LHR *prior* to the procedure (OR, 1.490; $P = 0.019$) and gestational age at delivery (OR 1.024; $P = 0.007$). Early delivery typically is the consequence of Preterm Premature Rupture Of the Membranes (PPROM), occurring within 3 weeks occurred in 16.7% cases. Mean gestation at delivery was 35.3 weeks; only one in three delivers prior to 34 weeks. Interestingly, survival for those delivering at 32–33 weeks is equal to that at 34 weeks

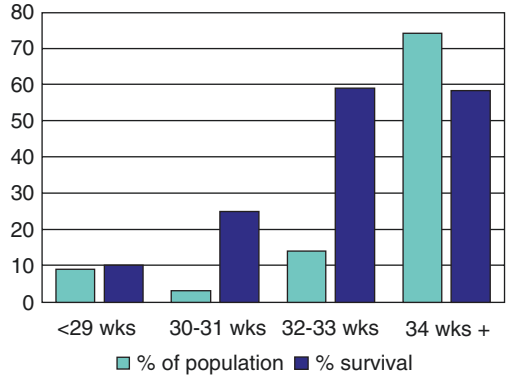

Fig. 4.16 Graphical display of number of patients delivering (*light blue bars*) and number of fetuses surviving (*dark blue bars*) as a function of gestational age. Modified from Deprest J, Nicolaides K, Done E, et al.: Technical aspects of fetal endoscopic tracheal occlusion for congenital diaphragmatic hernia. J Pediatr Surg 46:22–32, 2011 (Deprest, Nicolaides et al. 2011), with permission from the authors and the publisher

or later (60%; left sided cases only) (Fig. 4.16). Short term morbidity in survivors is better than expected: it is close to that of cases with *moderate* pulmonary hypoplasia, that were managed expectantly during pregnancy [147].

The early clinical experience has shown few demonstrable clinical side effects of the balloon on the developing trachea, except in very early occlusions and complications arising at the time of removal [48]. However, the neonates and infants do have obvious tracheomegaly, that does not seem to have a clinical impact, except for a barking cough on effort [48, 49]. Over time, the widening seems to become less important [49]. Most newborns require surgical patching of the diaphragm, indicating the rather large size of the defect in this selected group. The use of patch has previously been shown to be a predictor of outcome. High patch rates will increase the number of patch related complications, so that we felt research on engineering a diaphragmatic patch is now really required [150].

4.6.7 Trials on FETO Versus Expectant Management

Our initial experience has meanwhile been confirmed in other hands [151–153]. There is even one Brazilian randomized trial that showed an increased survival following FETO, though the survival rate in expectantly managed cases was very low (5%), which is not representative for most institutions [154]. Also right and left sided cases were pooled, which does not seem appropriate. In Europe there are now two trials ongoing (www.totaltrial.eu) (Table 4.7). One is in severe hypoplasia, with insertion of the balloon at 27–30 weeks and its removal at 34 weeks (NCT01240057). This protocol is based on our existing experience. A few items are worth mentioning. (1) We have slightly moved the time point of insertion from 26–28 to 27–30 weeks. This will lessen the risk for delivery prior to 32 weeks, the latter having a negative impact on survival (Fig. 4.16). The reason why we do not insert the balloon later, is that we have evidence for a less vigorous lung response with insertion beyond 30 weeks [155]. (2) We chose for in utero balloon removal (3) at 34 weeks. Prenatal removal was associated with a higher survival

Table 4.7 Criteria for fetal intervention for left sided CDH, as used in the TOTAL trial (www.totaltrial.eu). In that trial, FETO needs to be done within a certain window of gestation, as specified. Right CDH has been treated as well based on poor survival rates observed in the CDH antenatal registry [122]

Isolated left sided congenital diaphragmatic hernia	
Severe hypoplasia	Moderate hypoplasia
Severity: O/E LHR <25%, irrespective of liver position	Severity: O/E LHR 25–34.9% (included) irrespective of the liver position, or O/E LHR 35–44.9% (included) with intrathoracic herniation of the liver
Gestational age at randomization[a]: At the latest 29 weeks + 5 days → FETO between 27 weeks + 0 day and 29 weeks + 6 days	Gestational age at randomization[a]: At the latest 31 weeks + 5 days → FETO between 30 weeks + 0 day and 31 weeks + 6 days
Isolated right sided congenital diaphragmatic hernia	
Severe pulmonary hypoplasia	
O/E LHR < 45% and liver into the thorax[b]	

[a]Fetal evaluation ideally at 26 weeks or beyond. For consistency a posthoc determination of severity will be done on archived images, that need to be submitted to the principal investigator

[b]Based on observations in the antenatal CDH registry [122]

[145, 147]. Moreover survival does not increase with gestation at delivery, once beyond 34 weeks. Timely and elective balloon removal avoids unexpected emergency balloon retrieval. However, in the two Brazilian series there was no apparent difference in survival with balloon removal at the time or prior to birth. The trial in foetuses with moderate hypoplasia has started earlier (NCT00763737)(Table 4.7). In this group occlusion is done at 30–32 weeks. For both trials, our neonatal colleagues from all over Europe designed a standardised consensus postnatal management protocol [156] (Table 4.8). In right sided cases, the cut off is at O/E LHR <45%.

4.7 Fetal Cardiac Interventions

Antenatal interventions for congenital heart disease remain experimental, despite a well-defined rationale, with only a few expert centres worldwide developing expertise. The Children's Hospital of Boston has led this research. In this Chapter, we will review critical valvular aortic stenosis with evolving hypoplastic left heart syndrome (HLHS) in the fetus, which is considered the sentinel pathology for potential intervention. For readers interested in the experimental intervention for pulmonary atresia and hypoplastic right ventricle, we refer to the Boston group's two recent publications as well as one from Linz [157–160].

4.7.1 Definition and Epidemiology

Critical aortic stenosis is a congenital obstruction to the left ventricular outflow tract. It occurs most commonly as a result of fusion or one or both aortic commissures, thereby reducing leaflet mobility [26]. The incidence is 3.5 in 10,000 births, and represents 5% of childhood cardiac disease. HLHS is a lethal congenital heart abnormality, whereby the left ventricle is unable to support the systemic circulation. It usually occurs due to obstruction to left ventricular outflow, with aortic atresia the most common (Fig. 4.17). The degree of the ventricular hypoplasia is proportional to the

Table 4.8 Summary of the most important items in the postnatal treatment of patient with CDH according, based on the consensus statement of the CDH-EURO consortium [156]

Treatment in the delivery room	• No bag masking • Immediate intubation • Peak pressure below 25 cmH_2O • Nasogastric tube
Treatment on the NICU/PICU	• Adapt ventilation to obtain preductal saturation between 85–95% • pH > 7.20, lactate 3–5 mmol/L • Conventional ventilation (CMV) or high frequency oscillation (HFOV) maximum peak-pressure 25–28 cmH_2O in CMV and mean airway pressure 17 cmH_2O in HFOV • Targeting blood pressure: normal value for gestational age • Consider inotropic support
Treatment of pulmonary hypertension	• Perform echocardiograhy • Inhaled nitric oxide (iNO) first choice in case of non response stop iNO • In the chronic phase: phosphodiesterase—inhibitors, endothelin antagonist, tyrosine kinase inhibitors
ECMO (extracorporeal membrane oxygenation)	• Only starting if the patient is able to achieve a preductal saturation > 85% • Inability to maintain preductal saturation above 85% • Respiratory acidosis • Inadequate oxygen delivery (lactate>5 mmol/L) • Therapy resistant hypotension
Surgical repair	• Fraction of inspired oxygen (FiO_2) below 0.5 • Mean blood pressure normal of gestational age • Urine output >2 mL/kg/h • No signs of persistent pulmonary hypertension

From Deprest, J.A., et al., Antenatal prediction of lung volume and in-utero treatment by fetal endoscopic tracheal occlusion in severe isolated congenital diaphragmatic hernia. Semin Fetal Neonatal Med, 2009. 14(1):8–13

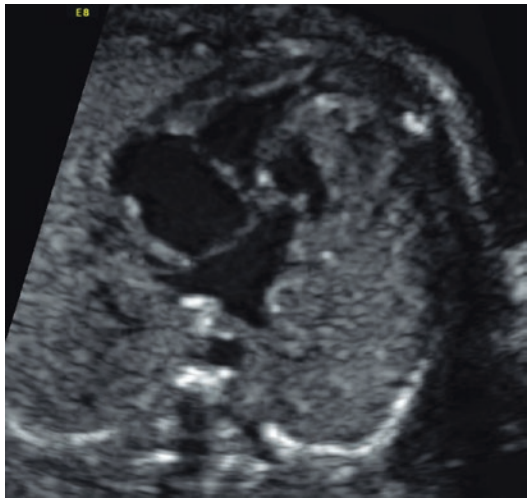

Fig. 4.17 Hypoplastic left heart syndrome

degree of outlet obstruction, unless an escape mechanism exists such as a ventricular septal defect [161].

4.7.2 Genetics

Aortic stenosis is associated with Turner, Noonan and William's syndrome. Aneuploidy is present in 5% of cases of congenital heart disease [22]. It is more common in males, 4:1. Recurrence is 2% with one affected sibling and 6% with two affected siblings. HLHS occurs in 10,000 births, with males twice as likely as females to be affected [22]. It is most commonly sporadic.

4.7.3 Pathophysiology and Natural History

Most fetuses with aortic valve stenosis will not sustain fetal compromise during pregnancy. However, a subset with critical stenosis (ductus dependent) may result in decreased right to left shunting between atria and thereby retard normal left ventricular development and result in HLHS. A pressure effect from the obstructed outflow tract first enlarges the left ventricle, coronary perfusion falls and cardiac function is impaired. Chronically raised ventricular pressures cause endocardial fibroelastosis and left sided structures such as the aortic root, mitral valve and left ventricle then fail to develop with advancing gestation [22, 162, 163]. Indeed, a preferential return of oxygenated blood towards the right ventricle and lower body rather than towards the left ventricle and the brain may also lead to suboptimal brain oxygenation *in utero*, which may be in part responsible for poorer neurodevelopmental outcomes [164, 165]. Significant restriction of the foramen ovale is present in 22% of patients with HLHS [166] and in 6% the atrial septum is completely closed. This drives increased pulmonary vein pressure and left atrial hypertension, as well as to pulmonary venous arterialization (abnormal vascular musculature) and hydrops. After birth, pulmonary venous return to the left atrium is increased, and obstruction to pulmonary venous drainage results in a further rise in pulmonary pressure, with severe hypoxemia, pulmonary oedema and haemorrhage. Emergency atrial septostomy is required.

About 5% of HLHS develop in the second trimester and are progressive [167]. Intrauterine growth restriction and hydrops may similarly develop. In Sharland and coauthors' series of 30 fetuses with left ventricular dysfunction, five fetuses with aortic stenosis developed into HLHS. There appears to be an overlap of diseases of primary left ventricular endocardial fibroelastosis, critical stenosis of the aortic valve and the HLHS [163].

Despite improvements in neonatal surgical and intensive care, the outcome of fetuses with hypoplastic left heart syndrome (HLHS) remains poor. Postnatal surgery, which for many results in a far from perfect single ventricle Fontan-type circulation [168], has a significant mortality rate, leading to a total survival of less than 65% [167]. Without it survival is not possible. The surgical choice is Norwood's three staged procedure or neonatal transplantation. For some fetuses with critical aortic stenosis, biventricular repair remains a possibility, with the therapeutic options including open and balloon valvulotomy [169].

4.7.4 Antenatal Diagnosis

Critical aortic valvular stenosis may be diagnosed antenatally, however sonographic features

for milder forms may be unreliable [22]. An early clue may include dilatation of the ascending aorta [26]. With critical obstruction, the left ventricle becomes hypokinetic and may appear dilated and hypoplastic on a standard 2D four chamber view. With advancing gestation however, ventricular size will become relatively smaller. Endocardial fibroelastosis may become evident. In cases of aortic and mitral atresia, the ventricle has a "slit" like appearance or may even appear absent, whereas aortic stenosis with mitral stenosis there is a small and very round or "tense" left ventricle, with the apex of the heart formed by the right ventricle [170]. Colour Doppler will reveal poor or absent filling of the diminutive ventricle. The aortic valve leaflets may be thickened with reduced motion and reveal turbulent and increased antegrade velocity on Doppler imaging. An absence of antegrade flow across the aortic valve confirms atresia. With severe stenosis, there may be hypoplasia of the mitral valve and aortic arch, or mitral stenosis and coarctation [26]. Mitral regurgitation can be determined by colour Doppler. The right ventricle and tricuspid valve should be inspected for regurgitation. The patency of the foramen ovale should be demonstrated by colour Doppler. Flow may become reversed across the atria, from left to right, with consequences for the pulmonary vasculature [26]. Doppler examination of the pulmonary veins then complements this assessment. In fetuses with a restrictive foramen ovale, the venous *a wave* is increased and peaked, with reversal of flow in the pulmonary veins during atrial systole [170]. Moving the transducer to the sagittal view will demonstrate retrograde flow in the ascending aorta and transverse aortic arch. Here, a coarctation may be visualised. At the three-vessel view, colour Doppler will show flow in the opposite direction of the adjacent pulmonary artery and arterial duct, confirming retrograde flow in the transverse aorta from the arterial duct. The Doppler profile in the arterial duct will similarly be altered. It is important to note here that the brain receives oxygenated blood via retrograde filling of the head and neck vessels from the arterial duct. Accordingly, the middle cerebral artery Doppler pulsatility index should be examined for central redistribution, or a fall in resistance, in an attempt to maintain fetal cerebral perfusion and guard against cerebral hypoxia. Fetal growth and amniotic fluid index may indicate IUGR. Sonographic evidence of additional abnormalities, aneuploidy and hydrops should all be meticulously sought.

4.7.5 Antenatal Prediction of Prognosis

For fetuses with critical valvular aortic stenosis, accurate prediction of evolving HLHS is imperative for parental counselling regarding continuation of the pregnancy, antenatal care, timing and patient selection for potential fetal intervention, to plan resuscitation and postnatal surgery. Mäkikallio and co-authors [171] from the Children's Hospital in Philadelphia, recently published anatomic and physiological variables in the mid gestation fetus with aortic stenosis and normal left ventricle size that are predictive of progression to HLHS. In their study on 43 fetuses diagnosed with aortic stenosis and normal left ventricular length at less than 30 weeks gestation, there were 23 live-born patients of which 17 developed HLHS and six having a postnatal biventricular circulation. All fetuses that progressed to HLHS had retrograde flow in the transverse aortic arch, 88% had left-to-right flow across the foramen ovale, 91% had monophasic mitral inflow, and 94% had significant LV dysfunction. With regard to all six fetuses who successfully achieved a biventricular circulation postnatally, they had antegrade flow in the transverse aortic arch, biphasic mitral inflow and normal LV function. These echocardiographic indices may help refine patient selection and assist prenatal counselling for progression of aortic stenosis to HLHS.

As with other fetal pathologies, the presence of hydrops suggests a bleak outlook. Similarly, the presence of tricuspid regurgitation conveys a poor prognosis for both survival and postnatal surgical success [170]. An added layer of complexity comes with a restrictive foramen ovale. Fetuses with a restrictive or intact foramen have a worse prognosis and may not respond to medical therapy in the postnatal period. This is a result of

abnormal pulmonary vasculature that develops from high atrial pressures. Hypoxaemia can develop quickly at birth and cardiovascular collapse is likely without immediate balloon atrial septostomy or surgery. Antenatal prediction of emergency atrial septostomy (or fetal intervention described below) is therefore essential to plan resuscitation and cardiac intervention at birth. The Cincinnati group have developed a pulmonary venous Doppler forward/reverse velocity time integral (FR VTI) ratio, that when less than three, optimizes specificity for predicting emergency atrial septostomy [158]. Others have performed a maternal hyperoxygenation challenge to study the response of the fetal pulmonary vasculature. Less than a10% decrease in the branch pulmonary artery pulsatility index after 10 min of 60% inspired oxygen administered to the mother is a non-reactive test and is predictive of emergency intervention at birth [172].

Furthermore, as introduced earlier, half of the long-term survivors have poor neurodevelopmental outcome [173], which may in part have an antenatal origin. Reduced middle cerebral artery pulsatility index may be a marker of such cerebral hypoxia, however this has not been specifically correlated with neurodevelopmental follow up in infants with HLHS.

4.7.6 Obstetric Management

Referral of suspected cases to an expert tertiary centre is required. Multidisciplinary counselling with maternal fetal medicine specialists, neonatologists, paediatric cardiologists and cardiothoracic surgeons are necessary. The diagnosis should be confirmed by fetal echocardiography as discussed above, including predictive indices. Additional abnormalities should be excluded and an amniocentesis performed to evaluate chromosomes. After counselling, termination of pregnancy should be offered to parents due to the poor prognosis and significant surgical morbidity that is necessary to sustain life. Expectant management may also be offered, whereby the pregnancy is conservatively cared for without intervention to spontaneous labour. At birth, comfort care to the neonate is offered. A clear plan from neonatology colleagues and parental support is clearly necessary. This may become more of an option as the pregnancy continues and repeat echocardiograms from 28 weeks gestation reveal progressive HLHS.

In some cases of evolving HLHS due to outlet valve obstruction, timely fetal balloon valvuloplasties offer the attractive rationale of ventricular recovery *in utero* and further growth (Fig. 4.18).

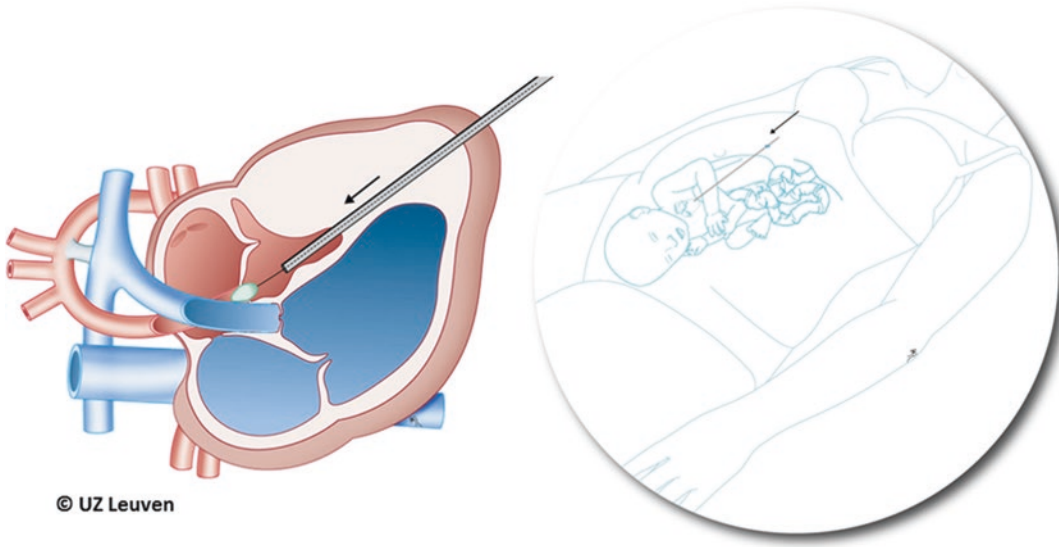

Fig. 4.18 Schematic drawing of in utero percutaneous aortic valve dilatation. Drawing: Myrthe Boymans. Reproduced, with permission from the UZ Leuven

Antenatal intervention theoretically reduces intraventricular pressure, improves coronary perfusion, reduces pulmonary pressures, promotes ventricular growth, and avoids development of myocardial fibroelastosis, thus all enabling improved cardiac function and potential biventricular postnatal repair [18].

Standardised needle-based procedures to access the fetal heart have been developed from groups in Boston (Massachusetts, US) [174] and Linz (Austria) [159]. A cardiocentesis is performed using a Seldinger technique to advance the working sheath into the target area under ultrasound guidance. Most cases can safely be performed under maternal local or locoregional anesthesia with fetal analgesia and immobilization. Maternal laparotomy rates are now therefore uncommon, falling from 27 to 10% in the Boston experience [160]. For the procedure, an 18 or 19 gauge needle is inserted into the fetal left ventricle at the level of the apex and in alignment with the left ventricular outflow tract (Fig. 4.18). A guide wire and a catheter with a coronary dilatation balloon are advanced through the aortic valve, which is dilated to 120% of the valve annulus. Fetal valves differ to children's valves, in that they are less complex structures, difficult to dilate and likely to re-stenose. Fetal resuscitation with inotropic medication, other vasoactive agents, or blood must be anticipated early to correct fetal acidosis or anaemia. Fetal complications include bradycardia requiring fetal resuscitation (17–38%), hemopericardium (13%), ventricular thrombosis (15–20%) and fetal death (8–13%) [159]. Maternal morbidity is rare, except when uterine exposure is needed for the procedure or emergency delivery. Rupture of membranes occurs in 2–7% of cases [175, 176].

In their largest series published in 2009 [174], the Boston group examined prenatal aortic valvuloplasty in 70 fetuses with aortic stenosis and evolving HLHS. The intervention was technically successful in 52 (74%) of treated fetuses, of whom 17 (33%) achieved biventricular circulation postnatally. However, prenatal aortic valvuloplasty altered the growth and function of some left heart structures (aortic valve, ascending aorta, mitral valve), but surprisingly did not change the growth velocity of the left ventricle. This may alter the approach to fetuses with evolving HLHS. Nevertheless, in fetuses with a larger left ventricle at enrolment, aortic valvuloplasty did increase the likelihood of a biventricular circulation. The authors developed a multivariate threshold scoring system of valvular and ventricular size and pressure to predict fetuses able to survive postnatally with a biventricular circulation. This may improve patient selection for fetal intervention. Of note, *in utero* atrial septoplasty for a highly restrictive foramen ovale has also been described, however the numbers remain small at this stage [177].

For otherwise continuing pregnancies, the fetal heart should be examined at 28 weeks gestation and then fortnightly thereafter for progression and the development of hydrops. The pregnancy should otherwise be allowed to continue to term. Delivery should occur in an experienced tertiary centre with immediate neonatal, cardiology and cardiothoracic surgery teams present. There appears to be no significant advantage of caesarean delivery when compared to vaginal birth. The Children's Hospital of Philadelphia compared 79 cases of HLHS delivered either vaginally or by caesarean section [178]. They found those delivered by elective caesarean had lower pH and higher partial pressure of CO_2 on arterial cord blood gas analysis, however no other differences in 1- and 5-min Apgar scores, markers of end organ function, echocardiographic parameters, length of hospitalization, and survival to discharge. It is even possible that vaginal delivery may prove advantageous, given that the fetus has a relatively fixed stroke volume and relies on heart rate to drive cardiac output. The physiological demands from vaginal delivery may protect the fetus by augmenting cardiac output from the single functioning ventricle [178]. Some centres plan induction of labour close to term to ensure a neonatal intensive care bed and appropriate staff are available and prepared to care for the neonate.

Others however, have advocated planned caesarean section for cases with restricted foramen ovale. It is argued a scheduled delivery facilitates immediate transfer of the neonate to an already well-prepared

team for emergency atrial septoplasty [158, 179]. An ex-utero intrapartum treatment (EXIT) procedure has also been reported to initiate extracorporeal membrane oxygenation before placental separation. Once stabilized, the neonate then underwent radiofrequency perforation of the atrial septum with a good outcome [180].

Prostaglandin E_1 therapy, often in conjunction with inotropes and correction of acidosis, is required for severe stenosis and HLHS [26]. If the stenosis is less severe and left ventricular function appears adequate and the condition is not duct dependent, the ductus arteriosus is allowed to close under close supervision.

4.8 Amniotic Band Syndrome

4.8.1 Definition and Epidemiology

Amniotic band syndrome (ABS) is a group of disruptive abnormalities and limb amputations; the likely consequence of early rupture of the amnion [26]. The reported incidence is 1 in 1300 live births.

4.8.2 Genetics

Considered sporadic. Associations with Ehlers-Danlos syndrome and osteogenesis imperfecta have been reported [22, 26]. There is no known risk of recurrence in future pregnancies.

4.8.3 Pathophysiology and Natural History

At first glance of our simple definition of early amnion rupture, one might expect the pathophysiology to be rather simple. However, there is a wide range of clinical manifestations and several theories have been developed to try and understand the observed complexity. Indeed there is a spectrum of many anomalies involving limbs, craniofacial structures, trunk, constrictive bands, and visceral and body wall abnormalities [22]. It is fair to say the exact cause remains unclear.

Of the proposed theories, Streeter in 1930 [181] suggested an intrinsic defect in the embryonic germinal disk and amniotic cavity, which resulted in later amniotic bands. This explains central anomalies of viscera, limb body wall complex and craniofacial structures, but is less satisfactory for extremities [182]. Torpin in 1965 [183] described an extrinsic theory, whereby early rupture of the amnion partially dislodges the fetus to the extra-amniotic space, with secondary amniochorionic mesodermal bands developing. A vascular disruption theory has also been proposed [184]. Most recently Moerman and colleagues [185] in Leuven, synthesised this work by proposing three distinct lesions: constrictive amniotic bands, amniotic adhesions and limb-body wall complex. This was based on their pathological study of 18 cases of ABS. In this series, four cases had constrictive bands presumed to be from amnion rupture that resulted in limb entanglement in shrivelled amniotic strands. This type may also be associated with cord entanglement and fetal death. In other cases, adhesive bands were observed to be the result of a broad fusion between disrupted fetal parts (mostly cephalic) and an intact amniotic membrane, while the limb-body wall complex is likely the result of vascular disruption. The authors suggest that the observed craniofacial defects (encephalocoeles and/or facial clefts) in these fetuses were not caused by constrictive amniotic bands, but were the result of a vascular disruption with or without cephalo-amniotic adhesion. Accordingly, the theories of Streeter and Torpin are not mutually exclusive and in fact may overlap. Timing of amnion rupture may also help to explain the variation in clinical manifestations. Huang and colleagues [186], suggested more severe visceral and skull abnormalities are likely to occur if rupture occurs before 45 days gestation.

Chorioamniotic separation, although considered normal until 16 weeks gestation, may occur either spontaneously, or following extrachorionic haemorrhage or invasive procedures such as amniocentesis, amnioreduction or fetal surgery [22, 187]. This may also increase the likelihood of ABS [188].

The natural history is difficult to predict. The degree of developmental disruption will determine the clinical outcome. Not unexpected with a definition of ruptured membranes is preterm

birth, with an average gestational age of 32 weeks in cases of ABS [22]. Low birth weight is also more common [189].

4.8.4 Antenatal Diagnosis

Sonographic features may be either isolated or appear in combination, reflecting the numerous forms of ABS. The bands themselves may be evident sonographically (Fig. 4.19), or more commonly, their effect on the fetal tissue can be seen. For example, bands may be inferred by absent or amputated digits or portions of limbs and constrictive bands from swollen distal limbs (Fig. 4.20). Similarly Doppler ultrasound may reveal compromised flow. Clubfeet or hands may occur. Craniofacial abnormalities may include cleft lip and palate, microphthalmia, encephalocoele and anencephaly. Encephalocoele can be attributed to ABS when they occur off the midline and anencephaly when some portion of the calvarium is present [22]. Gastroschisis, omphalocoele (less commonly) and limb body wall complex can all be associated with ABS [26]. Severe spinal defects, particularly when associated with abdominal wall defects, are consistent with ABS. Umbilical cord Doppler flow is essential to exclude cord involvement.

The sonographic presence of amniotic bands is not necessary to complete a diagnosis of ABS however, provided characteristic features are present. Fetal MRI has also been shown to be complementary to routine ultrasound [190].

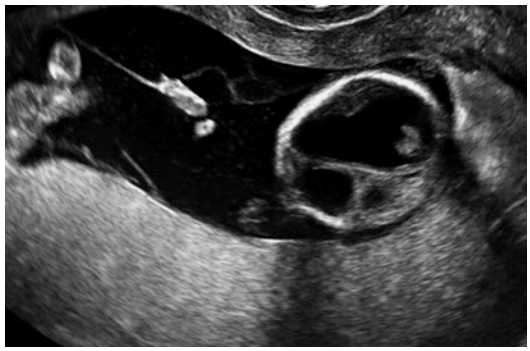

Fig. 4.19 Amniotic band syndrome, evidenced by ultrasound. Image: courtesy UZ Leuven

4.8.5 Antenatal Prediction of Prognosis

Prediction of prognosis is not well established, however is likely to be proportionate to the

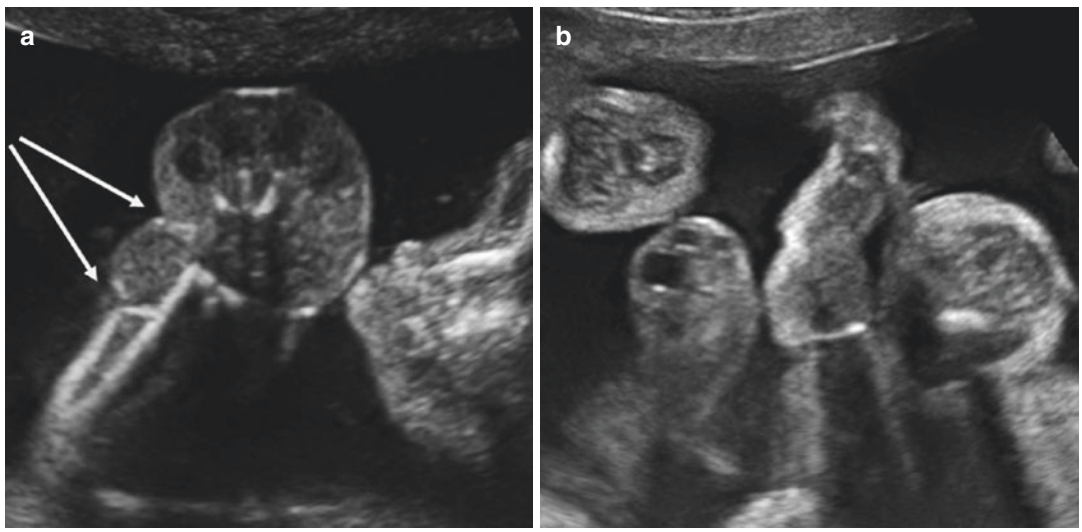

Fig. 4.20 Limb in Amniotic band syndrome. (**a**) Right forearm at 23 weeks: significant edema at the distal part and visualization of two notches created by the amniotic band (*arrows*). (**b**) Ultrasound image of the right arm and hand 1 month after fetoscopic release of the band. There is a decrease of the edema, with still two notches visible due to the amniotic band (*arrows*). c. At birth, there is still amniotic band tissue present around the arm, infiltrating into the subcutis. Images: courtesy UZ Leuven

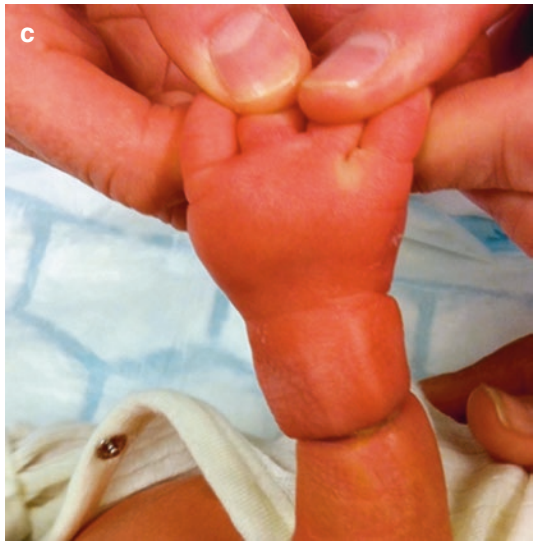

Fig. 4.20 (continued)

Table 4.9 prenatal classification of Amniotic Band Syndrome by Hüsler (2009)

1. Amniotic bands without signs of constriction
2. Constriction without vascular compromise (normal vascular Doppler studies compared to opposite site)
(a) Without or only mild lymphoedema
(b) With severe lymph oedema
3. Severe constriction with progressive arterial compromise, flow measurements distal and proximal of the constriction band
(a) Abnormal distal Doppler studies when compared to contralateral extremity
(b) No vascular flow to extremity
4. Bowing or fracture of long bones at constriction site
5. Intrauterine amputation

complexity of the ABS. Tadmor and colleagues (1997) [191] serially observed lower limb amputation from 21 weeks gestation, with evolving sonographic signs of a constriction ring, oedema, patent then absent limb arterial Doppler, bending, breaking and finally resorption of both tibia and fibula. However, other reports have shown resolution [192]. Serial Doppler ultrasound forms an important part of clinical assessment, particularly with regard to cord involvement. Reversed end diastolic flow of the umbilical artery Doppler may become evident with worsening constriction [193]. Hüsler and colleagues (2009) [194] proposed a prenatal classification to reflect stages of ABS involving extremities, which is based on Weinzweig's postnatal classification [195] (Table 4.9).

4.8.6 Obstetric Management

Referral to a dedicated fetal medicine centre is appropriate. A detailed sonographic survey and fetal echocardiogram is essential. Amniocentesis for karyotype is recommended for cases of diagnostic uncertainty. Obstetric management is dependent on whether the ABS is isolated or more complex. For isolated cases, expectant management is the norm. Weekly Doppler surveillance in comparison to the contralateral side for constrictive progression seems appropriate. When progression is identified, fetoscopic intervention may salvage the developing limb. However, given the natural history is not well established, patient selection is not established. Compromised but present flow is probably the appropriate time for intervention. Richter and colleagues (2012) [182] recently reviewed all published cases of intrauterine release of amniotic bands to rescue fetal limbs. The outcomes were generally favourable, although it might not always be possible to visualize and/or dissect and cut the bands, without risk for collateral damage. The bands may be covered within a constrictive ring in an oedematous area. After the procedure partial to full disappearance of the signs, flow and/or functional recovery may be obtained, but postnatal surgery remains often necessary. In their series of ten cases, preterm prelabour rupture of the membranes occurred in 78% prior to 34 weeks, with 67% of cases delivering preterm. Ruptured membrane rates were higher following fetoscopic band release when compared with fetoscopy for other indications, which may be related to the inherent pathology of ABS. In 90% of cases (8/9), the band could be cut to some extent, but only in three cases (33.3%) there was complete release possible. Functional salvage of the limb occurred in 6/9 cases (67%). In the other three, secondary postnatal amputation was required in one and in two cases there was persistent reduced mobility.

For more complex ABS with multiple abnormalities, multidisciplinary counselling with geneticists, neonatologists and paediatric surgeons are essential. Options of expectant management and termination of pregnancy should be discussed with parents.

4.9 In Conclusion: From Tinkering to Translation

For the field of fetal intervention and surgery to continue to translate into improved and meaningful outcomes for our fetal and neonatal patients, training and research collaborations between maternal-fetal medicine specialists, neonatologists and paediatric surgeons must become fluid across multiple centres. Effective collaboration is necessary to ensure cohorts of fetal patients with rare diseases are identified and streamlined into formalised trials in specialised centres to evaluate our novel interventions. This chapter is but one example of the necessary dialogue needed across different medical specialties if we are to help improve the lives of our unborn fetal patients.

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How Pathology Helps the Neonatal Surgeon

5

Michael Ashworth

Abstract

It is axiomatic that good pathology is essential for good patient care. For too long, pathologists have viewed their central role in diagnosis and clinical management as self-evident to all. Alas, the benefits of high-quality pathological investigation are not always self-evident, and much good work has gone unrecognized or unappreciated. To some extent we have ourselves to blame in that there has been a retreat of the pathologist to the autopsy room or the laboratory with a consequent lack of visibility in the clinical arena. The reduction in the volume and scope of pathology teaching in some undergraduate curricula has led to a lessening of the background pathological knowledge of many clinicians and, thus, the common meeting ground of clinician and pathologist has diminished. In pediatrics perhaps as nowhere else, is the need for a commonality of interest so great. Fortunately, in pediatrics the pathologist, by and large, is more visible in the clinical arena than in any other area. It is necessary for us all to strive to increase the commonality of interest for the benefit of the patient.

Keywords

Pathology • Newborn surgery • Paediatric surgery

5.1 Introduction

It is axiomatic that good pathology essential for good patient care. For too long, pathologists have viewed their central role in diagnosis and clinical management as self-evident to all. Alas, the benefits of high-quality pathological investigation are not always self-evident, and much good work has gone unrecognized or unappreciated [1]. To some extent we have ourselves to blame in that there has been a retreat of the pathologist to the autopsy room or the laboratory with a consequent lack of visibility in the clinical arena. The reduction in the volume and scope of pathology teaching in some undergraduate curricula has led to a lessening of the background pathological knowledge of many clinicians [2] and, thus, the common meeting

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_5

ground of clinician and pathologist has diminished. In pediatrics perhaps as nowhere else, is the need for a commonality of interest so great. Fortunately, in pediatrics the pathologist, by and large, is more visible in the clinical arena than in any other area. It is necessary for us all to strive to increase the commonality of interest for the benefit of the patient.

5.1.1 Biopsy Handling

Ideally the sample should be submitted to the pathology laboratory fresh and as soon as possible after removal from the patient. It is important that the tissue is contained in a sterile container labelled with the patient's details and that it is accompanied by a request form giving basic demographics, a short summary of the clinical history and any notable features together with any particular points that the surgeon wishes to be addressed [3].

Submission of fresh tissue permits taking of samples for microbiological culture, for molecular biological analysis and for electron microscopy, all important and all increasingly being used for diagnosis and prognostication. The temptation on the part of the surgeon to open the specimen to have a sneak preview should be firmly resisted! This distorts the anatomy, particularly if the specimen is then placed in fixative, and makes assessment of resection margins very difficult, if not impossible.

5.1.2 Frozen Sections

The standard method of dealing with tissues for histopathological examination is fixation in formalin, followed by dehydration of the specimen in graded alcohols and embedding in paraffin wax to permit cutting of sections at 3–5 μm thickness. While this gives excellent preservation of detail for the pathologist, it does have several disadvantages:

Time. Fixation is a slow process with penetration of the tissues by the fixative at the rate of only several millimeters per day. Very small specimens fix rapidly; larger ones do not. To a certain extent this difficulty can be obviated by rapid fixation techniques such as microwaving where urgency is required [4]. However, even with the best techniques several hours are required. Where more rapid diagnosis is required the frozen section must be used.

Loss of enzyme activity and antigenicity with fixation. Enzyme activity is abolished with formalin fixation and if an enzyme histochemical technique is required the sample must be received fresh and then frozen. Some antigens are lost, or their expression is greatly reduced, by fixation. Newer techniques are being developed and antibodies optimized and antigen retrieval systems perfected to permit antigens previously undetectable on paraffin sections now to be seen [5]. Nonetheless the optimum expression is still seen on frozen section. Immunofluorescence techniques also still require frozen section.

In the frozen section technique the tissue is rapidly frozen to prevent ice crystal formation;, Ice crystals destroy tissue morphology and make the specimen worthless. Isopentane and liquid nitrogen are the most commonly used materials for rapid freezing. Once frozen the specimen needs to be cut in a special freezing microtome—the cryostat. Frozen sections are cut at a greater thickness than conventional paraffin section. This means that the cellular detail is not so good. Also tissues that contain a lot of air (such as lung) can become very distorted on frozen section [6].

In routine pediatric practice frozen sections are used for:

- assessment of ganglion cells on rectal suction biopsy
- acetylcholinesterase staining of rectal suction biopsies
- Identification of level of aganglionic zone in Hirschsprung pull-through
- muscle enzyme histochemistry
- intra-operative assessment of clearance of surgical resection margins

5.1.3 Histochemistry

Enzyme activity in a tissue is preserved after removal and can be detected by cutting frozen sections of the tissue and applying the enzyme

substrate, permitting the enzyme to work and then demonstrating the enzyme product by means of a color marker.

This is used most specifically for muscle biopsy where oxidative enzymes are employed and ATPase is used to identify fiber types. Latterly, immunohistochemistry is being increasing used in this field [7]. The demonstration of acetylcholinesterase activity in rectal suction biopsies is very useful in the assessment of Hirschsprung disease [8]. Multiple other enzymes can be demonstrated but their use is limited to large specialist, or research, centers.

5.1.4 Immunohistochemistry

The past 30 years has seen histopathology revolutionized by the introduction of immunohistochemistry. This employs the antibody-antigen interaction by using antibodies labelled with a coloring system and directed at specific antigens in the tissues. There are a vast number of antigens that can be identified and the list grows almost daily. The significance of demonstrating antigens in the tissue lies in the possibility of using an antigen profile to identify the origin of the tissue and yield diagnostic and prognostic information about its behavior. Nowadays most immunohistochemical techniques can be used on formalin fixed paraffin embedded tissue, although a few still require fresh frozen tissue. It is important to realize that a single antigen rarely, if ever, is specific to a single diagnosis and that panels of antibodies are required and even then must be interpreted in the context of the case [9].

5.1.5 Molecular Techniques

Molecular techniques can now be applied to tissue [10]. Again the point must be emphasized that the results of all these tests must be interpreted in the context of the case. If this is not followed then mistakes will be made [11]. The two most commonly employed techniques in molecular diagnosis are Fluorescent In-situ Hybridization (FISH) and Reverse-transcriptase Polymerase Chain Reaction (RT-PCR). High quality nucleic acid is required usually from fresh or frozen tissue, although techniques are now available for use on formalin fixed and paraffin embedded tissue. FISH can be used on tissue imprints, frozen sections or paraffin embedded sections. It requires the target DNA to be denatured and then hybridized with fluorescent-labelled DNA probes for target specific sequences of DNA. This technique is suitable for detection of translocations by using sequences that flank the breakpoint; if a translocation is present in the tissue then the probe sequences are separated. If fusion probes are used, then if a translocation is present the probes will be brought together. FISH can also be used for detection of amplification or regions of DNA, DNA gain or DNA loss.

In RT-PCR RNA is extracted from the tissue and the extracted nucleic acid is mixed with oligonucleotide primers and the enzyme DNA polymerase. This leads to amplification of large quantities of DNA highly specific to the primers used. This amplified product is then visualized by various techniques such as gel electrophoresis, restriction fragment length polymorphisms, Southern blotting or sequence analysis. The technique is exquisitely sensitive, and great care must be taken to avoid contamination with even minute amounts of extraneous nucleic acid. This requires meticulous attention to detail and use of appropriate controls.

FISH and PCR detect slightly different things and in practice are complementary techniques, each supplying the others deficiencies.

Pediatric tumors in which molecular biology is used routinely in the clinical setting [10] include neuroblastoma where the MYCN status of the tumor is used for prognostication, rhabdomyosarcoma where detection of the PAX-FKHR fusion transcript permits the diagnosis of alveolar rhabdomyosarcoma and primate neuroectodermal tumor (PNET) where the detection of EWS gene fusion transcripts is used in diagnosis.

5.1.6 Team Work

Running through all that has been written above is the need for teamwork. The pathologist is part of the clinical team. The information available to the pathologist needs to be of the best to permit

them to select the correct techniques of examination and correctly to interpret their result. There needs to be dialogue between surgeon, radiologist, pediatrician/neonatologist and pathologist in formulating diagnosis and approach to treatment and its monitoring. Constant feedback and regular meetings are essential for all to permit the maximum effectiveness of the team.

5.2 Developmental Disorders of the Gastrointestinal Tract

5.2.1 Oesophagus

True maldevelopments of the esophagus include esophageal atresia (with or without tracheoesophageal fistula), diverticula, webs and duplication cysts.

5.2.1.1 Esophageal Atresia and Tracheoesophageal Fistula

Esophageal atresia (OA) has an incidence of 1:3000–1:5000 live births and there is a high incidence of associated maternal polyhydramnios (50%). The commonest variants are proximal OA with distal tracheoesophageal fistula (TOF) (85%), OA without fistula (10%), "H-shaped" TOF without atresia (3%). In proximal OA with distal TOF, the esophagus is a blind ending pouch, ending a short distance from the cricoid cartilage [12]. The gap is in the order of 1–2 cm and the fistula usually takes origin from the carina posteriorly (Fig. 5.1). In Pure OA the gap much wider than with above. There is a high incidence of trisomy 21. The "H" type usually do not have associated abnormalities. Diagnosis is usually late.

Fig. 5.1 Oesophageal atresia with tacheo-oesophageal fistula. A hand-drawn illustration from the Archives of Great Ormond St Hospital for Children. This is a child who presented in 1901 with regurgitation after feeding. Attempts to place a tube in the stomach failed and a gastrostomy was fashioned. He died aged 5 days of pneumonia. A post-mortem was performed and the hand-written report (still extant) reads "a probe passed from the stomach up the oesophagus appeared through the larynx. A probe passed down the oesophagus from above was stopped one half-inch above the bifurcation of the trachea". The illustration shows the blind-ending upper oesophageal pouch behind the larynx, and the distal oesophagus taking origin from the carina of the trachea. Of the two probes in the larynx, one emerges from the left main bronchus and the other through the stomach wall close to the cardia

5.2.1.2 Esophageal Diverticulum

Congenital diverticula are rare and most are acquired. Histologically they consist of all layers of esophageal wall.

5.2.1.3 Esophageal Stenosis and Webs

These are very rare and usually have tracheobronchial remnants in the wall of the esophagus. True congenital lesions are akin to esophageal

atresia. They may be associated with OA or TOF. Webs are commoner in mid esophagus and stenosis commoner in lower esophagus. Webs consist of mucosal and submucosal tissue only.

5.2.1.4 Duplication Cyst

This may present with respiratory distress or feeding difficulties [13]. They may be detected antenatally [14]. Doubling of the esophagus may be tubular or spherical (Fig. 5.2). The cyst has a muscle coat (usually with two layers) and the lining epithelium is ciliated, non-ciliated, squamous or gastric or combinations of these. For the purposes of classification, if a duplication cyst is associated with vertebral defect it is best regarded as a neurenteric cyst. If the wall of the cyst contains cartilage the lesion is best classified as a bronchogenic cyst. (Fig. 5.3).

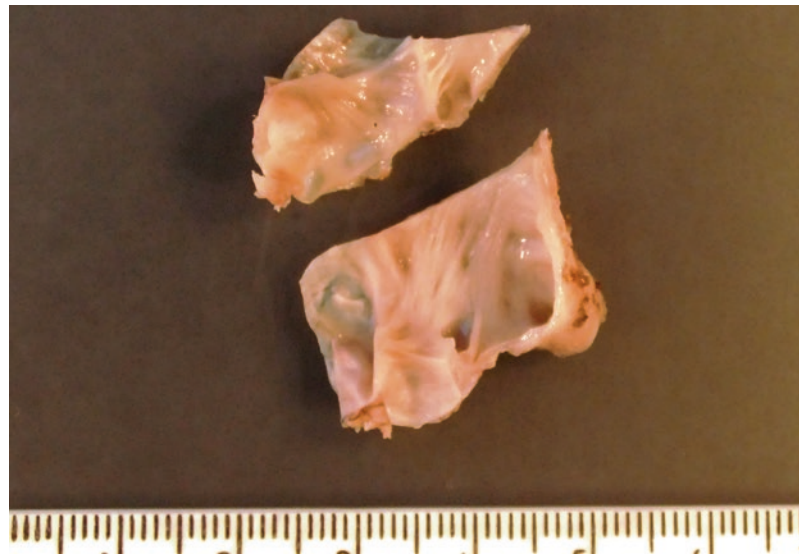

Fig. 5.2 Oesophageal duplication cyst. A 7-month old boy with a right-sided mediastinal cyst. The cyst was a mass 3.5 × 3.0 × 3.0 cm and contained thick mucus. The lining is white and trabeculated. Histologically it was covered by respiratory and squamous epithelium. The wall contained smooth muscle but no cartilage

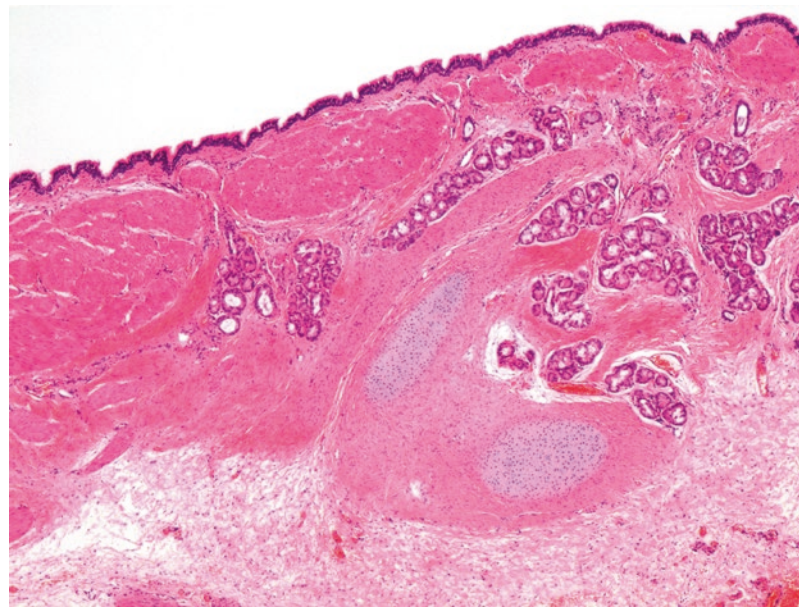

Fig. 5.3 Bronchogenic cyst. A left-sided chest mass 3.0 cm in diameter that has a wall composed of smooth muscle with sero-mucinous glands and hyaline cartilage. The lining is of ciliated respiratory epithelium

5.2.2 Stomach

5.2.2.1 Gastric Duplication Cysts

These are rare and may present as gastric outlet obstruction [15], abdominal mass, abdominal pain or failure to thrive. They are associated with duplication of esophagus or duodenum and vertebral abnormalities. Histologically they have a smooth muscle coat in continuity with that of the stomach wall and the cyst lumen may communicate with the gastric lumen. The mucosal lining is usually of gastric mucosa (Fig. 5.4).

5.2.2.2 Heterotopias

These include pancreatic tissue in wall of antrum (usually submucosa or muscle coat) that may cause gastric outlet obstruction. It is sometimes seen endoscopically as a dome-shaped nodule with a central punctum. It consists histologically of pancreatic acini and Brunners glands and may show prominent smooth muscle hyperplasia [16]. If Brunner's glands and smooth muscle alone are seen, the lesion is best termed an adenomyoma [17].

5.2.2.3 Hypertrophic Pyloric Stenosis

In this common condition of infants the pyloric portion of the stomach becomes abnormally thickened. It manifests as gastric outlet obstruction. There are few pathological descriptions; and these describe morphologically unremarkable smooth muscle. There is possible absence of sarcoglycans within hypertrophied pyloric muscle [18].

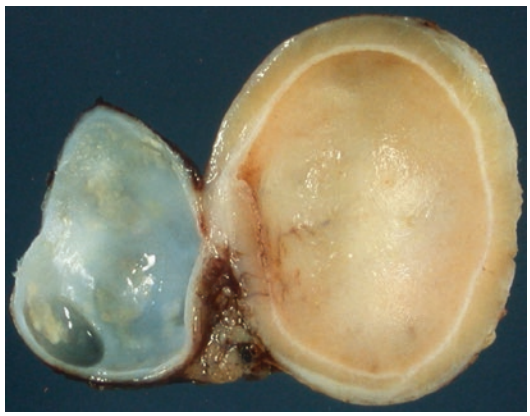

Fig. 5.4 Gastric duplication cyst. A 2.5 cm diameter cyst from the wall of the stomach. It is bi-lobed with a smooth lining and a muscular wall

5.2.3 Small Intestine

5.2.3.1 Intestinal Atresia

Intestinal atresia is an intrauterine process resulting in an incomplete bowel lumen. Duodenal atresia is mainly associated with trisomy 21. Usually it is treated with duodeno-duodenostomy and only rarely submitted for pathological assessment. Intestinal atresia is presumed to be due to intrauterine insult, either an ischemic or a hypotensive episode. The jejunum and ileum may also be affected. It may be isolated or multiple. Jejuno-ileal atresia is more commonly submitted for pathological assessment, because it is treated with resection and anastomosis. The specimen (Fig. 5.5) shows a discontinuous lumen and the atretic segment shows fibrosis [19] with focal muscularis replacement, dystrophic calcification and pigment-laden macrophages (Fig. 5.6).

5.2.3.2 Meckel's Diverticulum and Related Vitello-Intestinal Remnants

The vitellointestinal duct in the embryo joins the lumen of the midgut to the yolk sac. It is usually obliterated early in development. It can persist as a fistula between umbilicus and ileum; only parts of it may persist, the proximal part as Meckel's diverticulum or the distal part as an umbilical sinus or cyst. Meckel's diverticulum is present in between 1 and 4% of the population. It may be completely asymptomatic. There are symptoms in about one-fifth of cases: there may be ulceration either in the diverticulum or adjacent small bowel. It may cause hemorrhage, it may perforate or a foreign body may lodge in it to cause perforation. It may form the lead point for intussusception or it may have fibrous attachment to umbilicus and cause constriction of bowel with obstruction or volvulus [20]. The diverticulum is situated on the antimesentreic border of terminal ileum approx. 30 cm from

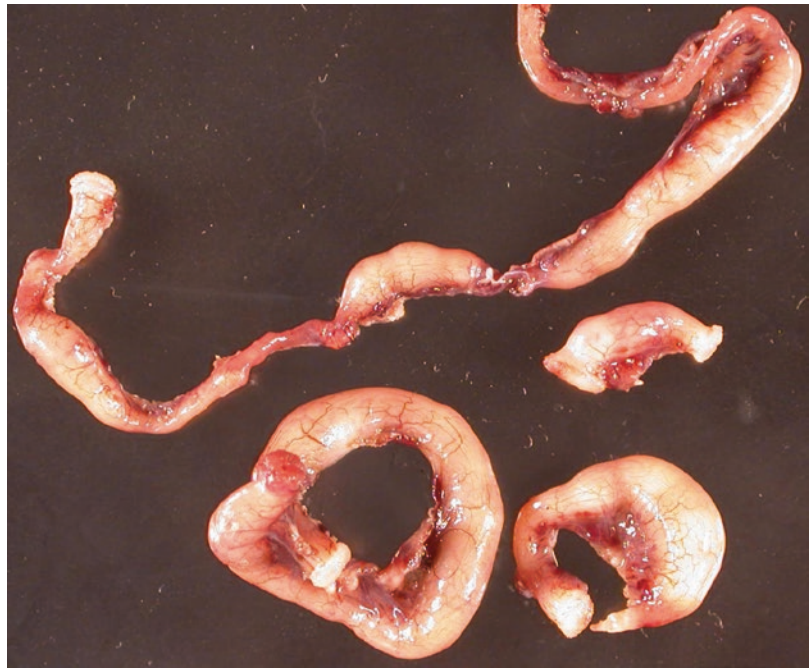

Fig. 5.5 Jejunal atresia. A 5-day old male infant with multiple segments of jejunal atresia. The specimen shows four pieces of small intestine. The longest is 14 cm long and it shows areas of thread-like narrowing. The other pieces also show tapered ends

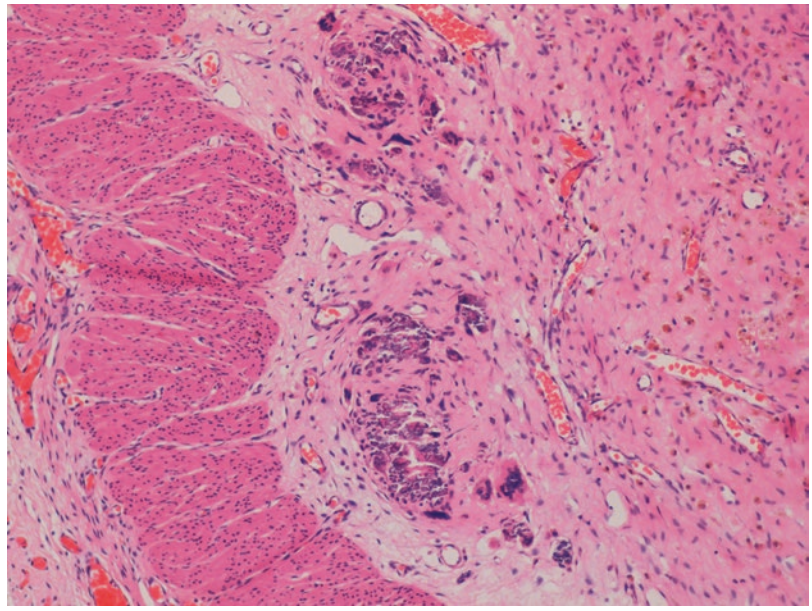

Fig. 5.6 Ileal atresia. Six-day old male infant with mid-ileal atresia. A 5 cm length of small bowel was resected that ended blindly. The section from the blind end shows that the muscle coat is still intact, but there is fibrous obliteration of the lumen and the presence of dystrophic calcification and haemosiderin-laden macrophages

ileocaecal valve. The diverticulum may be up to 8 cm long, but is usually much shorter (Fig. 5.7). It may be long and tubular or squat and almost cystic. The tip may be bifid or nodular. All components of normal bowel wall are present. The muscle coat may be very attenuated at the tip or distorted by heterotopic tissue. It is lined, usually, by ileal mucosa, but may have gastric body mucosa lining it [21]—Helicobacter organisms may colonise it. Rarely, colonic tissue is present or one may see ulceration or a bleeding point. There may be nodules of pancreatic tissue (including islets) in the wall and the serosa may show fibrosis or inflammation (Fig. 5.8).

5.2.3.3 Omphalomesenteric Cysts and Sinus

These present as umbilical discharge or granulation tissue. They are lined by small bowel, gastric or colonic mucosa (Fig. 5.9) and may contain pancreatic tissue. The lesions may ulcerate with replacement of the lining by granulation tissue to form an umbilical granuloma [22].

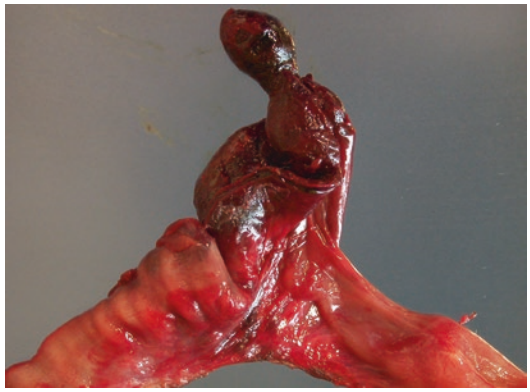

Fig. 5.7 Meckel's diverticulum. A 2-month old girl who underwent laparotomy for irreducible intussusception. A segment of ileum 21 cm long was resected. Protruding from the antimesenteric borer there is a Meckel's diverticulum 1.5 cm long and 0.8 cm in diameter that has undergone haemorrhagic infarction

5.2.3.4 Duplication Cysts

The cysts have a two-layered muscularis propria with outer layer fused with normal intestine (Fig. 5.10). The muscle coat contains a myentric plexus. The mucosal lining is usually enteric mucosa, but gastric mucosa is also common.

5.2.4 Large Bowel

5.2.4.1 Anorectal Anomalies

These are complex developmental defects with variable anatomy. While the treatment is largely operative, it is not usual for the pathologist to receive surgical specimens from these operations. Small segments of stenotic anal canal or rectum or small fistulae may be received showing disorganized musculature with variable fibrosis. Nephrogenic elements are sometimes seen in the distal bowel wall [23].

5.2.4.2 Currarino Triad

This is an autosomal dominant condition with incomplete penetrance comprising: teratoma, meningocoele, anorectal malformation and sacral bony defect. Approx. 50% of the cases also have Hirschsprung disease [24].

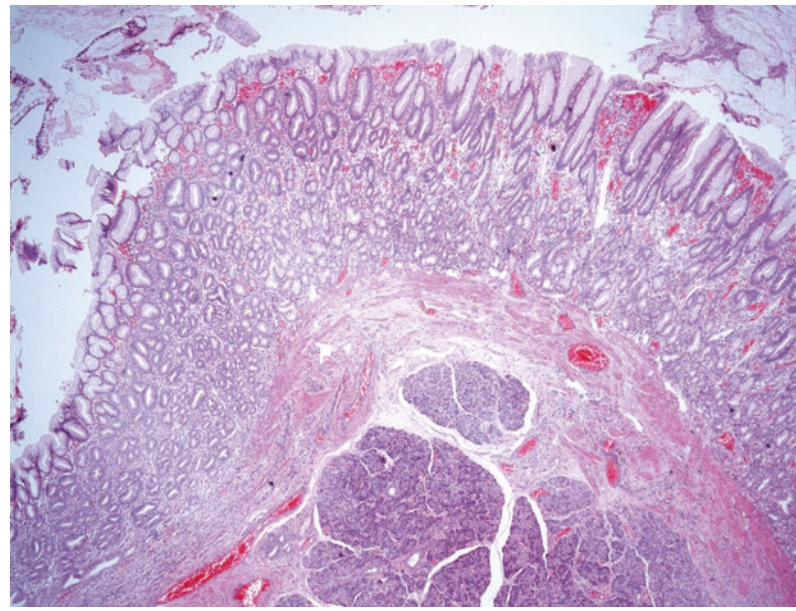

Fig. 5.8 Meckel's diverticulum—heterotopic pancreas. A 5-month old girl with ileo-colic intussusception. The lead point was a Meckel's diverticulum and histological examination of the tip of the diverticulum shows that it is lined by gastric antral type of mucosa, beneath which there is a nodule of heterotopic pancreatic tissue. The pancreatic tissue extended through the muscle coat of the diverticulum to its serosa

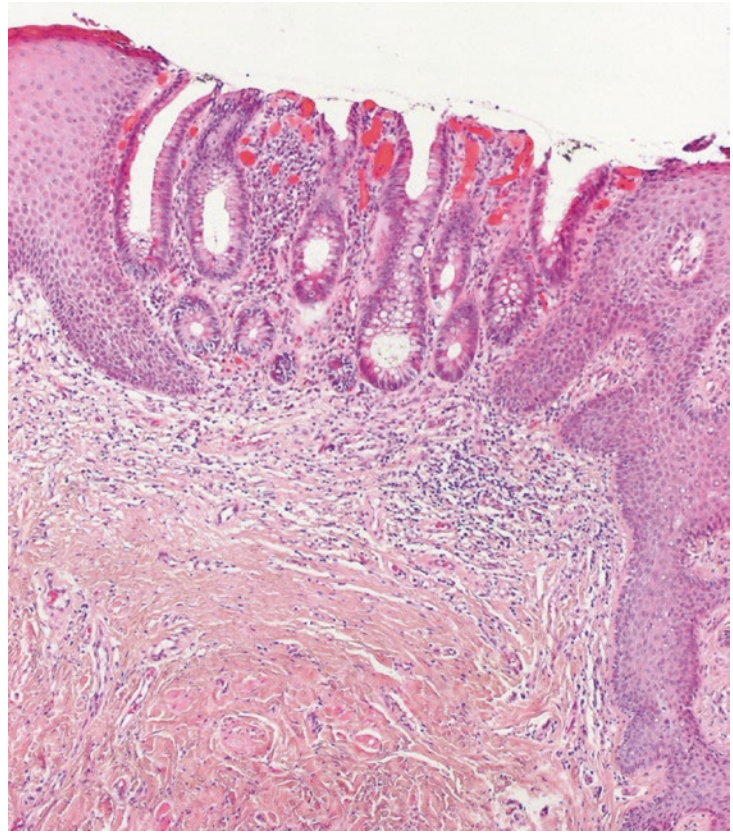

Fig. 5.9 Umbilical polyp—omphalomesentreic duct remnant. A polyp, partly covered by skin and partly by small bowel mucosa showing superficial capillary congestion and deeper chronic inflammation. Although the tissue may appear red and weeping, it is not, in fact, ulcerated

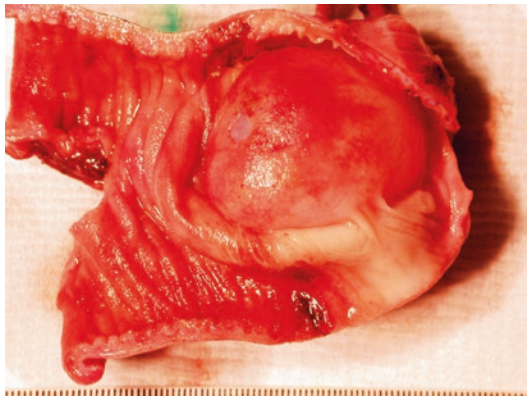

Fig. 5.10 Ileal duplications cyst. A 5-month old boy who presented with intestinal obstruction and at examination had an ileo-caecal mass. At laparotomy the mass was resected. The illustration shows the opened specimen. Protruding into the bowel lumen is a smooth-domed mass 3 cm in diameter that represents the cyst. Histologically it was composed of a two-layered muscularis propria with the outer layer fused with the normal bowel wall. The mucosal lining of the cyst was an admixture of simple cuboidal enteric-type mucosa and non-specialised gastric-type epithelium

5.3 Intestinal Obstruction

5.3.1 Intussusception

Although intussusception is rare in neonates, it does occur [25] and, especially in the premature infant may be misdiagnosed as necrotizing enterocloitis [26]. Only those cases that cannot be reduced medically come to pathological attention. The resected mass comprises:

- an outer layer of thinned distended bowel—the intussuscipiens
- an inner layer of everted, invaginated bowel—the intussusceptum

The mesentery of the intussusceptum is stretched and congested. The lead part of the intussusceptum may show a mass that may be lymphoid hyperplasia, sometimes secondary to infection with Adenovirus. It may also be due to

a polyp, a Meckel's diverticulum, a duplication cyst, a tumor or heterotopic pancreas (Figs. 5.11 and 5.12). The intussusceptum is frequently infarcted and hemorrhagic.

Histologically the intussusceptum shows edema and hemorrhagic infarction. Adenovirus inclusions may be seen in hyperplastic bowel surface epithelium. Other pathology associated with the cause of the mass may be recognized. The cause may not be identified other than lymphoid hyperplasia. The intussuscipiens shows thinning of its wall and it may also show hemorrhage.

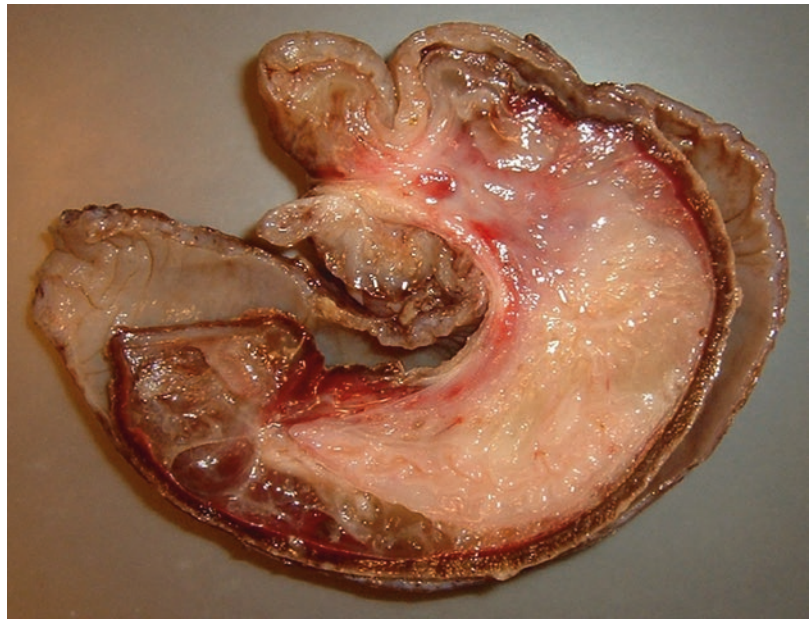

Fig. 5.11 Intussusception. A 5-month old girl with failed reduction of ileo-colic intussusception. The opened specimen shows the invaginated and everted small bowel contained within a sleeve of large intestine. The intussusceptum is infracted and there was a Meckel's diverticulum at its lead point that contained heterotopic pancreas in its wall

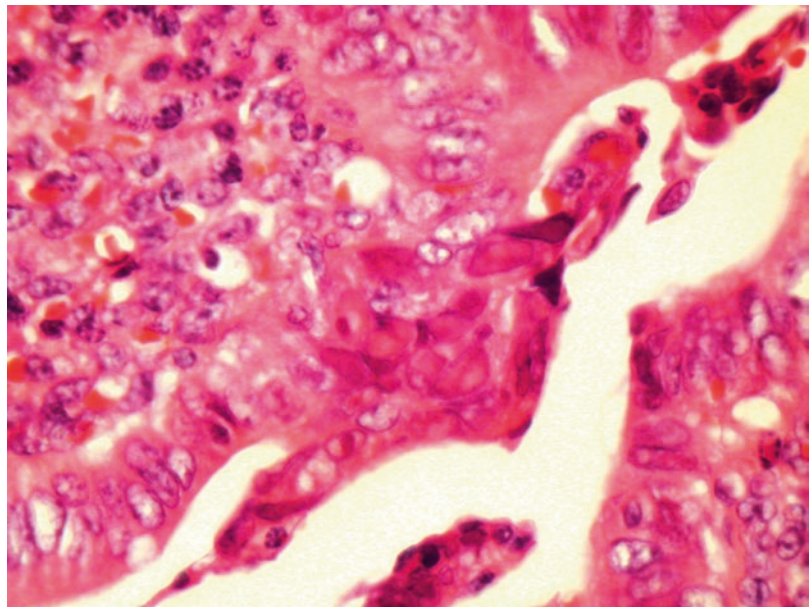

Fig. 5.12 Intussusception. An 8-month old boy with ileo-colic intussusception. The resected specimen showed lymphoid hyperplasia. A high-power view of the mucosal surface of the small bowel shows epithelial cell hyperplasia and numerous Adenovirus intranuclear inclusions

5.3.2 Volvulus

This refers to twisting of the bowel on its mesentery to such an extent as to compromise the mesenteric blood supply. It is associated with malrotation [27] with abnormally long mesentery showing a short attachment to the abdominal wall, with congenital bands or inflammatory adhesions. It may be fatal. Pathologically, the affected bowel is distended and shows hemorrhagic infarction with sharp demarcation from the unaffected bowel (Fig. 5.13). It is rare for the pathologist to identify a cause of volvulus in the submitted specimen.

5.3.3 Meconium Ileus

This refers to neonatal bowel obstruction due to impacted meconium, most commonly in the terminal ileum. There may have been intrauterine obstruction or perforation. Meconium ileus is typically associated with cystic fibrosis, affecting about 15% of neonates with cystic fibrosis. However, about 10–20% of apparent meconium ileus cases do not have cystic fibrosis. Very low-birth weight and premature infants especially can develop meconium obstruction in the absence of cystic fibrosis [28]. The clinical picture may be mimicked by total colonic aganglionosis.

The resected surgical specimen show secondary features of perforation and meconium peritonitis with granulation tissue, dystrophic calcification and fetal squames, as well as pigment (Fig. 5.14). The intestinal lumen characteristically is filled with inspissated meconium, the mucus extending deep into crypts (plugging). A similar histological picture may be seen in premature infants with meconium plugging who do not have cystic fibrosis [29] (Fig. 5.15).

Fig. 5.13 Volvulus. An 11-month old with intestinal obstruction. Laparotomy showed volulus caused by adhesions because of previous Nissen fundoplication. A 25 cm length of bowel was resected. The image shows the resected bowel. The serosal surface is congested and shows a shaggy appearance caused by fibrinous exudate. The middle part of the specimen shows haemorrhagic infarction with very dark disclouration and haemorrhage. A perforation on the antimesenteric border is evident at bottom left. Note the sharp demarcation between infracted and non-infarcted bowel

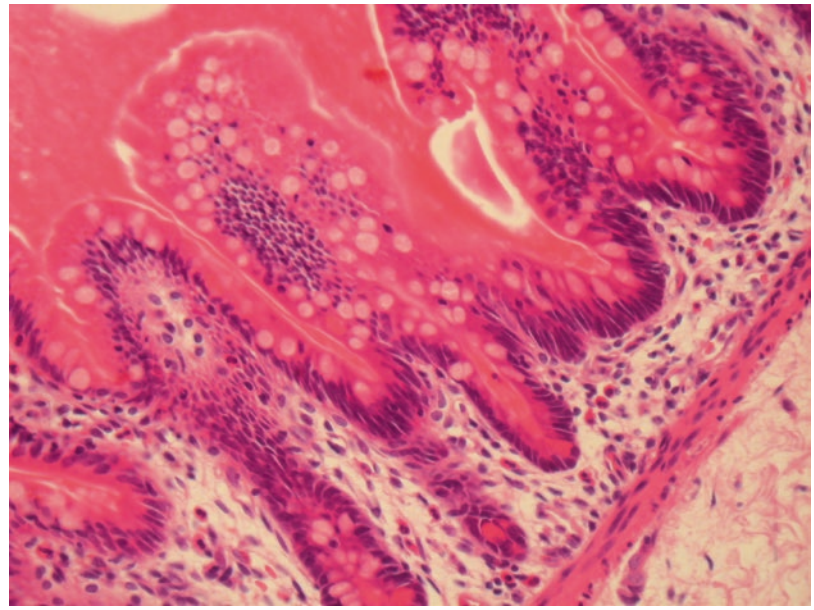

Fig. 5.14 Meconium ileus cystic fibrosis. Two day old boy with cystic fibrosis gene mutation who presented with meconium ileus and microcolon. There was associated ileal atresia. The resected specimen shows small bowel mucosa with inspissated mucus in the crypts

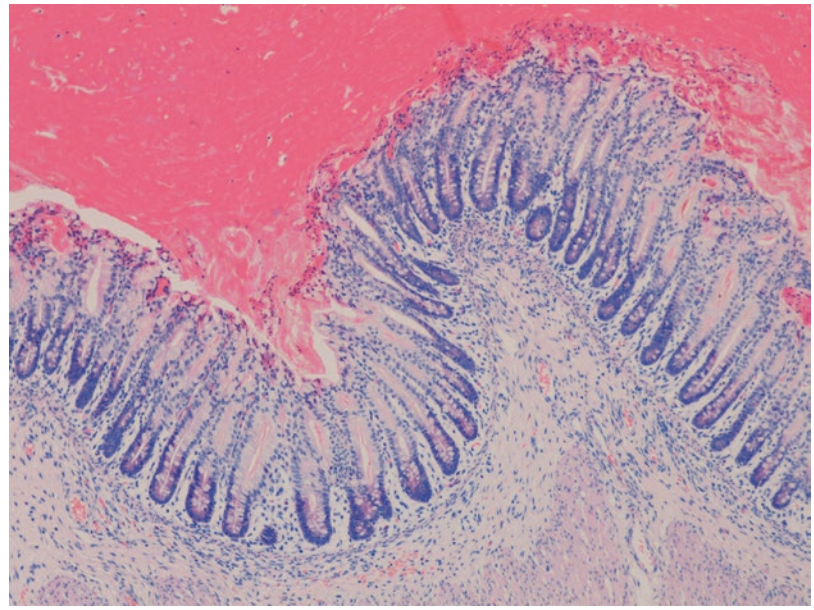

Fig. 5.15 Meconium ileus in a premature infant. Five day old premature male infant with meconium ileus. Cystic fibrosis screening negative. The histological section of the resected bowel shows dilated bowel with inspissated meconium in the crypts, identical to that seen in patients with cystic fibrosis

5.4 Hisrchsprung Disease

Hisrchsprung disease is a developmental disorder in which there is absence of ganglion cells in the distal rectum and a variable length of contiguous proximal bowel. Caused by failure of neural crest cells to migrate, proliferate, and/or differentiate during development of the enteric nervous system.

In most cases of Hisrchsprung disease the diagnosis is straightforward, but in a small number the diagnosis can be difficult to the extent of being one of the most difficult areas in pediatric pathology practice. This area is the commonest cause of litigation in pediatric pathology practice. Meticulous examination and documentation are essential. Pitfalls abound for the unwary.

There are three stages in the care of Hisrchsprung disease in which there is histopathological involvement:

1. primary diagnosis
2. intraoperative guidance of resection of the aganglionic segment
3. evaluation of the resected bowel

The histopathologist may, of course, also be involved in further evaluation if the patient continues to have symptoms after the definitive surgical procedure.

5.4.1 Primary Diagnosis on Rectal Suction Biopsy

The diagnosis of Hisrchsprung disease is made or excluded on rectal suction biopsy: the quality of the biopsy sample critically depends on the skill and experience of the operator. The diagnosis rests on demonstrating the absence of submucosal ganglion cells in an adequate sample (Fig. 5.16), with or without accompanying hypertrophic submucosal nerves (diameter greater than 40 μm). An abnormal acetylcholinesterase (AChE) staining pattern is diagnostic—there are increased numbers of coarse fibers in the muscularis mucosae and lamina propria mucosae with transversely running nerve fibers in lamina propria (Fig. 5.17).

Laboratories differ in their approaches to these biopsies. Acetylcholinesterase staining can be demanding and difficult and cannot be employed on formalin fixed, paraffin embedded tissue. It is not used in all laboratories. Many laboratories rely on H&E staining of serial paraffin sections; In some, enzyme histochemical staining for lactic and succinic dehydrogenase and nitric synthase are also used [30]. Some groups use enzyme histochemical staining for nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase [31]. Immunohistochemical staining for many

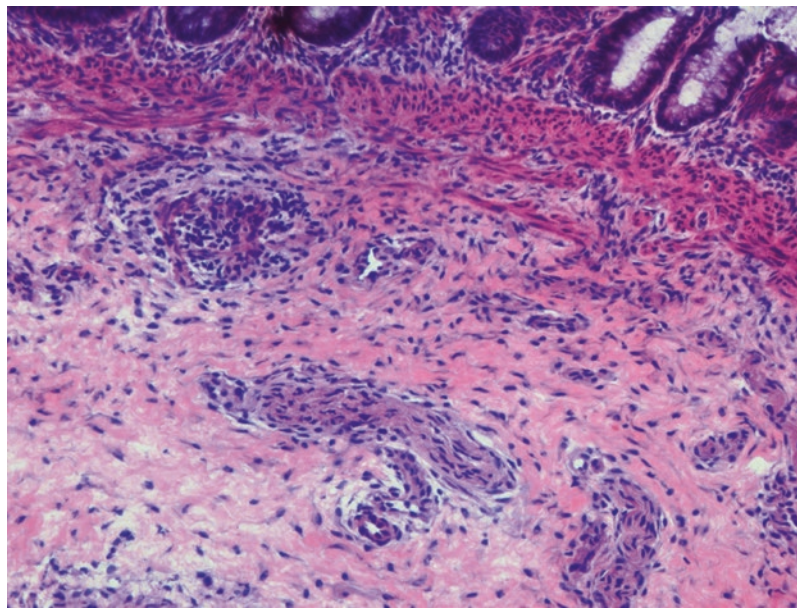

Fig. 5.16 Hirschsprung disease—rectal suction biopsy. The image shows an H&E stained section of a rectal suction biopsy in a neonate with Hirschsprung disease. The bases of the mucosal crypts and the muscualris mucosae are visible in the upper part of the image. The rest of the field represents submucosa. As is normal in the neonate the tissue is cellular, but there are no ganglion cells. There are however, multiple, abnormally thick submucosal nerves. While this picture is typical of Hirschsprung disease, in reality, multiple serial sections need to be viewed to be certain of the absence of ganglion cells. Acetylcholinesterase staining greatly assists the interpretation

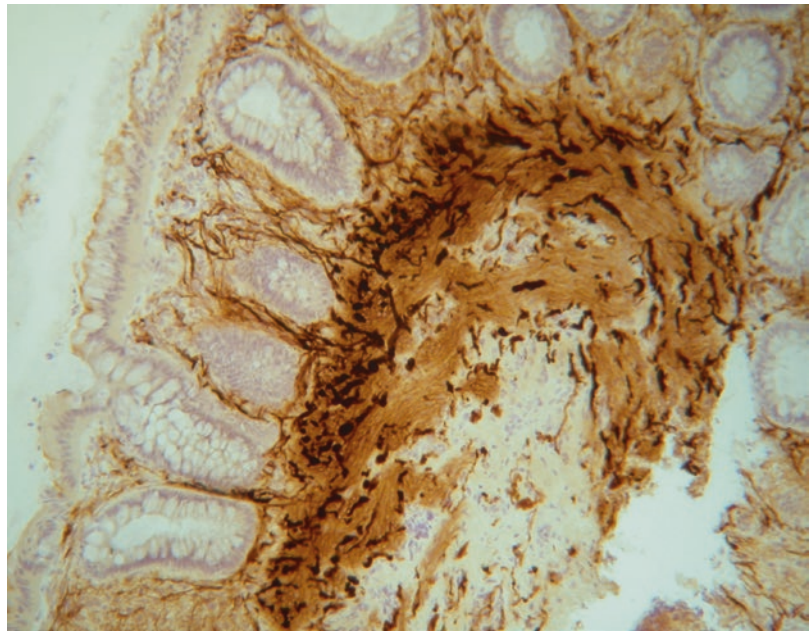

Fig. 5.17 Hirschsprung disease—acetyl cholinesterase. Neonatal rectal suction biopsy snap frozen, sectioned and stained for acetlycholinesterase activity. Positive reaction product is stained *dark brown*. There are large irregular and knotty nerve fibres in the muscularis mucosae and a marked increase in fibres in the lamina propria mucosae, including nerve fibres running parallel to the biopsy surface. This appearance is characteristic of Hirscshsprung disease

different antigens has been described. Most facilitate recognition of ganglion cells, but in practice add little to the H&E-based interpretation of an experienced pathologist. Recent interest has centered on Calretinin immunohistochemistry [32]. Loss of calretinin immunoreactive nerves correlates spatially with aganglionosis (Figs. 5.18 and 5.19). This has the advantage of being employable on formalin fixed paraffin embedded tissue. Many laboratories have switched to this technique and are pleased with the results. The technique, however, does have the theoretical disadvantage that it relies on absence of staining for a positive result.

At least two rectal suction biopsy specimens at different levels above the dentate line (e.g. 2, 3, 5 cm) are required and should be received fresh on saline-moistened filter paper. If an urgent diagnosis is required, the specimens are processed immediately. The specimen from the lowest level (distal) should be cut first. Specimens are oriented with the submucosal side up, frozen rapidly and serial sections cut without trimming. Rapid H&E staining is performed and when many sections with submucosa are present, the slides are passed to the pathologist. Two further frozen sections are then cut and a rapid Acetylcholinesterase stain is performed (45 min). If the specimen is ganglionic, a standard acetylcholinesterase stain is performed later. A report can be issued to the surgeon in less than 1 h from receipt of the specimen. After the acetylcholinesterase stain is reported, the remainder of specimen is fixed in 10% buffered formalin for paraffin processing. A ribbon of at least 60 serial sections is cut with the specimen orientated in usual way and stained with H&E.

5.4.2 Assessment of Rectal Suction Biopsy Specimens for Hirschsprung Disease and Its Pitfalls

Ganglion cells must be identified on H&E stained sections. Ganglion cells in a neonatal biopsy are small with neuroblastic morphology and more difficult to identify than mature ganglion cells (Figs. 5.20 and 5.21). Histiocytes and endothelial cells may mimic them and it is important to check neighboring sections. Cytomegalovirus infected cells in the submucosa can be mistaken for ganglion cells. This may seem an unlikely possibility,

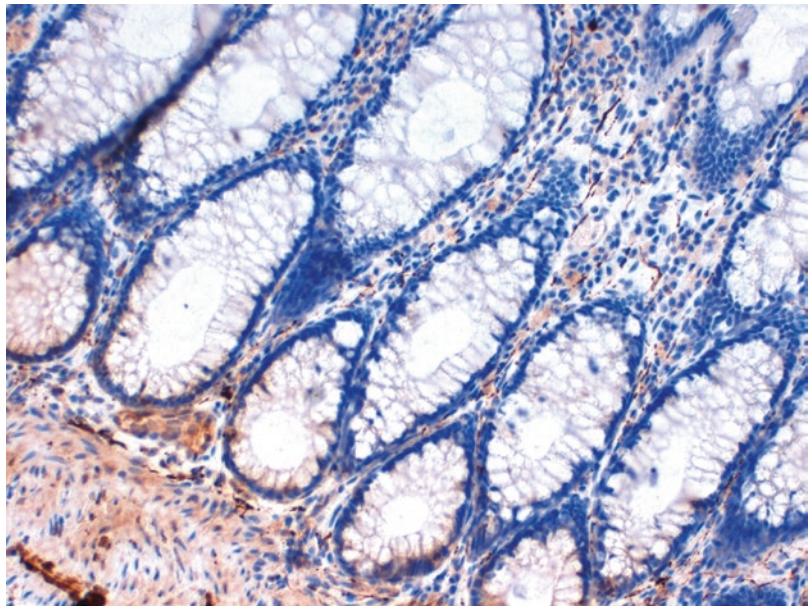

Fig. 5.18 One year old girl with constipation. Rectal suction biopsy to exclude Hirschsprung disease. The specimen was normal A section from the biopsy specimen stained immunohistochemically for Calretinin. The picture shows a view of the mucosa with a small amount of musclularis mucosae and submucosa to the lower left of the field. *Dark brown* nerve fibres are evident in the lamina propria mucosae (running vertically). A few small fibres are evident in the muscularis mucosae and part of the strongly stained body of a ganglion cell is seen at the lower edge of the field

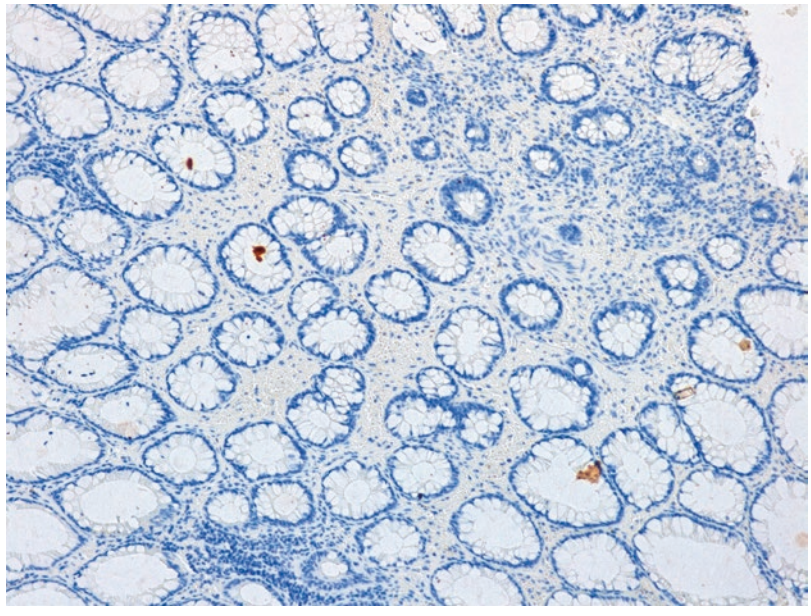

Fig. 5.19 Hirschsprung disease. Five day old boy with Hirschsprung disease. Rectal suction biopsy stained for calretinin. The biopsy is superficial and shows no muscularis mucosae or submucosa, precluding assessment of the presence or absence of ganglion cells. The absence of positive staining of nerve fibres for calretinin indicates that this is a case of Hirschsprung disease. In the absence of submucosa it is not possible to be sure whether this represents aganglionic or transition zone

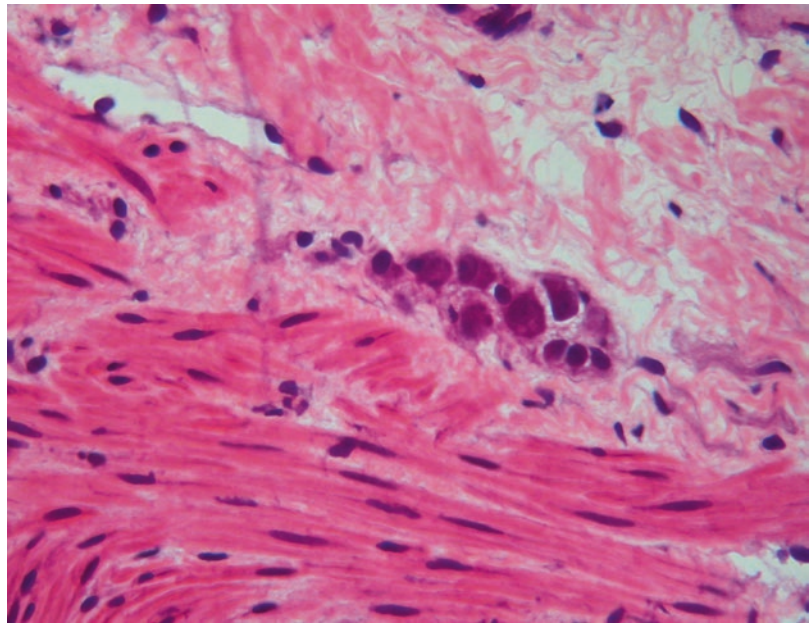

Fig. 5.20 Normal mature submucosal ganglion cells. A high-power view of an H&E stained section of a rectal suction biopsy from an infant without Hirschsprung disease. A group of approximately six ganglion cells is present close to the muscularis mucosae. The characteristics of mature ganglion cells are well seen; large size, basophilic cytoplasm, eccentric, round nucleus, prominent nucleolus and surrounding satellite cells

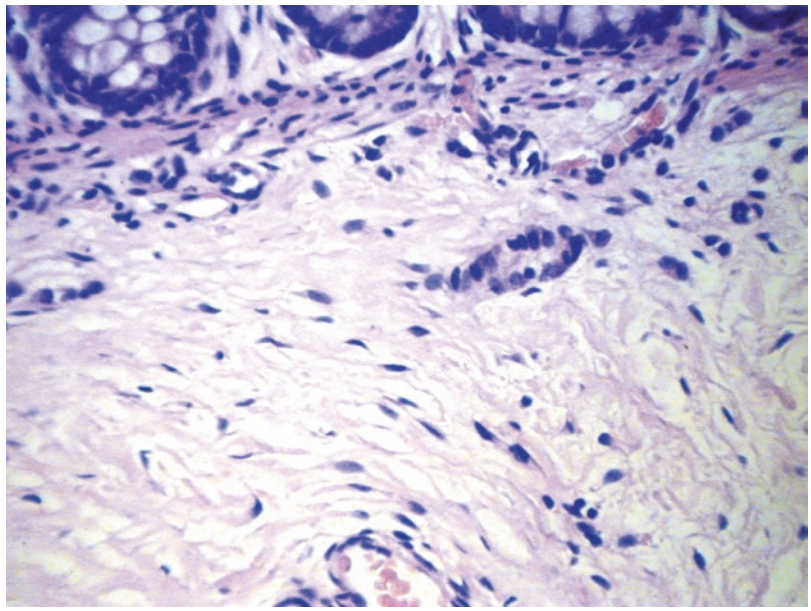

Fig. 5.21 Normal immature submucosal ganglion cells. A high-power view of an H&E stained section of a rectal suction biopsy from a neonate. The bases of the mucosal crypts and the muscularis mucosae are visible at the top of the field. There is a single group of immature ganglion cells lying close to the muscularis mucosae in the centres of the field. In contrast to the mature ganglion cells they show little cytoplasm and the nuclei do not contain prominent nucleoli. When ganglion cells are this immature, they are recognised by their disposition in a characteristic horseshoe pattern. Adjacent sections should be checked to ensure that this structure is not a blood vessel or a group of other cells. Acetylcholinesterase staining greatly aids in the interpretation

but it has happened to me! Such infected cells usually show surrounding inflammatory cells [33].

When ganglion cells are identified with certainty, the report is formulated as "ganglionic at the level of this biopsy" especially if only one specimen is received. This allows for the possibility of short segment disease which may become apparent if symptoms continue and further biopsies are taken at lower levels.

If ganglion cells are present but there are large hypertrophic nerves in the submucosa, the possibility of intestinal ganglioneuromatosis should be suggested.

In a biopsy from the physiological hypoganglionic zone 1–2 cm proximal to dentate line ('low biopsy') there may be extremely sparse ganglion cells, often single rather than in usual clusters. Usually there are associated prominent thick-walled blood vessels. There are also prominent nerves, but they are not hypertrophic. Splayed muscle fibers of sphincter may also give a clue to the low site of the specimen. There may be squamous epithelium or transitional anal mucosa present (Fig. 5.22). The acetylcholinesterase pattern is normal. If no ganglion cells are identified in such a specimen it is reported as: "Morphologic low biopsy. Normal acethylcholinesterase. Repeat biopsy recommended if clinically indicated".

If the biopsy specimen has inadequate submucosa for assessment of the presence of ganglion cells, the acetylcholinesterase staining pattern is crucial. If the acetylcholinesterase pattern in the muscularis mucosae is typical of Hirschsprung disease, then the report to the surgeon is: "Superficial biopsy. No ganglion cells identified. Acetylcholinesterase pattern suggestive of Hirschsprung disease." If the biopsy specimen has inadequate submucosa and the acethylcholinesterase pattern is normal, then the report is: "Superficial biopsy. No ganglion cells identified. Normal acethylcholinesterase. Repeat biopsy advised if clinically indicated" If the acethylcholinesterase staining is equivocal, a repeat biopsy is advised.

There is variability of the morphological patterns. No hypertrophic nerves are present in some cases of Hirschsprung disease.

5.4.3 Short Segment Hirschsprung Disease

The definitions vary. Together with our surgeons we define short segment Hirschsprung disease as

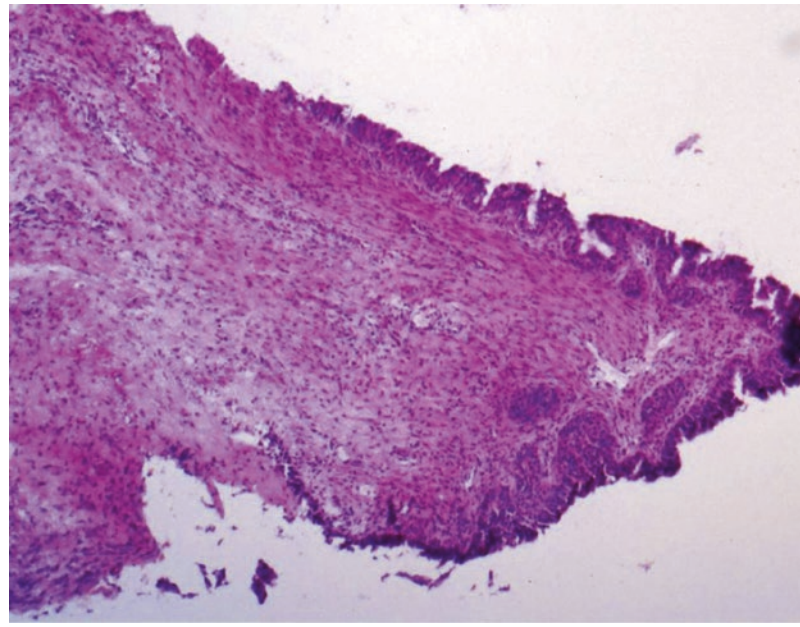

Fig. 5.22 Rectal suction biopsy for suspected Hirschsprung disease. The specimen shows an H&E stained section. It is composed of anal mucosa covered by transitional epithelium. The biopsy is too low for adequate assessment of ganglion cells

Hirschsprung disease in which the length of aganglionic bowel is less than 2 cm. The diagnosis is made when only the most distal rectal suction biopsy or part of the biopsy shows the appearances of Hirschsprung disease. The more proximal biopsies show normal ganglionic bowel with normal acetylcholinesterase staining.

5.4.4 Ultra-short Segment Hirschsprung Disease

Again, definitions vary, but together with our surgeons we define this as a clinical syndrome with functional abnormality of internal anal sphincter (internal sphincter achalasia) diagnosed on anorectal manometry and with no detectable morphological abnormality on rectal suction biopsy.

5.4.5 Intestinal Neuronal Dysplasia (IND)

This has been very controversial over the years. It is now recognized as a morphological description of a normal variant of the submucosal plexus [34, 35]. The finding of 'giant ganglia' containing more than seven nerve cells is a normal feature of biopsies in infants under the age of 1 year. The only situation in which the changes of IND may be of clinical significance is proximal to an aganglionic segment in a patient with Hirschsprung disease.

5.4.5.1 Reporting on Frozen Sections of Intra-operative Biopsies

Treatment of Hirschsprung disease is by surgical removal of the aganglionic segment. The procedure is guided by intraoperative frozen section diagnosis to determine the level at which bowel is ganglionic. Seromuscular biopsies consisting of two layers of muscularis propria and intervening plexus are submitted for urgent frozen section. The level from which the biopsy was taken should be indicated. Submission of appendix for identification of ganglion cells is not recommended since the appendix does not always have a well-defined myenteric plexus and ganglion cells can be difficult to locate in frozen section. For seromuscular biopsy specimens the orientation is such that the two muscle layers can be easily distinguished. A ribbon of serial sections is cut and stained with H&E. A fully ganglionic specimen should contain clusters of readily identifiable ganglion cells with associated neuropil and no nerves (Fig. 5.23). If ganglion cells are present but are accompanied

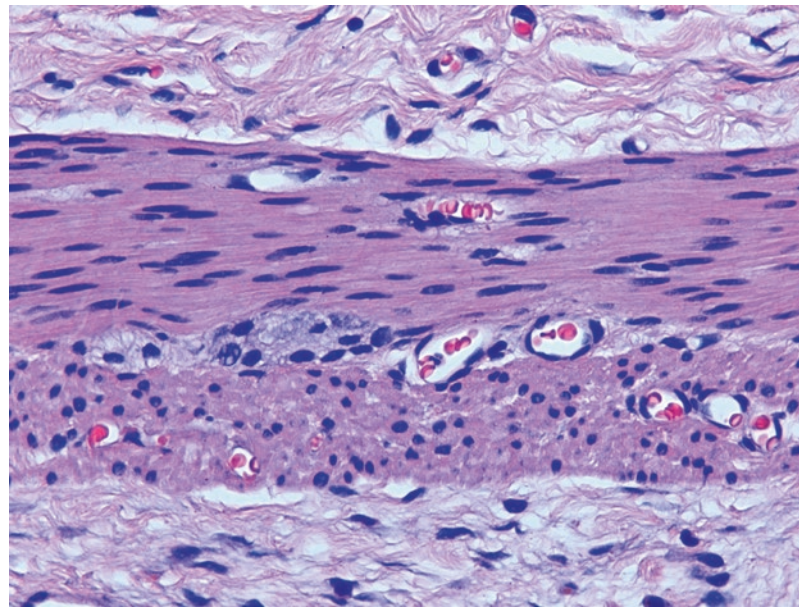

Fig. 5.23 Hirschsprung disease. A neonate with Hirschsprung disease. A section of normally ganglionic myenetric plexus proximal to the aganglionic zone. The two layers of the myenteric plexus are visible, the outer layer running longitudinally in the upper part of the picture and the inner layer in the lower part of the picture. A group of at least two ganglion cells with surrounding support cells is visible between the two layers. There are no enlarged nerves

by hypertrophic nerves, this represents transitional zone (Fig. 5.24) and biopsy from a more proximal level is advised. If ganglion cells appear sparse (i.e. clusters are small or more widely spaced than usual), this also probably represents transitional zone and biopsy from a more proximal level is advised. If ganglion cells are absent, and there are hypertophic nerves biopsy from a more proximal level Is advised. If there are no ganglion cells present, but no hypertrophic nerves and the muscle layers are closely apposed, the appearances are suggestive of long segment disease or total colonic aganglionosis (Fig. 5.25) and biopsy from more proximal level is advised. The pathologist reporting these biopsy specimens must be absolutely confident

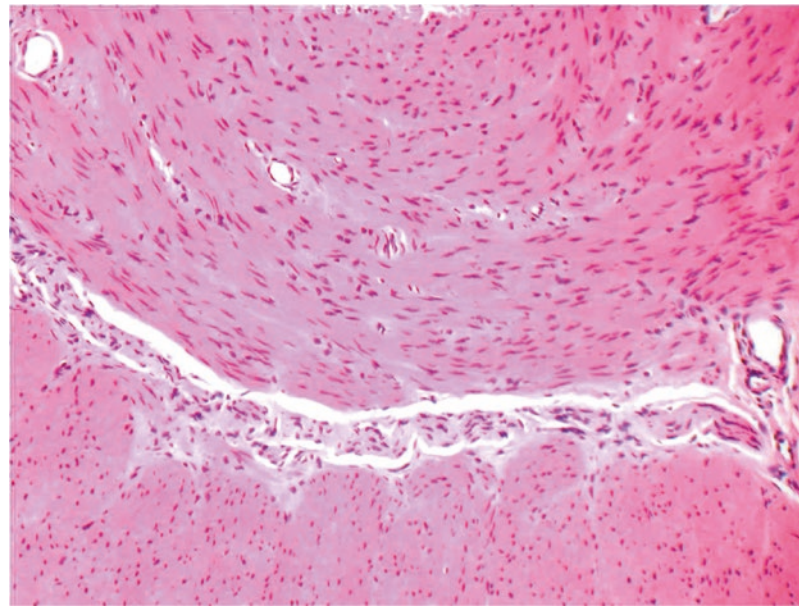

Fig. 5.24 Hirschsprung disease. Seromuscluar biopsy—H&E stained section The myenteric plexus contains enlarged wavy nerves. This appearance may be seen in the aganglionic zone. If ganglion cells are present in addition to enlarged nerves, then this suggests that the specimen is from the transition zone between aganglionic and normal bowel

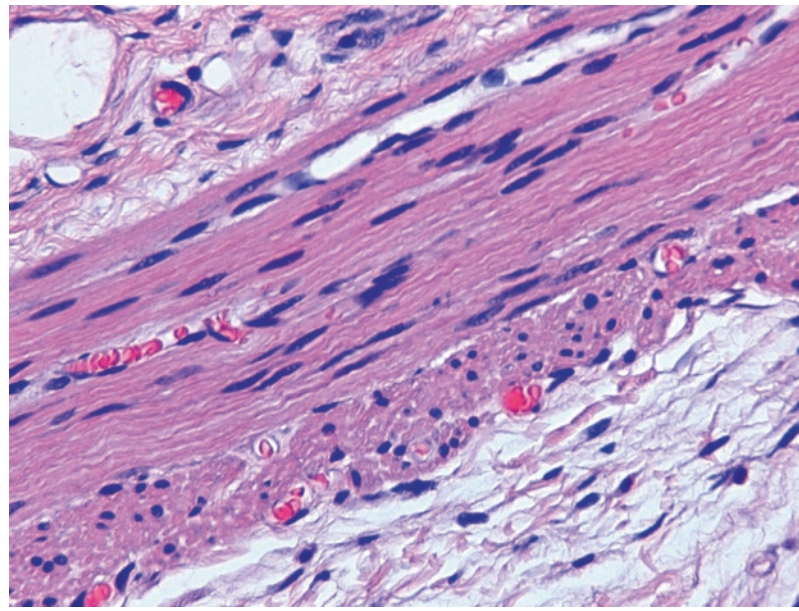

Fig. 5.25 Hirschsprung disease. A seromuscular biopsy from a neonate with total colonic aganglionosis. The outer muscle coat is visible in the upper part of the picture and the inner layer beneath it. They are closely apposed with no intervening tissue and the myenteric plexus is empty. The absence of enlarged nerve fibres is typical of total colonic aganglionosis

that two muscle layers can be distinguished: the serosa can be mistaken for the intermyenteric layer.

5.4.5.2 Evaluation of Resected Bowel

In about 80% of cases of Hirschsprung disease the affected segment is confined to the rectosigmoid. About 10% of cases have long segment disease and 5% have total colonic aganglionosis. The disease may involve small intestine. A further 5% have short segment disease. The transitional zone between normally innervated intestine and aganglionic intestine shows hypoganglionosis and occasional hypertophic nerves. It can be of very variable length. Depending on the clinical circumstances, the resected bowel may be received all in one piece or in multiple parts. Sutures should be applied by the surgeon to indicate orientation. Ideally the specimen should be received fresh, opened on arrival and circumferential samples of proximal margin taken for frozen sections and AChE staining, the remainder should be pinned out and fixed in formalin. Sampling of the proximal margin is most important: we perform circumferential sampling of the proximal end. Since the neuronal population may have spiral architecture, despite intraoperative sections showing ganglionic bowel at one point, the specimen may occasionally reveal transitional zone. There is an association between proximal segment histology and postoperative outcome [36]. ganglionic, this generally predicts good postoperative bowel function, 10% have constipation. If there is intestinal neuronal dysplasia (IND) of the proximal segment, the overall clinical result is unchanged but the constipation rate is higher. If there is proximal segment hypoganglionosis there is impaired postoperative function. If there is proximal aganglionosis there is a complicated postoperative course with secondary bowel resections and episodes of enterocolitis. Acetylcholinesterase activity in the proximal resection margins is a useful indicator [37].

Further sampling of a complete longitudinal full thickness strip of the entire resected bowel documents the lengths of aganglionic segment, transitional zone of hypoganglionosis and occasional hypertrophic nerves and fully ganglionic bowel. Skip segments may be present, recognized as segment of ganglionic bowel in an otherwise aganglionic segment.

5.4.6 Procedures in Other Institutions

Not all laboratories carry out circumferential sampling of proximal resection margins. Some laboratories take representative samples along the resected bowel rather than sampling the entire length.

5.4.7 Assessment of Biopsies from Patients with Failed Pull-through Procedure for Hirschsprung's Disease

One of the reasons for a failed pull -through procedure for Hirschsprung disease is a retained aganglionic segment [38]. Biopsies may be taken to assess whether or not the aganglionic segment has been fully excised. The pathologist needs to be familiar with the surgical pull-through procedure which has been performed. The operation with which we are familiar in our institution is the Duhamel operation [39] in which the anterior wall of the neorectum is aganglionic and the posterior wall is ganglionic. Biopsies are performed of the anterior and posterior rectal wall. It is expected that the anterior rectal wall biopsy will be aganglionic and will show the appearance of Hirschsprung disease. The posterior rectal wall biopsy will be normally ganglionic. If the posterior wall biopsy is aganglionic than the aganglionic segment has not been fully excised.

5.4.8 Hirschsprung's-Associated Enterocolitis (HAEC)

Colitis occurring in children with Hirschsprung disease is a major cause of morbidity and mortality in this group of children [40]. Classic presentation is a neonate with history of constipation. Post-pull through Hirschsprung disease associated enterocolitis is typically seen within 2 years

following pull through. The histopathological features [41–43] show several discrete phases used to grade pathologic severity:

Normal mucosa—grade 0
Crypt dilatation, mucin retention—grade 1
Cryptitis or <2 crypt abscesses/HPF—grade 2
Multiple crypt abscesses/HPF—grade 3
Fibrinopurulent debris and mucosal ulceration—grade 4
Transluminal necrosis or perforation—grade 5
Grade I may show marked mucus streaming from crypts similar to cystic fibrosis. Grades III–V may appear similar to ulcerative colitis (Fig. 5.26)

5.4.9 Hypoganglionosis

The diagnostic criteria are not strictly defined. It is usually a secondary condition being situated proximal to a segment of typical aganglionosis in Hirschsprung disease. Primary hypoganglionosis is rare. The signs and symptoms are indicative of Hirschsprung disease, but the rectal suction biopsy is normal. There are manometric and neurophysiologic tests suggestive of neuropathic process. It is often segmental and may be progressive. It is usually managed by stoma to relieve symptoms. At stoma placement, the surgeon may take a length of full thickness bowel to evaluate for primary hypoganglionosis or other neuromuscular pathology. Pathologically, the submucosal plexus is normal. The myenteric plexus shows a range of appearances including decreased numbers of ganglion cells in ganglion cell clusters, small hypoplastic ganglion cells, decreased numbers of clusters that are widely spaced. There may be decreased numbers of nerves in the muscularis propria on AChE staining [44]. The mean density values of myenteric ganglion cells in childhood is:

jejunum 3.6/mm (TS), 3.7/mm (LS)
ileum 4.3/mm (TS, LS)
colon 7/mm (LS), 7.7/mm (TS)

Ganglion cell density values outside two standard deviations from normal correlate with continuing pseudo-obstructive symptoms [45].

Interpretation in these cases is often subjective and not evidence-based. It is difficult to find normal age-matched controls. Long standing neu-

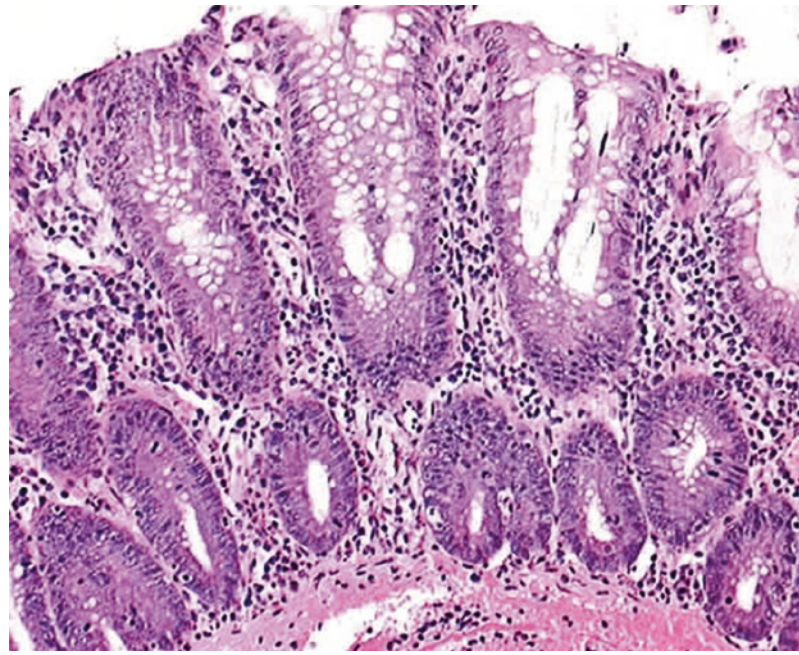

Fig. 5.26 Hirschsprung disease. Enterocolitis. A section from the resected colon shows mucosa with hyperplasia of the crypt epithelium and a diffuse inflammatory cell infiltrate in the lamina propria mucosae. There is also infiltration of the crypt epithelium by inflammatory cell. The histological picture resembles acute ulcerative colitis

ropathy may induce secondary myopathic change and it is consequently difficult to determine which is primary and which secondary process.

5.4.10 Megacystis Microcolon Intestinal Hypoperistalsis Syndrome

A rare, congenital and usually fatal condition of unknown etiology, presenting with abdominal distension, a distended, non-obstructed urinary bladder and intestinal hypoperistalsis resulting in functional intestinal obstruction.

Pathologically, the bowel may appear normal on routine H&E staining. However, connective tissue stains such as Picrosirius Red show that the collagenous fiber network of the muscularis propria is not well-formed [46]. There are vacuolar degenerative changes in the smooth muscle cells of the bladder [47]. There is markedly increased connective tissue between smooth muscle cells of the bladder on Masson Trichrome and van Gieson staining and reduced smooth muscle actin, desmin and dystrophin immunoreactivity in bladder smooth muscle. Electron microscopy shows vacuolar degenerative changes in smooth muscle cells and abundant connective tissue between these cells.

5.5 Necrotising Enterocolitis

Necrotizing enterocolitis is a common medical emergency, particularly in low birth weight infants. The pathogenesis is uncertain but associated risk factors include prematurity, birth weight and enteral feeding, especially milk formula. The pathophysiology is complex and unresolved but involves abnormal or immature gut motility and digestion with abnormal or mature circulatory regulation [48]. There is in addition, abnormal intestinal bacterial colonization, abnormal intestinal mucosal barrier function and abnormal intestinal immunity. About half of all cases require surgical intervention.

The disease can affect any part of the gastrointestinal tract but mainly involves the distal small intestine and right side of the colon. It shows patchy areas of wall thickening and dilatation leading to perforation (Fig. 5.27). There is coagulative necrosis affecting the partial-thickness or full-thickness bowel wall [49, 50]. Intestinal pneumatosis may be evident with representing intramural gas bubbles (Fig. 5.28). If there has been perforation, then acute peritonitis will be evident. There are frequently associated reparative changes with granulation tissue and fibrosis. The lesion heals by fibrosis which may lead to stricture or dysmotility. Healed cases may show features similar to other cases of healed ischemic gut damage, namely loss of muscularis mucosae in areas of previous ulceration, hemosiderin-laden macrophages in the submucosa (indicating previous hemorrhage at this site) or submucosal or muscular coat fibrosis (Fig. 5.29).

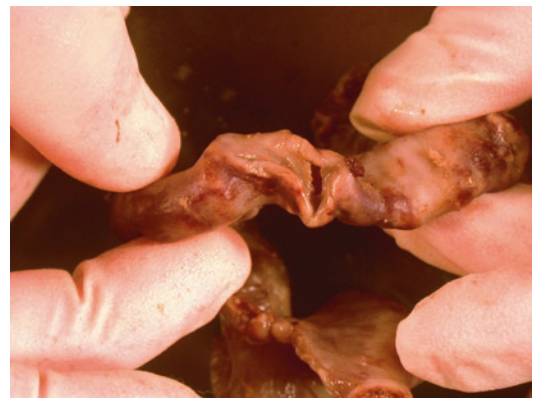

Fig. 5.27 Necrotising enterocolitis—bowel perforation. A seven-week old boy born at 31 weeks. Laparotomy and resection of 27 cm of ileum for perforated necrotising enterocolitis. There is extensive necrosis of the wall and the figure shows an area of perforation. Three such perforations were present in the specimen. The wall in the vicinity of the perforation is paper-thin. This patchy thinning is typical of NEC

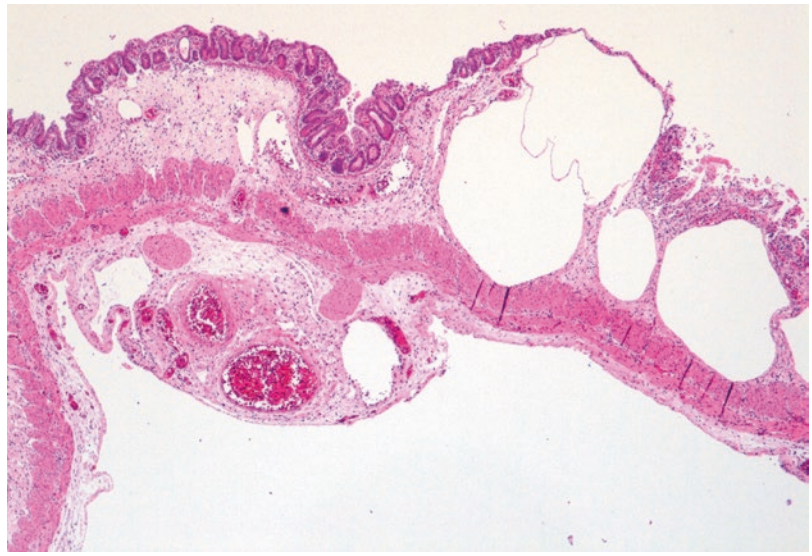

Fig. 5.28 Necrotising enterocolitis. A 28 day old premature female infant with necrotising enterocloitis. A 24 cm segment of ileum was removed. The bowel was pale and thin and appeared "bubbly". A low power H&E section of the affected area shows numerous gas cysts in the submucosa of the bowel, representing Intramural gas. There is ulceration to the right of the field and inflammation with mucosal villous blunting to the left

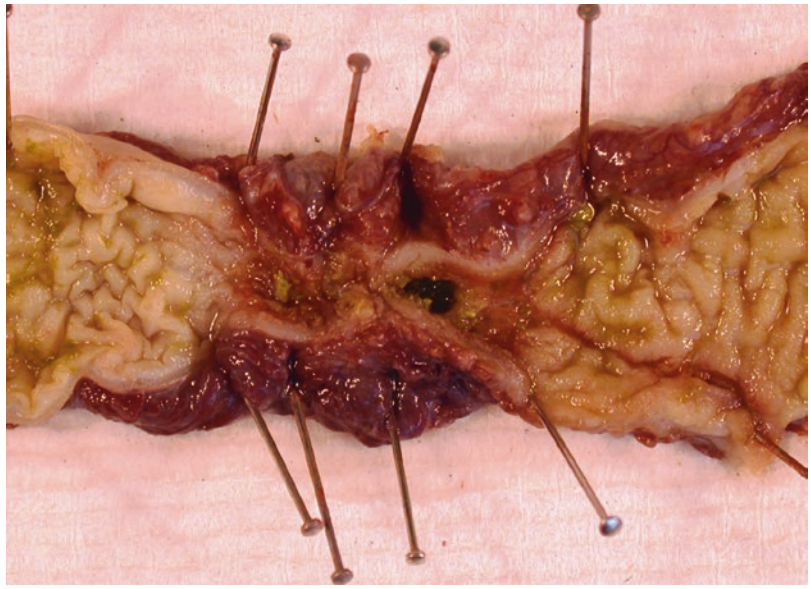

Fig. 5.29 Necrotising enterocolitis—bowel stricture. A 6-week old born prematurely and with intrauterine growth restriction. He developed necrotising enterocolitis that was medically treated, but never managed to establish feeds. He developed abdominal distension and contrast enema suggested right colon hold-up. A 7.5 cm long segment of ascending and transverse colon was resected. The image shows the opened specimen pinned out to permit fixation. There is a central stricture 2 cm long in which the mucosa is ulcerated and the luminal diameter is less than 0.1 cm. The mucosa of the bowel to the right of the stricture shows linear ulcers parallel to the axis of the bowel. Histologically the stricture showed replacement of the mucosa by granulation tissue and fibrous replacement of the muscle coat. Some calcified debris was present in the serosa suggesting possible previous perforation. These appearances are of an iscahemic stricture in keeping with previous necrotising enterocolitis

5.6 Biliary Atresia and Choledochal Cyst

Extrahepatic biliary atresia is characterized by total or segmental obliteration of the extrahepatic bile ducts. Liver biopsy is indicated for the diagnosis. The liver in extrahepatic biliary atresia shows cholestasis with plugging of the small bile ducts [51]. There is proliferation of small ductules at the edges of the portal tracts and there is progressive fibrosis of the "biliary" type. There may be associated giant cell hepatitis with a variable degree of chronic inflammatory cell infiltration in the portal tracts. There is absence or paucity of intralobular bile ducts [52] (Fig. 5.30).

Choledochal cyst is a localized cystic dilatation of the common bile duct. The dilatation may be fusiform or may be present as a diverticulum. There is frequent association with pancreatic or biliary anomalies [53]. The liver biopsy shows features similar to extrahepatic biliary atresia. The cyst wall shows thickening and fibrosis and inflammation with bile staining (Fig. 5.31). There may be dystrophic calcification. There is usually no epithelial lining [54].

5.7 Congenital Neck Cysts in Infants

The majority of such lesions are accounted for by thyroglossal duct cysts and branchial cleft cysts; thyroglossal duct cysts are about three times more common than branchial cleft cysts. Other congenital neck cysts that occur in children are dermoid cyst, cervical thymic cyst, bronchogenic cyst and cystic hygroma.

5.7.1 Thyroglossal Duct Cyst

In the fourth week of embryonic life the thyroid gland develops as an area of epithelial proliferation at the tip of the foramen caecum in the posterior tongue. It migrates inferiorly to its final site in the anterior neck by the seventh week. The thyroid gland remains connected to the foramen caecum by the thyroglossal duct which normally disappears by the end of the fifth week. Failure of involution of this structure gives rise to thyrolossal duct cysts anywhere along the original tract of the thyroglossal duct.

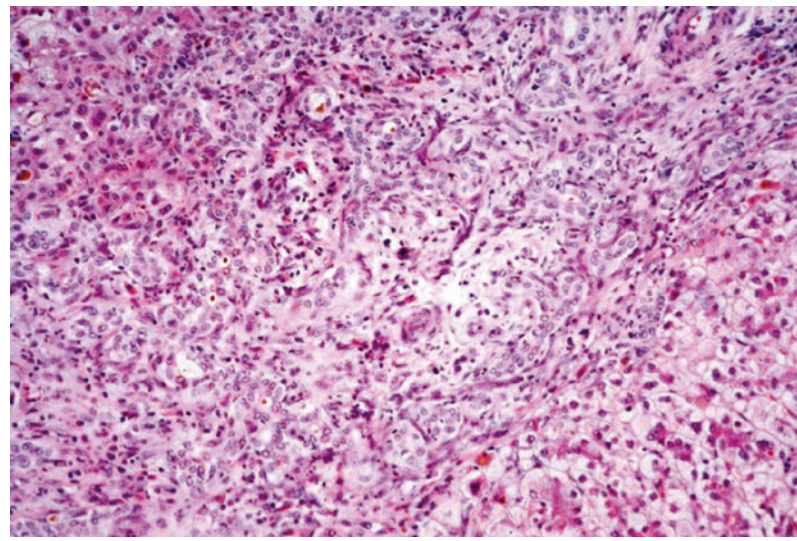

Fig. 5.30 Biopsy of liver from an infant with extrahepatic biliary atresia. The section is stained with H&E. The hepatocytes are swollen and there are bile plugs in canaliculi. A large portal tract at the centre of the field shows oedema and an indistinct demarcation from the surrounding liver. There is proliferation of bile ductules at the periphery of the portal tract

About one-quarter of cases of thyroglossal duct anomalies are sinuses rather than cysts [55]. Sinuses predominant in children and cysts in adults. The thyroglossal duct remnants are located in the midline anywhere between the base of the tongue and the pyramidal lobe of the thyroid gland. Most commonly they are located at the level of, or just, below the hyoid bone. Because of the attachment to hyoid bone, the cysts rise on swallowing or on protrusion of the tongue. They manifest during childhood as asymptomatic neck masses, most commonly before the age of 5 years. The cysts are lined by pseudostratified columnar epithelium in 60% cases and squamous epithelium in 40% (Fig. 5.32). It is important to emphasize that only about 20% have associated, recognizable thyroid tissue (Fig. 5.33). Epithelial tissue is commonly found within the hyoid bone or its periosteum (Fig. 5.34). A sinus may form to the skin surface.

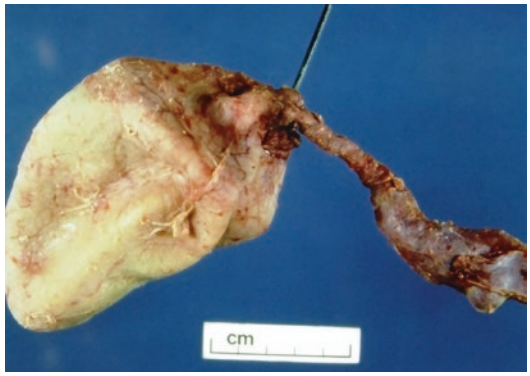

Fig. 5.31 Choledochal cyst. The excised cyst of the bile duct shows a fusiform unilocular swelling up to 12 cm in maximum diameter. The wall was composed largely of fibrous tissue with a haemorrhagic lining

5.7.2 Branchial Cleft Cysts

By the fourth week of embryonic life there are four well developed (and another two rudimentary) pairs of ridges in the cervical area of the embryo; these are termed the branchial arches. Externally the troughs separating the arches are termed clefts and internally (on the endodermal

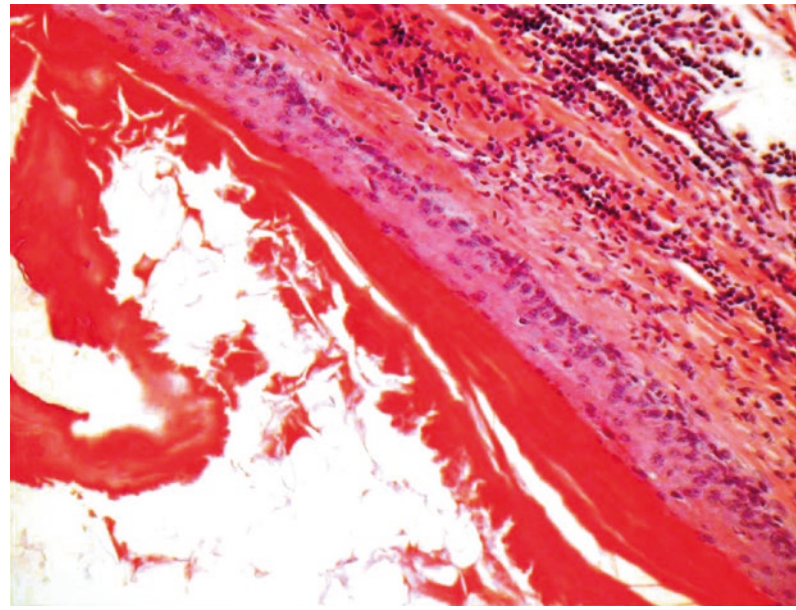

Fig. 5.32 Thyroglossal cyst. A high power view of an H&E stained section of the wall of a thyroglossal cyst. The lining is of keratinising stratified squamous epithelium. The lumen contains keratin, the wall is fibrous and shows a chronic inflammatory cell infiltrate

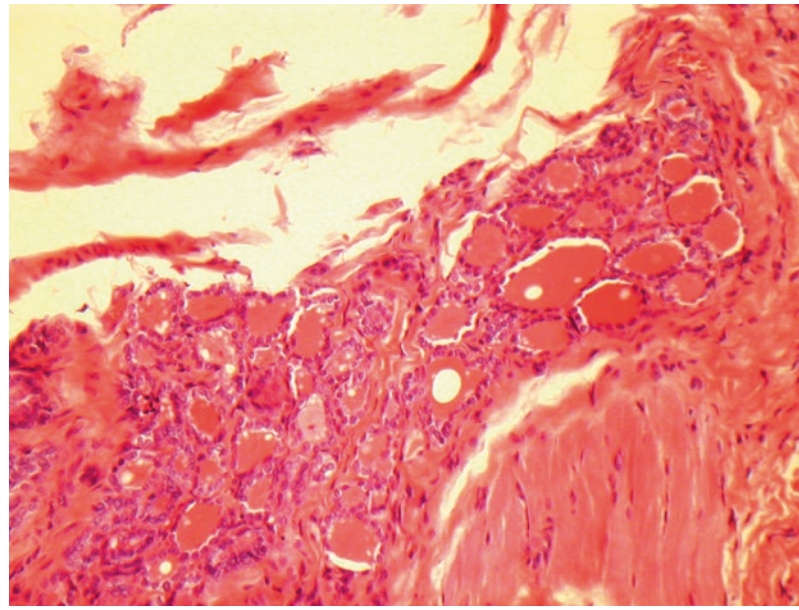

Fig. 5.33 Thyroglossal cyst. An H&E stained section from the wall of a thyroglossal cyst. It shows a collection thyroid follicles identified by heir characteristic content of eosinophilc colloid. Thyroid tissue is identified in only approximately half the case of thyroglossal cyst

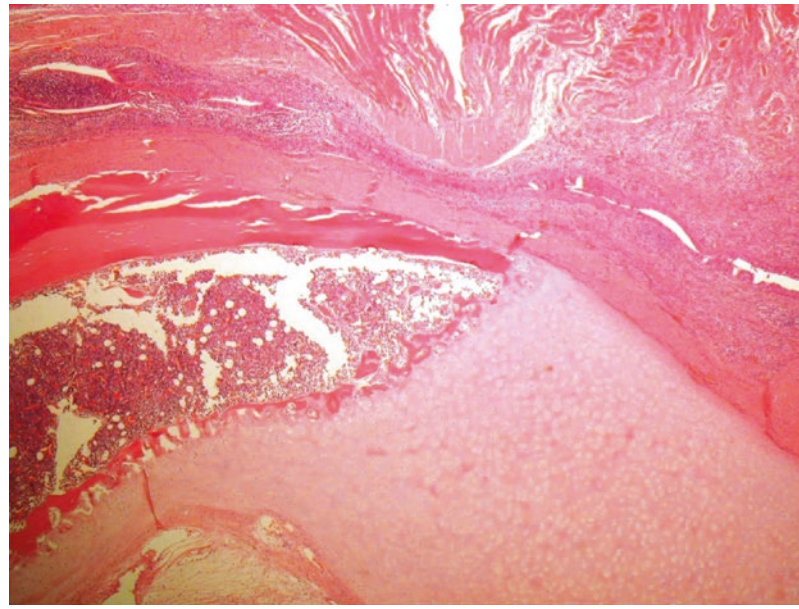

Fig. 5.34 Thyroglossal cyst. A section of the hyoid bone removed with the cyst. The cartilage and the bone are visible and abutting the perisoteum of the bone (in the upper part of the field) is part of the sinus tract. The tract is lined by upper respiratory type of epithelium and shows a lymphocytic infiltrate in its wall. This emphasises the intimate relation of the tract to the bone

surface) the separating depressions are termed pouches. Branchial anomalies are the remnants of the branchial arches and their associated clefts that fail either to regress or to develop normally. Branchial cleft lesions present as either a cyst in the lateral aspect of the neck or as a sinus draining the lower part of the lateral neck. It is the internal opening of the sinus that determines the cleft or pouch of origin. Internally, the first arch derivatives are connected to the external auditory meatus or the middle ear. Second arch anomalies connect internally to the tonsil or supratonsillar area and third and fourth arch derivatives open internally into the pyriform fossa [56].

Lesions derived from the second branchial cleft account for about 95% of all cases; those

derived from the first cleft make up about 1% and the remainder are very rare. Derivatives of the third and fourth arches are almost always left-sided. First cleft anomalies present as a cyst, sinus or fistula opening on the skin between the external auditory meatus and the suprahyoid submandibular area. They are intimately associated with the parotid gland and the branches of the facial nerve. They must be differentiated from preauricular sinuses which are lined only by squamous epithelium and do not communicate with the ear [57].

Second cleft anomalies present as either a fistula or cyst opening along the anterior border of the sternocleidomastoid muscle. Fistulae are commoner than cysts in children. The skin opening is occasionally marked by skin tags or small nodules of cartilage (Fig. 5.35). About 10% of second cleft cysts are bilateral. They are lined by respiratory and squamous epithelium, either alone or in combination. The cysts more frequently show a squamous lining while sinuses and fistulae have a respiratory epithelial type of lining. Other tissues are present in the wall such as lymphoid tissue, sebaceous glands or salivary tissue. The fluid within the cysts contains cholesterol clefts. About one in five lesions has become infected by the time of surgical excision. The

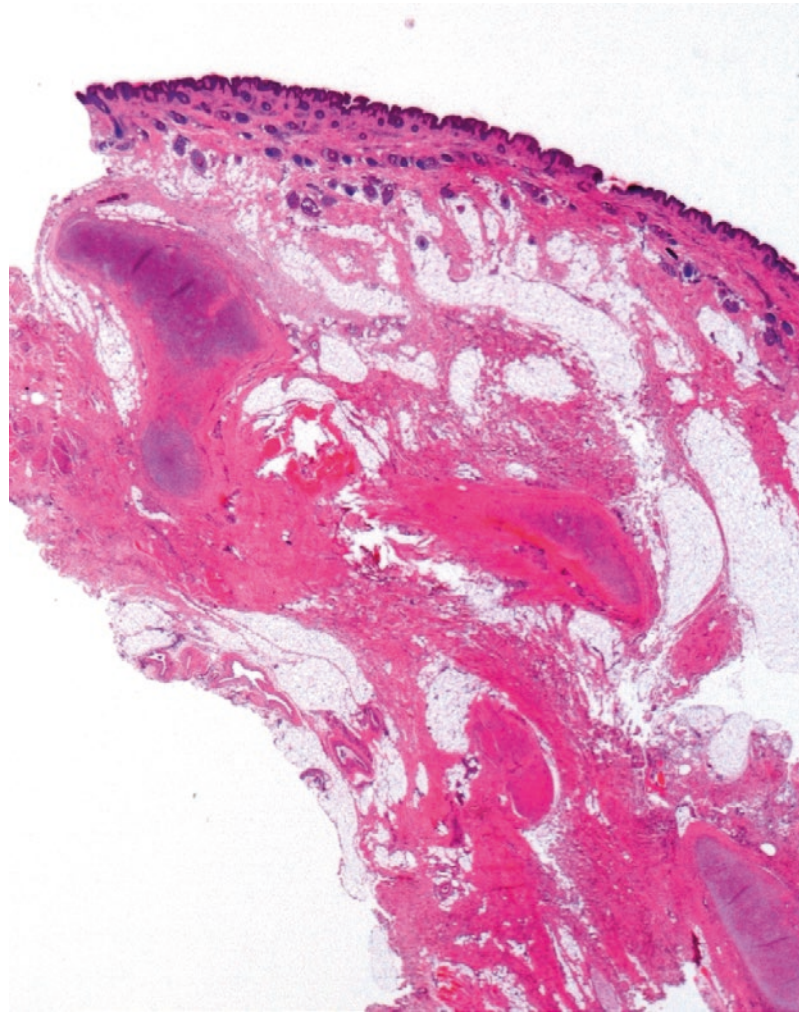

Fig. 5.35 Branchial cleft sinus—A 1 year old boy with a left neck sinus and preauricualr tag. An H&E stained section of the tag shows three plates of elastic cartilage in the subcutaneous tissue

treatment of choice is surgical excision. Incomplete excision results in a high rate of recurrence.

5.7.3 Dermoid Cyst

These account for about 25% of midline cervical anomalies. There are subcutaneous in location and do not move on swallowing or protrusion of the tongue [58]. The cysts, like all dermoid cysts have a lining of keratinizing stratified squamous epithelium and epidermal appendages are present in the wall (Fig. 5.36). The lining may be ulcerated and show a foreign body granulomatous reaction to the keratin contents.

5.7.4 Bronchogenic Cyst

Primarily a lesion of the chest, bronchogenic cyst may occasionally be found in close association with the cervical trachea in the lower neck [59]. It usually indents the trachea and presents with stridor [60]. It is not connected to the tracheal lumen. The cyst is a unilocular, thin-walled paratracheal cyst with a lining of upper respiratory type of epithelium with smooth muscle and sometimes hyaline cartilage (Fig. 5.3).

5.7.5 Cervical Thymic Cyst

They usually present after the age of 2 years, but may present in neonates [61]. They may be found anywhere along the normal descent route of the thymus gland from the mandible to the sternal notch; about half extend into the mediastinum [62]. Most patients are asymptomatic, although respiratory complications may occur. Preoperative recognition is unusual and the diagnosis almost always depends on histology. Histological investigation of the excised specimen shows thymic tissue remnants with Hassall's corpuscles (Fig. 5.37), and cholesterol clefts in the cyst wall [63]. Intact, complete surgical excision remains the treatment of choice.

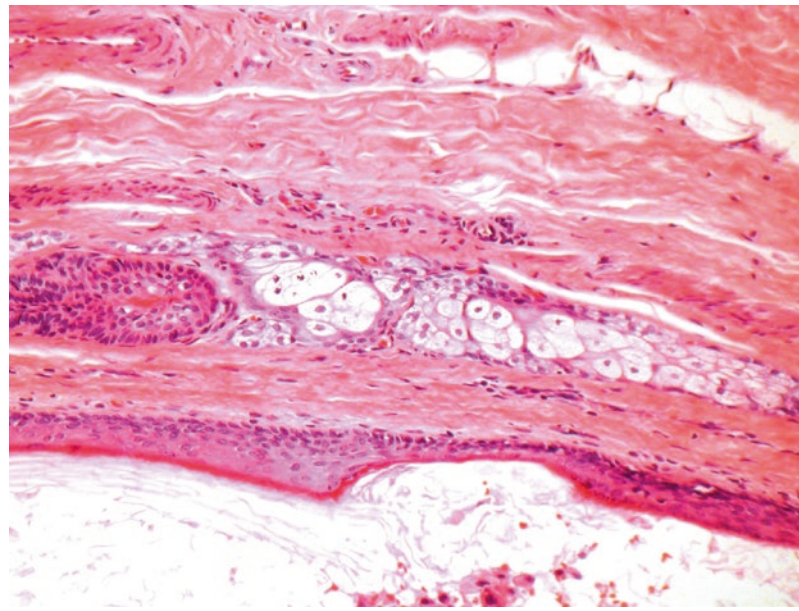

Fig. 5.36 Dermoid cyst. An H&E stained section of the wall of a dermoid cyst showing the characteristic lining of keratinising stratified squamous epithelium with a hair follicle and sebaceous glands in the fibrous wall. Keratin debris fills the cyst lumen in the lower part of the image

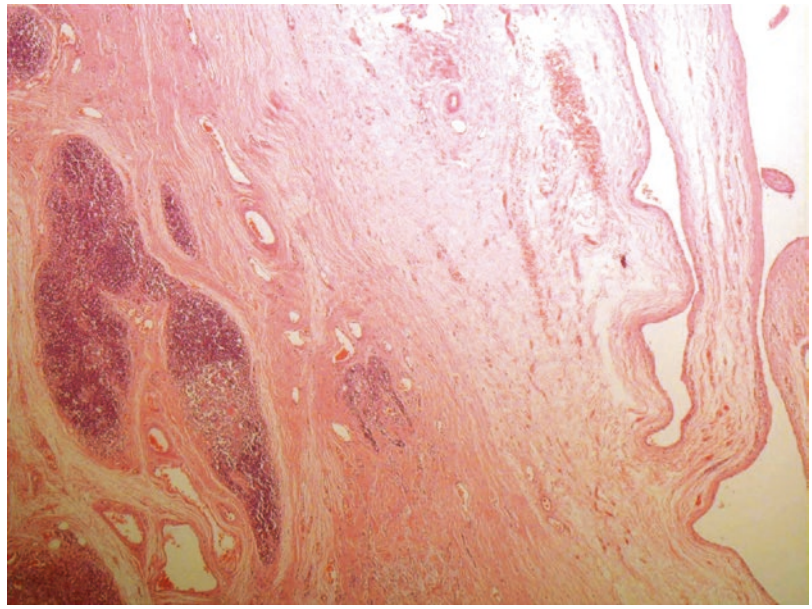

Fig. 5.37 Thymic cyst. An H&E stained section from the wall of a thymic cyst. The lumen is to the left of the picture and the lining is of non-keratinising stratified squamous epithelium. To the right of the field is an area of rather atrophic thymic tissue, composed of lymphocytes and Hassall's corpuscles

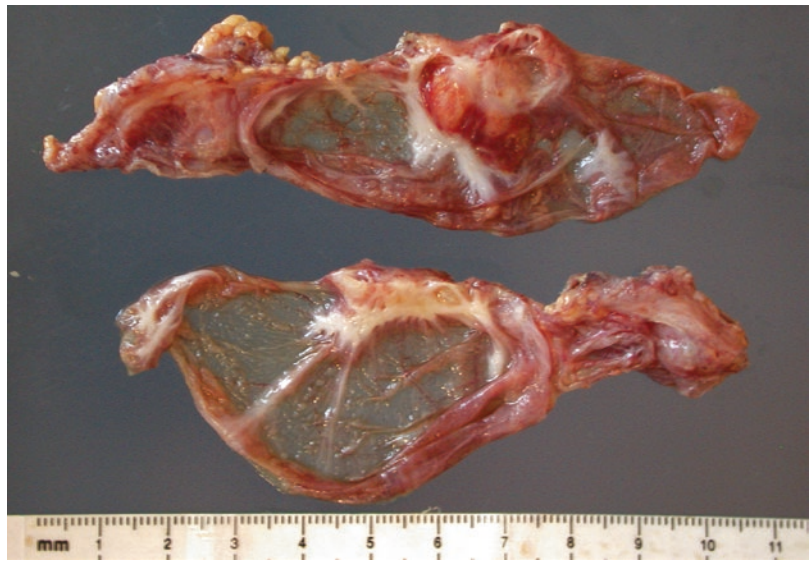

Fig. 5.38 Cystic hygroma. A 3-month old male with a cystic anterior neck mass. A multiloculated cystic mass 7 × 4.5 × 3 cm was resected. The cut surface of the specimen shows the multiple locules of variable size, some with near-transparent walls. Focal fibrous trabeculae are evident in the lining. Histologically the tissue showed multiple cystic spaces with small nodules of lymphocytes in the wall. The features are typical of lymphangioma\cystic hygroma

5.8 Cystic Hygroma

These are malformations of the lymphatic system in the neck [64]. Most present before the age of 2 years, the majority in the first year of life. More than three-quarters are situated in the posterior triangle of the neck. Histologically, they are composed of ectatic lymphatic vessels (Fig. 5.38) and contain small nodules of lymphoid tissue [65].

5.9 Neonatal Lung Pathology

5.9.1 Congenital Lung Cysts

The nomenclature of this group of lesions is confusing [66]; there is overlap of the various entities and similar lesions have been given different names, whereas different lesions have been labelled the same. Many cases are now detected antenatally by ultrasound scanning and followed up [67], permitting assessment of their development. There is disagreement among authorities about the detail and origins of these lesions. It is increasingly becoming apparent that narrowing or obliteration of the bronchial lumen is a common factor in many of them [68].

5.9.1.1 Congenital Pulmonary Airway Malformation

Stocker has provided a near-universally used classification of cystic lung malformations. He originally distinguished cystic lung lesions that he called Congenital Cystic Adenomatoid Malformation (CCAM) types I, II and III [69]. The term CCAM is still in common usage. In 2002, he expanded the original three types to five, termed 0–4 and renamed the entities Cystic Pulmonary Airway Malformation (CPAM) because not all lesions are cystic and with the exception of type 3 they are not adenomatoid [70]. The 2002 classification is based on the putative segment of the bronchial tree that is primarily affected, extending from proximal to distal. Type 0 is said to originate from the trachea\bronchi, while type 4 is said to originate from the pulmonary acinus.

This sometimes causes problems in trying to assign a particular lesion to one or other of these categories particularly in the more immature lung [71]. Type 4 CPAM is claimed by some to be a cystic form of pleuropulmonary blastoma [72].

Type 0 (Acinar Dysplasia)

This lesion is very rare and results in bilateral small firm granular lungs with solid parenchyma (Fig. 5.39) and numerous small spaces less than 0.1 mm diameter. Histologically (Fig. 5.40), the tissue consists of Irregular bronchus-like structure lined by pseudostratified, columnar epithelium, many surrounded by cartilage or smooth muscle. There is prominent, loose mesenchyme containing thin vessels, extramedullary haematopoiesis and basophilic debris. There may be associated cardiovascular abnormalities, renal hypoplasia or dermal hypoplasia. Affected infants usually die shortly after birth.

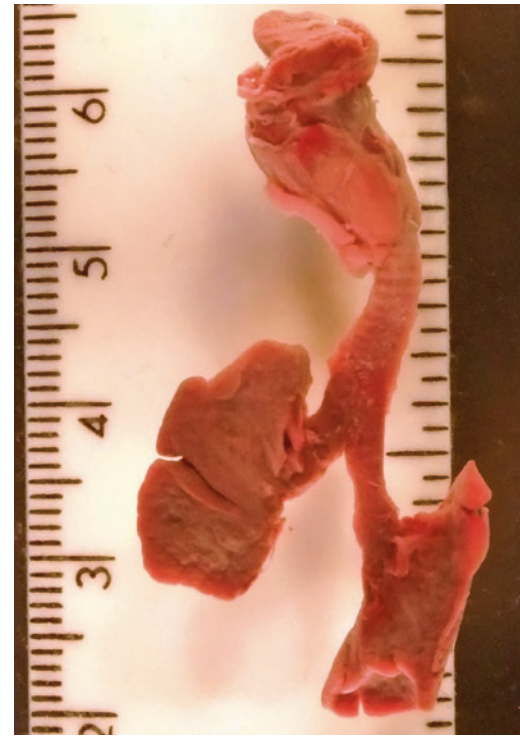

Fig. 5.39 Congenital acinar dysplasia (CPAM 0). Lungs from a fetus of 22 weeks' gestation with intrauterine growth restriction and fetal hydrops. The lungs are minute. The combined weight was 0.67 g (expected at 22 weeks' gestation is 11 g)

Type 1 (Large Cyst Type)

This accounts for the majority of cases. It may present in utero or postnatally with increasing respiratory distress in the first few days of life. Cysts are limited usually to one lobe with only rare bilateral involvement. The cysts measure 1–10 cm in diameter (Fig. 5.41) and intercommunicate. They are lined by ciliated, pseudostratified columnar epithelium with walls of fibromuscular tissue and cartilage. About half of all cases show small foci of mucinous epithelial cells (Fig. 5.42) in the cyst lining.

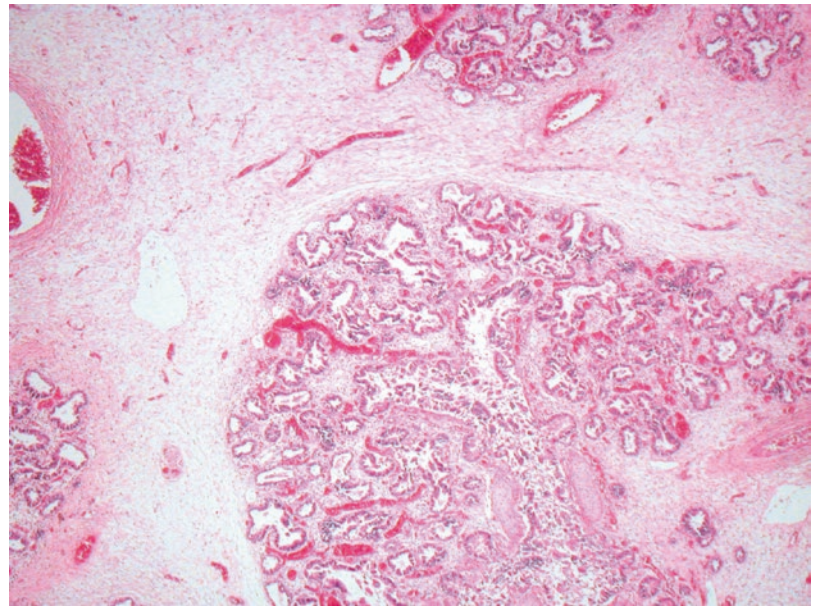

Fig. 5.40 Congenital acinar dysplasia (CPAM 0). Thirteen-day old female with congenital acinar dysplasia. There is oedematous stroma that contains proliferated bronchi, but no more distal differentiation of the lung tissue

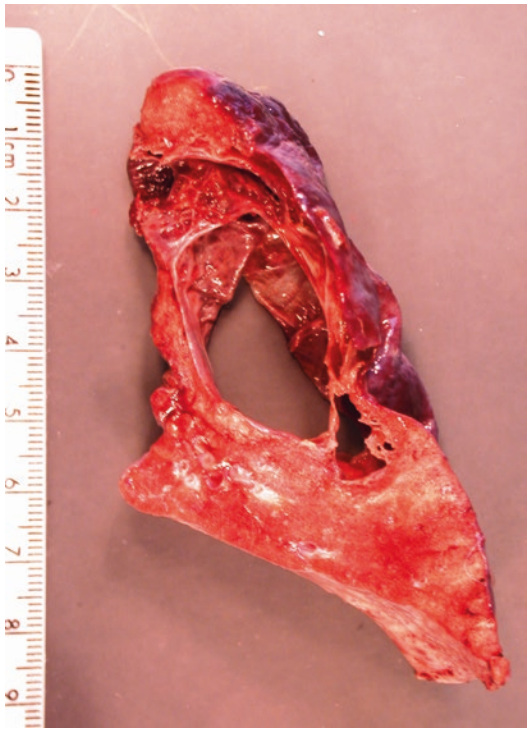

Fig. 5.41 Congenital pulmonary airway malformation Type 1 (CPAM 1). Six-month old boy. With a cyst in the lower lobe of the right lung. The specimen shows the cut surface of the excised right lower lobe. There is a unilocular cyst 5 cm in maximum dimension with a trabeculated lining. The cyst cavity communicated with the surrounding air spaces. Type 1 CPAM may show smaller subordinate cysts in the surrounding lung

Type 2 (Small Cyst Type)

Presents in first weeks of life and is the subtype most commonly associated with other congenital abnormalities. It comprises multiple small cysts (0.5–1.5 cm) (Fig. 5.43) that have back to back dilated bronchiole-like structures with reduction in alveolar structures in between (Fig. 5.44). The intervening parenchyma shows alveolar duct like structures. A subset contains striated muscle in the stroma (rhabdomyomatous dysplasia).

Type 3 (Adenomatoid Type)

This subtype occurs almost exclusively males and is associated with maternal polyhydramnios. It involves an entire lobe or the entire lung and is frequently a bulky mass with mediastinal shift (Fig. 5.45). Grossly, the lesion is firm and bulky and may have small cysts. These have branched bronchiolar or alveolar duct-like structures and are lined by low cuboidal epithelium (Fig. 5.46). There is a virtual absence of larger pulmonary arteries.

Type 4

This subtype present with respiratory distress or tension pneumothorax, and usually affects one lobe. There are large air filled cysts with displacement. The cysts have a flattened epithelial lining. This lesion is controversial [73] and is regarded by some as a type-1 pleuropulmonary blastoma.

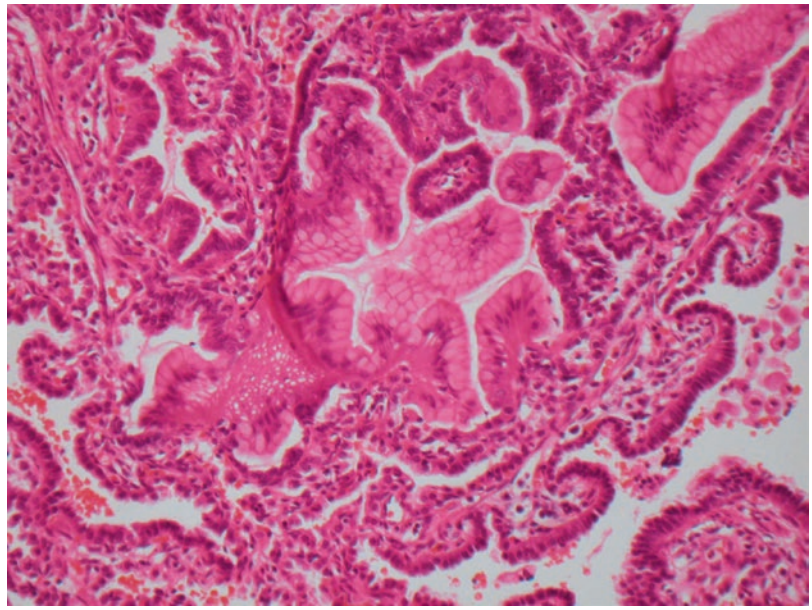

Fig. 5.42 Congenital pulmonary airway malformation Type 1 (CPAM 1). Photomicrograph of the lining of a CPAM type 1. The cuboidal lining typical of this cyst is seen. In addition there are areas of pale, mucin-secreting epithelium, characteristic of Type 1 CPAM

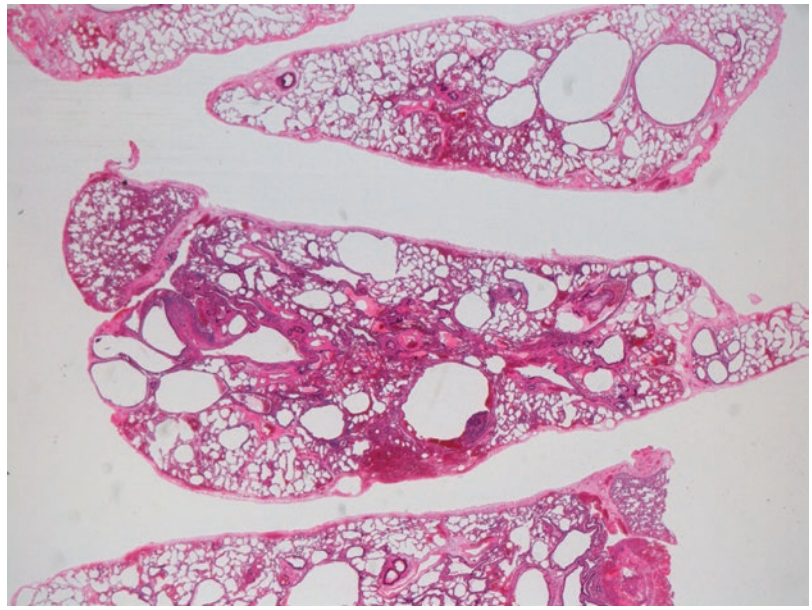

Fig. 5.43 Congenital pulmonary airway malformation Type 2 (CPAM 2). Male with antenatally detected cystic mass in the right middle lobe, removed when aged 5 months. A whole mount section shows that most of the lobe is replaced by multiple small rounded cysts with some intervening normal parenchyma

5.9.1.2 Bronchial Atresia

Can occur at any level from lobar to subsegmental bronchus. There may be a mucocoele at the level of obstruction [66] with an obliterated bronchial lumen. There is dilatation of the distal parenchyma with accumulation of mucus and macrophages in the air spaces. It is becoming increasingly evident that some form of bronchial atresia is present in association with sequestration, congenital pulmonary airway malformation (Fig. 5.47) and lobar emphysema [68].

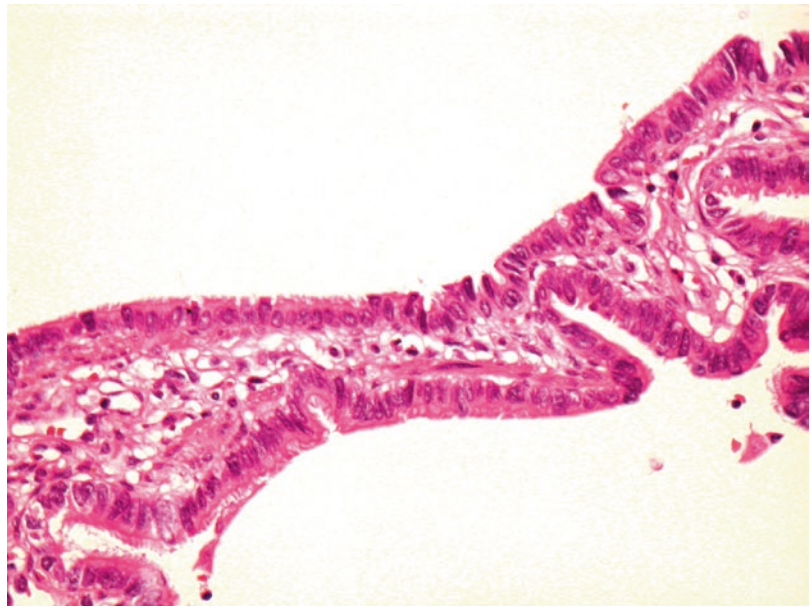

Fig. 5.44 Congenital pulmonary airway malformation Type 2 (CPAM 2). A photomicrograph of a septum separating two cysts. The cysts have a back-to-back arrangement and are lined by bronchiolar type epithelium. Sometimes in type 2 CPAM striated muscle cells are identifiable in the stroma—so-called rhabdomyomatous dysplasia

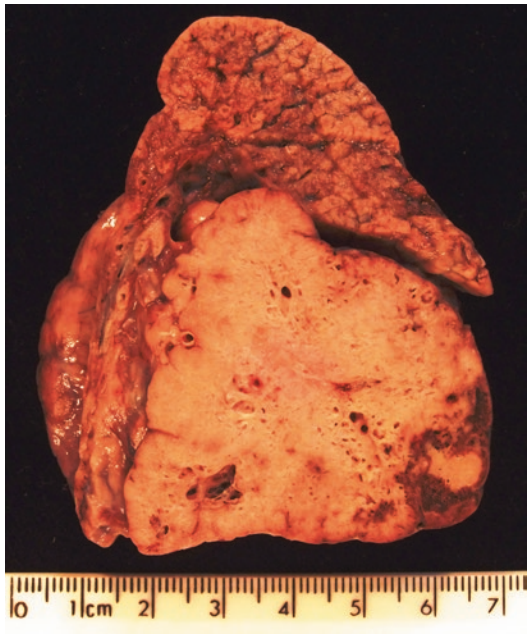

Fig. 5.45 Congenital pulmonary airway malformation Type 3 (CPAM 3). Two week old female infant with an antenatal diagnosis of right cystic lung mass. There was associated polyhydramnios and hydrops. The right lung shows the lower lobe replaced by a solid mass 8 cm in maximum dimension with a few scattered cysts

5.9.1.3 Pulmonary Sequestration

Pulmonary sequestration refers to lung tissue that lacks a connection to the bronchial tree. Generally there is an anomalous systemic arterial supply [74] (Fig. 5.48). The sequestered segment of lung may be within the lung, where it is termed intralobar sequestration, or outside the lung or even outside the thorax, the lesion then being termed extralobar sequestration. Very rarely, there is a connection to the gastrointestinal tract (usually esophagus) this lesion then being termed a "bronchopulmonary foregut malformation" [75].

Extralobar sequestration usually presents in the first year of life and occurs more commonly in boys. Two-thirds of cases are situated on the left side of the body (thorax, retroperitoneum or even pericardium) and there is a frequently association with diaphragmatic defects. The retroperitoneal examples may be mistaken for tumor e.g. neuroblastoma. Histologically extralobar sequestration is a pyramidal airless mass with a systemic arterial supply, venous drainage to the pulmonary veins, systemic veins or portal veins. It is composed of lung parenchyma, usually covered by pleura. The lung parenchyma shows sec-

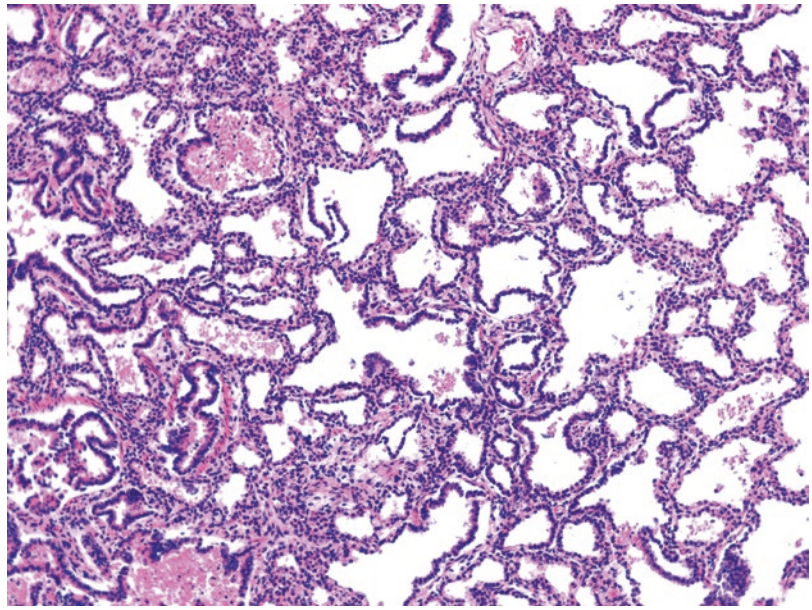

Fig. 5.46 Congenital pulmonary airway malformation Type 3 (CPAM 3). Photomicrograph of the lesion in Fig. 5.45. It is composed of distended air spaces lined by cuboidal epithelium with no normal lung parenchyma

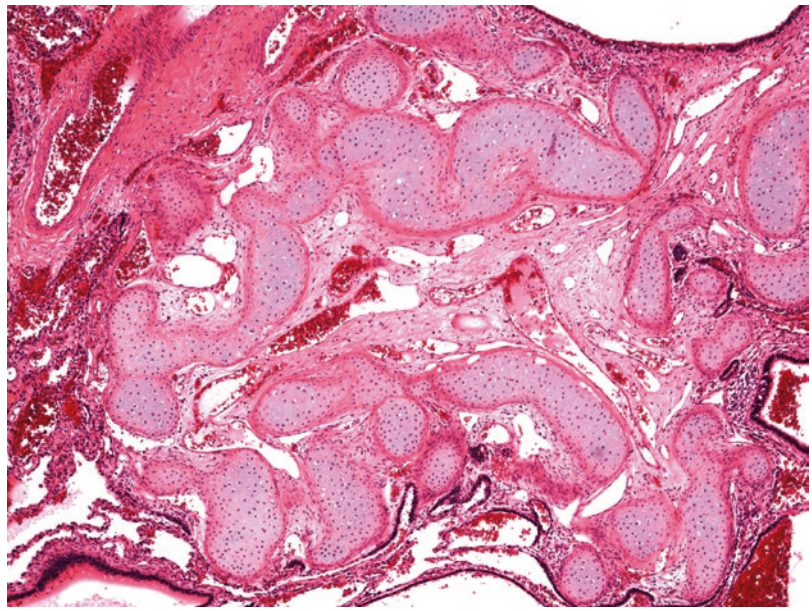

Fig. 5.47 Bronchial atresia. Photomicrograph of a section taken from close to the resection margin of a type 2 CPAM of the right middle lobe in a 6-month old boy. There is a garland of irregular cartilage plates around a fibrovascular core. The appearances suggest occlusion of the lumen of a bronchus

ondary inflammatory changes with secondary lymphangiectasia and may also show features indistinguishable from CPAM [76].

Intralobar sequestration frequently does not present until adult life although antenatal presentation is recorded. It shows no sex preference and affects both sides equally. The lower lobes are most frequently affected. It is situated within the pleural investment of the lung, lacks a demonstrable bronchial connection but contains air. It has a

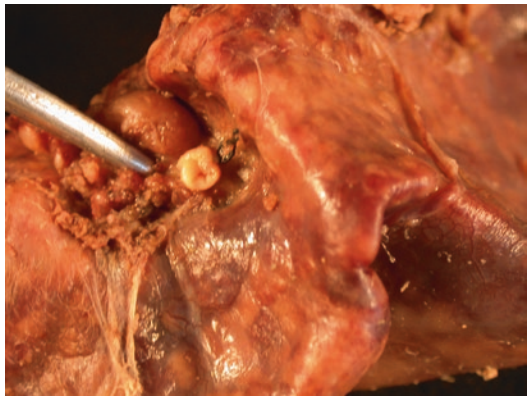

Fig. 5.48 A 7-week old boy with multiple congenital anomalies, including gastroschisis, bladder exstrophy and asplenia, and a left intralobar sequestration causing high-output cardiac failure. Left thoracotomy with excision of the sequestration. The excised specimen shows a large systemic artery entering the lung through the pleural surface well away from the lung hilum

systemic arterial supply (Fig. 5.49) with venous drainage to the pulmonary veins. It frequently shows such secondary changes as, fibrosis and inflammation and may show changes indistinguishable from CPAM. The pulmonary arteries in the sequestered segment may show evidence of pulmonary arterial hypertension [77].

Dr. Langston [66] has proposed an overarching classification of all cystic lung lesions.

5.9.1.4 Congenital Lobar Overinflation

This a more accurate term than the previous designation of congenital lobar emphysema. There is overinflation of a lobe of lung, usually middle or upper lobe, with compression of the surrounding normal lung [78]. It may demonstrate partial bronchial obstruction, but more frequently no anatomical cause can be found for the overdistension. The surgically excised lobe is filled with air and does not collapse after removal. Microscopically, the cut surface shows distended air spaces that may appear normal. Only when compared with an age-matched control lung section is the distended nature of the alveoli apparent (Fig. 5.50).

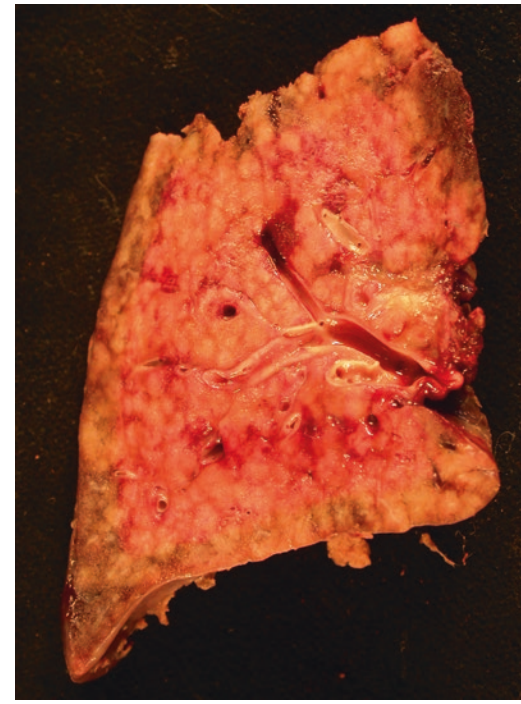

Fig. 5.49 Intralobar sequestration. Same case as Fig. 5.48. The cut surface shows the systemic artery affording the blood supply to the sequestered segment. No connection to the bronchial tree was demonstrated

5.9.1.5 Interstitial Emphysema

This refers to dissection of gas from the respiratory tree into the interstitium of the pleura, interlobular septa and bronchovascular bundles. It is frequently associated with pneumothorax and is usually associated with mechanical ventilation in neonates [79]. A localized form may cause respiratory embarrassment or may mimic CPAM [80] or congenital lobar overinflation. It usually does not require lung resection [81] but may be present in lung removed for other reasons.

It consists of irregular spaces in the lung interstitium around the bronchovascular bundles, veins and pleura that may be cystically enlarged. The lymphatics may be involved. It may be of such severity that bronchovascular bundles apparently 'hang' within clear spaces (Fig. 5.51). It may be confused with lymphangiectasia mor-

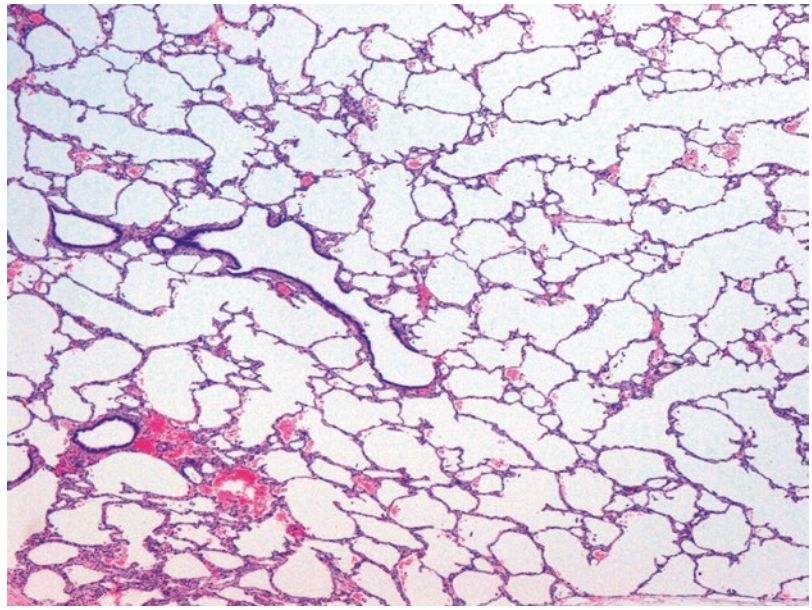

Fig. 5.50 Congenital lobar emphysema (overdistension). A 20 day old male infant who required resection of the right middle and lower lobe. The lung was bulky but without focal abnormality. A photomicrograph shows what appears to be normal lung. The airspaces are, however, distended when compared with a normal lung

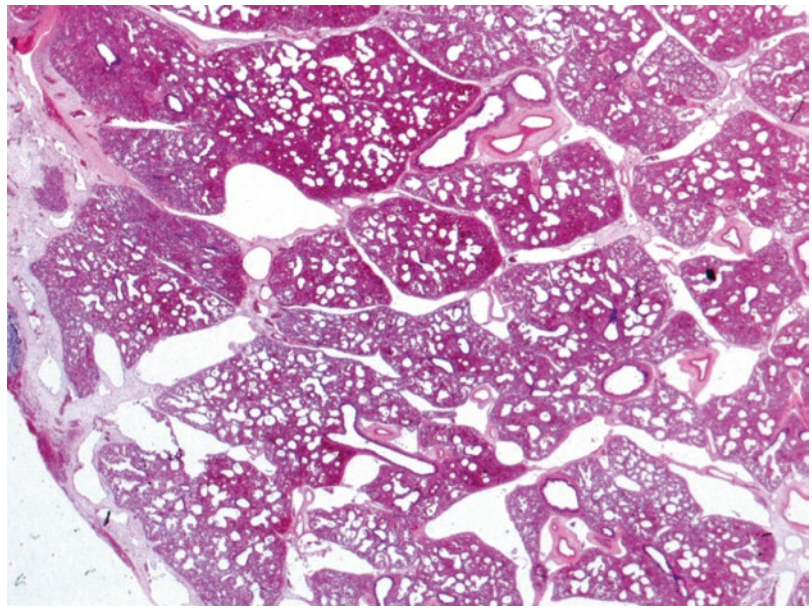

Fig. 5.51 Pulmonary interstitial emphysema. A 1 month old female infant with congenital heart disease, sepsis and multi-organ failure who spent her short life in intensive care and on artificial ventilation. The lung shows extensive pulmonary haemorrhage. In addition, there are large clear spaces in the interlobular septa and around bronchovascular bundles that represent interstitial air—pulmonary interstitial emphysema

phologically. If persistent, a surrounding florid foreign-body giant cell reaction occurs.

5.9.2 Alveolar Capillary Dysplasia

This is one of the commonest indications for neonatal lung biopsy and the condition at present can only be diagnosed on biopsy. The child may have other congenital defects such as congenital heart disease or bowel malformations [82], but from the respiratory point of view, is usually normal at birth. The child develops respiratory difficulty in the subsequent days. Typically, there is extreme difficulty in oxygenation despite ease of ventilation. Death is almost invariable. Familial cases are described. Causative mutations in the FOX F1 gene on chromosome 16q have been described

in cases with associated malformations [83], raising the possibility that in future the condition may be diagnosed on gene testing.

On biopsy, there are two main components:

- Misalignment of pulmonary veins. This can be detected on frozen section. Thin-walled veins run in the same fibrous tissue sheath as the arteries and bronchi (Fig. 5.52). The veins are of a comparable diameter to the arteries they accompany. They should not be mistake for dilated lymphatics that are a common feature of many pulmonary disorders.
- Greatly thickened alveolar septa that contain large numbers of capillary blood vessels not in contact with the overlying alveolar epithelium (Fig. 5.53). If in doubt cytokeratin and CD31

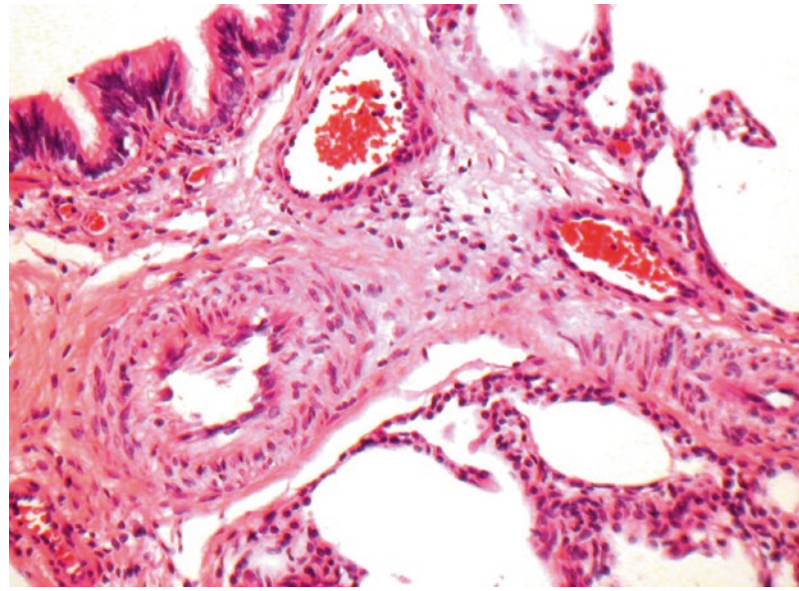

Fig. 5.52 Congenital alveolar capillary dysplasia. Open lung biopsy from a 19-day old female infant with respiratory failure. There is misalignment of the pulmonary veins. A thick-walled intra-acinar artery is present in the centre of the picture and accompanies a bronchiole whose epithelial lining is visible at the top of the field. In addition, two vein branches (filled with blood) accompany the artery. This is abnormal and should prompt a search for alveolar capillary dysplasia

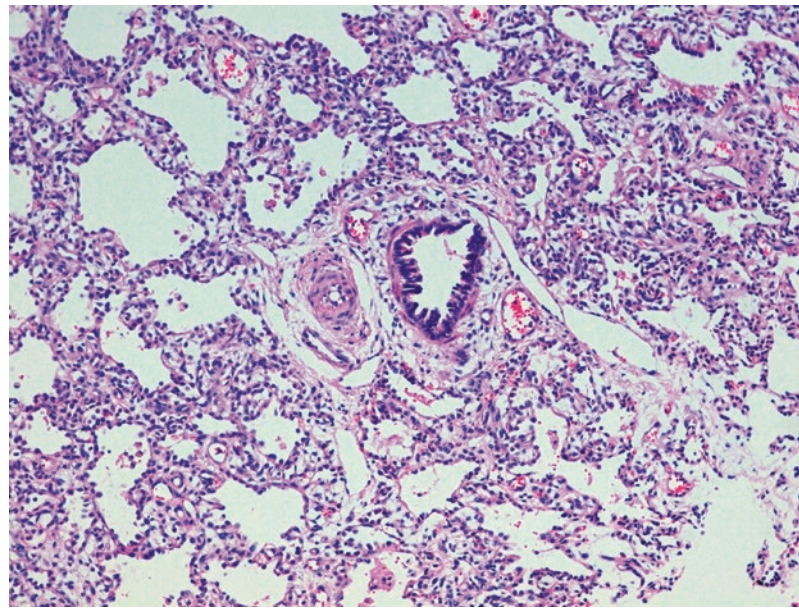

Fig. 5.53 Congenital alveolar capillary dysplasia. A 9-day old male infant with pulmonary hypertension. The section shows lung with misalignment of the pulmonary veins—the vein accompanies the artery and bronchus. In addition, there is thickening of the alveolar septa, and the small alveolar capillaries sit, not immediately beneath the alveolar epithelium, but rather in the centre of the thickened septa—so-called alveolar capillary dysplasia

staining highlights the epithelial and vascular components.

There is pulmonary arterial hypertension with medial hypertrophy in the muscular pulmonary arteries and muscularization of the arterioles.

5.10 Genito-urinary Abnormalities

5.10.1 Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease characteristically presents in the neonatal period or, indeed, antenatally [84]. There is bilateral enlargement of the kidneys by cysts associated with congenital hepatic fibrosis. [85, 86]. There is bilateral massive renal enlargement (Fig. 5.54). There may be severe pulmonary hypoplasia. Histologically there is replacement of the normal renal structure by fusiform cysts extending from the cortex to medulla displayed in radial fashion with preservation of the overall shape of the kidney (Fig. 5.55). The liver shows ductal plate malformation with fibrosis (Fig. 5.56). There may be occasional small glomerular cysts [87], although these are not a prominent feature.

5.10.2 Nephronophthisis

Nephronophthisis is an autosomal recessive condition due to abnormality in the urine concentrating capacity that progresses to end-stage renal failure [88]. An infantile form occurs. Histologically it is characterized by dilated tubules and collecting ducts with the formation of cysts (Fig. 5.57). There is chronic inflammatory change in the interstitium. There may be secondary glomerulosclerosis but glomerular cysts are not prominent.

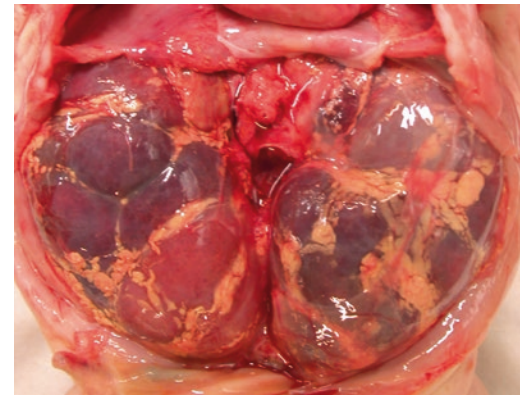

Fig. 5.54 Autosomal recessive polycystic kidney disease. A term infant who died aged 1-day. Renal cystic disease was diagnosed antenatally and there was associated oligohydramnios. The infant died of pulmonary hypoplasia. This is a photograph from the post-mortem showing massive enlargement of both kidneys. The kidneys retain their shape but occupy the entire posterior abdominal wall from diaphragm to pelvis

5.10.3 Renal Dysplasia

Renal dysplasia is a developmental abnormality are also associated with reflux in the ureters or lower urinary tract. [89, 90]. Histologically, the kidneys are small and scarred with numerous immature cysts surrounded by cuffs of immature mesenchyme (Fig. 5.58). There may be metaplastic cartilage in the stroma, a useful histological future (Fig. 5.59). There is often extramedullary hemopoiesis the abnormality may be focal, segmental or affect the whole kidney sometimes associated with hydronephrosis.

5.10.4 Reflux Nephropathy

Reflux nephropathy, is due to vesico-ureteric reflux shows a combination of fibrosis, interstitial inflammation, tubular atrophy and loss of the glomeruli (Fig. 5.60). In utero the features may overlap with those of renal dysplasia. The ureter is usually thick walled.

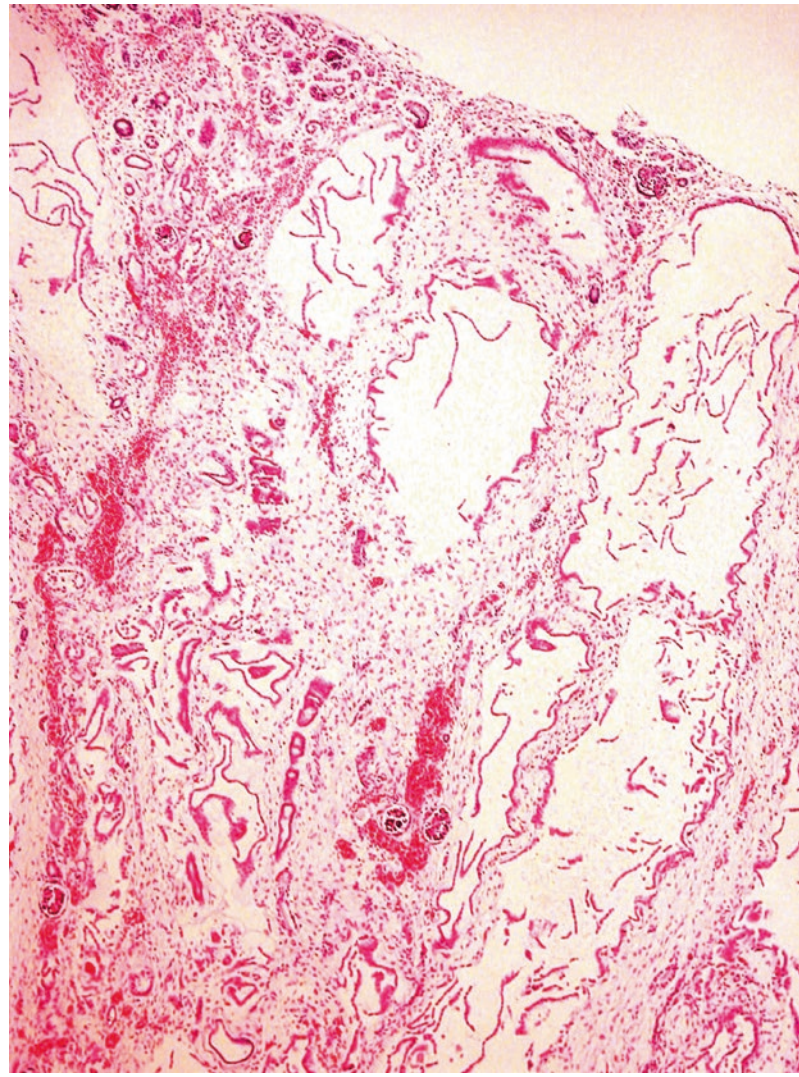

Fig. 5.55 Autosomal recessive polycystic kidney disease. Same case as Fig. 5.54. A histological section of one of the kidneys. The cortex is uppermost, covered by renal capsule. There is post-mortem autolysis. Nevertheless, multiple cystically dilated renal tubules are visible running perpendicular to the capsule. There is focal sloughing of their epithelial lining. The stroma is oedematous with focal haemorrhage. A few glomeruli are visible. The appearance is typical of ARPKD

5.10.5 Testicular Torsion

Testicular torsion is well reported infancy [91] and many cases may represent torsion of the testicular appendage rather the testis itself. If the testis is affected there is congestion and edema and interstitial hemorrhage which progress to frank hemorrhagic infarction of the organ (Fig. 5.61). If the testicular appendage only is affected there is congestion and interstitial hemorrhage although rarely frank necrosis. If the torsion occurs in utero the testicular tissue may regress and no testis may be identifiable (Fig. 5.62). At inguinal exploration a cord like structure is identified with sometimes a small nodule remaining. There is no identifiable normal testicular tissue, although vas deferens and epididymis are identified and histologically there may be scattered areas of hemosiderin laden macrophages or dystrophic calcification [92].

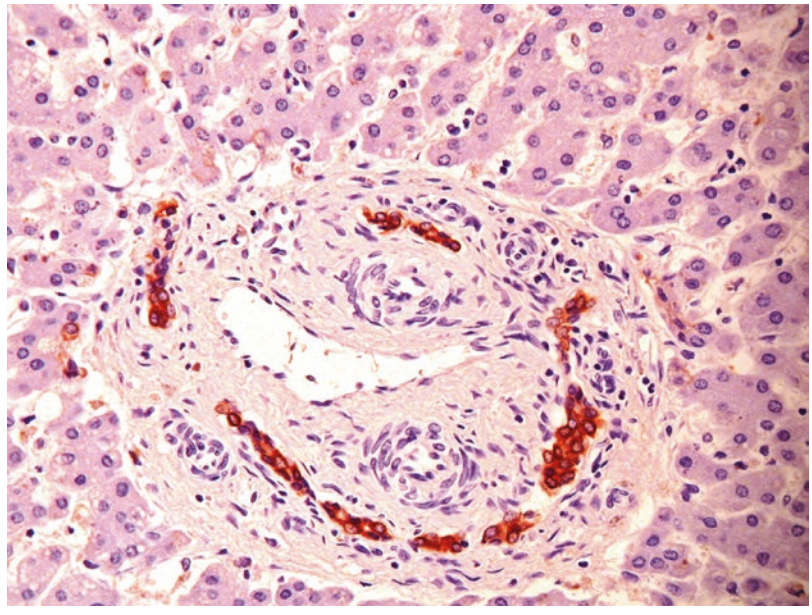

Fig. 5.56 Ductal plate malformation liver. A histological section of the liver stained immunohistochemically for cytokeratin 19. This highlights the biliary epithelium (stained *brown*) in a portal tract. Instead of a single profile of the bile duct to accompany the artery, the bile duct is a garland of tissue around the periphery of the portal tract—the so-called ductal plate malformation. After 16 weeks of gestation this appearance is abnormal and is strongly associated with ARPKD

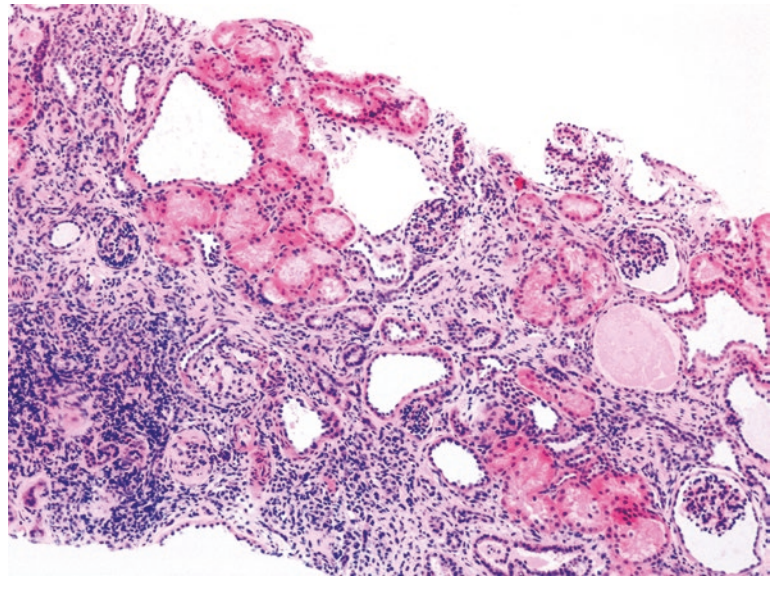

Fig. 5.57 Nephronophthisis. Biopsy from a child with cystic renal disease. There is marked interstitial chronic inflammation and dilatation of tubules. The features are not specific for nephronopthisis and genetic confirmation is required

5.10.6 Cryptorchid Testis

Cryptorchid testis removed during infancy may show minimal or no abnormalities [93].

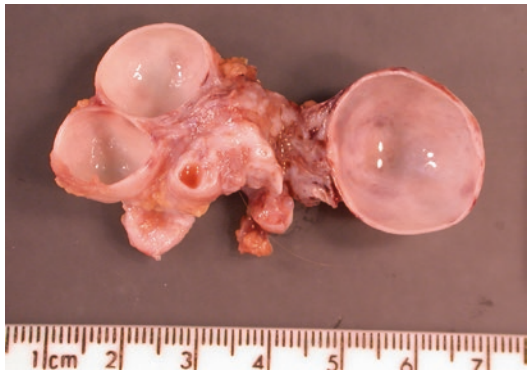

Fig. 5.58 Renal dysplasia. One-year old female with multicystic renal dysplasia. The excised kidney shows loss of the normal renal tissue and replacement by multiple cysts up to 2 cm in diameter

5.11 Neonatal Tumours

Congenital malignancies are rare [94]. They account for approximately 2% of all childhood cancers. About 40% of congenital tumors are histologically malignant. Of these the commonest are neuroblastoma, leukemia and congenital brain tumors. Neuroblastoma comprises 30–40% of congenital tumors and is the commonest congenital malignancy. Spontaneous regression may occur in 40% of the antenatally detected cases. Congenital acute leukemia is the second, commonest congenital malignancy.

5.11.1 Teratoma

Teratomas in the neonate are usually benign and occur mainly in the sacrococcygeal area (Fig. 5.63) followed by the anterior mediastinum [95]. They may also be found in the peri-

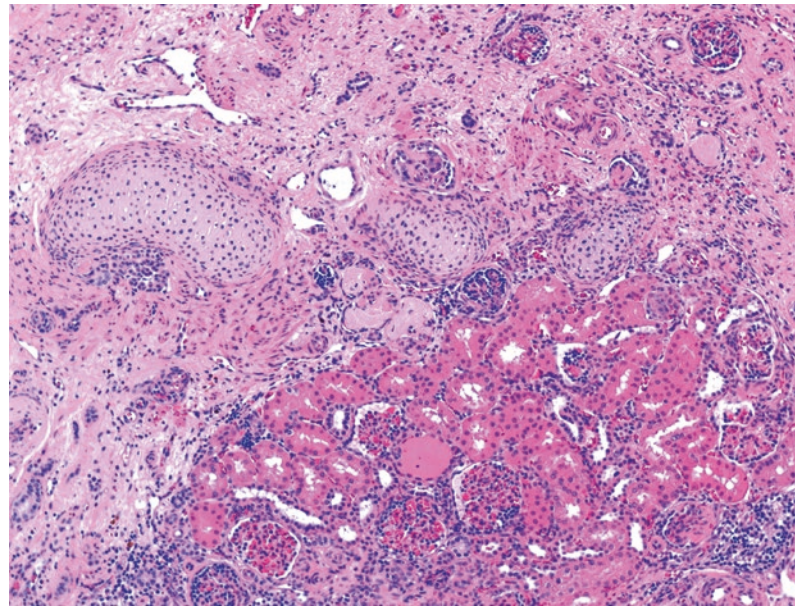

Fig. 5.59 Renal dysplasia. Histological section from a dysplastic kidney (H&E stain). The lower part of the field shows relatively normal kidney. The upper part shows loss of tubules and fibrosis. There are three small irregular bars of hyaline cartilage—feature very typical of renal dysplasia

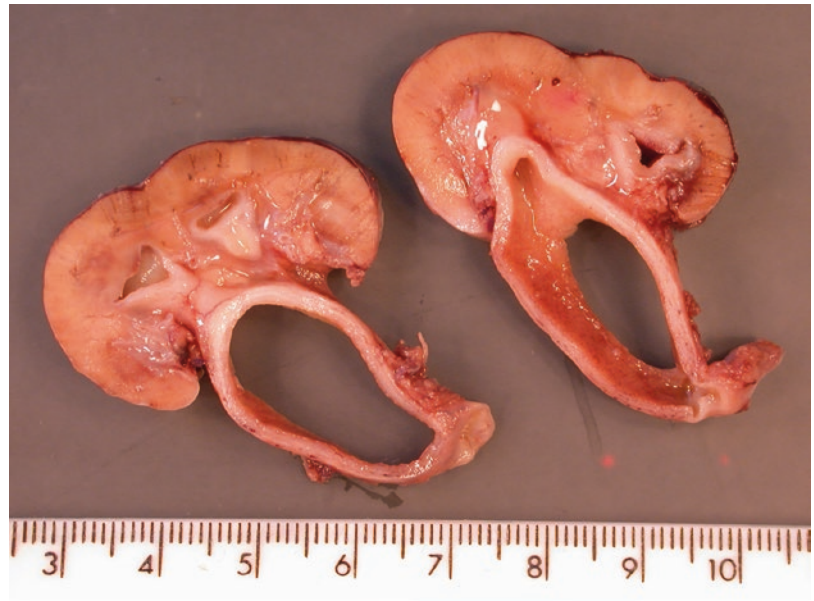

Fig. 5.60 Reflux nephropathy. Eleven-month old female infant with right duplex ureter and vesicoureteric reflux into lower pole moiety. Resection of lower pole. The cut surface of the specimen shows a normal thickness of cortex but there is blunting of the pyramids, mild calyceal dilatation and marked expansion of the pelvis

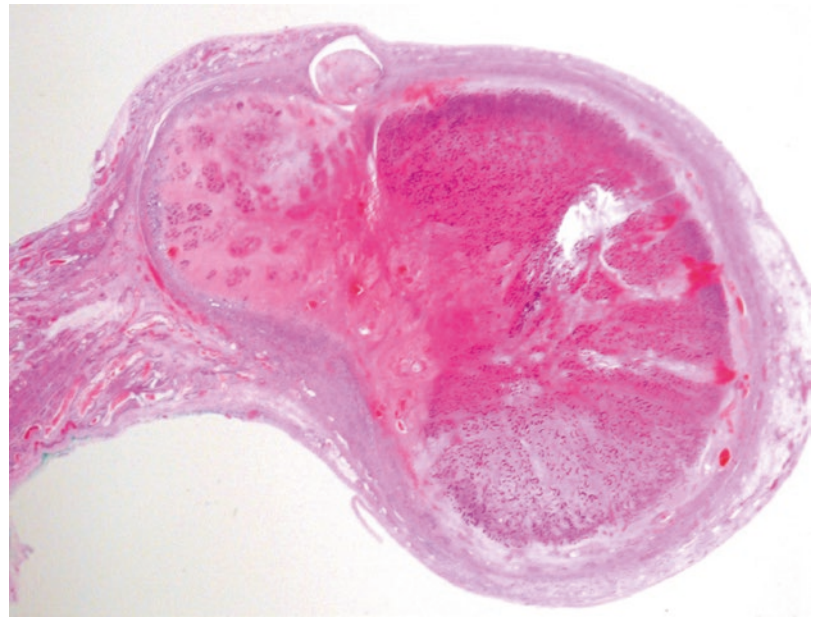

Fig. 5.61 Testicular torsion. Six-month old male with testicular torsion. A section of the entire specimen shows the spermatic cord to the left, the testis to the right and the epididymis and appendix testis in the centre of the field. The tissue is oedematous and shows haemorrhage and necrosis. Much of the cellular detail is obscured because of necrosis

cardium [96]. Diagnosis is usually established prenatally and may require intervention in a compromised fetus. Alpha fetoprotein is the tumor marker of choice and is particularly useful for assessing the presence of residual or recurrent disease. Grossly the tumors may reach a large size (Fig. 5.64) and many are cystic. The cut surface will frequently reveal multiple tissues including adipose tissue, mucus and keratin and frequently hair, cartilage, bone or teeth. Histologically the tumors are composed of tissues derived from all three germ layers. There is usually adipose tissue, skin, mature neuroglial tissue, smooth muscle, glan-

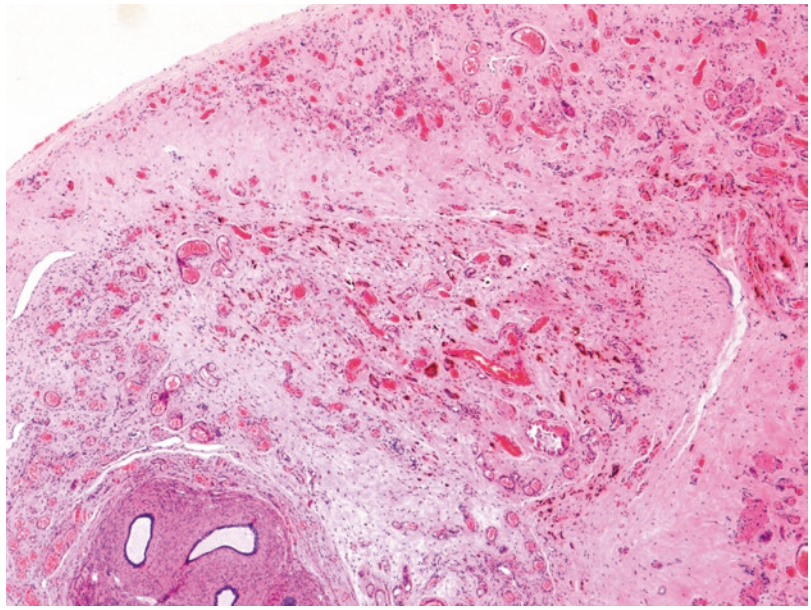

Fig. 5.62 Vanishing testis. Removal of an "atrophic testis" from a 1-year old boy. The specimen was a tubular structure 2.0 cm long and 0.4 cm in diameter. Histologically it consists of vas deferens with epididymis. At the expected site of the testis (shown) there is a nodule of loose vascular tissue with a small focus of calcification and numerous macrophages that contain *dark brown* haemosiderin pigment. No testicular tissue is identified. The appearances are those typical of so-called vanishing testis

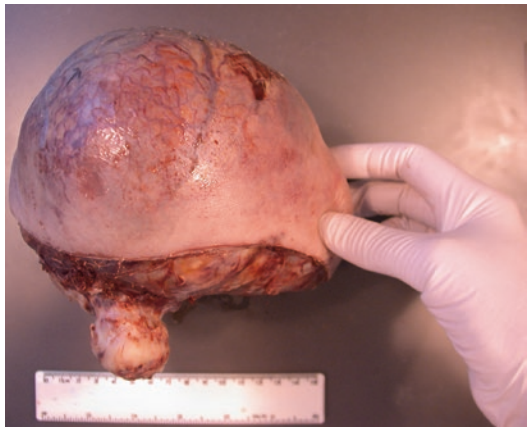

Fig. 5.63 Sacrococcygeal teratoma. An antenatally diagnosed sacrococcygeal tumour removed from a 5 day old boy. The specimen weighed nearly 1.5 kg and was 22 cm in maximum dimension. The stretched skin with distended veins over the surface of the tumour can readily be appreciated. Histologically the tumour was a teratoma that contained some immature elements but there was no evidence of malignancy

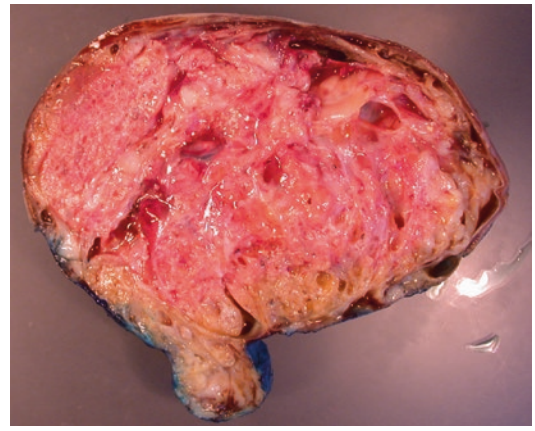

Fig. 5.64 Sacrococcygeal teratoma. The same case as Fig. 5.63. The cut surface of the tumour is predominantly solid, but with cystic areas. There are variable amounts of tissue with a myxoid appearance, while other areas are fleshy and some are fatty

dular tissue, cartilage and sometimes bone (Fig. 5.65). Less frequent are tissues such as retina, pancreas, thyroid and pancreas. About three-quarters of all sacrococcygeal teratomas are benign, containing no immature elements. A further 10–15% will have immature elements, usually immature neural tissue (Fig. 5.66). A small percentage will contain frankly malignant elements, most frequently yolk-sac tumor (Fig. 5.67).

5.11.2 Neuroblastoma

Neuroblastoma is an embryonic tumor that occurs at the site of the sympathetic ganglia from the neck to the pelvis [97]. The adrenals are the most common site with lesser numbers in the abdomen, thorax, head and neck. It is the most common congenital malignancy [94] and the most common intra-abdominal cancer in children. Paraneoplastic syndromes including

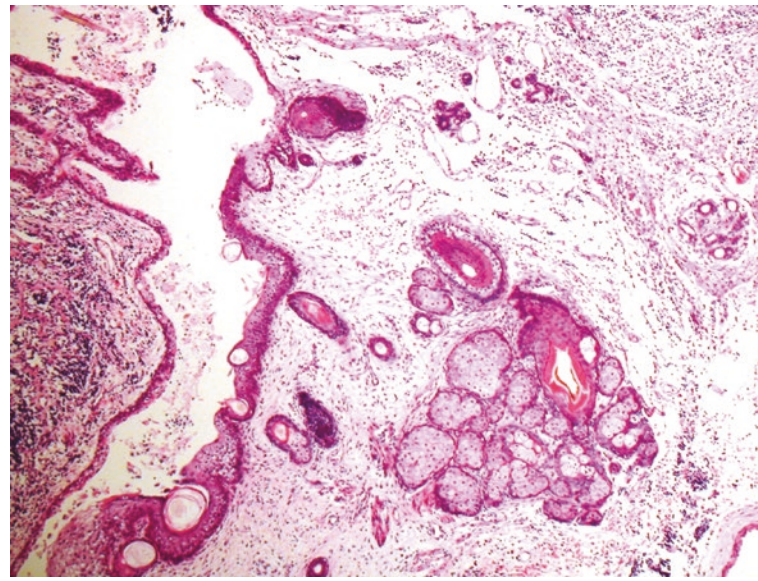

Fig. 5.65 Sacrococcygeal teratoma. A field from a scarococcygeal teratoma showing skin and adnexa, smooth muscle, glandular tissue and loose mesenchyme. There are no immature elements

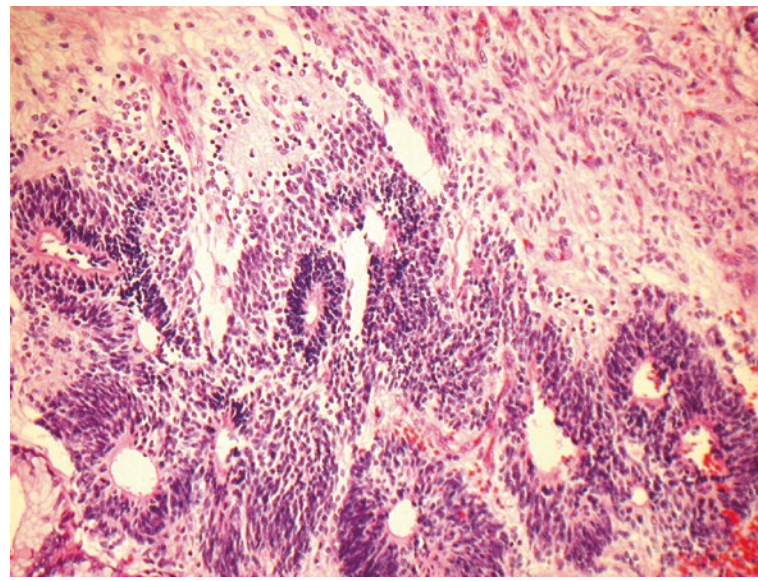

Fig. 5.66 Sacrococcygeal teratoma—immature elements. Another field from the same case showing numerous ependymal rosettes with surrounding immature neural tissue. Such immature neural tissue is frequently found in sacrococcygeal teratomas, and provided the tumour is completely excised, does not adversely affect the outcome

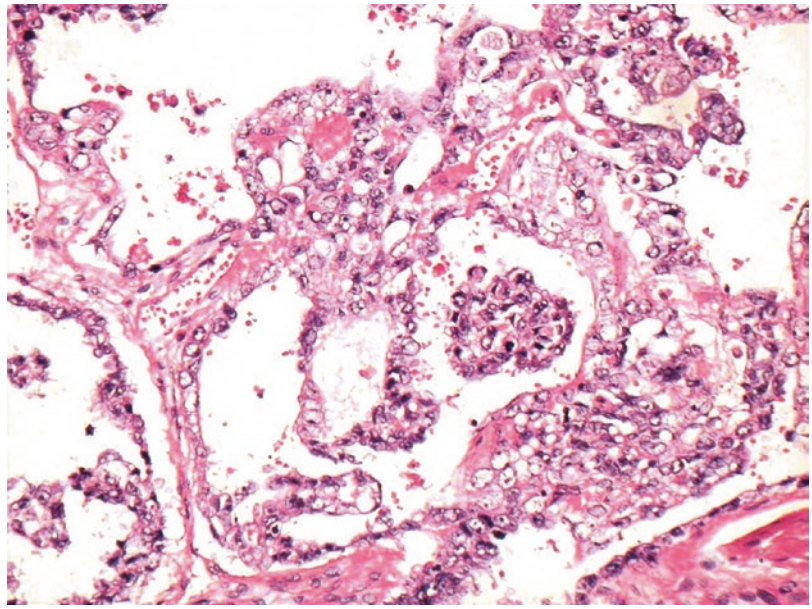

Fig. 5.67 Sacrococcygeal teratoma—1 year old with a sacrococcygeal mass 4 × 3 × 2.5 cm. Raised AFP level. The cut surface was cystic and solid. Histologically there was extensive yolk-sac tumour. A high power view of one such focus shows a cystic space lined by malignant cells and showing a polypoid projection of malignant tissue into the lumen. This is a Schiller-Duval body, diagnostic of yolk sac tumour

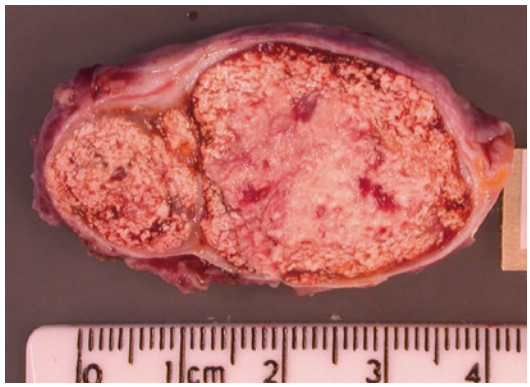

Fig. 5.68 Neuroblastoma. An 11 month old boy with resection of a primary adrenal neuroblastoma—Stage 4—following chemotherapy. The mass weighed 108 g and measured 4 × 3 × 2 cm. The tumour has a fibrous capsule in which remnants of the adrenal gland are visible as bright yellow areas. The tumour is nodular and very heavily calcified with a granular appearance. Histologically there was no viable tumour

hypertension, myclonus and Horner syndrome may be present. Metastasis is to bone marrow, regional lymph nodes and liver. The spinal canal is frequently involved by contiguous spread. Congenital cases may have placental involvement [98].

The tumors are typically bulky and fleshy typically show hemorrhage and are composed of small round blue cells with focal calcification (Fig. 5.68). There is primitive neural tissue with varying maturation. The degree of maturation varies (Fig. 5.69) from totally undifferentiated cells (small round blue cells) to lesions which show abundant Schwann cell differentiation and mature ganglion cells. The poorly differentiated lesions are commoner. By immunohistochemistry the cells stain with antibodies to NSE, NB84 and CD56. The behavior of the tumor depends upon its biological features such MYCN amplification and deletion of chromosomle 1p [99]. In the congenital cases (Fig. 5.70) spontaneous regression may occur in up to 40%. In children under 1 year of age, a particular form of metastatic disease occurs termed stage 4S, where a unilateral tumor shows metastasis limited to skin, liver and bone marrow (but not bone). These tumors have a much better prognosis that neuroblastoma metastatic to other sites [100].

5.11.3 Liver Tumours

Liver tumors account for about 5% of all tumors in the fetus and newborn [101]. The most frequent are benign vascular tumors and mesenchymal hamartoma. Hepatoblastoma is the commonest

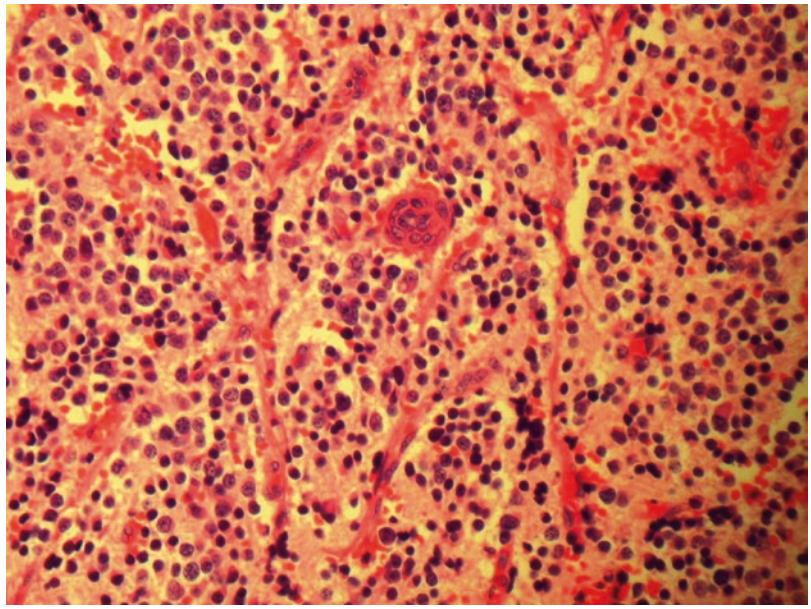

Fig. 5.69 Neuroblastoma—a 10-month old girl with resection of a stage III left adrenal neuroblastoma following chemotherapy. An H&E stained section (high power) shows the packeted arrangement of the tumour cells, separated by incomplete, thin fibrovascular septa. The cells are poorly differentiated neuroblasts and there is a background of fine fibrillary eosinophilic material—neuropil. This appearance is very characteristic of neuroblastoma

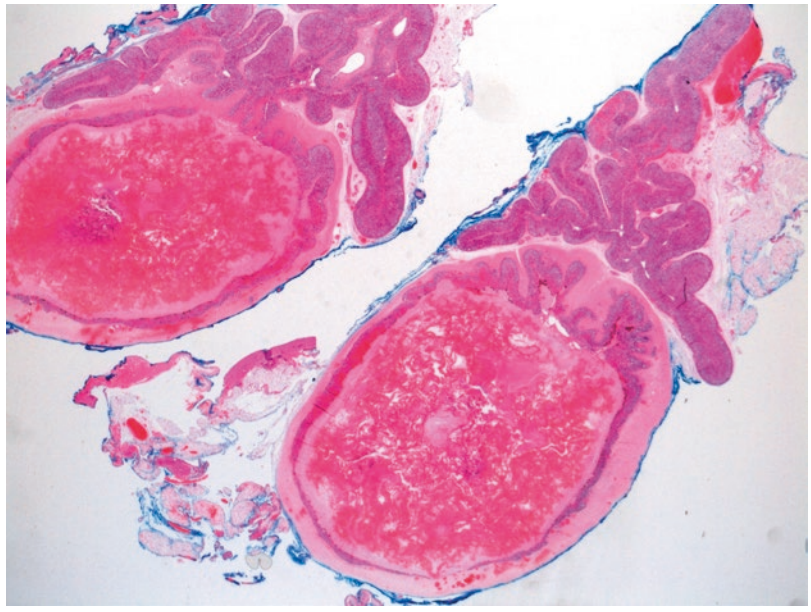

Fig. 5.70 Congenital neuroblastoma. An antenatally diagnosed tumour in the right adrenal gland of a male infant. Removed at 1 year of age. The excised adrenal gland showed a calcified nodule 1.0 cm in diameter. A whole mount section shows the adrenal gland that contains a rounded nodule of necrotic and calcified tissue. No viable elements are seen but the appearance is in keeping with a congenital neuroblastoma. The *blue* colour is ink, painted on the specimen to assess the resection margins

malignant tumor. In utero tumors may be associated with polyhydramnios, fetal hydrops and extreme cases the maternal mirror syndrome. Hepatoblastoma usually presents as a single liver mass (Fig. 5.71), although up to one fifth cases may show multiple lesions. There is usually associated anemia and sometimes raised platelet count. Lung metastasis is present at the time of diagnosis in up to one-fifth of cases. The histopathologic features show great variability. The tumors are predominantly epithelial and generally consists of fetal or embryonal components resembling respectively fetal and embryonic liver (Fig. 5.72). There is a variable amount of associated connective tissue which may show heterologous elements such as osteoid, skeletal muscle and sometimes squamous epithelium or melanocytic epithelium (Fig. 5.73). A small cell undifferentiated type is described. The presence of embryonal or undifferentiated cell types is indicative of a poor prognosis. Many cases are not submitted for pathological examination until after chemotherapy and in these cases there is usually extensive regressive change with fibrosis, necrosis, hemosiderin deposition and frequently a predominance of heterologous elements.

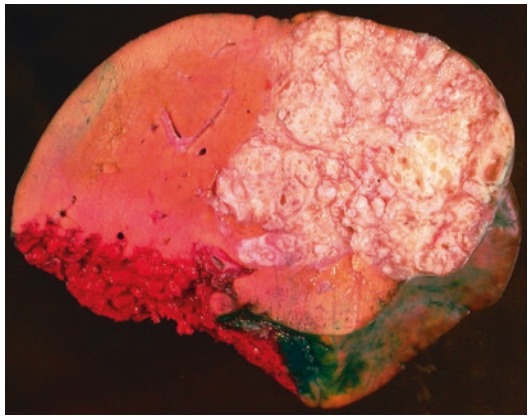

Fig. 5.71 Heaptoblastoma. Nine moth old boy with resection of a liver tumour following chemotherapy. The tumour was in segments IV, VI, VII and VIII. The cut surface shows a heavily calcified nodular pale mass 6 × 5 × 3 cm bulging onto the capsular surface. The *green* and *red* inks are used to identify the resection planes. Microscopically the tumour was predominantly mesenchymal with extensive osteoid. Resection was complete

Mesenchymal hamartoma is solid or cystic and recognized histologically by a myxoid stroma that contains islands of hepatocytes and dilated biliary structures (Fig. 5.74) [102]. There is an association with placental mesenchymal dysplasia [103].

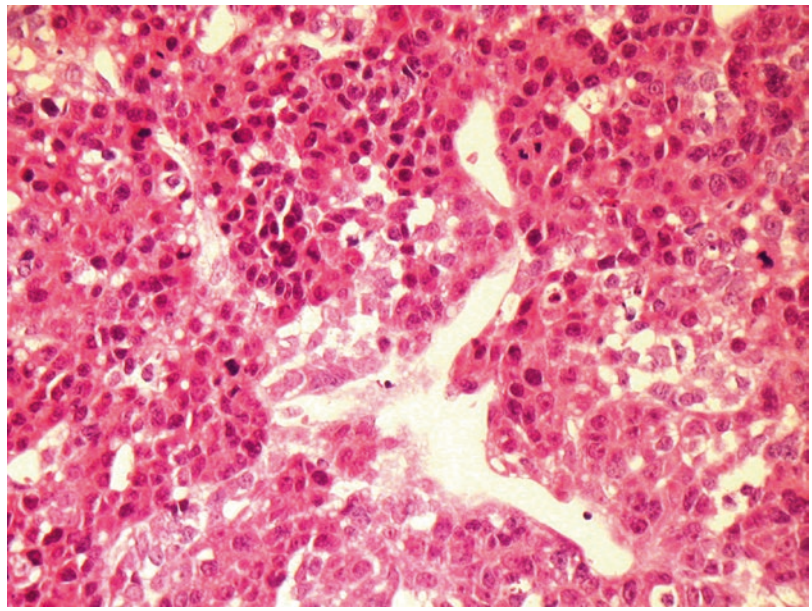

Fig. 5.72 Hepatoblastoma. A 7 month old girl with a mass in the right lobe of the liver and alpha feto-protein level of around 300,000. A needle biopsy core of the mass shows a mixture of embryonal and fetal hepatocytes, typical of hepatoblastoma

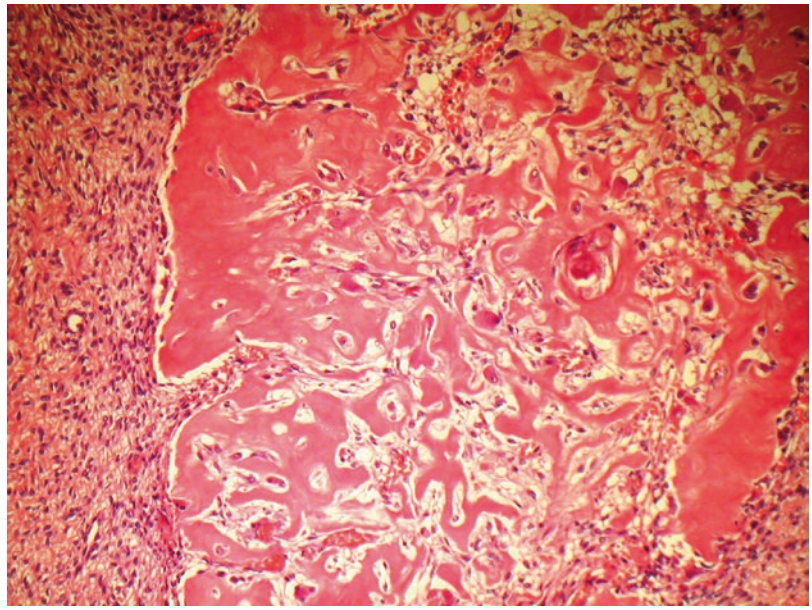

Fig. 5.73 Heaptoblastoma heterologous elements. Same case as in Fig. 5.71. There is extensive osteoid, visible as irregular bands of pink eosinophilic material, set in a spindle cell stroma

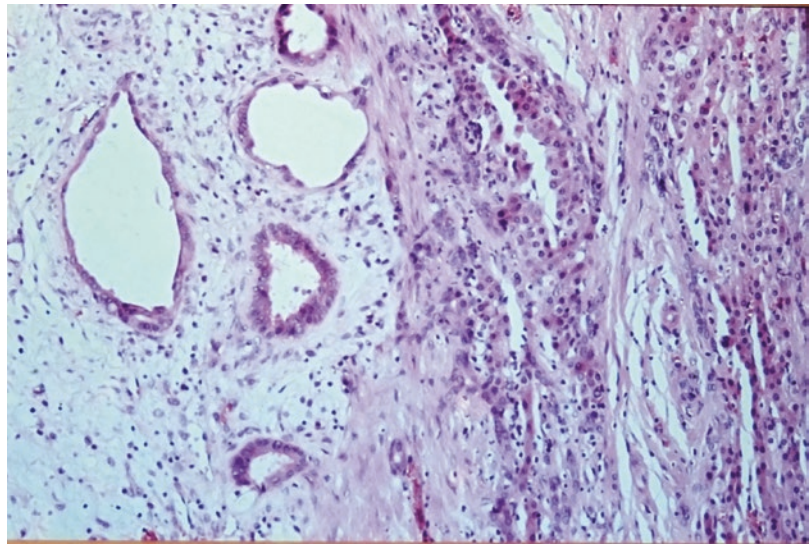

Fig. 5.74 Mesenchymal hamartoma liver. A 6-month old boy with a mass in the right lobe of the liver. A high-power H&E stained section shows dilated biliary structures set in a mesenchymal stroma with enclosed islands of hepatocytes

5.11.4 Renal Tumours

Renal tumors account for approx. 7% of all neonatal tumors [104]. Mesoblastic nephroma (Fig. 5.75) is the most common tumor to be found at this age accounting for between 2 and 5% of all pediatric renal tumors, but Wilms' tumor and other malignant and benign tumors occur.

Congenital mesoblastic nephroma is a tumor of the kidney occurring typically within the first 3 months of life particularly in the neonatal period [105]. The tumor is usually unilateral. Two main subtypes are described—the classical type with a with a distinct resemblance to infantile fibromatosis (Fig. 5.76) and the cellular type that resembles infantile fibrosarcoma (Fig. 5.77) and shares with it the same t(12:15) ETV6-NTRK3 translocation [106]. Macroscopically it has an appearance resembling a uterine fibroid (Fig. 5.75), but with indistinct margins because

of infiltration of the surrounding kidney. Necrosis and hemorrhage are not found but there may, however, be cystic change. It is present at the renal hilum and projects on the medial aspect of the kidney. Microscopically the tumor is composed of spindle cells. Entrapped renal tubules are present within the tumor. There may be immature cartilage, a metaplastic phenomenon.

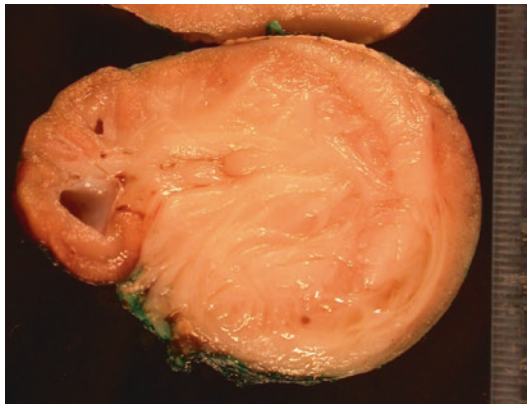

Fig. 5.75 Mesoblastic nephroma. A 17 day old hypertensive female with a congenital left renal mass. The excised specimen weighed 44 g and contained a tumour 5 cm in diameter that bulges from the medial aspect of the kidney. The cut surface has a whorled grey appearance resembling a uterine fibroid. The appearance is typical of congenital mesoblastic nephroma. There is moderate dilatation of the renal calyces

Wilms' tumor (nephroblastoma) is a malignant neoplasm derived from the nephrogenic blastema [105]. The majority of cases are sporadic but there is an association with inherited syndrome some associated with abnormalities of the WT1 gene. Most tumors are unilateral, but may be bilateral. The tumor is a solid mass that is well demarcated from the surrounding uninvolved kidney (Fig. 5.78). Nephrogenic rests may be present in the surrounding kidney. Histologically' Wilms' tumor have a classical triphasic appearance comprising epithelium, stroma and blastema (Fig. 5.79). Blastema refers to cellular immature tissue present in the embryo. The respective proportions of these three elements vary from tumor to tumor. There may be anaplasia in the tumor cells (Fig. 5.80) which may affect any of the three components. Following chemotherapy there is usually marked necrosis and regressive change. The tumor has a tendency to involve the renal vein and spread in that fashion. Local nodes may also be involved. The presence of diffuse anaplasia within the tumor renders it a high-risk tumor. Nephrogenic rests (Fig. 5.81) are abnormally persistent areas of immature cells in the renal cortex. Normally they disappear by 36 weeks of gestation and where they persist they give rise to Wilms' tumor. They are said to have a prevalence of

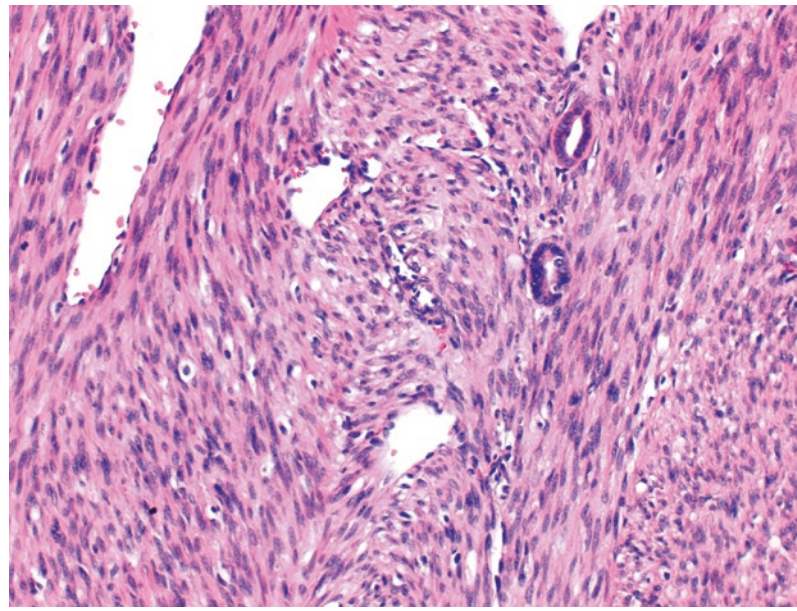

Fig. 5.76 Mesoblastic nephroma. A 7 week old boy with hypertension and a renal mass. A section from the excised kidney (H&E) shows regular fascicles of spindle cells without atypia. There are included entrapped normal, non-neoplastic, renal tubules

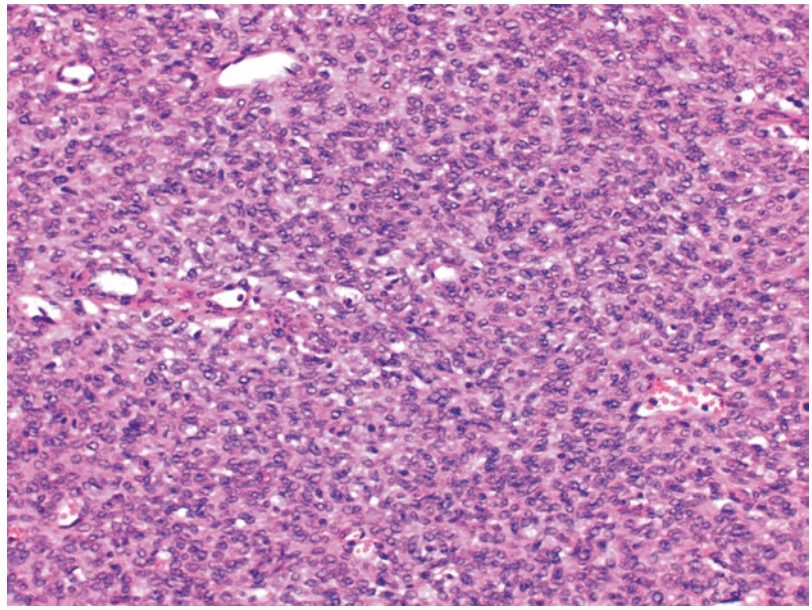

Fig. 5.77 Cellular mesoblastic nephroma. A 6 week old boy with a right renal mass 14 × 13 × 9 cm. A section of the mass taken at the same magnification as Fig. 5.76 shows it to be more cellular than that specimen with numerous mitotic figures. The specimen showed a positive transcript for ETV6-NTRK3 by RT-PCR

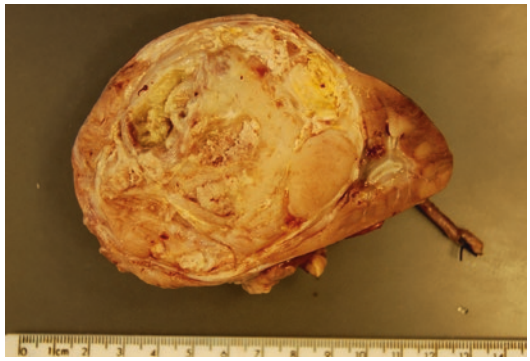

Fig. 5.78 Nephroblastoma (Wilms' tumour). A 3-month old boy with a right renal mass resected after chemotherapy. The excised specimen weighed 244 g and the tumour measures 7 cm in greatest diameter. The tumour is at the upper pole, well circumscribed and demarcated from the kidney by a fibrous pseudocapsule. Its cut surface shows fleshy areas and large areas of necrosis (approx. 60%). Histologically the tumour showed focal extracapsular spread but was completely excised (Stage 2)

approximately 1% in autopsies of children but they are probably much rarer than this.

5.11.5 Brain Tumours

Brain tumors in infants are rare, accounting for less than 5% of all pediatric brain tumors. Most are supratentotiral. These tumors are often histologically benign (teratoma, choroid plexus papilloma), but can be very large and are frequently situated in difficult locations [107, 108].

5.11.6 Tumours of the Chest Wall and Lung

5.11.6.1 Congenital Peribronchial Myofibroblastic Tumor

This is a very rare, but very striking, tumor that presents in utero with polyhydramnios and fetal hydrops [109]. It can present in the neonate as respiratory distress. There is a large mass on chest X-ray occupying most of the lung field. Grossly, there is a well-circumscribed solid mass up to 10 cm in diameter. Microscopically, the tumor is composed of fascicles of uniform spindle cells (Fig. 5.82) without pleomorphism [110]. Mitotic figures are present, but are not atypical. There is a very striking peribronchial infiltration with infiltration of the surrounding lung parenchyma. It has benign behavior, but the infant may die as a consequence of the hydrops [111].

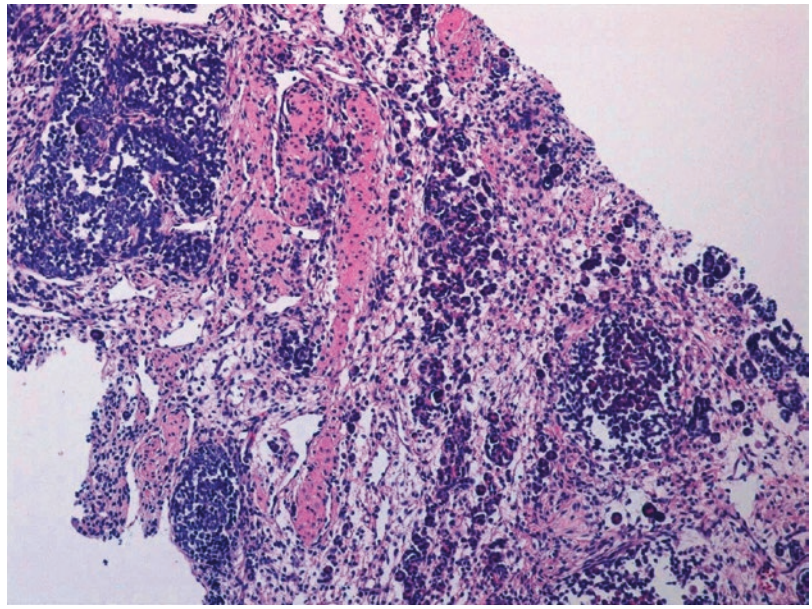

Fig. 5.79 Needle biopsy specimen of a right renal mass in a 1-year old girl. The sections show a high-power view of one of the cores stained with H&E. There is a loose myxoid stroma in which are set primitive tubules and areas of cellular blastema (most evident in the left upper part of the field) The appearance is typical of nephroblastoma (Wilms' tumour). By immunohistochemistry the tumour cell nuclei were stained positively with antibody to WT1

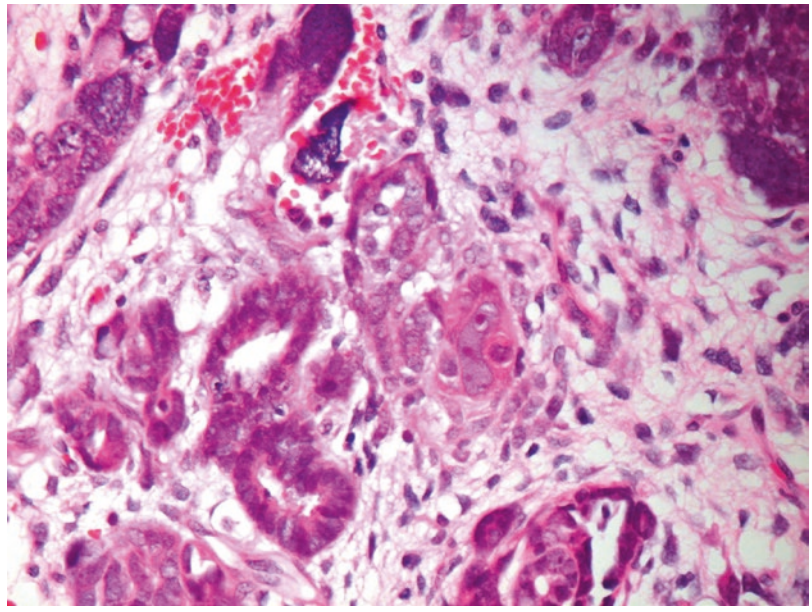

Fig. 5.80 Nephroblastoma (Wilms' tumour) anaplasia. A high-power field from a Wilm's tumour showing that the epithelial elements have bizarre, enlarged and hyperchromatic nuclei—anaplasia. This child was 8 years old. Anaplasia is much commoner with increasing age and is rare in infants

5.11.6.2 Fetal Lung Interstitial Tumor

This entity has only recently been reported [112]. The authors describe ten cases in infant's (seven males and three females) of mixed solid and cystic lung masses. The infants presented with variable respiratory distress developing shortly after birth. Imaging studies showed a well circumscribed mass (right lower lobe × 4, left lower lobe × 2, right upper lobe × 2 and one each in the right middle and left upper lobes). No local recurrence or metastatic disease was noted in up to 3 years of follow up. The mass is described as solid to spongy with well-defined borders. Histologically there was fibrous border between

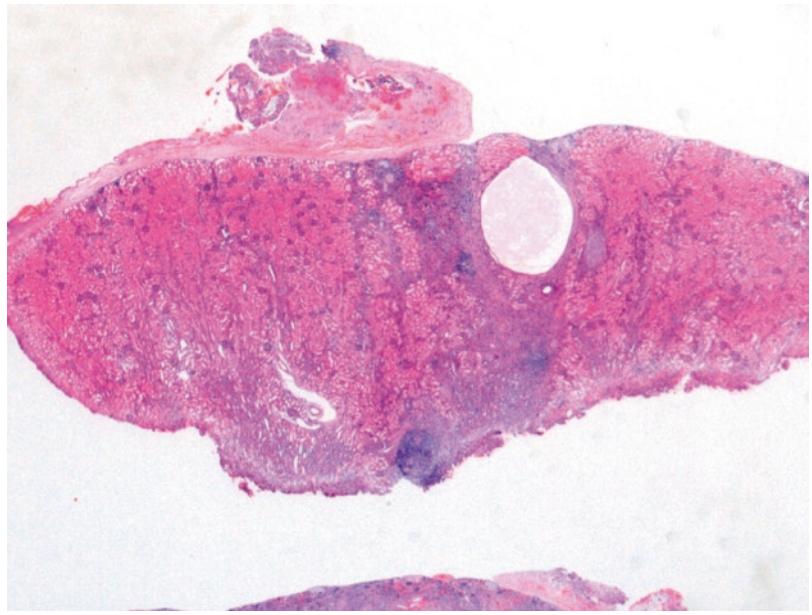

Fig. 5.81 A 1 year old boy with previous resection of nephroblastoma (Wilms' tumour) of the right kidney. A lesion was noted in the left lower pole and excised. It shows a wedge of immature and darkly staining renal tissue 0.8 cm in diameter. There is focal cystic dilatation of some tubules. The appearance is of a nephrogenic rest (H&E stain)

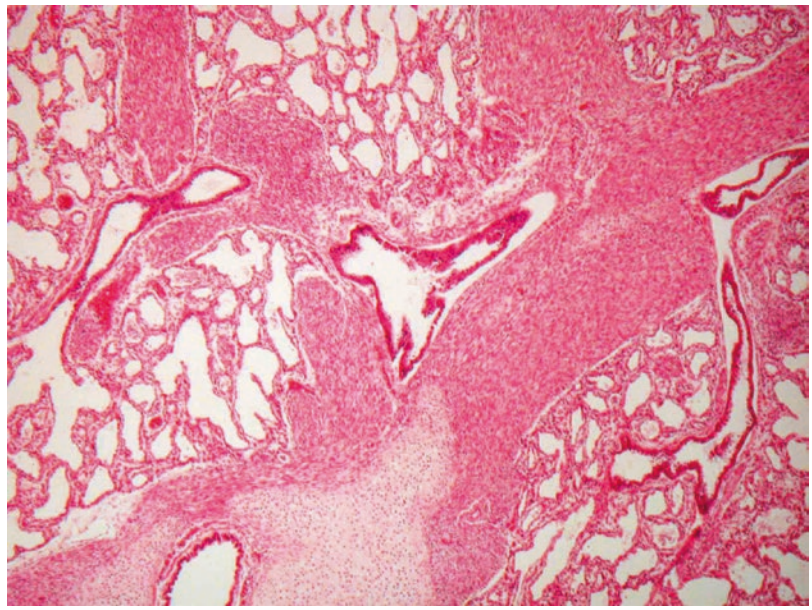

Fig. 5.82 Peribronchial myofibroblastic tumour. A section from the lung of a newborn with hydrops and a large right lung mass. The photomicrograph shows marked expansion of the bronchovascular connective tissue sheaths by thick bundles of bland spindle cells

the lesion and surrounding lung and the tumor is described as resembling fetal lung at 20–24 weeks gestation. There were cystic spaces lined by epithelium and a cellular stroma.

5.11.6.3 Pleuropulmonary Blastoma

The mean age of development of this malignant tumor lies outside the neonatal period but it may, nonetheless, present in the neonate. It is divided, pathologically into three types: I–III corresponding to cystic, solid and cystic, and solid morphology respectively and representing a spectrum of increasing aggressiveness [113]. Type I pleuropulmonary blastoma is the type most likely to present in the neonatal period (its median age of occurrence is 9 months) and is often confused, both on

imaging and pathologically with congenital pulmonary airway malformation (CPAM) [73]. Pleuropulmonary blastoma an association with cystic nephroma [114] and may be part of a familial cancer syndrome associated with mutations in the gene DICER1 [115]. Grossly it is cystic with thin walls (Fig. 5.83). There is no macroscopic thickening or solid areas. The cysts are lined by benign epithelium [72]. Focal subepithelial condensation of primitive cells (Fig. 5.84) may show rhabdomyoblastic differentiation (rhabdomyosarcoma-like). The muscle cells stain with vimentin, desmin and myogenin. The absence of rhabdomyoblastic differentiation does not exclude the diagnosis. There is variable pleomorphism. Primitive cell collections may be very sparse and multiple sections may be required to make the diagnosis and differentiate from type 4 CPAM [73]. The tumor may contain small nodules of immature cartilage which is very useful for diagnosis. It is treated by complete surgical excision with adjuvant chemotherapy. If incompletely excised, it may recur as type II or III pleuropulmonary blastoma.

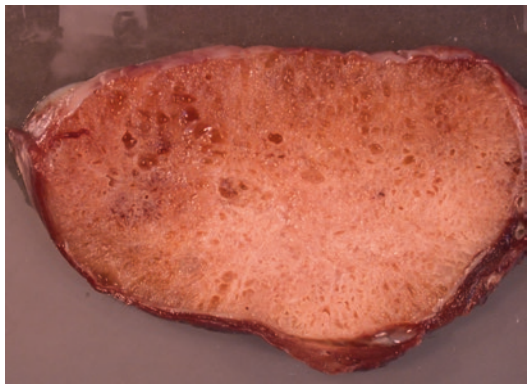

Fig. 5.83 Pleuropulmonary blastoma type 1. A 6-day old boy with a mass in the lower lobe of the left lung. The resected specimen measured 7 × 5 × 4 cm and had a spongy cut surface

5.11.6.4 Infantile Chest Wall Mesenchymal Hamartoma

This is a very rare, but benign disorder of the ribs that may involve a single rib or more than one rib; it may be bilateral. It occurs in infants and usually present at birth as an asymptomatic chest wall mass or with respiratory distress and cyanosis. It may be fatal because of respiratory impairment, but more usually follows a benign course [116]. Radiology shows a cystic and solid mass with fluid levels in the cysts. Grossly, it is a well-delineated, lobulated mass with blood-filled cystic spaces and areas of cartilage. Histopathologically, it consists of areas of hyaline cartilage, both mature and immature, a spindle cell stroma. Osteoid and aneurysmal bone cyst-like areas.

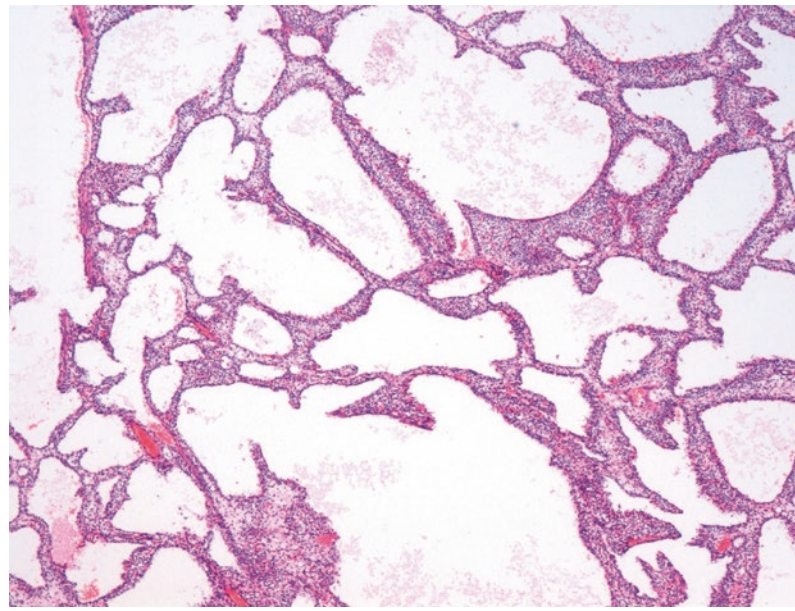

Fig. 5.84 Pleuropulmonary blastoma type 1. Same specimen as Fig. 5.83. The histology shows multiple cystic spaces lined by bland respiratory epithelium. Within the rather rigid septa there is condensation of rather primitive cells beneath the epithelium

5.11.7 Vascular Tumours

Vascular abnormalities are common, occurring about 1% of children. There is considerable confusion about their terminology. They can be broadly classified into hemangiomas and vascular malformations. The hemangiomas represent tumors, they show rapid growth during infancy followed by progressive involution, the basic underlying defect being abnormal endothelial cell proliferation. The vascular malformations, on the other hand, represent lesions that are present at birth (whether evident clinically or not) and grow with the child and do not show spontaneous regression; their basic underlying pathology is abnormal vascular development. Vascular malformations can be further subclassified according to the predominant type of vascular channels present in the lesion, such as capillary, venous, arterial and lymphatic, or a combination of these. They can also be classified according to the blood flow within them as either high-flow or low-flow lesions. The International Society for the Study of Vascular Anomalies, in 1996 produced a classification of vascular anomalies [117] incorporating these distinctions. In the classification, the tumors encompass:

- infantile hemangioma
- congenital hemangiomas (rapidly involuting and non-involuting forms)
- lobular capillary hemangioma (pyogenic granuloma)
- tufted angioma
- kaposiform haemangioendothelioma
- haemangiopericytoma

The malformations are either:

- simple with slow flow (capillary, venous, lymphatic) or high flow (arterial)
- combined lesions with either slow flow (lymphovenous malformation or capillary lymphovenous malformation) or high flow (arteriovenous malformation or capillary arteriovenous malformation).

Infantile hemangioma is the most common vascular tumor of children (Fig. 5.85) [118] characterized pathologically by staining of the lesional endothelium with the antibody GLUT-1 which recognizes the antigen Glucose Transporter Protein 1. The antigen is strongly expressed in all the lesional endothelial cells (Fig. 5.86) at all stages of their natural history [119]. It has greatly simplified the diagnosis of these tumors.

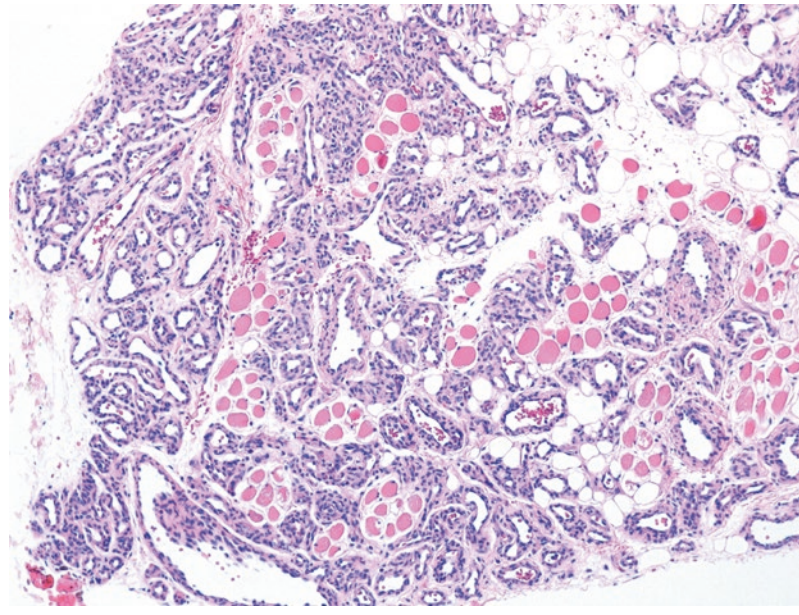

Fig. 5.85 Infantile hamangioma. Needle biopsy of a lump from the left thigh in a 5 month old female infant. The lesion shows multiple, small, capillary-sized vascular channels set among adipose tissue and striated muscle

Kaposiform haemangioendothelioma resembles juvenile hemangioma but shows no tendency to spontaneous regression and is frequently associated with Kasabach-Merritt syndrome, characterized by profound thrombocytopenia and hemorrhage. The lesion is most common in the extremities and is occurs in superficial and deep soft tissues [120]. The lesion is nodular and can resemble infantile capillary hemangioma histologically, but contains spindle cells. The cells are negative for GLUT 1, but are CD31 and CD34 positive. They are focally smooth muscle actin positive, but characteristically show positivity for the lymphatic marker D2–40 [121] (Fig. 5.87).

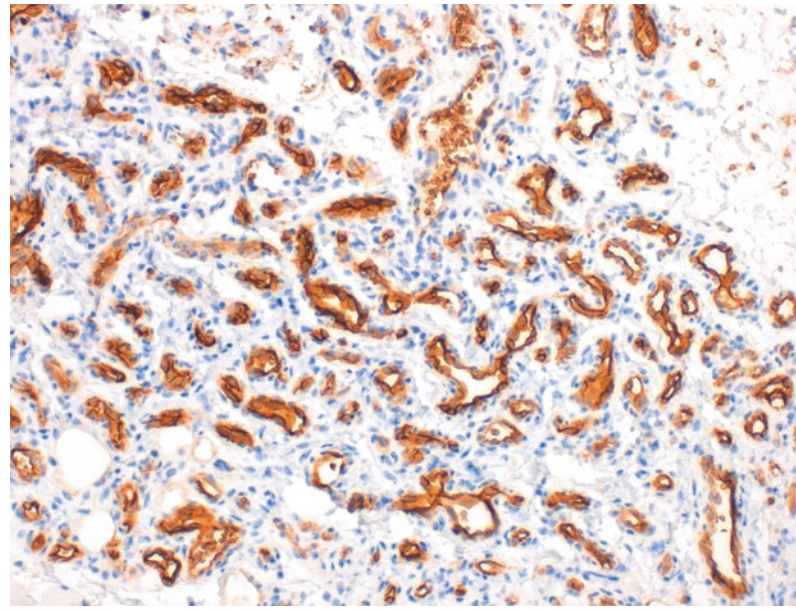

Fig. 5.86 Infantile haemangioma. Same case as Fig. 5.85 stained immunohistochemically with antibody to GLUT1. There is strong staining of the endothelium of the vascular spaces indicating that this is an infantile haemangioma

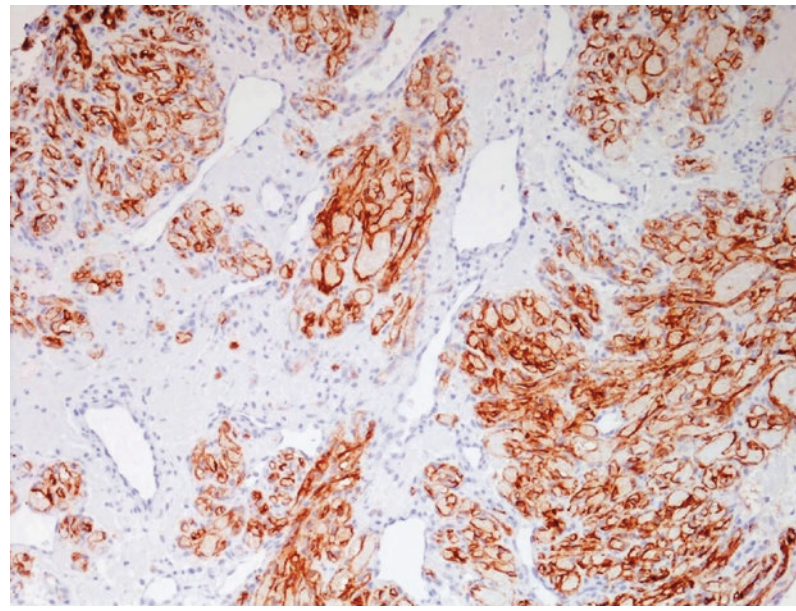

Fig. 5.87 Kaposiform haemangioendothelioma. A lesion composed of spindle cells with vascular spaces that stain strongly with antibody D2–40

5.11.8 Rhabdomyosarcoma

Rhabdomyosarcoma, a malignant tumor with differentiation towards a striated muscle phenotype, is the commonest soft tissue tumor in children, but is rare in the neonate [122]. Nevertheless, it may occur and has even been described in utero [123]. The tumor may arise in many sites but has a predilection to involve the head and neck and parameningeal area, proximal limbs and the viscera including bile duct and genitourinary tract (Fig. 5.88). Two histological subtypes are identified, the embryonic form and the alveolar form, the latter having a more aggressive clinical course. Alveolar rhabdomyosarcoma is characterized by a specific translocation affecting the PAX-FKHR genes [124]. Histologically embryonal rhabdomyosarcoma shows a spindle cell appearance with alternating areas of cellular and myxoid appearance (Fig. 5.89). Rhabdomyoblastic differentiation, that is to say recognizable differentiation toward striated muscle is uncommon, although cells may appear strap-like and have abundant eosinophilic cytoplasm. Cross-striations are not usually seen. The alveolar subtype has a small round blue cell phenotype with aggregation of the cells with a fibrovascular connective tissue stroma. Disaggregation of the cells from the fibrous septa in some cases imparts a pseudo-alveolar pattern that first gave this subtype its name (Fig. 5.90). Immunohistochemically, the tumor cells show strong cytoplasmic staining for the muscle protein desmin and display nuclear positivity for myogenin (Fig. 5.91)—alveolar rhabdomyosarcoma showing a greater percentage of positive nuclei than embryonal rhadomyosarcoma [125]. Increasingly molecular methods are being employed to make the diagnosis of alveolar rhabdomyosarcoma.

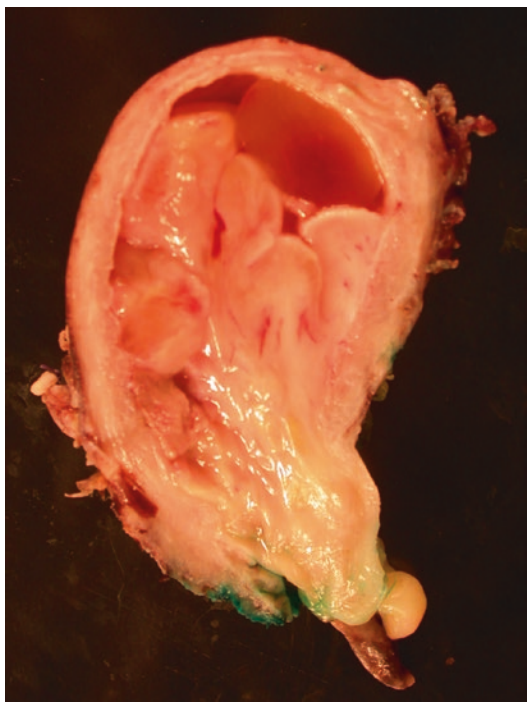

Fig. 5.88 Rhabdomyosarcoma. Two year old boy who had an embryonal rhabdomyosarcoma of the prostate glands treated with chemotherapy and radiotherapy. Cystoprostatectomy following recurrence. The Bladder is sectioned in the sagittal plane. A myxoid, polypoid tumour mass replaces the prostate gland and anterior lower bladder wall and distends the bladder lumen

5.11.8.1 Infantile Fibrosarcoma

This is a tumor of the infant: approximately 50% of cases are congenital. There is a characteristic t(12;15)(p13;q26) translocation resulting in an abnormal ETV6-NTRK3 fusion transcript, that is very helpful for diagnosis [126]. The commonest site is the distal extremities, but other sites may be involved, including head and neck. The lesion presents as a rapidly growing mass and may be mistaken for a hemangioma [127]. Histologically, it comprises interlacing bundles of spindle and ovoid cells (Fig. 5.92). The lesion is responsive to chemotherapy but may recur in up to half of the cases.

5.11.8.2 Infantile Myofibromatosis

Infantile myofibromatosis is a myofibroblastic proliferation and may be solitary or multiple and diffuse. It presents as a superficial painless subcutaneous mass in the head and neck, trunk or extremities. Deeper masses may occur in the muscle or viscera. Histologically it has a nodular appearance with zoning, the central zone showing a haemangiopericytoma-like appearance, while the periphery is more cellular

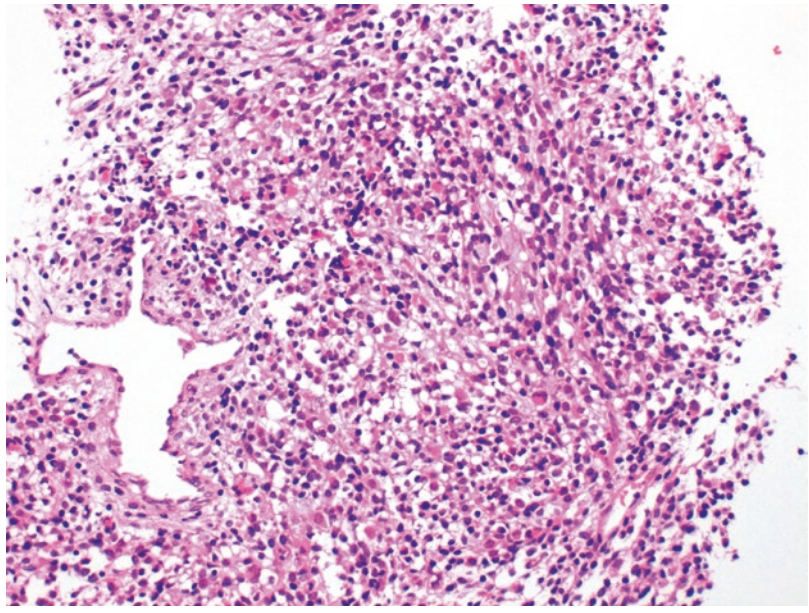

Fig. 5.89 Rhabdomyosarcoma—embryonal subtype. A 9-month old girl with a soft tissue mass in the face, a needle core biopsy shows a cellular lesion composed of spindle cells loosely arranged. Scattered cells with opaque eosinophilic cytoplasm are present, indicating a more mature muscle phenotype. Myogenin staining showed only 30% of tumour nuclei stained positively and there was no FOX01 gene rearrangement

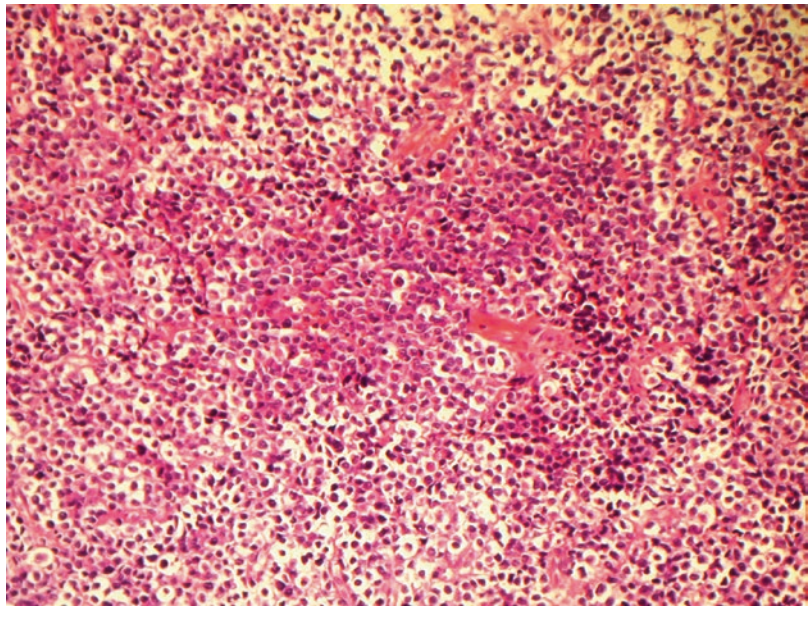

Fig. 5.90 Alveolar rhabdomyosarcoma. A 5-month old girl with a neck mass. A biopsy specimen shows a cellular tumour with a vaguely packeted arrangement of the cells. The centres of the packets show disaggregation of the cells—a feature typical of alveolar rhabdomyosarcoma. The cells showed strong cytoplasmic staining with antibody to desmin and almost all the tumour cell nuclei showed strong staining for myogenin. PCR analysis showed a PAX7-FKHR (t1;13) fusion transcript

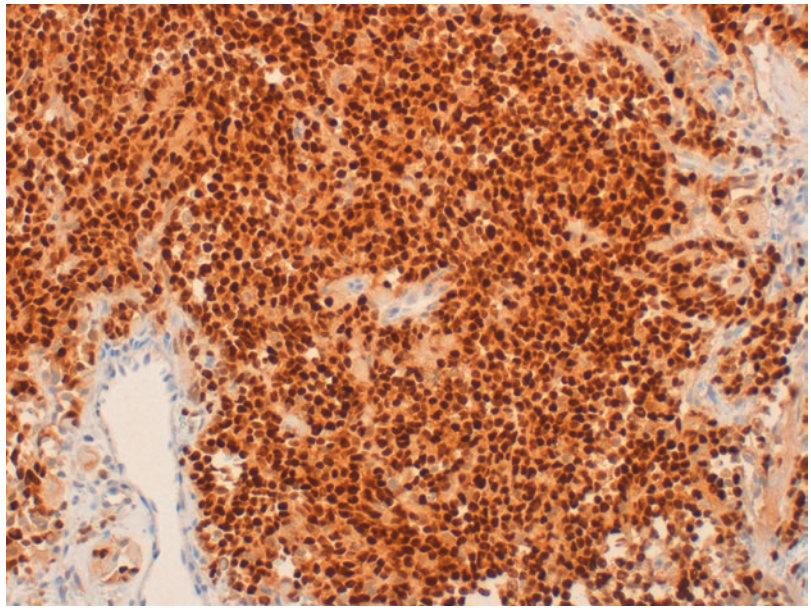

Fig. 5.91 Rhabdomyosarcoma. Immunohistochmical staining of a biopsy specimen with antibody to myogenin. There is nuclear staining of approximately 90% of tumour cell nuclei. Such a high percentage of staining is strongly indicative of the alveolar subtype of rhabdomyosarcoma

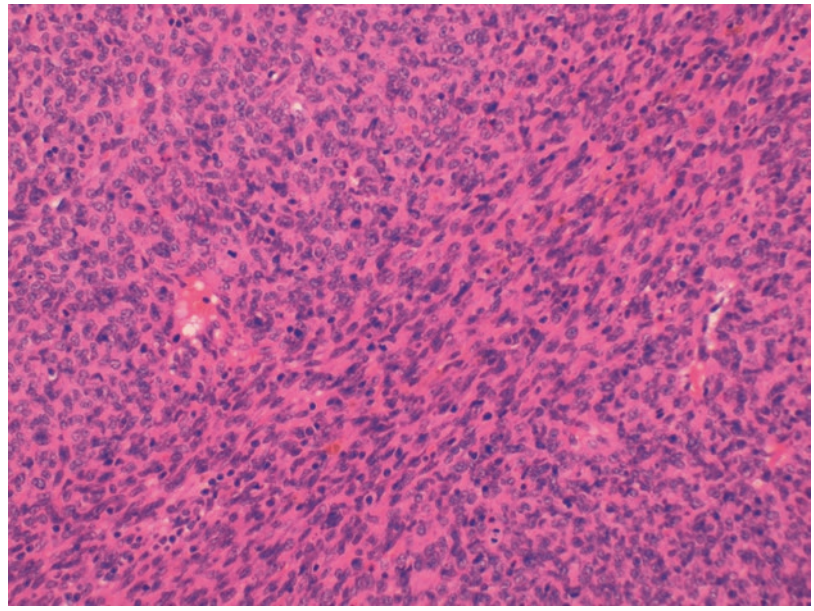

Fig. 5.92 Infantile fibrosarcoma. Twenty-six day old boy with a right thoracic cystic and solid mass, The lesion is composed of spindle cells arranged in fascicles with frequent mitotic figures. PCR analysis showed a ETV6-NTRK3 transcript, confirming the diagnosis of infantile fibrosarcoma

(Fig. 5.93). There is no atypia. There is some histological overlap with haemangiopericytoma and infantile fibrosarcoma [128] but, crucially, it had lacks the typical translocation of infantile fibrosarcoma.

5.12 Autopsy

Inevitably, babies will die of their disease or its complications. In this setting, an autopsy carried out by a competent pediatric\perinatal pathologist

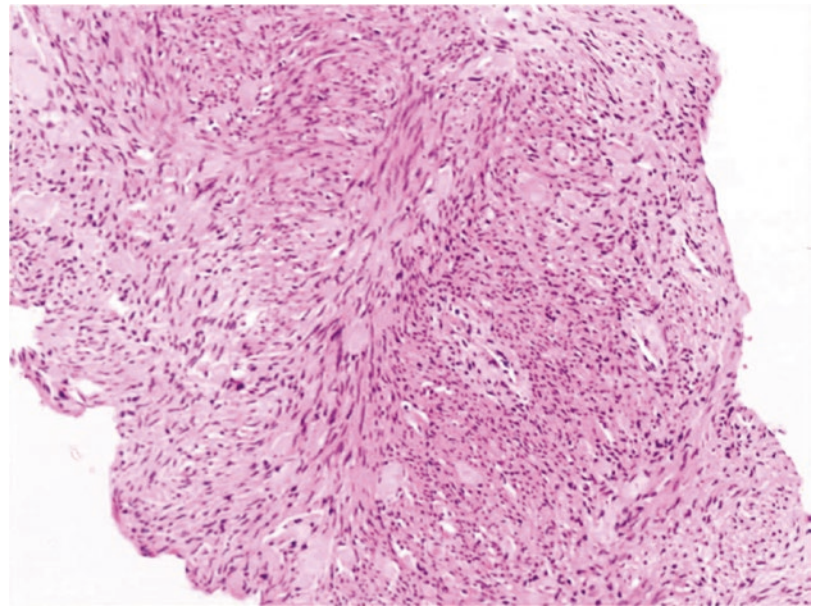

Fig. 5.93 Infantile myofibromatosis. An H&E stained section shows interlacing fascicles of spindle cells with eosinophilic cytoplasm

can be very useful in answering hitherto unanswered questions. It is important to realize that not all questions can be answered by the autopsy—even in the twenty-first century there are areas of biology where understanding is still at a primitive stage. The more precisely formulated the question that the pathologist is posed, the more likely it is that meaningful information can be obtained by the autopsy. Although the preference will always be for a full autopsy, it may well be that the question to a particular query may be answered by a limited post-mortem, for example limited to the operation site, to the heart and lungs or to the brain. This emphasizes again the importance of team work. Possibly nowhere else is teamwork as important as in managing the expectation of the family in relation to post-mortem. Indeed, many of the problems relating to post-mortem have arisen not because of malpractice but because of a lack of appreciation by all parties of the needs and expectations of others.

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6 Developmental Physiology and Pharmacotherapy in Pediatric Surgical Newborns

John N. van den Anker and Dick Tibboel

Abstract

Human development consists of a continuum of physiologic events that includes somatic growth, neurobehavioral maturation and eventual reproduction, and is often divided into infancy, childhood, adolescence and early adulthood. Across this period of time organ size and function change as does body composition, protein expression, and cellular function. Some tissues may be more sensitive to effects early in life whereas later in life function may decline. This holds true in particular when organ development has resulted in major congenital anomalies. As these developmental changes in function and form occur, their implications with respect to the clinical pharmacology of drugs and their appropriate place in pediatric therapy must be considered.

Keywords

Newborn physiology • Pharmacology • Newborn surgery

6.1 Introduction

Human development consists of a continuum of physiologic events that includes somatic growth, neurobehavioral maturation and eventual reproduction, and is often divided into infancy, childhood, adolescence and early adulthood. Across this period of time organ size and function change as does body composition, protein expression, and cellular function. Some tissues may be more sensitive to effects early in life whereas later in life function may decline. This holds true in particular when organ development has resulted in major congenital anomalies. As these developmental changes in function and form occur, their implications with respect to the clinical pharmacology of drugs and their appropriate place in pediatric therapy must be considered.

The impact of these developmental changes in drug disposition is largely related to alterations in body composition (e.g. body water content, plasma protein concentrations) and function of organs important in metabolism (e.g. the liver)

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_6

and excretion (e.g. the kidney). During the first decade of life, these changes are dynamic and can be non-linear and discordant making standardized dosing inadequate for effective drug dosing across the span of childhood. Consequently, "standard dosing" of many drugs during rapid phases of growth/development where both drug disposition and response may be altered are generally inadequate for the purpose of optimizing drug therapy. This goal can only be achieved through fundamental and integrative understanding of how ontogeny influences pharmacokinetics and pharmacodynamics. Throughout development, the impact of ontogeny on pharmacokinetics and pharmacodynamics is, to a great degree, predictable and follows definable physiologic "patterns" that will be described in the sections that follow. Significant impairment of normal physiology as occurs in intestinal atresias and gastroschisis (absorptive capacity) as well as renal function (obstructive uropathy) have major implications for optimal dosing.

Developmental pharmacokinetics must take into account normal growth and developmental pathways [1, 2]. A better understanding of the various physiologic variables regulating and determining the fate of drugs in the body and their pharmacologic effects has dramatically improved both the safety and the efficacy of drug therapy for neonates, infants, children, and adolescents [3, 4]. The impact of development on the pharmacokinetics of a given drug is dependent, to a great degree, upon age-related changes in the body composition and the acquisition of function of organs and organ systems that are important in determining drug metabolism as well as drug transport and excretion [5, 6]. Although it is often convenient to classify pediatric patients on the basis of postnatal age for the study and provision of drug therapy (e.g., newborn infants aged 1 month or less, infants between 1 and 24 months of age, children between 2 and 12 years of age, and adolescents between 12 and 16–18 years of age), it is important to recognize that changes in physiology that characterize development may not correspond to these age-defined breakpoints and also are not linearly related to age. In fact, the most dramatic changes in drug disposition occur during the first 12–18 months of life, when the acquisition of organ function is most dynamic [3, 4]. Additionally, independent from developmental aspects, it is important to mention that the pharmacokinetics of a given drug may be altered in pediatric patients also due to intrinsic (e.g., genotype, inherited diseases) and/or extrinsic (e.g., acquired diseases, diet, co-medication) factors that may occur during the first months and years of life [7–12]. To study pediatric pharmacokinetics it is very useful to examine the impact of development on those physiologic variables that govern drug Absorption, Distribution, Metabolism, and Excretion [1, 2, 5] which is summarized by the commonly used term ADME. Especially the surgical newborn with major gastrointestinal and/or renal anomalies forms a very complicated patient in this respect.

6.2 Drug Absorption

For therapeutic agents administered by extravascular routes, the process of absorption is reflected by the ability of a drug to overcome chemical, physical, mechanical, and biological barriers. Developmental differences in the physiologic composition and function of these barriers can alter the rate and/or extent of drug absorption [3, 4]. While factors influencing drug absorption are multifactorial in nature, developmental changes in the absorptive surfaces (e.g., gastrointestinal tract, skin) can be determinants of bioavailability [3, 4].

The most important factors that influence drug absorption after oral administration from the gastrointestinal tract are related to the physiology of the stomach, intestine and biliary tract. During the first few years of life there are significant changes in gastric pH related to parietal cell density and function. Parietal cells are present early in fetal life in the antrum and body of the stomach. However, at term only about 20% of neonates possess the same proportion of parietal cells as observed in adults [13]. The highest gastric pH levels (6–8) occur in the neonate immediately after birth and within hours drop to 2–3. These levels return to neutral over the next 24 h, and remain that way for the next 10 days [1].

These initial changes do not occur in premature infants, who seem to have little or no free acid during the first 14 days of life [1]. However, sick preterm infants have been shown to have a lower gastric pH than healthy preterm infants [14]. In addition, one must also consider the impact of feeding on gastric pH and effects on drug absorption. Feedings with infant formula have been found to increase gastric pH, buffering it to levels >4 for up to 90 min after a feeding. As a consequence, the oral bioavailability of drugs that are acid labile (e.g., beta-lactam antibiotics) may be increased due to reduced degradation. With parietal cell maturation over the next few years, gastric pH gradually decreases to adult values by 3–7 years of age.

Gastric emptying rates also show significant ontogenic differences. The time of gastric emptying is delayed in the period immediately after birth for both full term and preterm neonates. It approaches adult values within the first 6–8 months of life [15]. For drugs with limited water solubility (e.g., phenytoin), gastric emptying rate may significantly influence the rate and extent of bioavailability. Delayed gastric emptying can result in delayed absorption of drugs, since most drugs are absorbed in the small intestine.

Especially in newborns following major loss of intestinal length, either congenital or acquired (NEC), hypergastrinemia has a significant effect on stomach function.

Intestinal transit time is prolonged in neonates because of reduced motility and peristalsis, but appears to be reduced in older infants as a result of increased intestinal motility [15, 16]. Other factors that may play a role in intestinal drug absorption are immaturity of the intestinal mucosa leading to increased permeability, immature biliary function, high levels of intestinal β-glucuronidase activity, reduced first-pass metabolism, maturation of carrier mechanisms and variable microbial colonisation [16]. Additionally, the ability to solubilize and subsequently absorb lipophilic drugs can be influenced by age-dependent changes in biliary function. Immature conjugation and/or transport of bile salts into the intestinal lumen result in low intraduodenal levels despite blood levels that exceed those seen in adults.

Unfortunately, few studies have systematically evaluated the effect of developmental changes in gastric emptying and intestinal motility on drug absorption in infants and children. Anderson et al. showed that the oral acetaminophen absorption rate was significantly lower in the first days of life before stabilizing 1 week after birth [17]. Another study showed that the time to reach the maximum concentration (t_{max}) of cisapride was significantly longer in preterm infants compared with term neonates [18]. Generally, the rate at which most drugs are absorbed is generally slower and thus, the time to achieve maximum plasma concentrations is prolonged in neonates and young infants relative to older infants and children. Despite their incomplete characterization, developmental differences in the activity of intestinal drug metabolizing enzymes and efflux transporters have the potential to markedly alter drug bioavailability.

So far only very few studies have systematically evaluated the effect of ultrafast transit time on drug absorption or intestinal hormone profiles such as gastrin, CCK and peptide YY in newborns with short bowel.

Development can also alter the systemic exposure to drugs given by other routes of administration such as dermal, intramuscular, rectal, and intrapulmonary. The morphologic and functional development of the skin as well as factors that influence the penetration of drugs through the skin have been reviewed [19]. Basically, the percutaneous absorption of a compound is directly related to the degree of skin hydration and relative absorptive surface area and inversely related to the thickness of the stratum corneum [19]. The integument of the full-term neonate possesses an intact barrier function and is similar to that of an older child or adolescent. However, the ratio of surface area to body weight of the full-term neonate is much higher than that of an adult. Thus, the infant will be exposed to a relatively greater amount of drug topically as has been proven in case of local application of drugs-containing ointments to protect (giant) omphaloceles for infection in the past (mercury; jodide, etc.). In contrast, data of human skin from preterm infants indicates

an inverse correlation between permeability and gestational age. Permeability rates were 100- to 1000-fold greater before 30 weeks gestation as compared with full-term neonates, with a three- to fourfold greater permeation rate seen beyond 32 weeks [20]. *In vivo* studies suggest that this increased dermal permeability in preterm infants is a short-lived phenomenon with the permeability barrier of even the most premature neonates similar to that of full-term neonates by 2 weeks of postnatal life [20]. There are numerous reports in the literature underscoring the importance of skin absorption in neonates primarily showing toxicity after exposure to drugs or chemicals [21]. These include pentachlorophenol-containing laundry detergents and hydrocortisone [22, 23]. Therefore, extreme caution needs to be exercised in using topical therapy in neonates and young infants.

In infants absorption of rectally administered agents may be reduced due to a greater number of high-amplitude pulsatile contractions in the rectum, relative to adults, leading to premature expulsion of solid rectal drug formulations (e.g., suppositories). In contrast, rectal solutions of drugs such as diazepam are readily and rapidly absorbed in children, achieving therapeutic plasma concentrations within 4 min of administration [24].

Developmental differences in airway surface area, chest wall compliance, functional residual capacity and hypoxic drive have the potential to influence the local and systemic exposure of drugs that are administered via inhalation. For example, lung deposition increases and oropharyngeal deposition decreases with increasing age (lung deposition from same inhaler/spacer combination 1–2% in infants, 4–6% in 2–6 year old children, and 12% in 10 year old child). Aerosol particles are typically designed for adults and older children and these large-particle aerosols are typically not suitable for newborns, infants and toddlers who have smaller pulmonary passages.

6.3 Drug Distribution

Drug distribution is influenced by a variety of drug-specific physiochemical factors, including the role of drug transporters, blood/tissue protein binding, blood and tissue pH and perfusion [1, 3, 4]. However, age-related changes in drug distribution are primarily related to developmental changes in body composition, the concentration of available binding proteins, and the capacity of plasma proteins to bind drugs. Age-dependent changes in body composition alter the physiologic "spaces" into which a drug may distribute [25]. When expressed as a percentage of total body mass, neonates and young infants have significantly higher extracellular fluid and total body water spaces (e.g., 80% in infants vs. 60% in adults). In contrast, the percentage of intracellular water as a function of body mass remains stable from the first months of life through adulthood. Age-dependent changes in body composition can alter the apparent volume of distribution for many drugs, both hydrophilic and lipophilic in character. Larger extracellular and total body water spaces in neonates and young infants, coupled with adipose stores that have a higher water/lipid ratio than in adults, produce lower plasma concentrations for drugs that distribute into these respective compartments when administered in a weight-based fashion. The surgical newborn suffering from ongoing fluid losses in the abdominal cavity (intestinal obstructions, volvulus NEC) in combination with generalized edema can still suffer from intravascular hypovolemia. This has major consequences for renal function. In clinical practice the amount and quantification of changes in extracellular fluids is very difficult. Several hydrophilic drugs such as gentamicin and linezolid have a significantly larger volume of distribution in neonates than in infants or adults [26, 27].

The extent of drug binding to proteins in the plasma may influence the volume of distribution of drugs [1]. Only free, unbound, drug can be distributed from the vascular space into other body fluids and, ultimately, to tissues where drug-receptor interaction occurs.

Albumin, total protein, and total globulins such as α[alpha]1 acid-glycoprotein are the most important circulating proteins responsible for the drug binding in plasma. The absolute concentration of these proteins is influenced by age, nutrition, and disease. Changes in the composition and amount of these circulating plasma proteins can also influence the distribution of highly bound drugs [1, 5]. A low plasma albumin is commonly

observed in newborns with gastroschisis, intestinal atresia, and NEC postoperatively. A reduction in both the quantity and binding affinity of circulating plasma proteins in the neonate and young infant often produces an increase in the free fraction of drug, thereby influencing the availability of the active moiety and potentially, its subsequent hepatic and/or renal clearance. For example, phenytoin is extensively (~94–98%) bound to albumin in adults as compared to 80–85% in the neonate and the resultant six to eightfold difference in the free fraction can result in CNS adverse effects in the neonate when total plasma phenytoin concentrations are within the generally accepted "therapeutic range" (10–20 mg/L).

Other factors associated with development and/or disease such as variability in regional blood flow, organ perfusion, permeability of cell membranes, changes in acid-base balance and cardiac output can also influence drug binding and/or distribution. Finally, drug transporters such as the ABC efflux pump P-glycoprotein (MDR1/ABCB1) can influence drug distribution because these transporters can markedly influence the extent to which drugs cross membranes in the body and whether drugs can penetrate or are secreted from the target sites (e.g., cerebrospinal fluid). P-glycoprotein has been found to be expressed in the human central nervous system as early as 27 weeks of gestation with expression intensity during the neonatal period becoming most prevalent at 33 weeks of gestation. This is particular relevant in the large number of premature born infants treated for NEC. Within the CNS there is also differential expression within various regions of the brain in relation to age [28]. P-gp in the liver also follows a developmental pattern of expression whereby activity increases during the first few months of life and adult levels are reached by 2 years of age [29].

6.4 Drug Metabolism

Drug metabolism exhibits marked developmental dependence, especially during fetal and early postnatal life. Hepatic development begins in the fetus at the fourth week of gestation as a duodenal diverticulum. By the sixth week of fetal life hepatic lobules are present and by the ninth week, the organ represents 10% of the fetal weight [30]. Drug metabolism reflects the biotransformation of an endogenous or exogenous molecule by one or more enzymes to moieties, which are more hydrophilic and thus can be more easily excreted [1, 3, 4]. While metabolism of a drug generally reduces its ability to produce a pharmacologic action, it also can result in a metabolite that has significant potency, and thereby, contributes to the overall pharmacological effect of the drug. A good example being morphine in which the M3-and M6-glucuronide metabolites have extensive anti- and equal morphinomimetic effects. In the case of a pro-drug such as codeine, biotransformation is required to produce the pharmacologically active metabolite morphine. Although drug metabolism takes place in several tissues (e.g., intestine, skin, kidney, lungs, liver), hepatic metabolism has been investigated most intensively and this metabolism has been divided conventionally into two phases [1, 3, 4]. Phase I hepatic metabolism usually results in modifying the therapeutic agent or xenobiotic (e.g., through oxidation) in order to make the molecule more polar. Phase II hepatic metabolism usually results in addition of a small molecule (e.g., glucuronide) to the therapeutic agent in order to make it more polar. As the architecture of the liver develops, so do the families of enzymes responsible for the biosynthesis and metabolism of both endogenous and exogenous substrates. While there are many enzymes that are capable of catalyzing the biotransformation of drugs, the quantitatively most important are represented by the cytochromes P450 (CYP450). The specific CYP450 isoforms responsible for the majority of human drug metabolism are represented by CYP3A4/5, CYP1A2, CYP2B6, CYP2D6, CYP2C9, CYP2C19, and CYP2E1.

Development has a profound effect on the expression of CYP450. Distinct patterns of isoform-specific developmental CYP expression have been observed postnatally. As reflected by recent reviews, distinct patterns of isoform-specific developmental changes in drug biotransformation are apparent for many Phase I and Phase II drug metabolizing enzymes [31–34]. Very recently, Hines [35] has categorized the

development of enzymes involved in human metabolism in three main categories: (1) those expressed during the whole or part of the fetal period, but silenced or expressed at low levels within 1–2 years after birth, (2) those expressed at relatively constant levels throughout fetal development, but increased to some extent postnatally and (3) those whose onset of expression can occur in the third trimester, but substantial increase is noted in the first 1–2 years after birth. Based on literature data CYP3A7, flavin-containing monooxygenase 1 (FMO1), sulfotransferase 1A3/4 (SULT1A3/4), SULT1E1, and maybe alcohol dehydrogenase 1A (ADH1A) belong to the first group. To the second group belong CYP2A6, 3A5, 2C9, 2C19, 2D6, 2E1, and SULT1A1. The third group includes ADH1C, ADH1B, CYP1A1, 1A2, 2A 6, 2A7, 2B6, 2B7, 2C8, 2C9, 2F1, 3A4, FMO3, SULT2A1, glucoronosyltransferases (UGT) and N-acetyltransferase 2 [35–37].

In addition to these *in vitro* data, there has been an explosion in the amount of information generated about metabolism of therapeutic agents in children during the last two decades. *In vivo* data have been generated largely through two means [38, 39]. One is through dedicated ontogeny studies in which a probe drug (e.g., dextromethorphan or acetaminophen/paracetamol) is given to children of various age groups or to the same children over a period of time [38, 39]. The other manner in which these *in vivo* data have been developed is serendipitously over the course of industry-sponsored or investigator-initiated pediatric clinical trials. The most important examples of studies that have resulted in clinically important insight into the ontogeny of drug metabolism are summarized in the following paragraph.

Midazolam plasma clearance, which primarily reflects hepatic CYP3A4/5 activity after intravenous administration [40, 41], increases approximately fivefold (1.2–9 mL/min/kg) over the first 3 months of life [42]. CYP2C9 and to a lesser extent, CYP2C19, are primarily responsible for phenytoin biotransformation [43]. Phenytoin apparent half life is prolonged (~75 h) in preterm infants but decreases to ~20 h. in term infants less than 1 week postnatal age and to ~8 h. after 2 weeks of age [44]. Also for caffeine developmental changes is elimination have been describes [45]. Saturable phenytoin metabolism does not appear until approximately 10 days of postnatal age, demonstrating the developmental acquisition of CYP2C9 activity.

It is well established that infants who are barely into their second trimester of gestational life and are born with a weight of just a few hundred grams (400–500 g) can survive and will develop into a surgical newborn by chance. On the other extreme, by the end of the first month of postnatal life, large for gestational age infants may weigh upwards of several kilograms. Indeed, the 95th weight percentile is approximately 5 kg. No other age groups can be defined in differences measured logarithmically. As one might expect, there are similar tremendous developmental changes in hepatic drug metabolizing enzymes during this time frame. Understanding these implications is important for individualized dosing in critically ill surgical newborns.

6.5 Phase I Enzymes

6.5.1 CYP3A

The CYP3A subfamily represents the majority of CYP total content in the liver. Indeed, it has been shown that over one-half of all drugs administered to pediatric patients (e.g., tacrolimus, midazolam, fentanyl) are metabolized by CYP3A [46]. The CYP3A subfamily consists of CYP3A4, 3A5, 3A7 and 3A43. CYP3A43 is not known to play a significant role in hepatic metabolism. It has been established that CYP3A4 is the predominant CYP3A enzyme in adults, whereas CYP3A7 is the predominant CYP3A enzyme in the fetus and infants. Moreover, there is a great deal of overlap of specificity of ability for CYP3A4 and CYP3A7 to metabolize therapeutic agents. In 2003, Stevens et al. published the results of examining the largest collection of fetal and pediatric liver samples to date [47]. The study included 212 samples. Stevens and colleagues demonstrated that CYP3A7 is highest between 94 and 168 postconceptional days on a pmol/mg basis of total hepatic protein [47]. The

level at birth is less than half that of the high prenatal value. However, it remains higher than that of even adult CYP3A4 levels. Furthermore, these hepatic samples demonstrated that there is minimal CYP3A4 activity prenatally that continues to increase after birth. Nevertheless, CYP3A7 content remains higher than CYP3A4 content until at least 6 months of age. The high activity of CYP3A7 early in fetal life is associated with its function in forming a precursor for estriol biosynthesis, a hormone that is important in fetal growth and timing of child birth. CYP3A4 and CYP3A5 have overlapping substrate specificities and in the case of CYP3A5, polymorphic expression with racial differences in the genotype-phenotype relationship exists that can have significant effects on the biotransformation of drugs that are substrates for this isoform [48]. A clear developmental pattern for CYP3A5 expression has not yet been fully elucidated.

To date, two probe drugs have been researched extensively, which have demonstrated the lower activity of CYP3A4 at birth and in neonates. In 2001, de Wildt et al. published the results of midazolam metabolism given to 24 preterm infants [40]. Only 19 of 24 preterm infants produced detectable levels of 1-OH-midazolam. Furthermore, these results firmly established that premature infants had lower CYP3A4 activity than full-term infants, than did children and adults historically. In conclusion, CYP3A7 activity is very high before birth and continues to have high activity after birth and is even present into adulthood. CYP3A4 possesses very low activity at birth and very slowly increases in the neonatal period. Thus, when designing studies and dosing with substrates for CYP3A4 in young infants and children, great care needs to be taken to adjust for this low activity in order to achieve the goal of the FDA guidance that in children exposure and Cmax are not higher than that in adults.

6.5.2 CYP1A2

One of the first CYP enzymes to be studied utilizing a probe drug in the first year of life is CYP1A2. Two methylxanthines (caffeine and theophylline) have been utilized extensively to evaluate CYP1A2 in vivo in young children [49–51]. Theophylline and caffeine are two commonly utilized medications in neonates for the treatment of apnea. These medications are frequently continued form the neonatal period during the first year of life. At birth, caffeine-3-demethylation, a measure of CYP1A2 activity, is very low. Consequently, Erenberg et al. published that the efficacious dose of caffeine is 10 mg/kg every day [50]. The half-life of caffeine is 72–96 h in infants compared to approximately 5 h in older children and adults. Similarly, 8-hydroxylation of theophylline is reduced at birth. Specific effects on intestinal circulation of premature borns with NEC are not available. Nevertheless, longitudinal data indicate a rapid maturation process for CYP1A2, as it appears to reach adult levels within the first year of life, often within the first 6 months of life.

In conclusion, it is evident that CYP1A2 activity is highly reduced in young infants. Additionally, activity of the enzyme is highly inducible. Finally, maturation of CYP1A2 activity is rapid in the first year of life.

6.5.3 CYP2D6

CYP2D6 is one of the most polymorphically expressed enzymes in humans [52, 53]. Some estimates indicate the fewer than 90% of individuals are homozygous for the wild-type allele. In 1991, Treluyer et al. published the results of liver samples from fetuses aged 17–40 weeks postconception [54]. These results demonstrated that the concentration of hepatic CYP2D6 protein was very low or undetectable in these fetuses. This lack of CYP2D6 activity at birth led to the hypothesis that birth-related events may trigger maturation of the enzyme. In 2007, Blake et al. published in vivo results that provided further understanding of CYP2D6 activity in the first year of life [38]. Dextromethorphan results demonstrate indeed that there is low activity at birth, but that there is rapid acquisition of CYP2D6 activity in the first year of life. Already within the

first 2 weeks of life there is measurable acquisition of CYP2D6 activity. Despite the discussion in the literature about the fact that the increase in renal function might conceal the enzyme development resulting in an apparent plateau of the metabolic ratio after 2 weeks [55], very recent data show that an infant with a postmenstrual age of 52 weeks has already mature hepatic CYP2D6 activity [56].

6.5.4 CYP2C9/CYP2C19

Lee et al. [57] and Koukouritaki et al. [58] have published the most extensive reviews to date on CYP2C activity in humans. They demonstrate that the two main representatives of the CYP2C subfamily of enzymes (CYP2C9 and CYP2C19) conveniently follow the CYP2C rule of 20%. Approximately 20% of hepatic CYP content of adult livers is CYP2C and these CYP2C enzymes metabolize 20% of pharmaceuticals developed to date.

Although not to the same extent as CYP2D6, the two main CYP2C representatives are polymorphically expressed. To date, over ten genetic polymorphisms of CYP2C9 have been identified and at least 15 genetic polymorphisms of CYP2C19 have been reported in the literature [57, 58]. Just as with CYP2D6, these polymorphisms may result in poor metabolizer status, which may confound studies in infants and young children.

The ontogeny of CYP2C9 is much better established than CYP2C19. Indeed, hepatic liver samples have shown that CYP2C9 activity is functionally very low just prior to birth. However, much like CYP2D6, this activity increases quickly in the first year of life. The classic example of the effects of this very low level of CYP2C9 activity at birth can be seen with phenytoin [59]. Indeed, the recommended daily dose for newborns is 5 mg/kg/day, but by 6 months to 3 years of age this increases to 8–10 mg/kg/day consequent to increased CYP2C9 activity.

Two major pharmaceutical classes of drugs (i.e., benzodiazepines and proton pump inhibitors) have major representative therapeutic agents that are metabolized by CYP2C19 [60, 61]. Indeed, characteristic representatives from these classes are used in the literature to indirectly ascertain the ontogeny of CYP2C19 activity. Hydroxylation of diazepam is attributed to CYP2C19 activity and is a classic example of the effects of the maturation process of CYP2C19 [62]. In neonates, the half-life of diazepam is reported to be 50–90 h. Within the first year of life, that half-life of 40–50 h is much closer to the adult value. The surgical ELBW infant with a high risk of CNS-related problems (convulsions; intracranial hemorrhage) can easily be overdosed once these phenomena are not taken into account. More recently, the effects of the ontogeny on proton pump inhibitor metabolism have been reviewed. To date, all proton pump inhibitors other than rabeprazole are metabolized by CYP2C19. Of the drugs in this class, the biotransformation of pantoprazole is predominantly dependent upon CYP2C19 activity. As expected, exposures of the CYP2C19 metabolism-dependent proton pump inhibitors are universally increased in the youngest infants when genetic polymorphisms of CYP2C19 are fully accounted for [61, 62].

Taken together, these results demonstrate an important trend when designing pharmaceutical studies that depend on hepatic metabolism through the two major CYP2C enzyme pathways. It is extremely important to be cognizant of the limited activity of these enzymes in early childhood and its potential differences in case of serious hepatic disease such as biliary atresia and TPN-associated cholestasis. Moreover, much like with CYP2D6, it is important to recognize the impact of genetic polymorphisms when studying individuals who take substrates of these enzymes [63]. Finally, the first 3 months of life represents a dramatic maturation time for the activity of many drug metabolizing enzymes. When considered in the context of a similar dramatic, nonlinear increase in body size (i.e., both weight and length), individualization of drug dose based on pharmacokinetic data is often a real challenge, especially for agents where attainment of critical target plasma concentrations (or systemic exposures) is necessary.

6.5.5 CYP2E1

CYP2E1 is being increasingly recognized for its importance in the oxidative metabolism of a wide variety of pharmaceuticals (e.g., acetaminophen, halothane, and ethanol) [64]. However, only in the last 5 years has the developmental patterns of this important enzyme been well understood [65]. Nevertheless, human hepatic CYP2E1 developmental expression is difficult to appreciate due to the multiple levels of regulation in its activity. Finally, an increasing number of genetic polymorphisms, which lead to lower CYP2E1 protein concentration, have been demonstrated in the literature [66].

To date, Johnsrud et al. have published the largest study of the activity of fetal and pediatric liver samples to determine the ontogeny of CYP2E1 [65]. Measurable CYP2E1 activity was demonstrated in 18 of 49 second trimester livers and 12 of 15 third trimester samples. Moreover, measurements of mean concentrations of CYP2E1 protein as part of total milligrams of microsomal protein found that second trimester infants averaged 0.35 pmol/mg, third trimester infants 6.7 pmol/mg, newborns 8.8 pmol/mg and older infants aged 30–90 days 23.8 pmol/mg, and finally children aged 90 days to 18 years 41.4 pmol/mg. Thus, this implies a rapid maturation starting in late fetal life and continuing through early infancy in CYP2E1 activity. It would appear that these data demonstrate that careful attention would be required in studies of new CYP2E1 substrates in infants under the age of 90 days.

Of the cytochrome P450 isoforms quantitatively important for drug metabolism in humans, all studied till now appear to have a developmental pattern with respect to the attainment of activity.

As with chloramphenicol, morphine, acetaminophen, and zidovudine, all UGT substrates have a requirement for alteration of dosing regimen to compensate for reduced enzyme activity in the first weeks and months of life. In premature infants (gestational age 24–37 weeks) the plasma clearance of morphine was found to be fivefold lower relative to older children. The clearance of morphine, a predominant UGT2B7 and UGT1A1 substrate, generally reaches adult levels between 2 and 6 months of life. However, considerable variability exists [67]. Acetaminophen glucuronidation (a substrate for UGT1A6 and UGT1A9) is present in the fetus and newborn at very low levels (1–10% of adults). Following birth, activity steadily increases with levels approaching (~50%) by 6 months of age and full maturation by puberty.

6.6 Drug Excretion

Drug excretion or elimination in pediatric patients can occur via multiple routes which include biliary excretion, exhalation, and renal clearance. Of these, the kidneys are quantitatively the most important. The kidney is the primary organ responsible for the excretion of drugs and their metabolites. Maturation of renal function is a dynamic process that begins early during fetal organogenesis and is complete by early childhood [68, 69]. The developmental increase in glomerular filtration rate (GFR) involves active nephrogenesis, a process that begins at 9 weeks and is complete by 36 weeks of gestation, followed by postnatal changes in renal and intrarenal blood flow. Following birth, the GFR is approximately 2–4 mL/min/kg in term neonates and as low as 0.6–0.8 mL/min/kg in preterm neonates [70]. GFR increases rapidly during the first 2 weeks of life followed by a steady rise until adult values are reached by 8–12 months. This increase in GFR in the first weeks of life is mainly because of an increase in renal blood flow. Similarly, tubular secretory pathways are immature at birth and gain adult capacity during the first year of life.

There is a clear controversy regarding the use of serum creatinine to predict renal function in children [71]. Serum creatinine depends on many factors and residual maternally derived creatinine interferes with the assay in the first days of life in neonates [72]. In addition, factors that have a negative influence on the use of plasma creatinine to predict renal function are renal tubule integrity issues and GFR values of less than 20 mL/

min/1.73m^2. In these individuals GFR is probably overestimated. If creatinine is measured with the Jaffé reaction ketoacids, serum bilirubin and cephalosporins interfere with the reaction and therefore the use of an enzymatic method should be advised because of less interference as compared to the Jaffé method [73]. A more direct approach to estimate the GFR is to use a marker that is freely permeable across the glomerular capillary and neither secreted nor reabsorbed by the tubulus. Markers that have been mentioned to measure the GFR are inulin, polyfructosan S, cystatin C, ^{51}Cr-EDTA, ^{125}I-iothalamate or mannitol [71, 74]. A marker to estimate the active tubular secretion in children is p-aminohippuric acid [74].

However, a comparison between serum creatinine with inulin clearance in preterm infants showed a good and clinical useful correlation and supported serum creatinine as an appropriate measure of GFR in preterm infants already on day 3 of life [73].

Collectively, the aforementioned changes in GFR dramatically alter the plasma clearance of compounds with extensive renal elimination and thus, provide a major determinant for age-appropriate dose regimen selection. Pharmacokinetic studies of drugs primarily excreted by glomerular filtration such as ceftazidime and famotidine have demonstrated significant correlations between plasma drug clearance and normal, expected maturational changes in renal function [70, 75]. For example, tobramycin is eliminated predominantly by glomerular filtration, necessitating dosing intervals of 36 to 48 h in preterm and 24 h in term newborns [76]. Failure to account for the ontogeny of renal function and adjust aminoglycoside dosing regimens accordingly can result in exposure to potentially toxic serum concentrations. Also, concomitant medications (e.g., betamethasone, indomethacin) may alter the normal pattern of renal maturation in the neonate. Thus, for drugs with extensive renal elimination, both maturational and treatment associated changes in kidney function must be considered and used to individualize treatment regimens in an age-appropriate fashion. The amount of illness especially in ELBW-infants with a hemodynamic important open ductus arteriosus should be taken into account as a contributing factor resulting in overdosing of for instance aminoglycosides.

As denoted above, development produces profound differences in processes that collectively, can influence all facets of drug disposition (i.e., absorption, distribution, metabolism and excretion). Knowledge of the impact of ontogeny on the physiologic determinants of drug disposition enables prediction of how development per se can impact pharmacokinetics and also, enables the clinician to use this information as a tool for designing age appropriate drug regimens. A recent review by van den Anker, et al. describes the implications of developmental pharmacokinetics on pediatric therapeutics [4].

6.7 Other Factors Influencing the Absorption, Distribution, Metabolism and Excretion of Drugs in Neonates and Young Infants

In addition to growth and development there are several other major variables that will influence the pharmacokinetic parameters of drugs such as inborn or acquired diseases, environmental influences such as body cooling, and pharmacogenomics. It is outside the scope of this chapter to provide extensive information on these important variables but a few will be highlighted here.

Hypoxic-ischemic events are encountered regularly in sick neonates and these events might result in a decrease in the rate and amount of drug absorption as well as impaired renal function. There are data to show that after perinatal asphyxia the GFR in neonates is 50% less as compared to neonates born without asphyxia, resulting in a decreased clearance of renally cleared drugs [77]. The persistence and/or closure of a patent ductus arteriosus has a major impact on both the volume of distribution and elimination of frequently used drugs in the newborn [78]. This has been shown for drugs such as ceftazidime where the existence of a patent ductus and or the exposure to indomethacin to close

this ductus was associated with a decreased GFR and a larger volume of distribution of ceftazidime, a solely renally cleared drug. In another study investigating ibuprofen there was a significant increase in the clearance of ibuprofen after closure of the ductus [79]. Finally, total body cooling is a new treatment modality that is being used to improve the neurological outcome of neonates who suffered from perinatal asphyxia. In a study investigating the pharmacokinetics of morphine in neonates with and without body cooling a clinically impressive decrease in morphine clearance was seen in neonates on body cooling [80].

6.8 Pharmacogenomics: Impact for Pediatric Populations

The contribution of genetic factors to explain heterogeneity of drug response in infants and children is another important issue with the ultimate goal for better treatment of children based on the individual genetic make-up. One of the major tasks is to optimally adapt the choice and amount of a drug to the individual need of a patient and for instance to prevent overdosing with the risk of adverse drug reactions. Genetic variability influences almost all ADME processes including drug absorption (e.g. via the intestinal drug transporter P-glycoprotein/ABCB1), drug metabolism (e.g. cytochrome P450 enzymes 2C9, 2C19, 2D6) and drug elimination, thereby resulting in alteration of pharmacokinetics and subsequently of pharmacodynamic processes.

There is an increasing body of evidence that genetic variants in drug metabolizing enzymes (e.g. CYP450 enzymes; http://www.cypalleles.ki.se/) as well as in drug transporters (e.g. ABCB1/P-gp, SLCO1B1/OATP1B) [80–82] are functional relevant (e.g. loss of function variants or gain of function polymorphisms) with in part dramatic changes in mRNA and/or protein expression and function. Genetic variants in drug targets such as receptor molecules or intracellular structures of signal transduction and gene regulation directly and/or indirectly may also influence drug response and tolerability in the neonate and young infant. Based on several novel and promising genomic technologies such as high-throughput genotyping (e.g. MALDI TOF mass spectrometry), genome-wide association studies and next generation sequencing, pharmacogenomic knowledge will improve our understanding of pharmacotherapy in children but will also stimulate the drug development process for innovative agents in the future [83, 84].

At present we know that age and genetic determinants of CYP2D6 expression constitute significant determinants of inter-individual variability in CYP2D6 dependent metabolism during ontogeny. Very recently it was documented that the in vivo phenotypic CYP2D6 activity was concordant with the genotype from 42 weeks postmenstrual age onwards [9, 38]. This indicates that for clinicians treating neonates, young infants, children and adolescents the genetic variation in CYP2D6 is the major player to consider if prescribing CYP2D6 substrates.

In summary, both genetic and environmental factors contribute to inter-individual variability in the PK of medications metabolized by CYP2D6 [10, 11]. In this context a recent paper using a whole body physiology-based pharmacokinetic (PBPK) modelling approach to investigate the contribution of CYP2D6 genetics on codeine administration in breastfeeding mothers and their babies supports the evidence that pediatric pharmacogenomics comprises more than a single gene, and developmental aspects of physiological processes need to be considered [85].

6.9 Developmental Pharmacodynamics

Developmental pharmacodynamics has been described as the study of age-related maturation of the structure and function of biologic systems and how this affects drug response. Relative to pharmacokinetic data there is paucity of information regarding developmental pharmacodynamics.

There is evidence that differences in receptor number, density, distribution, function, and ligand affinity differ among children of differing

ages and adults. Much of the data demonstrating these differences is acquired from studies of the central and peripheral nervous systems. A recent study in humans found that the $GABA_A$ receptor, which binds benzodiazepines and barbiturates, has significantly higher expression levels in the brain at 2 years of age as compared to older children and adults. These data suggest that the GABA receptors have a rapid increase in expression early in infancy that subsequently declines with age. In addition there is evidence in animal models that this inhibitory transmitter has excitatory functions early in development. Early in development chloride concentrations in the neuron are relatively high which leads to excitation (depolarization) of the cell upon opening of the chloride channels by GABA. With maturation, intracellular chloride concentrations decrease which result in inhibition (hyperpolarization) of the cell upon opening of the channel by GABA. These changes may explain observed differences in dosing in infants (require relatively larger doses of antiepileptic medications e.g. midazolam) and furthermore explain seizures experienced by infants upon benzodiazepine exposure. In animal studies, neonatal exposure to GABAergic agents (anticonvulsants, IV and inhaled anesthetics) during synaptogenesis accelerates apoptotic cell death in the CNS [86].

Another example in the CNS resides with the μ-opioid receptor, the numbers of which are markedly reduced (i.e., >50%) in newborn as compared to adult rats [87]. Regional opioid receptor distribution in the brain also exhibits developmental differences. In neonates receptor density is lower in the areas of the brain responsible for analgesic effect (e.g. cortex, thalamus, hippocampus) as compared to those areas of the brain where autonomic/side-effects are produced (e.g., pons, medulla, hypothalamus) as receptor density in these areas approximates that observed in adults [87]. These data suggest that differences may exist regarding the analgesic potency of opiates in neonates as compared to adults.

It is important of expanding pediatric pharmacology studies beyond descriptions of age-dependence in pharmacokinetics to include data on pharmacodynamics. A hindrance in accomplishing this goal in surgical newborns is the interaction and relative contribution of (altered physiology) and the "defective" (multi)organ function in this population. In most institutions the annual number of specific diagnoses seriously hampers clinical studies of appropriate size to reach an acceptable level of evidence. To address this disparity in pharmacodynamic data will require the development of pharmacodynamic "biomarkers" which are sufficiently robust that they can be used as surrogate endpoints to assess the relationship of drug exposure and response across the developmental continuum and specific conditions.

Creative and selective use of non-invasive surrogate endpoints and validated biomarkers can add to the current body of knowledge pertaining to the ontogeny of pharmacodynamic response.

Conclusions

The surgical newborn population shows unique differences in pharmacokinetic parameters as compared to adults and therefore requires specific dosage recommendations. While the paucity of pharmacokinetic and physiological data makes it difficult to precisely determine drug doses, knowledge of the effects of growth, maturation, environmental influences, and pharmacogenetic background on absorption, distribution, metabolism, and elimination of frequently used medicines will allow more appropriate dosing recommendations for this patient population. Clearly, much more research is needed to fully understand the impact of (abnormal) development on specific organ function and its consequences for short term (pharmacotherapy) and long term effects (neurodevelopmental outcome; pharmacovigilance).As described in this chapter, studies with substrates as markers for hepatic metabolic activity or renal function and *in vitro* data are very useful for a better understanding of this impact. Finally, there is an urgent need to better understand the metabolic activity, carrier mechanisms and drug transporters related to the gastrointestinal tract, forming a major area of interest given the pathology for pediatric surgeons taking care of these vulnerable patients.

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Transfer of the Surgical Neonate

7

Christopher P. Driver

Abstract

Neonatal surgery is increasingly delivered in regional or even supra-regional centres with the specific aim of improving short and long-term outcome for complex congenital conditions. This arrangement permits the concentration of a multidisciplinary team of experts equipped with the wide range of skills required to successfully manage the specific challenges posed by the newborn surgical patient. Neonatal intensive care for these patients may need to commence immediately after delivery or may be only required following surgical intervention. It is essential therefore that nurses and clinicians in units which may potentially receive surgical neonates have the appropriate competencies required for the initial stages of management.

This chapter will discuss in utero transfer, the general principles of neonatal stabilisation prior to and during transfer, important principles of the transfer itself and condition specific considerations for common neonatal surgical conditions.

Keywords

Neonatal surgery • Neonatal transport • Guidelines

7.1 Introduction

Neonatal surgery is increasingly delivered in regional or even supra-regional centres with the specific aim of improving short and long-term outcome for complex congenital conditions. This arrangement permits the concentration of a multidisciplinary team of experts equipped with the wide range of skills required to successfully manage the specific challenges posed by the newborn surgical patient. Neonatal intensive care for these patients may need to commence immediately after delivery or may be only required following surgical intervention. It is essential therefore that nurses and clinicians in units which may potentially receive surgical neonates have the appropriate competencies required for the initial stages of management [1].

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_7

This chapter will discuss in utero transfer, the general principles of neonatal stabilisation prior to and during transfer, important principles of the transfer itself and condition specific considerations for common neonatal surgical conditions.

7.2 In Utero Transfer

With increasing antenatal diagnosis of congenital anomalies there is often the opportunity to plan the transfer arrangements in advance. Most babies born with complex surgical conditions are relatively stable and can therefore be delivered and initially managed safely in any appropriately equipped and staffed neonatal unit. There are however specific advantages of in utero transfer in certain conditions. The most significant of these is the ability to deliver a baby with a known complex condition in an environment where all potential therapeutic requirements (staff and equipment) are readily available. This enables optimal timing of appropriate specialist interventions without the need for a potentially difficult postnatal transfer in a high risk newborn. An example of this would be in a fetus with an antenatally diagnosed congenital diaphragmatic hernia who may need immediate specialist ventilatory management and rapid access to extracorporeal membrane oxygenation.

It is not without its own risks however. Transferring a mother pre-delivery can lead to a prolonged antenatal hospital stay, far from friends and family in an unfamiliar environment and with unfamiliar staff. In utero transfer should therefore only be considered if the local unit cannot provide appropriate immediate care or a postnatal transfer is considered to be high risk.

7.3 Pre-Transfer Stabilisation

Many complex surgical conditions are not diagnosed antenatally—and even pre-diagnosed babies don't always follow pre-considered plans—so any hospital offering maternity services must be fully prepared to initiate resuscitation and stabilisation prior to transfer to a specialist surgical unit for definitive repair. The general principles of management of a baby born with a surgical condition are initially little different to those applied to a medical neonate [2]. The initial aims are to ensure optimisation of blood pressure, oxygen saturation, blood glucose and blood gases to minimise the risk of secondary injury as result of poor resuscitation, ensuring a baby is in the best possible clinical condition prior to the transfer occurring [3].

The key features of stabilisation are:

- Appropriate airway and respiratory management
- Adequate monitoring of Heart Rate, Blood Pressure and Oxygen Saturation
- Appropriate lines and tubes in place, functioning and secure
- Condition specific management initiated when vital signs stabilised

A checklist for stabilisation may be a useful *aide memoire* [2] (Fig. 7.1).

7.4 General Principles of Transfer

Transfer of the surgical neonate is often provided by specialist neonatal retrieval teams based in the regional centre. These teams should comprise of an appropriately trained and experienced doctor and neonatal intensive care nurse who can guide initial resuscitation, initiate an appropriate level of neonatal intensive care and stabilise the surgical neonate prior to transfer back to the regional unit. As detailed above appropriate prior stabilisation permits a controlled and safe transfer, minimizing risk to the patient and the transfer team. Again, a Transport Checklist (Fig. 7.2) may be useful.

Airway
Is airway patent and secure?

Breathing
Is endotracheal intubation and mechanical ventilation required prior to transfer?

Circulation
Has baby been adequately fluid resuscitated to place heart rate and BP within an acceptable range? Is inotropic support required to maintain adequate perfusion?

Temperature
Ideally skin-core perfusion should be monitored to aide assessment of peripheral perfusion. The baby should be stabilised in a thermoneutral environment where possible. It should be remembered that heat loss is considerably increased with exposed viscera (e.g. gastroschisis)

Metabolic
Electrolyte, glucose and acid-base balance should be optimised prior to transfer ideally

Infection
Have appropriate antibiotics been given either for treatment or prophylaxis?
Has this been clearly documented?

Comfort
Has the need for analgesia been considered or given prior to transfer?
Has this been clearly documented?

Safety
Is all necessary equipment for transfer available and working?
Is the baby clearly identified with two name bands?

Tubes
Does the baby require a nasogastric tube to be passed for decompression aide ventilation and to reduce the risk of aspiration?
Is vascular access adequate and secured?
Is a urinary catheter required?

Parents
Are parents informed of the condition of their baby?
Has a provisional plan been discussed with them?

Condition specific treatments
Are any condition specific interventions required prior to transfer?

Fig. 7.1 Stabilisation Checklist. From: Scottish Neonatal Transfer Service Stabilisation Handbook. Greig C, Mitchell A, et al. 2007; used with permission

7.5 Mode of Transfer

The decision on the appropriate mode of transfer is dependent on a number of issues such as geography, weather, distance to travel and the condition of the infant. All have specific advantages and disadvantages. Road transfer is cheap, quick to initiate, with good patient accessibility and relatively weather immune but can be slow. Helicopters are quick, can fly at low altitude if necessary but require an appropriate landing site, have limited space, can compromise patient assessment with noise and vibration, are expensive and are weather limited. Fixed wing aircraft are quieter, quicker over long distance and can have more space but are also expensive, take longer to organise and need a land transfer to and from the airport to the hospital.

Transport incubator. The modern transport incubator should be capable of providing high

Fig. 7.2 Transfer Checklist

Medical and nursing record
Has all relevant initial resuscitation and management been documented and copied for the transport team to take?

Drugs
Have all drugs administered been documented?
Has Vitamin K been given and documented?

Results of investigations
Are all relevant results available including biochemistry, haematology, microbiology and blood gases?

Imaging
Are copies of relevant imaging available to be taken by the transport team?

Maternal Blood sample
This may be required for testing if neonatal blood transfusion is required.
Is it must be accurately and appropriately labelled with all maternal details?

Parents
Are parents informed of the condition of their baby? Has a provisional plan been discussed with them? Do they know where their baby is being transferred to and have arrangements been made for them to get there? Do parents and transport team have accurate contact phone numbers?

performance respiratory support with optimal thermoregulation during transfer. It should have facilities for continuous monitoring of heart rate, blood pressure and oxygen saturation and ideally advanced ventilatory monitoring. It requires both air and oxygen cylinders and suction equipment, battery operated pumps to administer drugs and fluids together with the ability to access external power and gases when available. It should be robust and must have the facility for secure fixation to the transport vehicle of choice during transfer. It should carry a full range of emergency equipment and drugs required for maintaining and if necessary escalating intensive care during transfer. The transport team must be familiar with all aspects of the equipment and have the ability to "trouble shoot" during the transfer if required.

7.6 Parents

In the difficult period of initial resuscitation and stabilisation it is easy to overlook the parents. They may have had an antenatal diagnosis and subsequent counselling to prepare them for what is likely to happen but with many surgical conditions the diagnosis is only made at delivery. There is often—quite appropriately—considerable anxiety and concern about their newborn child and the need for a transfer to a regional centre will only increase that. It is essential therefore that parents are informed of and involved in decision making as much as is practically possible. It is important to discuss with parents the reason for transfer, a provisional plan, the mechanism and destination of the transfer and the likely time scale. In addition parents need contact details of the receiving unit and travel directions, ideally in written form. They should get the opportunity to see their baby prior to transfer and ideally have a photograph taken. It is possible that a mother may have just undergone a surgical procedure herself and is unable to travel with her baby so the transferring team must make every effort to keep her informed.

7.7 Consent

Consent for any proposed surgical procedure may cause difficulty if a baby is transferred to specialist centre. If possible one parent (who has the legal right to consent) should accompany the baby to permit the operating surgeon to discuss the risks and benefits of surgery prior to obtaining informed consent. A consent form sent with a baby which has been signed by a parent without this discussion has limited legal standing. If a

parent cannot accompany the infant then consent can be obtained via a telephone conversation with the operating surgeon.

7.8 Condition Specific Considerations

7.8.1 Gastroschisis

This is often diagnosed antenatally allowing a postnatal management plan to be in place. The significant risks are fluid and heat loss and kinking of the mesentery leading to venous congestion of the exposed bowel. Intravenous access with careful fluid management is essential, broad spectrum antibiotics should be started, Vitamin K given and a wide bore naso/oro gastric tube passed. This must be aspirated every 15 min during transfer to ensure the risk of aspiration of gut contents is minimised. The exposed bowel can be placed in a sterile "bowel bag" for transfer or the abdomen can be carefully wrapped in clear plastic film to both reduce fluid loss and stabilise the bowel. Avoid the use of saline soaked swabs as this can accelerate heat loss. The baby should be nursed in the left lateral position to prevent kinking of the vascular pedicle. Thermoregulation is optimised by nursing and transferring in a heated incubator.

7.8.2 Oesophageal Atresia and Tracheo-Oesophageal Atresia

Unless this is a pure oesophageal atresia this condition is rarely diagnosed antenatally. The major initial risk is aspiration of unswallowed saliva. To prevent this, the baby should be nursed in the lateral or prone position and a 10 Fr Replogle tube should be placed in the upper pouch [4]. This should be placed on continuous suction at low pressure (5 kPa (35–40 mmHg)) with frequent irrigation of the air channel to prevent blockage. If a Replogle is not available a wide bore feeding tube can be used but this must be aspirated every 15 min during transfer. The volume of aspirated saliva should be recorded and replaced. Intravenous access with careful fluid management is essential, broad spectrum antibiotics should be started and Vitamin K given. The risk of associated abnormalities, including cardiac, should be considered. Thermoregulation is optimised by nursing and transferring in a heated incubator.

7.8.3 Congenital Diaphragmatic Hernia

This is increasingly diagnosed antenatally but will still often present with severe respiratory distress at birth. If antenatally diagnosed an in utero transfer to an appropriate regional facility that can provide optimal management is the preferred option. If diagnosed at birth endotracheal intubation should be performed with minimal bag/valve/mask ventilation and early passage of an oro/nasogastric tube. Pre and post ductal arterial monitoring and venous access should be initiated and a ventilation strategy of permissive hypercapnia to minimise barotrauma instituted. There is an increased risk of pneumothorax so equipment necessary to inset a chest drain should be available during transfer.

7.8.4 Myelomeningocele

This condition is also is increasingly diagnosed antenatally permitting a postnatal plan to be prepared in advance. The exposed spinal lesion should be covered with a non adherent dressing and the baby nursed in the prone position. The use of saline swabs should be avoided as this can cause significant heat loss. Latex exposure should also be avoided as these children have a high incidence of latex allergy which may be due to early repeated contact.

7.8.5 Intestinal Obstruction

The general principles of transfer of a neonate with intestinal obstruction from any cause are

similar. The major risks are aspiration of intestinal contents and fluid depletion. A wide bore naso/oro gastric tube should therefore be passed and placed on free drainage. In addition it must be aspirated regularly during stabilisation and transfer. The volume aspirated should be accurately measured, documented and replaced. Intravenous access with careful fluid management is particularly important as fluid loss may be significant. Vitamin K should be given and broad spectrum antibiotics be considered. In addition it is important copies of all X-rays are sent with the patient.

7.9 Back Transfer of the Post-Operative Neonate

This should be considered as soon as the infant's condition permits it. Early back transfer has the advantage of returning child and parent close to home, freeing up specialist surgical cots and permits maintenance of medical and nursing skills in the referring units. For this to be considered the receiving unit should have the staff and facilities to provide for the infant's predictable future needs, the remaining estimated length of in hospital stay should is balanced the costs and risks of reverse transport and the parents views should be considered. It is rarely an emergency and can therefore be carefully planned. As the post-operative patient will usually be relatively well a reduced transport team can often provide this transfer.

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Fluid, Electrolyte and Nutritional Support of the Surgical Neonate

8

Simon Eaton, Paolo De Coppi, and Agostino Pierro

Abstract

The newborn infant is in a "critical epoch" of development. A healthy term infant grows at a rate of 25–30 g per day over the first 6 months of life, so that weight has doubled by the age of 5 months. This growth clearly requires adequate nutrition, but especially where medical or surgical conditions exist, must also be carefully managed together with fluid and electrolytes. Thus a significant period of inadequate nutrition, or inappropriate fluid and electrolyte administration, may not only affect short-term outcomes, but may also be a risk factor for the long-term menace of stunted mental and physical development. Amongst preterm infants, lower in-hospital growth velocity is associated with impaired neurodevelopmental outcome. Fluids and electrolytes undergo changes during the perinatal period, so an understanding of the perinatal changes in body composition is useful to understand the principles behind the fluid, electrolyte and nutritional management of surgical neonates. As well as providing the components necessary for increase in tissue mass, adequate provision of nutrients is also required to mount an appropriate immune response is extremely important, as infection and sepsis may impair growth and neurodevelopmental outcome.

Keywords

Fluids and electrolytes • Nutrition • Intravenous feeding • Parenteral nutrition

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8.1 Introduction

The newborn infant is in a "critical epoch" of development. A healthy term infant grows at a rate of 25–30 g per day over the first 6 months of life, so that weight has doubled by the age of 5 months. This growth clearly requires adequate

P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_8

nutrition, but especially where medical or surgical conditions exist, must also be carefully managed together with fluid and electrolytes. Thus a significant period of inadequate nutrition, or inappropriate fluid and electrolyte administration, may not only affect short-term outcomes, but may also be a risk factor for the long-term menace of stunted mental and physical development. Amongst preterm infants, lower in-hospital growth velocity is associated with impaired neurodevelopmental outcome [1]. Fluids and electrolytes undergo changes during the perinatal period, so an understanding of the perinatal changes in body composition is useful to understand the principles behind the fluid, electrolyte and nutritional management of surgical neonates. As well as providing the components necessary for increase in tissue mass, adequate provision of nutrients is also required to mount an appropriate immune response is extremely important, as infection and sepsis may impair growth and neurodevelopmental outcome [2].

8.2 Perinatal Changes in Body Composition

Newborn infants grow very rapidly, have higher energy expenditure and lower caloric reserves than adults and therefore do not tolerate prolonged periods of starvation. The body composition of newborn infants is markedly different from that of adults. The water in body tissues includes the intracellular fluid, which represents the water contained within the cells, and extracellular fluid. Extracellular fluid is further sub- divided into: intravascular fluid (plasma); interstitial fluid (fluid surrounding tissue cells); and transcellular fluid (e.g. cerebrospinal, synovial, pleural, peritoneal fluid). Total body water (TBW) as a percentage of body weight follows an inverse relationship with fat content, as fat cells contain very little water. During the first trimester, when only 1% of body mass is fat, 90% of body mass is TBW with 65% of body mass made up of extracellular fluid [3]. As fat % increases, TBW decreases from 87% of body weight at 24–25 weeks gestation to 75% at term (Fig. 8.1) [4], eventually falling to 65–50% in adulthood. This proportion varies not only with age, but also with weight, so that among preterm infants, small for gestational age infants have a significantly higher body water content (approximately 90%) than appropriate for gestational age infants (approximately 80%) [5]. These changes in TBW are accompanied by a decrease in the extracellular compartment fluid (ECF) to intracellular compartment fluid (ICF) ratio. The ECF is 65% of total body mass at 24–25 weeks gestation declining to 40% at term whereas ICF increases from 22% at 24–25 weeks gestation to 35% of body mass at term and then to 40% at 1 month of age. Although there is a gradual decline in the extracellular compartment, there is a more abrupt loss in the early post-natal period due to decreased interstitial fluid, which largely corresponds to the physiological early post-natal weight loss. Because extracellular fluid is more easily lost from the body than intracellular fluid and infants have a

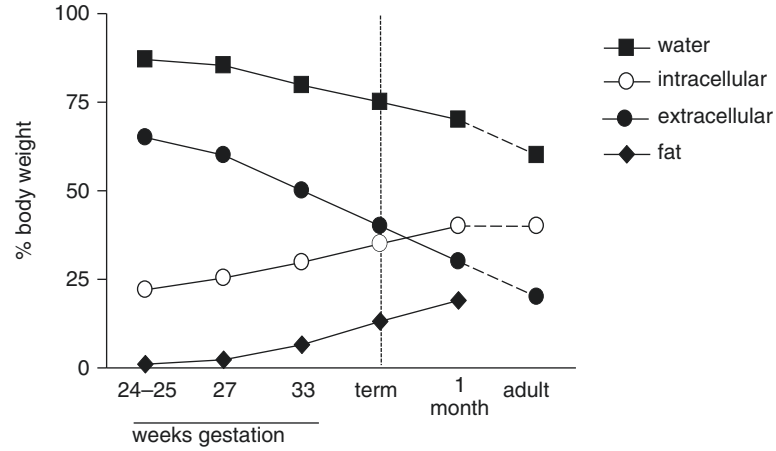

Fig. 8.1 Body composition changes with age [4–139]. Percentage body fat is not shown for adults because of the extremely wide range

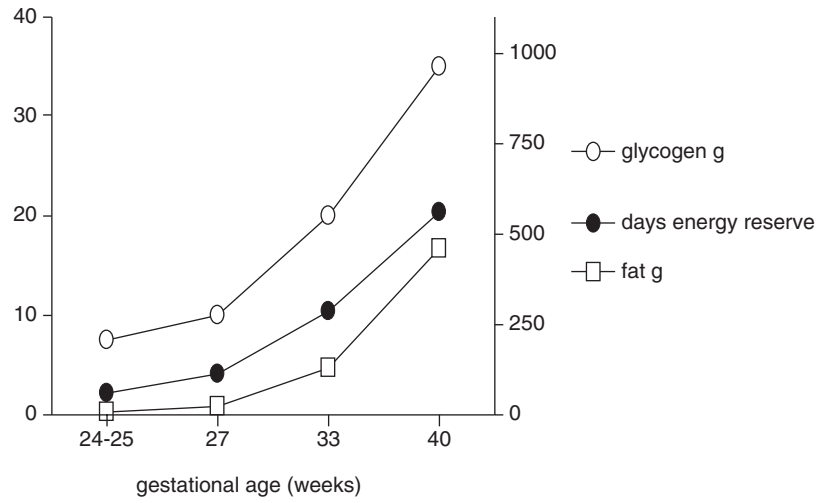

Fig. 8.2 Relationship between theoretical energy reserve and body stores of glycogen and fat [4, 140]

larger surface area to body mass ratio, they are more at risk of developing dehydration than older children and adults. This decline in body water reflects also an increase in energy content of the body. The ratio between resting energy expenditure (in kcal/kg/day) to non-protein energy reserve (in kcal/kg) gives an approximate estimate of the energy reserve of the infants. This is only ~2 days at 24–25 weeks gestation, increases to ~20 days at term as glycogen and fat stores increase (Fig. 8.2) [4] and is in excess of 50 days in the adult, hence the urgent need for adequate caloric intake in very-low-birth-weight (VLBW) and/or extremely-low-birth-weight (ELBW) infants after birth. Early PN in VLBW infants has been shown to be beneficial [6], although there is controversy on how "aggressive" nutritional intervention should be in preterm infants. Full-term neonates have higher content of endogenous fat (approximately 600 g) and therefore can tolerate a few days of undernutrition.

8.3 Energy Requirements of the Neonate

Newborn infants have a significantly higher metabolic rate and energy requirement per unit body weight than children and adults: the total energy requirement for an extremely-low birthweight (i.e. <1000 g) preterm infant fed enterally is 130–150 kcal/kg/day [7], and that of a term infant is 100–120 kcal/kg/day, compared to 60–80 kcal/kg/day for a 10-year old and 30–40 kcal/kg/day for a 20-year old individual [8–10]. Of the 100–120 kcal/kg/day required by the term infant, approximately 40–70 kcal/kg/day is needed for maintenance metabolism, 50–70 kcal/kg/day for growth (tissue synthesis and energy stored), and up to 20 kcal/kg/day to cover energy losses in excreta [11–13]. Newborn infants receiving total parenteral nutrition (TPN) require fewer calories (110–120 kcal/kg/day for a preterm infant and 90–100 kcal/kg/day for a term infant [14]), due to the absence of energy losses in excreta and to the fact that energy is not required for thermoregulation when the infant is in an incubator. These data are shown diagrammatically in Fig. 8.3, but it should be stressed that energy requirements vary greatly, depending on many variables such as ventilation, thermoregulation, physical activity, etc. Several equations have been used to estimate the resting energy expenditure, and therefore the energy requirements, of infants and children. The most frequently used are those of the World Health Organisation WHO [9] (which were revised in 2004 [10]), Schofield [15] and Harris and Benedict [16]. These are based on weight, height and/or age and are based on measurements of orally fed, healthy individuals, and thus take no account of the abnormal physiology and/or pathology of infants requiring artificial nutritional support.

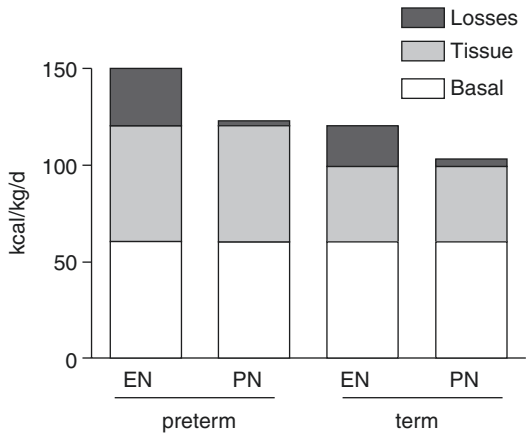

Fig. 8.3 Partition of energy metabolism in preterm and term infants receiving nutrition enterally (EN) or parenterally (PN) [7, 8, 11, 13, 14]. Energy "expended" includes basal metabolic rate, activity, the energy expended in laying down new tissue, and thermoregulation, "tissue" is the amount of energy actually stored in new tissue, "losses" include losses in stool, etc.

8.4 Energy Requirements of the Surgical and Septic Neonate

An equation has been developed to predict REE in stable surgical infants, to which the major contributing predictors are body weight, heart rate (providing an indirect measure of haemodynamic and metabolic status) and postnatal age [17]. Although adults show large increases in resting energy expenditure following trauma, surgery, burns or during severe infection [18], this does not appear to be true for infants, although there are few studies in this area. Critically-ill, post-surgical ventilated premature neonates [19], neonates with necrotizing enterocolitis [20] and surgical infants (with or without ECMO) [21] were shown to have similar REE values to healthy neonates, whereas others have suggested that REE is increased during neonatal sepsis [22] and that REE correlates with severity of illness during sepsis in neonates [23]. Another study, examining the immediate post-operative response to neonatal surgery, found that there is a peak in REE 4 h after surgery, which was short-lived, returning to baseline within 12–24 h after surgery [24]. There is no further increase in energy expenditure in the first 5–7 days following an operation [24, 25]. The timing of these changes corresponds with the postoperative changes in catecholamine levels and other biochemical and endocrine parameters [26]. It has been demonstrated that the postoperative increase in energy expenditure can, at least partially, result from severe underlying acute illness, which frequently necessitates surgery (i.e. sepsis or intense inflammation, see below) [27]. Interestingly, infants having a major operation after the second day of life have a significantly greater increase in resting energy expenditure than infants undergoing surgery within the first 48 h of life. A possible explanation for this may be greater secretion of endogenous opioids in the perinatal period blunting the endocrine and metabolic responses [26, 28, 29]. Thus, there is no clear indication that increased energy should be provided to septic or surgical neonates [14].

Resting energy expenditure is directly proportional to growth rate in healthy infants, and growth is retarded during acute metabolic stress. Studies in adult surgical patients have shown that operative stress causes marked changes in protein metabolism characterised by a postoperative increase in protein degradation, negative nitrogen balance [30, 31], and a decrease in muscle protein synthesis [32]. However, changes in whole body protein flux, protein synthesis, amino acid oxidation or protein degradation do not seem to occur in infants and young children undergoing major operations [33], which led us to speculate that infants and children divert protein and energy from growth to tissue repair, thereby avoiding the overall increase in energy expenditure and catabolism seen in the adult [20, 33, 34]. The existing knowledge on the metabolic response to sepsis in infants is limited. There are conflicting reports on whether critically-ill infants are hypermetabolic [21, 35–40]. However, most studies suggest that infants with sepsis do not become hypermetabolic [41, 42] and that septic neonates with necrotizing enterocolitis do not show any increase in whole body protein turnover, synthesis and catabolism [20]. However, the conflicting data may reflect measurements taken at different times in infants with differing degrees of sepsis [43].

8.4.1 Perinatal Changes in Fluid Balance and Renal Function

Before labour, pulmonary fluid production decreases while existing fluid is reabsorbed and efflux through the trachea increases and accelerates during labour, thereby drying out the lungs. During labour, arterial pressure increases and causes shifts in plasma from the vascular compartment and a slight rise in haematocrit. Placental transfusion can occur if there is delayed clamping of the cord and the neonate is placed at or below the level of the placenta, resulting in up to 50% increase in red blood cells and blood volume. This polycythaemia may have severe consequences such as neurological impairment, thrombus formation and tissue ischaemia [44]. Day one postpartum the neonate is oliguric. Over the following 1–2 days, dramatic shifts in fluid from the intracellular to extracellular compartment result in a diuresis and natriuresis which contributes weight loss during the first days of life. This is approximately 5–10% in the term neonate and 10–20% in the premature infant. The proportion of contributions from ECF and ICF to fluid lost is controversial and the mechanism is yet to be determined. This diuresis occurs regardless of fluid intake or insensible losses and may be related to a postnatal surge in atrial natriuretic peptide [45]. Limitations in the methodology of measuring ECF and ICF have limited our understanding of the processes. It has been demonstrated however that large increases in water and calorie intake are required to reduce the weight loss. Higher calorie intake alone reduces weight loss but the ECF still decreases. Subsequent weight gain appears to be the result of increases in tissue mass and ICF per kilogramme body weight but not ECF per kilogramme body weight. By the fifth day post-partum, urinary excretion begins to reflect the fluid status of the infant. The kidneys in neonates have small immature glomeruli and for this reason the glomerular filtration rate is reduced (about 30 mL/min/1.73 m^2 at birth to 100 mL/min/1.73m^2 at 9 months). Premature and low birth weight infants may have a lower GFR than term infants, and the initial rapid rise in GFR is absent. In neonates, the low osmolality in the renal medulla means the countercurrent system for urine concentration is less effective and urine concentration capacity is between 50 and 700 mOsm/kg compared with 1200 mOsm/kg in the adult kidney, and therefore has less tolerance for fluid imbalance.

8.4.2 Fluid and Electrolyte Requirements of the Neonate

Fluid administration varies with age as a consequence of the variation on total body water composition and the different compensatory mechanisms. In paediatric medicine, the widely used Holliday and Segar method for estimating fluid requirements allows 100 mL/kg/day for infants up to 10 kg [46]. However, newborn infants can have very wide range of maintenance requirements, depending on clinical conditions, such as ambient temperature/thermoregulation (e.g. incubator, Babytherm), phototherapy, pyrexia, patent ductus arteriosus, chronic lung disease. In addition, especially in preterm infants, fluid administration should also allow for the physiological weight loss over the first 7–10 days of life (up to a maximum of 10% of birth weight), always maintaining urine output ≥1 mL/kg/h (Table 8.1). Blood volume can be estimated as 106 mL/kg in preterm infants, 90 mL/kg in neonates, 80 mL/kg in infants and

Table 8.1 Normal maintenance fluid requirements

Premature infant	1st day of life	60–150 mL/kg/day
	2nd day of life	70–150 mL/kg/day
	3rd day of life	90–180 mL/kg/day
	>3rd day of life	Up to 200 mL/kg/day
Term infant	1st day of life	60–80 mL/kg/day
	2nd day of life	80–100 mL/kg/day
	3rd day of life	100–140 mL/kg/day
	>3rd day of life	Up to 160 mL/kg/day
Child > 4 weeks of age, up to 10 kg		100 mL/kg/day

children and about 65 mL/kg in adults [47, 48]. Adequate systemic perfusion depends (among other factors) upon adequate intravascular volume. However, infants and children can compensate for relatively large losses in circulating volume, and signs and symptoms of shock may be difficult to detect if a child has lost less than 25% of the circulating volume. The movement of fluid between the vascular space and the tissues depends on osmotic pressure, oncotic pressure, hydrostatic pressure, and changes in capillary permeability. Understanding these factors is important when trying to anticipate changes in the child's intravascular volume [49].

Not only the amount of fluids but also the type of fluid administered varies according to age. In newborn infants, 10% dextrose solution is recommended. Sodium supplementation is not usually required in the first 24 h (low urine output), and after that time can be given at 2–4 mmol/kg/day (adjusted primarily on serum sodium values and changes in weight). Potassium (1–3 mmol/kg/day) and Calcium (1 mmol/kg/day) are usually added after the first 2 days of life. In Infancy and childhood there is a variety of intravenous solution used (Table 8.2), probably the most common is 5% dextrose with ½ normal saline. Potassium is not usually necessary, except if intravenous fluid is given for a longer period of time. Fluids can be administered intravenously (IV) via peripherally or centrally placed catheters. In newborn infants, or other conditions where dextrose is administered at >10%, peripheral administration is not recommended because of complications due to hyperosmolar solutions.

8.4.3 Common Fluid and Electrolyte Disturbances and Their Treatment

8.4.3.1 Sodium

Serum sodium is the major determinant of serum osmolality and therefore extracellular fluid volume. Urinary sodium excretion is dependent on the GFR and therefore is low in neonates when compared with adults. Normal neonatal serum sodium levels are 135–140 mmol/L, controlled by moderating renal excretion. During the period of oliguria on day one of life, sodium supplementation is not normally required. Normal maintenance sodium requirement following normal diuresis is 2–4 mmol/kg/day.

Hyponatraemia

Hypo-natraemia is defined when serum sodium concentrations is less than 135 mmol/L. Treatment depends on the fluid status of the patient and in case of hypo- or hypervolaemia, fluid status should be corrected first. When normovolaemic, serum sodium should be gradually corrected with NaCl infusion, but at a rate not exceeding 0.8 mEq/kg/h. Symptoms are not reliable for clinical management since they

Table 8.2 Common intravenous fluids

Intravenous fluid	Glucose (g/100 mL)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	Osmolality (mOsm/L)
5% dextrose	5	—	—	—	252/277
10% dextrose	10	—	—	—	505/556
Normal saline (0.9% NaCl)	—	154	—	154	308
½ Normal saline (0.45% NaCl)	—	77	—	77	154
5% dextrose with ½ normal saline	5	77	—	77	406
5% dextrose with ¼ normal saline	5	34	—	34	329
Lactated Ringer's	0	130	4	109	273
Hartmann's	0	131	5	111	278

are not often apparent until serum sodium falls below 120 mmol/L and their severity is directly related to the rapidity of onset and magnitude of hyponatraemia. If not promptly recognised it may manifest as the effects of cerebral oedema: apathy, nausea, vomiting, headache, fits and coma. Urine sodium can be useful to help determine the underlying cause of hyponatraemia as the kidneys respond to a fall in serum sodium by excreting more dilute urine but the secretion of ADH in response to hypovolaemia affects this. Urine sodium concentrations <10 mmol/L indicates an appropriate renal response to euvolaemic hyponatraemia. However, if the urinary sodium is >20 mmol/L this can indicate either sodium leak from damaged renal tubules or hypervolaemia.

Hypernatraemia

Hypernatraemia (serum sodium >145 mmol/L) may be due to haemoconcentration/excessive fluid losses (e.g. diarrhoea). Symptoms and clinical signs include dry mucous membranes, loss of skin turgidity, drowsiness, irritability, hypertonicity, fits and coma. Treatment is again via correction of fluid status with appropriate electrolyte-containing solutions. Other causes of hypernatraemia are renal or respiratory insufficiency, or can be related to drug administration.

8.4.3.2 Potassium

In the 24–72 h post-partum, a large shift of potassium from intracellular to extracellular compartments occurs resulting in a rise in plasma potassium. This is followed by an increase of potassium excretion until its normal serum concentration of 3.5–5.8 mmol/L is achieved. Therefore supplementation is not required in the first day of life but after neonatal diuresis, a maintenance intake of 1–3 mmol/kg/day is required.

Hypokalaemia

Hypokalaemia is commonly iatrogenic, either due to inadequate potassium intake or use of diuretics but can also be caused by vomiting, diarrhoea, alkalosis (which drives potassium intracellularly) or polyuric renal failure. As a consequence, the normal ion gradient is disrupted and predisposes to muscle current conduction abnormalities e.g. cardiac arrhythmias, paralytic ileus, urinary retention and respiratory muscle paralysis. Treatment employs the use of KCl.

Hyperkalaemia

Hyperkalaemia can be iatrogenic or due to renal problems but can also be caused by cell lysis syndrome (e.g. trauma), adrenal insufficiency, insulin dependent diabetes mellitus or severe haemolysis or malignant hyperthermia. As in hypokalaemia, hyperkalaemia alters the electrical gradient of cell membranes and patients are vulnerable to cardiac arrhythmias, including asystole. Treatment is with insulin (plus glucose to avoid hypoglycaemia) or with salbutamol.

8.4.3.3 Calcium

Calcium plays important roles in enzyme activity, muscle contraction and relaxation, the blood coagulation cascade, bone metabolism and nerve conduction. Calcium is maintained at a total serum concentration of 1.8–2.1 mmol/L in neonates and 2–2.5 mmol/L in term infants and is divided into three fractions. Thirty to 50% is protein bound and 5–15% is complexed with citrate, lactate, bicarbonate and inorganic ions. The remaining free calcium ions are metabolically active and concentrations fluctuate with serum albumin levels. Hydrogen ions compete reversibly with calcium for albumin binding sites and therefore free calcium concentrations increase in acidosis. Calcium metabolism is under the control of many hormones but primarily 1,25-dihydroxycholecalciferol (gastrointestinal absorption of calcium, bone resorption, increased renal calcium reabsorption), parathyroid hormone (bone resorption, decreased urinary excretion) and calcitonin (bone formation and increases urinary excretion). Calcium is actively transported from maternal to fetal circulation against the concentration gradient resulting in peripartum hypercalcaemia. There is a transient fall in calcium postpartum to 1.8–2.1 mmol/L and a gradual rise to normal infant levels over 24–48 h.

Hypocalcaemia

In addition to the physiological hypocalcaemia of neonates which is usually asymptomatic, other causes of hypocalcaemia are hypoparathyroidism, including DiGeorge syndrome, and parathryoid hormone insensitivity in infants of diabetic mothers which may also be related to hypomagnesaemia. Clinical manifestations are a tremor, seizures and a prolonged QT interval on electrocardiograph.

Hypercalcaemia

This is less common than hypocalcaemia but can result from inborn errors of metabolism such as familial hypercalcaemic hypocalcuria or primary hyperparathyroidism. Iatrogenic causes are Vitamin A overdose or deficient dietary phosphate intake. Less common causes in children are tertiary hyperparathyroidism, paraneoplastic syndromes and metastatic bone disease.

8.4.3.4 Magnesium

As an important enzyme cofactor, magnesium affects ATP metabolism and glycolysis. Only 20% of total body magnesium is exchangeable with the biologically active free ion form. The remainder is bound in bone or to intracellular protein, RNA or ATP, mostly in muscle and liver. Gastrointestinal absorption of magnesium is controlled by vitamin D, parathyroid hormone and sodium reabsorption. As previously stated, hypomagnesaemia is often related to hypocalcaemia and should be considered.

8.5 Acid-Base Balance

Acidosis (pH <7.35) and alkalosis (pH >7.45) can be generated by respiratory or metabolic causes. When the cause is respiratory—$PaCO_2$ is >45 mmHg (acidosis) or <35 mmHg (alkalosis)—treatment is via appropriate respiratory support. In case of metabolic—bicarbonate <21 mmol/L (acidosis) or >26 mmol/l (alkalosis), it is useful to check the anion gap [= $Na^{+-}(Cl^- + HCO_3^-)$, which is normally 12 ± 2 mEq/L] to understand the underlying cause. Treatment should be directed towards any underlying cause e.g. metabolic acidosis caused by dehydration or sepsis. The slow infusion of buffers such as sodium bicarbonate or tris-hydroxymethylaminomethane (THAM, a sodium free buffer) should be used as therapeutic adjuncts. The amount of sodium bicarbonate required can be calculated using the following equation:

$$\mathrm{NaHCO_3\,(mmol)} = \frac{\text{base excess} \times \text{body weight (kg)}}{3}$$

Acid-base balance is maintained by a complex system achieved by intracellular and extracellular buffer systems, respiration and renal function. Intracellular systems consist of conjugate acid-base pairs in equilibrium as shown by the equation below (A = acid, H = proton).

$HA \leftrightarrow H^+ + A$—The pH can be derived from the Henderson-Hasselbach equation.

$$\mathrm{pH} = \frac{\mathrm{pK} + \log\left[\mathrm{A}^-\right]}{\left[\mathrm{HA}\right]}$$

where pK is the dissociation constant of the weak acid, $[A^-]$ is the concentration of the dissociated acid and [HA] is the concentration of the acid. The most important of these systems is the carbonic anhydrase system:

$CO_2 + H_2O \leftrightarrow H^+ + HCO_3$—Extracellular buffer systems are similar but the proton is loosely associated with proteins, haemoglobin or phosphates and take several hours to equilibrate. Respiratory compensation occurs via the carbonic anhydrase system, ridding the body of carbon dioxide thereby shifting equilibrium to the left of the reaction and reducing the number of protons. The extent of the shift is influenced by the active transport of bicarbonate across the blood-brain barrier, thereby triggering central respiratory drive. Normal extracellular pH is maintained at 7.35–7.45. Normal metabolic processes produce carbonic acid, lactic acid, ketoacids, phosphoric acid and sulphuric acid all of which are either excreted or controlled by a number of buffer systems.

In the neonate, loss of the contribution of the feto-maternal circulation and maternal respira-

tory and renal compensation mechanisms force adaptation and maturation. There is a suggestion that increased sensitivity of the respiratory centres to fluctuations in pH changes allow the neonate to control acid-base balance more. Increases in the intracellular protein mass allow greater intracellular buffering. The extracellular buffer systems are already functional.

Respiratory compensation becomes active as respiration is established. It relies on pulmonary function and lung maturity and therefore neonates with lung disease may have impaired respiratory compensation. Carbon dioxide passes freely across the blood-brain barrier allowing almost immediate response from respiratory drive centres to respiratory acidosis. The response to metabolic acidosis is delayed as interstitial bicarbonate requires a few hours to equilibrate with the cerebral bicarbonate.

Renal compensation is the most important mechanism available to the neonate for acid-base balance. Adjustments in urine acidity have been seen as soon as a few hours post-partum but takes 2–3 days to fully mature. Consequent to the changes in renal function and perfusion described previously, the ability of the neonate to handle acid-base balance is limited in the first few days of life. Proximal tubules are responsible for the reabsorption of 85–90% of filtered bicarbonate but function less efficiently in the premature neonate. It can also be affected by some drugs used in neonates. Dopamine inhibits sodium/proton pump activity in the proximal tubules and therefore decreases the amount of bicarbonate that is reabsorbed. The remaining bicarbonate reabsorption takes place in the distal tubules but they differ from the proximal tubules in their absence of carbonic anhydrase. Aldosterone is the most important hormone affecting distal tubular function and stimulates proton excretion in the distal tubules. However, the distal nephrons of the premature infant are developmentally insensitive to aldosterone. Protons are excreted in the urine as phosphate, sulphate and ammonium salts. This increases with age and gestation. However, the introduction of phosphate containing drugs increases phosphate delivery to the distal tubules and therefore can increase the capacity to excrete H^+. Dopamine decreases the reabsorption of protons in the distal tubules thereby increasing proton excretion.

8.6 Parenteral Nutrition

8.6.1 Indications

Parenteral nutrition (PN) should be utilised when enteral feeding is impossible, inadequate or hazardous for more than 4–5 days. The most frequent indications in neonatal surgery are the intestinal obstruction due to congenital anomalies. Frequently after an operation on the gastrointestinal tract, adequate enteral feeding cannot be achieved for more than 1 week and parenteral nutrition becomes necessary. This modality of therapy has improved significantly the survival rate of newborns with gastroschisis, a condition which require intravenous administration of nutrients for 2–3 weeks. Although infants with some neonatal surgical conditions, such as gastroschisis, will all receive PN, there are some other congenital anomalies where the use of PN is more controversial. An example of this is duodenal atresia, in which many surgeons would routinely initiate PN, whereas some surgeons preferentially manage patients without PN by the use of trans-anastomotic tubes [50]. In addition to congenital bowel obstruction, PN may also be used in cases of necrotizing enterocolitis, short-bowel syndrome, gastroenterological indications, and respiratory distress.

8.6.2 Route of Administration

As phlebitis may develop with the use of peripheral veins with solutions exceeding 600 mOsm, it is not possible to administer adequate calories peripherally for the growth of extremely low birthweight infants, and peripheral veins are only used for short-term, partial, nutritional supplementation. In neonates, the umbilical vessels can be used for provision of PN centrally, although the risk of complications increases if umbilical catheters are used for more than 5 days (arterial),

or 14 days (venous) [51]. Central venous catheters can either be placed percutaneously directly in a deep vein, with subcutaneous tunnelling of the extravascular part of the line, or can be a peripherally inserted central catheter (PICC). Although there has been a systematic review comparing outcomes in neonates administered PN through percutaneous central venous catheters versus peripheral cannulae, the authors concluded that there was insufficient evidence to make form recommendations [52]. For consideration of technical aspects of placement and management, the reader is directed to the ESPGHAN/ESPEN guidelines [51].

8.6.3 Components of Parenteral Nutrition

The parenteral nutrition formulation includes carbohydrate, fat, protein, electrolytes, vitamins, trace elements and water. The caloric needs for total parenteral nutrition are provided by carbohydrate and lipid. Protein is not used as a source of calories, since the catabolism of protein to produce energy is an uneconomic metabolic process compared to the oxidation of carbohydrate and fat which produces more energy at a lower metabolic cost. The ideal total parenteral nutrition regimen therefore should provide enough amino acids for protein turnover and tissue growth, and sufficient calories to minimise protein oxidation for energy. Carbohydrates and fat provide the main energy sources in the diet, and this is reflected by their importance as a source of calories in parenteral nutrition.

8.6.3.1 Fluid Requirements

As described above, the hydration and proportion of extracellular fluid change rapidly in the neonate. In a surgical infant, these changes will also be occurring simultaneously with surgical intervention and in initiation of parenteral nutrition. Fluid overload is a possibility in these infants, and careful consideration of all fluids administered (parenteral nutrition and other prescribed drugs), together with daily monitoring of weight and electrolytes is mandatory, at least until PN has been stabilised. Excessive fluid administration can result in pulmonary oedema, or failure of closure of patent ductus arteriosus. A recent report by the National Confidential Enquiry into Patient Outcome and Death highlighted the poor fluid management of many neonates receiving PN [53]. Fluid restriction, or a requirement to administer other fluids in significant volume, can result in the delivery of macronutrients being less than current recommendations.

8.6.3.2 Glucose

Glucose is a main energy source for body cells and should be the primary energy substrate in parenteral nutrition, covering 60–70% of non-protein calories [54]. The amount of glucose that can be infused safely depends on the clinical condition and maturity of the infant, as the ability of neonates to metabolise glucose may be impaired by prematurity and low birth weight. Since (1) pancreatic islet cell function is relatively unresponsive for the first 2 weeks of neonatal life; (2) glycogen stores are limited (Fig. 8.2); (3) gluconeogenesis may be impaired; and (4) liver and peripheral tissues are relatively insensitive to insulin, premature neonates are at risk from both hypoglycaemia and hyperglycaemia [55]. Glucose infusion should be at least at a rate capable of maintaining blood glucose above 2.6 mmol/L, the current consensus definition of neonatal hypoglycaemia [56]. As the rate of endogenous glucose metabolism in neonates is of the order of 5 mg/kg/min, this should be considered the lowest infusion rate likely to avoid hypoglycaemia [54]. As glucose tolerance increases, the rate of glucose infusion can be increased. However, carbohydrate conversion to fat (lipogenesis) occurs when glucose intake exceeds metabolic needs. The potential risks associated with this process are two-fold: accumulation of the newly synthesised fat in the liver, and aggravation of respiratory acidosis resulting from increased CO_2 production, although whether these are clinically relevant in PN-fed infants is uncertain. In addition, hyperglycaemia in ELBW infants is a risk factor for late onset sepsis, mortality and the risk of developing advanced NEC [57]. A rapid increase in plasma glucose concentration precedes development of NEC [58], and infants with established NEC have both a high

prevalence of hyperglycaemia, and a worse outcome if hyperglycaemic [59]. Although there has been interest in the potential of insulin therapy to decrease hyperglycaemia-related morbidity and mortality in neonates, a large RCT on insulin therapy in very-low birthweight infants was stopped early due to an increased rate of hypoglycaemia and mortality in the insulin treated arm, and a recent systematic review concluded that current evidence does not support the use of routine use of insulin in very-low birthweight infants [60, 61]. The evidence base for or against control of glucose levels in surgical infants is lacking, although a large multicentre randomised controlled trial of tight glucose control in infants and children requiring intensive care (and including surgical infants) has recently completed recruitment [62]. Hypoglycaemia usually results from sudden interruption of an infusion containing a high glucose concentration.

8.6.3.3 Lipids

Lipids provide an energy-dense (9 kcal/g of fat), isotonic alternative to glucose as an energy source for PN, which also prevent essential fatty acid deficiency and facilitate provision of fat soluble vitamins. Combined infusion of glucose and lipids confers metabolic advantages over glucose, because it lowers the metabolic rate and carbon dioxide production and increases the efficiency of energy utilisation [63, 64]. There is a close interdependence of carbohydrate and lipid infusion rates on the one hand, and net fat deposition or oxidation on the other (Fig. 8.4). When the intake of glucose calories exceeds 18 g/kg/day (equivalent to resting energy expenditure), net fat oxidation is minimal regardless of fat intake, and net fat synthesis takes place [65]. At a carbohydrate intake of 15 g/kg/day, the proportion of energy metabolism derived from fat oxidation does not exceed 20% even with a fat intake as high as 6 g/kg/day. At a carbohydrate intake of 10 g/kg/day this proportion can be as high as 50% [65]. However, lipid utilisation is often low and unpredictable in neonates, and consequently, lipids are usually introduced slowly, especially in premature neonates [66].

The most commonly used fat emulsions for parenteral nutrition of surgical infants paediatrics

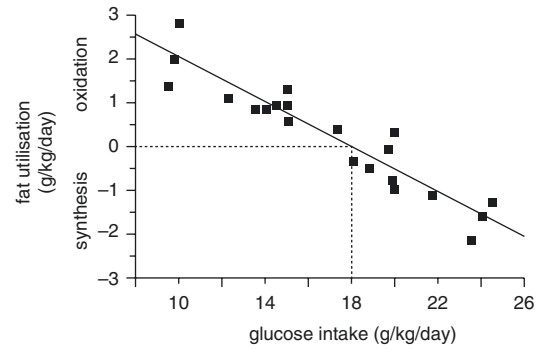

Fig. 8.4 Relationship between glucose intake and fat utilisation in surgical infants. Linear relationship between glucose intake and fat utilization ($r = -0.9$; $p < 0.0001$). Lipogenesis is significant when glucose intake exceeds 18 g/kg/day. From Pierro A, Jones MO, Hammond P, Nunn A, Lloyd DA. Utilisation of intravenous fat in the surgical newborn infant. Proceedings of the Nutrition Society 52, 237A. 1993; used with permission

are based on soybean oil, which in which the lipid is present as long-chain triglycerides (LCT). However, a frequent complication of long-term PN in surgical infants is parenteral-nutrition associated cholestasis (PNAC) and/or intestinal failure-associated liver disease (IFALD). These conditions, considered in more detail below, have been linked to the use of soybean oil, although other factors are thought to be involved. Soybean oil contains mostly Ω-6 fatty acids, which are thought to be pro-inflammatory compared with Ω-3 fatty acids. In addition, the amount of phytosterols delivered in soybean-based lipid emulsions is relatively high, and phytosterol accumulation has been postulated to cause PNAC/IFALD [67]. Hence in recent years, there has been great interest in adopting hepatoprotective lipid management strategies in PN of surgical infants. Several different approaches have been adopted:

- decreasing the amount of lipid administered [68, 69]. This can also be achieved by limiting the time on lipid, by lipid free hours or days. This could potentially result in poor growth due to inadequate calories.
- use of Omegaven®, a lipid emulsion of 10% fish oil. Fish oil is high in Ω-3 fatty acids and low in phytosterols, so has been suggested to

reverse cholestasis in surgical infants on long-term PN [70]. Use of Omegaven® as the only lipid source could, however, potentially result in essential fatty acid deficiency, due to lack of Ω-6 fatty acids, and could also result in poor growth, as the dose of Omegaven® is limited to 1.0 g/kg/day (compared with 3 g/kg/day for soybean-based lipid emulsions).

- use of lipid emulsions containing a mixture of long- (LCT) and medium-chain (MCT) triglycerides [71, 72]. This has the advantage of increasing fat utilisation [73], ability to use at up to 3 g/kg/day, and decreasing the phytosterols and Ω-6 fatty acids administered whilst ensuring adequate delivery of essential fatty acids.
- use of mixed lipid emulsions such as SMOF®, which is a mixture of **S**oybean, **M**edium-chain, **O**live and **F**ish triglycerides [71, 74, 75]. This has the advantages of lowered amounts of phytosterols and Ω-6 fatty acids, increased fat utilisation, delivery of Ω-3 fatty acids, ability to use at up to 3 g/kg/day.

Despite these different approaches, the evidence base supporting any lipid management strategy is lacking due to the paucity of RCTs in this area. It is difficult to design and implement good quality RCTs, as units already use a variety of alternate lipid management strategies [76]. It is also questionable whether maintaining an infant on a high dose of soybean-based lipid emulsion after the onset of PNAC/IFALD is ethical, so that it is difficult to decide on an appropriate comparison group.

High doses of lipid or an accidental rapid infusion of lipid may lead to fat overload syndrome, characterised by an acute febrile illness with jaundice and abnormal coagulation and respiratory problems [66, 77] and so lipids are usually advanced slowly, with close monitoring of triglyceride levels, especially in neonates with respiratory insufficiency or suspected infections [66]. Peroxidation in stored fat emulsions and the generation of free radicals during intravenous infusion of fat in premature infants have been reported [78]. However, the degree of free radical production is linked to the rate of lipid oxidation, as we have shown that a reduction in the carbohydrate to fat ratio in PN diet will result in increased oxidation of administered fat and a decrease in free radical–mediated lipid peroxide formation [79].

8.6.3.4 Amino Acids

In contrast to healthy adults who exist in a state of neutral nitrogen balance, infants need to be in positive nitrogen balance in order to achieve satisfactory growth and development. Preterm infants who are receiving glucose alone lose protein quickly (at the rate of 1–2% body protein per day), so should start to receive at least 1–1.5 g/kg/day amino acids parenterally if not receiving EN [80]. Infants are efficient at retaining nitrogen, and can retain up to 80% of the metabolizable protein intake on both oral and intravenous diets [81]. Protein metabolism, and deposition of body protein for growth, is dependent upon both protein and energy intake, so that above an energy intake of 70 kcal/kg/day, the major determinant of nitrogen retention in preterm infants is the amino acid intake [81]. The PN amino acid requirement of term newborn infants is between 2.5 and 3.0 g/kg/day, which allows for accretion of body protein [82]. Complications like azotemia, hyperammonaemia, and metabolic acidosis have been described in patients receiving high levels of intravenous amino acids [83] but rarely seen with amino acid intake of 2–3 g/kg/day [84]. In patients with severe malnutrition or with additional losses (i.e. jejunostomy, ileostomy), protein requirements are higher [85]. The nitrogen source of PN is provided as a mixture of amino acids, and mixtures specifically formulated for neonates are available. However, the ideal amino acid composition for term and preterm infants is uncertain. As well as the amino acids usually considered essential for adult humans, histidine is considered essential for infants, and the following amino acids have all been considered "conditionally essential" for neonates: arginine, cysteine, glutamine, taurine and tyrosine [86].

Cysteine is unstable in amino acid mixtures, but is central to sulphur amino acid economy and for glutathione synthesis. It is not certain whether newborn infants, especially those born prema-

turely, are capable of adequate rates of cysteine synthesis [86]. A meta-analysis of available trials in PN-fed neonates suggested that although cysteine-supplementation may improve nitrogen balance, there was insufficient data to evaluate the risks of cysteine addition, such as metabolic acidosis [87].

Like cysteine, glutamine is excluded from PN amino acid mixtures because of poor stability, although it can now be added as a dipeptide. Glutamine is important for the immune system and the intestine, as well as being essential as a nitrogen-carrier between organs [88]. It has been hypothesised that glutamine supplementation to parenterally fed neonates would decrease the incidence of infection and decrease to time to full enteral feeding. Two small studies examined the effects of PN glutamine supplementation in premature infants and found decreased duration of ventilation and decreased incidence of sepsis [89, 90]. However, a larger study in premature infants [91] found no benefit of glutamine supplementation. One randomised controlled trial [92] in surgical infants found that parenteral glutamine supplementation had no significant effect on intestinal permeability or nitrogen balance, although this study was not powered to detect differences in clinical endpoints such as incidence of sepsis or duration of PN. A large multicentre randomised controlled trial of glutamine-supplemented PN showed that although glutamine did not decrease the time to full enteral feeds, or the incidence of sepsis over the full period of PN, it did significantly decrease the incidence of sepsis during the period of exclusive parenteral feeding, i.e. before any enteral nutrition was introduced [93].

Arginine has also been considered conditionally essential to the neonate [86] and studies have shown low plasma arginine in infants with NEC [94–96]. Supplementation of PN, followed by EN, with arginine decreased the incidence of NEC in a randomised controlled trial [97], and is has been suggested that infants who have genetic polymorphisms which may alter arginine metabolism levels have an increased susceptibility to NEC [98].

Tyrosine synthesis from phenylalanine may be impaired in neonates [82, 86], and the measured tyrosine requirement for neonates is much greater than is available in current neonatal amino acid mixtures, due to poor solubility [99].

Taurine is a non-protein forming amino acid that has roles in the immune system, as an osmolyte, and in retinal and neurological function, and for bile acid conjugation [100, 101]. Neonates on PN may have poor taurine status due to poor renal reabsorption, impaired activity of synthetic enzymes, and low levels of cysteine, the immediate precursor for taurine [101]. Plasma taurine status of preterm infants has now also been suggested to affect neurodevelopmental outcome [102]. Despite the lack of strong evidence from RCT, most PN amino acid mixtures for neonates now contain taurine. This has been suggested to decrease the incidence of cholestasis in infants on PN (see below) [103].

8.6.3.5 Minerals, Vitamins and Trace Elements

Minerals, vitamins and trace elements are important structurally, as cofactors, or as components of enzymes, and provision of adequate supplies is important for the growing neonate. Fe, Ca, P and Mg should all be provided in adequate amounts for growth and development, but conversely, can cause problems if provided in excess of needs or if their metabolism is impaired. In addition, administration of adequate amounts can be problematic, because of lack of stability in solution or lack of compatibility with other components. Consequently, iron is often only supplemented in longer term PN [104] whereas calcium and phosphate supply depends on solubility in PN mixtures [104]. Vitamins and trace elements are particularly important in maintenance of the body's antioxidant defences [105]: vitamins C and E, selenium (for glutathione peroxidase), copper, zinc and manganese (all for superoxide dismutases), chromium, iodine and molybdenum can all added to parenteral nutrition. However, for many of these, the precise requirements are not known. Although there is evidence that selenium supplementation may be beneficial, selenium status varies widely geographically, so global recommendations are difficult [106]. It is suggested that if the duration of PN is less than

4 weeks, of the trace elements, only zinc needs to be added [104, 107]. There is little specific evidence for individual vitamin requirements, and the current recommendations are to continue with the available vitamin mixtures, which do not appear to cause toxicity or deficiency in the majority of neonates [107, 108]. Free radical production and lipid peroxidation will be considered in more detail below.

8.6.4 Complications of Parenteral Nutrition

8.6.4.1 Infectious Complications

In spite of significant improvement in the management of parenteral nutrition including the introduction of nutrition support teams, infection is still a major problem. More than 50% of surgical infants on PN have at least one suspected episode of sepsis, and around 30% of surgical neonates having at least one positive blood culture [93, 109]. Repeated episodes of sepsis may lead to impaired liver function [110, 111], critical illness and removal of central venous catheters. Although catheter-borne infections, which can be reduced by rigorous precautions [112], such chlorhexidine antisepsis [109], are important, microbial translocation from the intestine is also a significant source of infection in surgical infants on PN [110, 111]. Infection with enteric micro-organisms occurs significantly later than presumed catheter-related infection [113], supporting the hypothesis that a progressive impairment of host defences [114] and/or increased intestinal permeability may allow translocation of enteric organisms after an extended period of PN.

8.6.4.2 Mechanical Complications

Mechanical complications related to the intravenous infusion of nutrients are not uncommon. Extravasation of parenteral nutrition solution is a common complication of peripheral parenteral nutrition. Unfortunately, even a low osmolarity solution is detrimental for peripheral veins leading to inflammation and extravasation of the solution, which can cause tissue necrosis and infection. Extravasation injury is treated with occlusive dressings or hyaluronidase irrigation, but there is little evidence base for the best treatment in neonates [115]. Intravenous lines may become clogged from thrombus formation, calcium precipitates, or lipid deposition. There is disagreement on the ideal position of central venous lines (CVL) for parenteral nutrition in infants. Some authors advocate the atrium as the ideal position because this would give less chance of catheter dysfunction, whereas others believe that placement in the superior vena cava would reduce the risk of perforation. The current ESPGHAN/ESPEN recommendations are that the catheter tip should lie outside the atrium [51], but because complications of either approach are very rare (albeit potentially life-threatening), there is a paucity of evidence from RCTs.

8.6.4.3 Hepatic Complications

The hepatobiliary complications related to parenteral nutrition remain serious and often life threatening. The commonest hepatobiliary complication of parenteral nutrition in neonates is cholestasis. The clinical significance of this cholestasis itself is unknown, but if untreated, intestinal failure associated liver disease (IFALD) may occur, which can result in the need for liver transplantation, or can result in death. IFALD has been defined by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition [116] as:

- type 1 early IFALD—persistent elevation of alkaline phosphatase (ALP) and γ-glutamyl transferase greater than 1.5 times the upper limit of reference range for at least 6 weeks;
- type 2 established IFALD, elevation of ALP γGT as above, together with elevation of total bilirubin (>50 μmol/L), with a conjugated fraction of at least 50%;
- type 3 late IFALD—elevated ALP, total bilirubin, and clinical signs of end-stage liver disease.

Type 1 is thought to be reversible, type 2 is potentially reversible if enteral feeding is increased, PN reduced and repeated episodes of

catheter-related sepsis are prevented. The incidence of PNAC/IFALD depends on the length of time on PN, and occurs in up to 50% of infants receiving long-term PN [117]. Although the frequency of this complication seems to be diminishing [118], this is probably related to the more aggressive transition to enteral feeding rather than to an improvement in the intravenous diet. Various clinical factors are thought to contribute to the development of parenteral nutrition-related cholestasis. These include prematurity, low birth weight, duration of parenteral nutrition, immature entero-hepatic circulation, intestinal microflora, septicaemia, failure to implement enteral nutrition, short-bowel syndrome due to resection, and number of laparotomies (reviewed [119]). In addition to the effects of extremely low birthweight, and length of time on PN, infants receiving PN for either gastroschisis or jejunal atresia seem to be at particular risk [120]. Parenteral nutrition-related cholestasis has a higher incidence in premature infants than in children and adults. This may be due to the immaturity of the biliary secretory system since bile salt pool size, synthesis, and intestinal concentration are low in premature infants in comparison with full term infants [121]. PNAC and IFALD are diagnoses of exclusion without any specific marker yet available. Therefore, infants with cholestasis (conjugated bilirubin >2.0 mg/dL) who are receiving or have received parenteral nutrition must have an appropriate diagnostic evaluation to exclude other causes of cholestasis, such as bacterial and viral infections, metabolic diseases (e.g. alpha-1-antitrypsin deficiency, tyrosinaemia) and congenital anomalies (e.g. Alagille syndrome, biliary atresia, choledocal cyst) [122].

The aetiology of parenteral nutrition-related cholestasis remains unclear. Possible causes include the toxicity of components of parenteral nutrition, lack of enteral feeding, continuous non-pulsatile delivery of nutrients and host factors, infection and sepsis [119]. In particular, the lipid component of PN has been particularly implicated and many units now use alternative lipid management strategies (see discussion under lipid component of PN above). In addition to lipid management, careful management of these patients under a multi-disciplinary team seems to be beneficial [71, 116, 117, 123]. Bowel lengthening procedures, such as the STEP procedure or longitudinal intestinal lengthening may help transition to enteral nutrition [124, 125], whereas in those with advanced liver disease and no prospect of enteral autonomy, transplantation may be considered. Isolated liver transplantation [126], isolated intestinal transplantation and liver plus intestinal transplant are all feasible in children, and although results are improving, overall outcomes are still poor and organ availability is, of course, a problem [127].

8.7 Enteral Nutrition

The energy requirement of an infant fed enterally is greater than the intravenous requirement because of the energetic cost of absorption from the gastrointestinal tract and energy lost in the stools (Fig. 8.3). Enteral feedings should be used in preference to parenteral nutrition. The transition from parenteral to enteral feeding should be a short as possible. Neonates undergoing abdominal surgery for congenital or acquired intestinal dysfunction often require a period of parenteral nutrition, however the authors recommend to start introducing enteral feeding as soon as the gastric aspirate is less than approximately 24 mL/day even if the aspirate is still bilious. There is evidence that during parenteral nutrition of surgical infants, the introduction of minimal enteral feeding preserves immune function [128].

8.7.1 Feeding Routes

Alternative feeding routes where neonates are unable to feeds orally include naso-gastric or oro-gastric tubes, naso-jejunal tubes, gastrostomy tubes or jejunostomy tubes. Gastric feeding is generally preferable to intestinal feeding because it allows for a more natural digestive process i.e. allows action of salivary and gastric enzymes and the antibacterial action of stomach acid. In addition gastric feeding is associated with a larger osmotic and volume tolerance and a lower fre-

quency of diarrhoea and dumping syndrome. Thus, transpyloric feeds are usually restricted to infants (1) unable to tolerate naso- or oro- gastric feeds; (2) at increased risk of aspiration; (3) with anatomical contra-indications to gastric feeds, such as microgastria. Neonates are obligatory nose breathers and therefore oro-gastric feeding may be preferable over naso-gastric feeding in preterm infants to avoid upper airway obstruction. However, naso- gastric tubes are easier to secure and may involve a lower risk of displacement. In infants requiring gastric tube feeding for extended periods (e.g. more than 6–8 weeks) it is advisable to insert a gastrostomy, to decrease the negative oral stimulation of repeated insertion of nasal or oral tubes. The tube can be inserted using an open, endoscopic or laparoscopic approach. In infants with significant gastro-oesophageal reflux, fundoplication with gastrostomy tube or enterostomy tube placement is indicated [129]. In preterm infants with gastro-oesophageal reflux, enteral feeding can be established via a naso-jejunal tube inserted under fluoroscopy. Naso-jejunal feeding usually minimise the episodes of gastro-oesophageal reflux and their consequences. However, it is common for these tubes to dislocate back in the stomach. Regular analysis of the pH in the aspirate is essential to monitor the correct position of the tube. Feeding jejunostomy tubes can be inserted through existing gastrostomy or directly into the jejunum via laparotomy or laparoscopy.

8.7.2 Selection of Enteral Feeds

Breast milk is the ideal feed for infants because it has specific anti-infectious activities, aids gastrointestinal maturation and neurological development. When breast milk is not available chemically defined formulae can be used, which are designed either for term infants or specifically for preterm infants. If malabsorption is present and persists, an appropriate specific formula should be introduced. A soy-based disaccharide-free feed is used when there is disaccharide intolerance resulting in loose stools containing disaccharides. For fat malabsorption, a formula containing medium chain triglycerides (MCT) should be used. An elemental (free amino acids) or semi-elemental (protein hydrolysate containing di- and tri- peptides) formula may be indicated when there is severe malabsorption due to short bowel syndrome or severe mucosal damage as in NEC. Semi-elemental preparations have the advantage of a lower osmolality, are well absorbed and have a more palatable taste. Infants recovering from NEC pose a particular problem, as malabsorption may be severe and prolonged. These infants may have had small bowel resected, in addition to which the remaining bowel may not have healed completely by the time feeds are begun. Feeding may provoke a relapse of the necrotising enterocolitis and feeding should therefore be introduced cautiously. However, there is no strong evidence for the time to re-introduce enteral feeds in infants who have had NEC [130]. For persistent severe malabsorption, a modular diet may be necessary. Glucose, amino acid and MCT preparations are provided separately, beginning with the amino acid solution and adding the glucose and then the fats as tolerated. Minerals, trace elements and vitamins are also added. These solutions have a high osmolality and if given too quickly may precipitate dumping syndrome, with diarrhoea, abdominal cramps and hypoglycaemia. It is important therefore to start with a dilute solution and increase slowly the concentration and volume of each component. This may take several weeks and infants will need parenteral nutritional support during this period.

8.7.3 Administration of Enteral Feeds

Enteral feeds can be administered as boluses, continuous feeds or combination of the two. Bolus feeds are more physiological and are known to stimulate intestinal motility, enterohepatic circulation of bile acids and gallbladder contraction [131]; continuous enteral feeding leads to an enlarged, non-contractile gallbladder in infants [132]. Contraction is observed immediately after resuming bolus enteral feeds and

gallbladder volume returns to baseline after 4 days. Therefore the mode of feeding has important bearings on the motility of the extrahepatic biliary tree. Bolus feeds mimic or supplement meals and are easier to administer than continuous feeds since a feeding pump is not required. Bolus feeds are usually given over 15–20 min and usually every 3 h; term infants can tolerate a period of 4 h without feeds before hypoglycaemia occurs. In preterm neonates or in neonates soon after surgery 2-hourly feeds are occasionally given. Where bolus feeds are not tolerated, for example in the presence of gastro-oesophageal reflux, continuous feeds should be administered via an infusion pump over 24 h. This modality of feeding is used in infants with gastro-oesophageal reflux, delayed gastric emptying or intestinal malabsorption. Infants with jejunal tubes should receive continuous feeds and not bolus feeds as the stomach is no longer providing a reservoir.

8.7.4 Complications of Enteral Tube Feeding

Enteral tube feeding is associated with fewer complications than parenteral feeding. The complications can be mechanical including tube blockage, tube displacement or migration and intestinal perforation. Although infection is less of a risk than with parenteral nutrition, the risk of infected enteral feeds should not be ignored [133]. Other complications involve the gastrointestinal tract. These include: gastro-oesophageal reflux with aspiration pneumonia, dumping syndrome and diarrhoea. Jejunostomy tubes inserted at laparotomy can be also associated with intestinal obstruction. The use of hyperosmolar feeds has been associated with development of necrotizing enterocolitis, dehydration and rarely, intestinal obstruction due to milk curds [134].

In surgical infants, enteral feeding often results in vomiting, interruption of feeding, inadequate calorie intake and rarely in necrotizing enterocolitis. In infants with congenital gastrointestinal anomalies, exclusive enteral feeding is commonly precluded for some time after surgery due to large gastric aspirate and intestinal dysmotility. Therefore, appropriate calorie intake is established initially by total parenteral nutrition. Supplementary enteral feeding is introduced when intestinal motility and absorption improves. The percentage of calories given enterally is gradually increased at the expense of intravenous calorie intake. This transition time from total parenteral nutrition to total enteral feeding could be quite long. The presence of significant gastric aspirate often induces clinicians and surgeons not to use the gut for nutrition. However, minimal enteral feeding can be implemented early in these patients even if its nutritional value is questionable. Minimal enteral feeding may be all that is required to enhance some immunological function. This is supported by studies in animals [135] and infants [136]. Shou et al. [135] reported that supplementation of parenteral nutrition with just 10% enteral calories as chew diet improved rat macrophage and splenocyte function. Okada et al. [136] have shown that the introduction of small volumes of enteral feed improved the impaired host bactericidal activity against coagulase negative staphylococci and the abnormal cytokine response observed during total parenteral nutrition. The increase in bactericidal activity against coagulase negative staphylococci after the addition of small enteral feeds in patients on parenteral nutrition was significantly correlated with the duration of enteral feeding. This implies that stimulation of the gastrointestinal tract may modulate immune function in neonates and prevent bacterial infection.

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Neonatal Vascular Access

9

Colin T. Baillie

Abstract

Advances in the medical and surgical management of neonates are often predicated upon secure vascular access. Requirement for vascular access may be for physiological monitoring (arterial or central venous pressure), direct treatment (antibiotics, chemotherapy), supportive therapy (nutrition, transfusion, dialysis, ECMO), diagnostic radiological, and procedural purposes (drainage of CSF or chyle, minimally invasive cardiac interventions). It is important for the surgeon to have a broad working knowledge of this field, as, given the multidisciplinary nature of modern neonatal intensive care, the options for and scope of vascular access are expanding alongside the number of subspecialties with interests and relevant skills in this area.

Keywords

Vascular access • Central venous catheter • Newborn surgery

9.1 Introduction

Advances in the medical and surgical management of neonates are often predicated upon secure vascular access. Requirement for vascular access may be for physiological monitoring (arterial or central venous pressure), direct treatment (antibiotics, chemotherapy), supportive therapy (nutrition, transfusion, dialysis, ECMO), diagnostic radiological, and procedural purposes (drainage of CSF or chyle, minimally invasive cardiac interventions). It is important for the surgeon to have a broad working knowledge of this field, as, given the multidisciplinary nature of modern neonatal intensive care, the options for and scope of vascular access are expanding alongside the number of subspecialties with interests and relevant skills in this area.

Despite its obvious importance, neonatal vascular access has yet to attract a large specific evidence base in support of its related practices. Therefore, as the subject is explored, important inferences will be drawn from the paediatric and also adult literature which might reasonably be considered to have a bearing on the sub-

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_9

ject, or which might be worthy of future research to determine applicability to neonatal vascular access.

9.2 Historical Considerations

The history of intravenous access can be traced back to the seventeenth-century and the general description of the circulation by William Harvey. In the same century Sir Christopher Wren administered a potent mix of ale, opium and beer to dogs using a quill for intravenous access and a pig's bladder as a fluid reservoir. Access to the venous circulation became practical with the development of the hollow needle by Francis Rynd in 1845, and the use of these reusable steel needles continued into the 1950s. The modern IV catheter can be traced back to 1950s when the "Rochester plastic needle" was developed, rapidly to be superseded by the first generation of "over the needle" plastic catheters led by the Intracath™ (Beckton Dickinson 1957) and then in 1964, by the Angiocath™ [1].

Dr. Latta described the use of an IV solution for the treatment of cholera in a letter to the Lancet in 1832. This intravenous rehydration therapy saved thousands of lives in the Paris cholera epidemics of 1832 and 1849. Turning to intravenous nutrition, Elman and Weiner reported pioneering nutritional experiments in 1937 using intravenous infusions of carbohydrates and protein hydrolysates in adults. The major difficulties encountered were loss of peripheral access and the large volumes of fluid required to even approach provision of adequate calories. Further important advances in understanding the physiology of protein calorie malnutrition arose out of the horrors of World War II, including the appreciation of gut mucosal atrophy in starvation and the potential for reversing this process and inducing mucosal proliferation with "intravenous feeding". The modern approach to total parenteral nutrition (TPN) was developed in the Harrison Department of Surgical Research at the University of Pennsylvania initiated in the 1940s by Harry Vars, later championed by Jonathon Rhodes and finally "perfected" by Stanley Dudrick, who was the first to demonstrate in 1966 that reliable long term nutritional support could be provided using TPN in beagle puppies [2]. The same group applied this technique with spectacular success for nearly 2 years in an infant with ultra-short bowel syndrome [3]. The success of the Pennsylvania group was predicated both upon the development of a fat emulsion using cottonseed oil, and the development of polyvinyl central venous catheters which were biologically inert. (Central venous catheters in current usage are manufactured almost exclusively from silicon or polyurethane.)

The formal organization of neonatal intensive care began in the 1960s with the establishment of dedicated intensive care units and the development of technologies for neonatal ventilation, central venous access and TPN. During the subsequent half century significant advances have been made in improving the morbidity and mortality of premature infants. Much emphasis is rightly placed on evidence-based approaches to medical care, and an attempt has been made in the remainder of this chapter to emphasize these developments with respect to neonatal vascular access.

9.3 Commonplace Neonatal Vascular Access Procedures

Although the majority of the procedures outlined below are the prerogative of the neonatologist, a passing understanding is the minimum expected of the surgeon who might interfere with such access in the event of laparotomy, or who might be called upon to assist in the management of an occasional complication resulting from vascular access procedures.

9.3.1 Umbilical Venous and Arterial Cannulation

The neonatal umbilicus provides immediate reliable short term access to both arterial and venous circulations. The umbilical arteries and vein can readily be dilated to allow passage of a polyure-

thane catheter in the first 24 h of life. Measured graduations on the catheter allow for positioning which is later confirmed radiologically (Figs. 9.1 and 9.2). The catheters are secured by suture to the umbilical stump and fixed by tape to the abdominal wall.

With respect to umbilical venous catheterization (UVC), the formula for inserted catheter length (cm) is estimated by ***weight (kg) × 1.5 + 4.5 + length of cord above the skin***. The catheter tip should lie centrally at the level of or just above the diaphragm ie. within the inferior vena cava, but outwith the cardiac silhouette [4, 5]. Heparinization of the infusate is unnecessary as volume alone is usually sufficient to maintain patency. A study of 142 neonates with UVC's identified accurate central positioning in 75% and identified four life threatening complications (pericardial and pleural effusions, rupture into the liver parenchyma and rupture into the abdominal cavity causing ascites) [6]. There is now considerable experience with multi-lumen umbilical catheters suggesting that their use is associated with a significant reduction in the need for additional peripheral intravenous catheters, albeit at the price of increased catheter malfunction [7].

In the case of umbilical arterial catheterization (UAC), similar catheters are used (3Fr for babies <1500 g, 4Fr 1500–2000 g, and 5Fr >2000 g). The required insertion length (cm) is estimated by the formula ***weight (kg) × 3 + 9 + length of cord above the skin surface*** [5]. The preferred tip position is "high" (thoracic aorta T6—T9), [5, 8–10] although a "low" tip position *(abdominal aorta L3–4)* is also acceptable [10, 11]. A high position is thought to be associated with a lower incidence of ischaemic complications. Patency is ensured by continuous infusion of heparinised 0.45% saline (0.5 IU/mL). Circulation in the lower extremities should be documented hourly, and signs of significant vascular compromise should prompt rapid removal of the catheter. Damping of the arterial trace is often the first indication of an impending thrombotic problem and if persistent should prompt consideration of catheter removal.

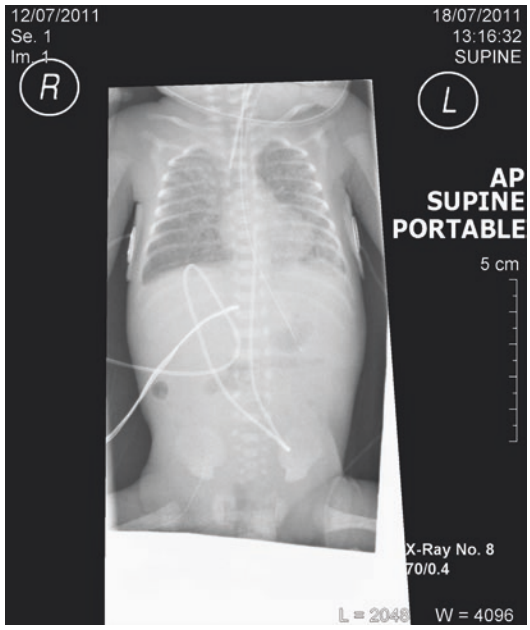

Fig. 9.1 Umbilical arterial catheter placed in ventilated neonate with tip in high position in thoracic aorta (T7–T8)

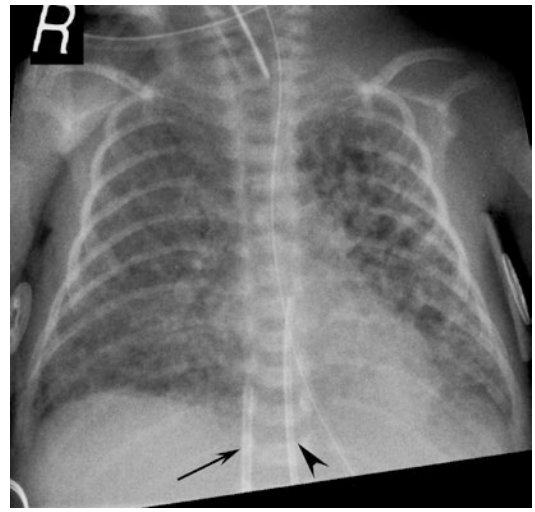

Fig. 9.2 Neonate with respiratory distress syndrome and unilateral pulmonary interstitial emphysema. The umbilical venous catheter (UVC) is positioned optimally and terminates at the diaphragmatic IVC (*arrow*). The UVC should not terminate in either the liver or the heart. The umbilical arterial catheter (arrowhead) lies to the left of the UVC and should terminate between T6 and T9 vertebral levels. *Image courtesy of Dr. Gurdeep S. Mann MRCP FRCP, Liverpool Women's Hospital*

These procedures are often used in emergency neonatal resuscitation. Infection and major vessel thrombotic complications become more common with increasing line longevity. Necrotizing enterocolitis is also associated with umbilical catheterization and when suspected, is similarly an indication for prompt line removal. Treatment of UAC-related thrombosis includes consideration of unfractionated (UFH) or low molecular weight heparin (LMWH) for 10 days. If life-, limb-, or organ-threatening symptoms result from UAC-thrombosis, thrombolysis with tissue plasminogen activator (tPA) [10], or even the option of surgical thrombectomy should be considered [12]. Currently there is no RCT evidence comparing thrombolysis with anticoagulation so firm conclusions about the relative merits of each treatment are impossible [13]. The risk of these medical interventions must be carefully weighed against the risk of haemorrhagic problems, particularly intra-ventricular haemorrhage.

9.3.2 Percutaneous Central Venous Cannulation

Peripherally inserted central lines (PICC's) are the preferred elective form of medium term vascular access in the premature neonate. The favoured routes are via the antecubital (basilic/cephalic), scalp (superficial temporal), or lower limb (saphenous) veins, although any peripheral vein can be used. Having accessed the vein, a long polyurethane catheter is "floated" into a central vein over a guidewire and the catheter tip position confirmed radiologically. There is clear guidance that the tip position of PICC lines should be outwith the cardiac silhouette to avoid the risk of tamponade [14]. The small diameter of these catheters often necessitates the use of radiological contrast to confirm tip position (Fig. 9.3).

The longevity of PICC lines is variable and is dependent on the neonate's co-morbidities in addition to prematurity. Judicious use of PICC lines includes appropriate and timely removal in the event of catheter complications, and the use of simple venous cannulae to "bridge the gap" to another PICC line insertion, when the neonate might have been compromised with respect to vascular access

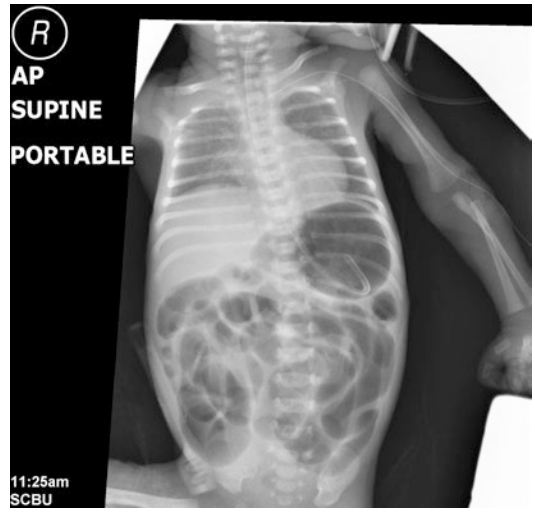

Fig. 9.3 Radiograph showing PICC line inserted via left cephalic vein with tip positioned optimally in the distal SVC but outwith the cardiac silhouette

(usually as a result of sepsis). This type of management in extremely premature neonates often obviates the need for surgical venous access and is a tribute to the skill of many a neonatologist.

There is increasing experience with central venous line insertion via internal jugular [15], femoral [16] and subclavian routes. Those with particular familiarity with the Seldinger approaches in these access locations often tunnel the catheter to the site of percutaneous access, thereby adding an extra level of protection from infectious catheter complications. There is an increasing willingness amongst surgeons to abandon the traditional open techniques of central venous access in favour of the percutaneous route, as it is thought that this approach is more likely to preserve the vein for future use. NICE guidelines now dictate that real time 2D ultrasound is mandatory (a gold standard) to assist catheterization via jugular (Fig. 9.4) and femoral routes in neonates over 3 kg, and that the operator (Fig. 9.5) should be appropriately trained in using ultrasound for the procedure [17]. A meta-analyses has been published which failed to show an advantage for US-guided as opposed to landmark insertions [18], but the patient base for this study was heavily weighted towards cardiac anaesthesia and as such is probably not completely representative of the population at large. This paediatric

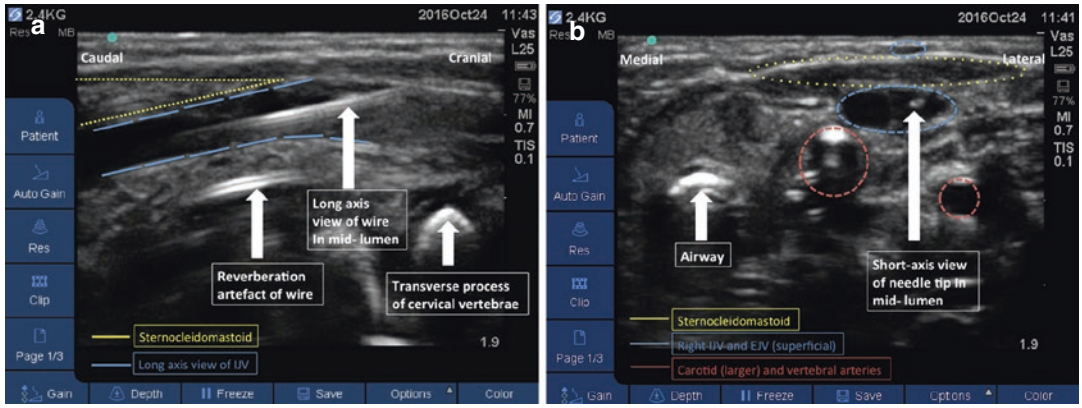

Fig. 9.4 (**a**) Ultrasound image of right side of neck in a 2.4 kg neonate. Note the proximity of significant other structures and the IJV midpoint is only 5 mm from skin. (**b**) Ultrasound image of right side of neck in a 2.4 kg neonate. Note the wire from a Seldinger CVP kit passing down the mid lumen of IJV. The wire can be followed distally into the thorax indicating correct placement. What cannot be appreciated from these static images is the significant compression of tissues that occurs during needle advancement. *Images courtesy of Dr. Peter Murphy, Consultant Anaesthetist, Royal Liverpool Children's Hospital NHS Trust*

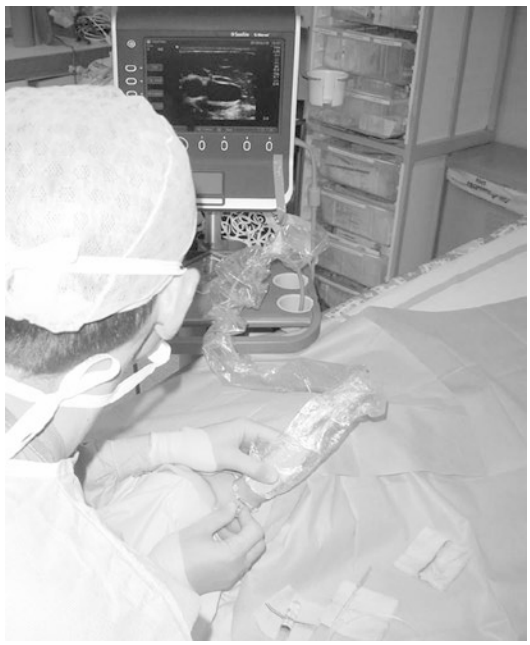

Fig. 9.5 Shows the technique of US-assisted venepuncture of the internal jugular vein. The operator uses the US probe to locate the vein and to follow continuously the progress of the needle tip/guide wire throughout the procedure. *Images courtesy of Dr. Peter Murphy, Consultant Anaesthetist, Royal Liverpool Children's Hospital NHS Trust*

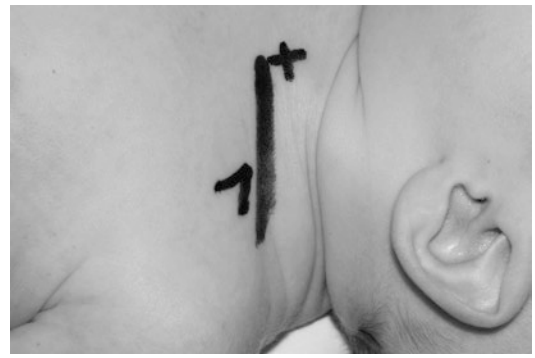

Fig. 9.6 Landmarks for percutaneous subclavian venous access. The insertion point is inferior to the clavicle at the junction of the medial two thirds with the lateral third of the clavicle (*arrow head*). The needle is advanced medially and cranially skirting just inferior to the clavicle and superior to the first rib, aiming in the direction of the suprasternal notch (*cross*)

meta-analysis and the "3 kg window" offered by NICE give some degree of flexibility to those favouring the "landmark approach" for smaller neonates (Figs. 9.6 and 9.7), but clearly a degree of familiarity with ultrasound-assisted central venous cannulation is becoming increasingly necessary.

9.3.3 Peripheral Arterial Catheterization

When arterial catheterization is required for invasive pressure monitoring outside the first 2 days of life, peripheral arterial cannulation is indicated. The radial and posterior tibial arteries are the preferred choice since catheterization of fem-

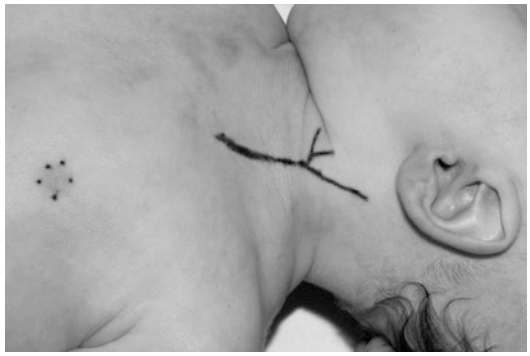

Fig. 9.7 Landmarks for percutaneous internal jugular venous access. The insertion point is over the sternomastoid muscle at the junction of its distal third with proximal two thirds (*arrow head*). The needle is advanced in the direction of the ipsilateral nipple at an angle of 30º to the skin surface whilst aspirating the syringe to confirm successful venepuncture

oral or brachial arteries carries significant risk of limb threatening consequences from distal thrombotic complications. These risks should always be carefully weighed against the potential benefits. The use of ultrasound or cold light transillumination may offer considerable assistance to arterial cannulation. As with umbilical arterial catheterization low dose heparin infusions are necessary to maintain arterial patency. In the event of distal ischaemic changes it is necessary to remove the catheter immediately. Where these changes are progressive options include passive observation, anticoagulation with UFH or LMWH, and thrombolysis usually with tPA. Not infrequently the risk of the intervention in terms of haemorrhage outweighs the potential benefit and non-viable tissues are frequently left to demarcate over time into dry gangrene before consideration of formal amputation.

9.3.4 Surgical Venous Access

As discussed earlier, technological improvements with catheters, new formulations of TPN, and the skills of both neonatologists and allied practitioners mean that surgical involvement in neonatal venous access is by no means inevitable even in the setting of extreme prematurity. However with increasing difficulty of access, requirement for "specialist" access (haemodialysis or ECMO), or when prolonged venous access is likely in a neonate undergoing surgery, surgical central venous catheterisation becomes mandatory. Additionally, when undertaking operative management of necrotising enterocolitis, complex meconium ileus or neonatal tumours (e.g. sacrococcygeal teratoma), a significant transfusion requirement may be anticipated. Under such circumstances it is advisable to insert a surgical venous catheter which allows for rapid volume expansion in the event of brisk haemorrhage.

Surgical central venous access is a routine procedure in a busy neonatal service and, although an excellent "training" operation, should not be undertaken without appropriate pre-operative planning, and meticulous attention to detail during surgery and in post-operative line management.

9.3.4.1 Pre-Operative Planning

As with any procedure undertaken under general anaesthetic, communication between neonatal, anaesthetic, surgical, laboratory, radiography and nursing personnel is vital. Clotting abnormalities should be corrected where possible and platelets should be available for peri-operative infusion should the platelet count be low ($<75 \times 10^9$/L). The size and type of line inserted, and whether single- or dual-lumen, both require careful consideration. A detailed knowledge of the vascular access history, and any requirement in the future for complex cardiac surgery will inform the choice of potential access sites. Clinical examination is mandatory as the sick neonate may have loss of epithelial integrity in neck flexural creases, or rarely a tracheostomy, which might similarly increase the risk of catheter infection at the time of surgery. Such considerations may suggest the use of (normally) second choice venous access sites.

Although urgent venous access may be required, where possible, surgery should not be undertaken without getting control of any prior catheter-related (or other) focus of sepsis, to avoid seeding microorganisms onto the newly inserted surgical line. Previous use of the intended

vascular access site is an indication for vascular imaging if the clinical situation permits. Ultrasound will determine patency of the relevant access vein but cannot provide information concerning "central run off". In practice, this is rarely a problem unless the central veins have been repeatedly accessed or there is clinical evidence of SVC or IVC thrombosis. Under such circumstances magnetic resonance venography (MRV) would be advisable to avoid predictable central access failure and consequent prolonged surgery.

9.3.4.2 Surgical Procedure: Open Technique

The internal jugular vein is most commonly the access vein of choice. The external vein is often useful but is less reliable in terms of achieving reliable access to the SVC. The procedure is performed supine under general anaesthesia, with both modest neck extension and the face turned away from the chosen side of access to expose the anterior and posterior triangles with the intervening sternomastoid muscle. A small transverse incision is made in the lower third of the neck over sternomastoid. Its two heads are split to reveal the internal jugular vein within the carotid sheath. The vein is controlled with an appropriately sized monofilament or silastic "sloop" (Fig. 9.8), taking care to handle the vein directly as little as possible as it readily undergoes venospasm. The catheter is tunnelled from the anterior chest to the cervical incision. Cutting the catheter to the appropriate length is a matter of judgement, but using the inter-nipple line as a guide, it usually needs to be trimmed a variable length above this. The venotomy can be made either with scissors or a venepuncture needle in an attempt to avoid the need for suture closure with fine prolene (Fig. 9.9). After passing the catheter, intra-operative fluoroscopic screening is required to determine the position of the catheter tip often with the aid of a bolus of radiological contrast medium should the catheter be smaller than 4.2Fr. The catheter is secured at the exit site by suture fixation and dressings. Access to the inferior vena cava is usually achieved using the saphenous vein just proximal to where it joins the femoral vein. It is important to control other tributaries of the sapheno-femoral junction to prevent the catheter from being misdirected. Other routes include the inferior epigastric vein and the external iliac vein approached extraperitoneally.

The literature concerning optimum tip position is reviewed in more detail later. In routine open surgical vascular access the "distal SVC to proximal atrium" (for upper extremity access) has been recommended [19], although this remains highly controversial [20]. When using lower extremity access the ideal tip position is in the IVC level with the base of the 12th thoracic vertebra (T12), corresponding to the diaphragmatic IVC.

Rarely surgical haemodialysis access is required in the neonate. The catheters (e.g.

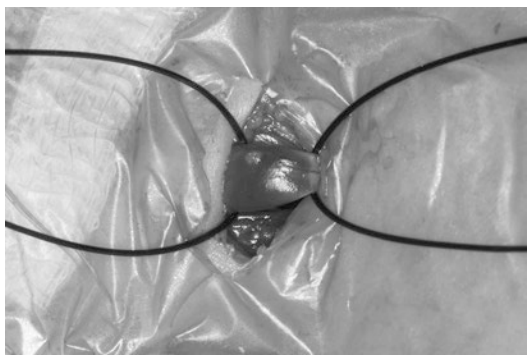

Fig. 9.8 Surgical exposure of the internal jugular vein between the heads of sternomastoid. The vein is "slooped" with silastic or monofilament suture prior to venotomy

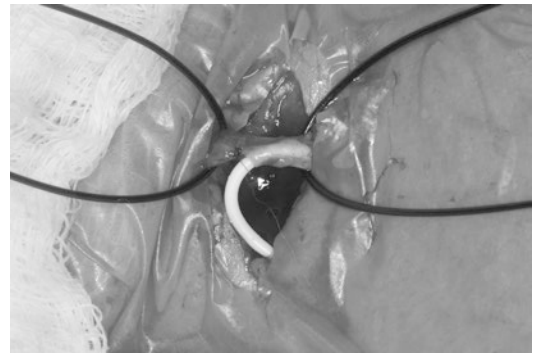

Fig. 9.9 The broviac line has been cut to length and passed via the venotomy to an estimated "junctional" position. The venotomy has been closed with fine prolene prior to confirming satisfactory tip position by fluoroscopy

Gamcath®) which are used for this purpose are of necessity quite rigid and therefore cannot exit on the chest wall when the internal jugular vein is accessed. For this reason an open procedure tunnelling the catheter is technically challenging and therefore these catheters are best inserted percutaneously. (Permcath® catheters, which are sufficiently flexible to exit the chest wall, are too large for most neonates.) To achieve and maintain long term adequate flow in the haemodialysis circuit it is advisable to use the largest internal lumen possible, preferably accessing the internal jugular vein rather than other access sites [21], and many (including the author) would argue in favour of having the catheter tip position preferentially sited within the proximal right atrium.

9.3.5 Percutaneous Versus Open Central Access

There is a developing body of opinion which believes that percutaneous access is superior to the open surgical approach [19, 22]. Given the lack of trauma to the vein associated with percutaneous access, this is an eminently reasonable proposition, especially with respect to the risk of thrombotic occlusion and potential future re-use of the vein. However there is no good supportive evidence in the literature to favour one approach over the other.

9.3.6 Complications of Venous Access

Venous access is associated with many complications. However, the three most frequent are catheter infection which may progress to septicaemia, occlusive complications such as fibrin sheath/vessel thrombosis and mechanical catheter complications such as dislodgement, migration and fracture.

9.3.6.1 Catheter Infection

The potential for the introduction of infection at the time of catheter insertion provides the rationale for consideration of the use of prophylactic antibiotics and other aseptic precautions at surgery. Although there is currently no strong evidence in relation to neonatal central line associated bloodstream infections (CLABSI's), level B evidence supports the following interventions to reduce the risk of CLABSI associated with whole population administration of TPN via central venous catheters; tunnelled/implanted catheters (confirmed only in long term use), antimicrobial coated catheters (demonstrated only in short term use), single lumen catheters, peripheral access as opposed to central access, appropriate central venous insertion site choice (internal jugular preferred to femoral vein), ultrasound guided venous access, maximal barrier precautions, and use of 2% chlorhexidene as a skin antiseptic [19]. Whether or not the benefits of these interventions will prove to be transferable to the neonatal cohort, we advocate the use of 2% alcoholic chlorhexidene pre-operative skin preparation, occlusive (opsite) draping, and a "no-touch" catheter handling discipline. At the very least, this focuses the mind of the surgeon on the danger of introducing infection. Logic also suggests that accurate fast surgery, minimal tissue handling, and the reduction of theatre "traffic" may also mitigate against primary catheter sepsis.

Cochrane reviews of systemic antibiotic prophylaxis at the time of central venous access in neonates [23] and in adult patients [19, 24] do not recommend their routine use. It has been suggested that fluconazole prophylaxis might be of value in certain high risk neonates. However a recent review of the literature has concluded that no trial has demonstrated a significant reduction in morbidity or mortality [25]. Contrary to generally received wisdom [19], and that of a prior Cochrane review in neonatal practice [26], a recent large RCT investigated the addition of 0.5 IU/mL Heparin to TPN administered through neonatal long lines (the HILLTOP trial) and demonstrated a significant reduction of culture-positive catheter-related sepsis [27]. Heparin-bonded catheters have failed to show any benefit in preventing catheter-related infection in children [28]. The use of antibiotic/heparin "locks" has also been shown to reduce the risk

of catheter-related infection in high risk groups [24, 29]. A neonatal study has recently recruited but not reported on the utility of a 15 min, 70% ethanol lock every third day. However, the benefit for neonates may be largely theoretical given that the requirement for continuous infusions effectively prevents the use of an antibiotic lock, or other form of lock for that matter.

Colonization of the exit site with microorganisms does not necessarily lead to invasive infection but provides a good rationale for tunnelling central catheters. It is advisable to monitor the skin flora at the exit site by regular swabs, thereby anticipating any invasive infection, and enabling active treatment of local cellulitis with an "informed choice" of intravenous antibiotics. There is no good evidence to suggest that any particular dressing is to be favoured in terms of preventing catheter-related infection [30]. Meticulous nursing care is essential both to keep the entry site infection free and to prevent the introduction of infection at the time of accessing the catheter. Where possible the line should not be used for routine sampling, and line interventions for treatment should be kept to the absolute minimum and performed with full aseptic technique. A Cochrane review investigating the use of in line filters has not conclusively demonstrated any benefit in terms of prevention of morbidity or mortality from introduction of secondary infection in neonates [31].

There is evidence that significant reductions in the incidence of CLABSI have been achieved in individual neonatal and paediatric intensive care units as a result of the implementation of "evidence-based catheter care bundles" [32]. This strategy postulates that CLABSI's result from lapses in technique at several levels of care [33]. Care bundles address multiple levels of intervention from insertion practice to daily line care. Level B evidence underlines the efficacy of such measures as; education and specific training, adequate hand washing policy, appropriate exit site care/dressing, hub disinfection/needle-free connectors, and regular changes of administration sets [19].

The incidence of catheter related sepsis is difficult to determine and depends critically on definition. The gold standard for line sepsis requires a positive culture from the catheter tip, once removed for presumed CLABSI. A positive blood culture, where the sample has been taken through the catheter, is a reasonable proxy, but does not exclude another potential source of blood stream infection. Exit site infection as evidenced by cellulitis or discharge of pus from the exit site may also be considered, but does not necessarily equate with colonization of the line and blood stream infection. Early diagnosis of CLABSI requires a high level of clinical suspicion and certainly should be considered in any neonate who is not "handling well". Changes in blood parameters such as C-reactive protein, liver function tests, white cell and platelet count, whilst all useful surrogate markers of infection, are frequently found to lag behind the onset of infection by 24 h or longer.

Quoted infection rates vary and are likely dependent on many variables. A recent large neonatal study of 294 peripherally inserted central catheters (PICC's) suggested a CLABSI rate of 17 per 1000 catheter days [34]. Another larger recent study of ultrasound guided percutaneous insertion of 500 Hickman® lines in children and neonates identified an infection rate of 3.2 per 1000 catheter days [22]. Local unpublished data from the author's institution of predominantly (87%) open surgical insertion of 336 central lines in children and neonates yielded an infection rate of 2.3 per 1000 catheter days. An exclusive study of 79 surgical neonates quoted a CLABSI rate of 9.9 per 1000 catheter days. A significant risk factor associated with CLABSI in this latter study was the presence of an intestinal stoma [35]. The inherent variability in the study populations, and variations in line type and mode of insertion, all conspire to make it difficult to draw firm conclusions about the factors that may be associated with neonatal CLABSI.

The commonest responsible organism is coagulase-negative *Staphylococcus* (representing 89% of blood culture isolations in a neonatal study [34]), thereby informing the choice of "best guess" antibiotic when treating suspected line sepsis. Other organisms such as coliforms are not infrequent culprits in surgical neonates. It has been

suggested that translocation of these organisms from the neonatal bowel may be the cause of such infection. Provided the neonate is not unduly compromised by the suspected line infection, an attempt to "sterilize" the line with a prolonged course of antibiotics is usually the first line of treatment. Overwhelming line sepsis demands urgent removal of the line. Where infection is due to more aggressive pathogens such as fungal species, *Pseudomonas* and *Staphylococcus aureus*, primary removal of the line is probably the best option. Failure to eradicate the organism after two attempts at sterilizing the line is another indication for line removal. However, in the setting of precarious venous access, or when venous access is likely to be prolonged (e.g. short bowel syndrome), consideration should be given to changing the line down the same track with appropriate antibiotic cover. Using this approach, the same vein can be used repeatedly over prolonged periods. Persistent low grade sepsis in the presence of a central line mandates the exclusion of bacterial endocarditis by echo-cardiography, since the consequences of missing this diagnosis may be disastrous. Timing of further central access following significant catheter-related sepsis ideally requires that the infection is appropriately treated before further surgical catheter manipulations are attempted.

9.3.6.2 Occlusive Catheter Complications

The presence of a catheter evokes the formation of a fibrin sheath around it which can usefully be employed to facilitate re-use of the catheter track for line "exchange" (see above). Sometimes, a fibrin sheath forms around the intravenous part of the catheter which, if extensive, can occlude the catheter lumen. Even in high-flow central veins the catheter can be a prothrombotic stimulus, resulting in partial or complete venous occlusion. Instillation of tissue plasminogen activator (tPA) or recombinant urokinase into a blocked catheter may be sufficient to re-establish patency. Sufficient urokinase (5000 units/mL saline) to fill the dead space of the catheter is left in situ for 30 min before attempting to aspirate the line. This procedure may be repeated once before removing the line and investigating to exclude line-related thrombosis if patency has not been restored. If successful, a contrast study through the line may reveal a fibrin sheath or local thrombosis, and give information both on tip position and adequacy of catheter "run off". The use of heparin "locks" to preserve line longevity in relation to occlusion is only of value when the line is accessed intermittently. There is grade 1B evidence to recommend against the prophylactic use of heparin in children with central venous catheters [10]. Similarly neonatal studies do not support the use of heparin in TPN as prophylaxis against catheter related thrombosis [26]. The use of heparin-bonded catheters cannot currently be recommended to prevent thrombosis or occlusive complications [28]. The general literature emphasizes (grade B) that thrombotic problems are reduced if the smallest possible catheter lumen size compatible with therapy is chosen, if an ultrasound-guided insertion technique is employed, and if the tip position is at or near the atriocaval junction [19].

When a neonatal central venous line or umbilical venous line is associated with confirmed thrombosis it should be removed. Management options include initial anticoagulation (grade 2C) with UFH or LMWH, or radiological monitoring alone (grade 2C). If thrombus propagation is demonstrated over time, anticoagulation with LMWH is recommended (grade 1B) for a minimum of 6 weeks [10].

The incidence of neonatal venous thromboembolism (VTE) is difficult to determine accurately, but data from Dutch and German national registries suggest an incidence of 0.1-0.5 cases per 10,000 births. The presence of a central line is the single most important contributory factor. It is often difficult to relate mortality directly to VTE, but certainly there is an appreciable mortality including stroke from paradoxical embolus [10].

9.3.6.3 Mechanical Complications

There is no fool-proof way of securing a central venous catheter before the Dacron cuff (if present) is firmly incorporated into the subcutaneous tissue. Reliance is usually placed on some form of exit stitch and the catheter dressing. Not infrequently incorrect application of the catheter

clamp to the non-reinforced part of the catheter results in fracture of the line. If sufficient undamaged external catheter is available distal to the fracture site, these can often be repaired with a commercially available kit. Prior to repair, the fracture site should be sealed with an adhesive clear dressing.

Extravasation of fluid into the subcutaneous tissue around the line track may similarly indicate fracture of the line or possibly occlusion due to a fibrin sheath (see above). A contrast study is indicated which usually identifies the underlying cause.

Removal of a central catheter can usually be performed under local anaesthetic at the cot side. This is not without risk and should not be left to the most junior member of the team. Usually the Dacron cuff can be dissected free via the entry site wound, but occasionally a second incision is required. Careful dissection on the fibrin sheath distal to the cuff allows the catheter to be retrieved. The major risk is cutting through the catheter beyond the cuff which might result in a catheter embolus (Fig. 9.10). Should this occur the retained catheter should be removed (size-permitting) by an interventional cardiologist using a snare inserted via the femoral vein.

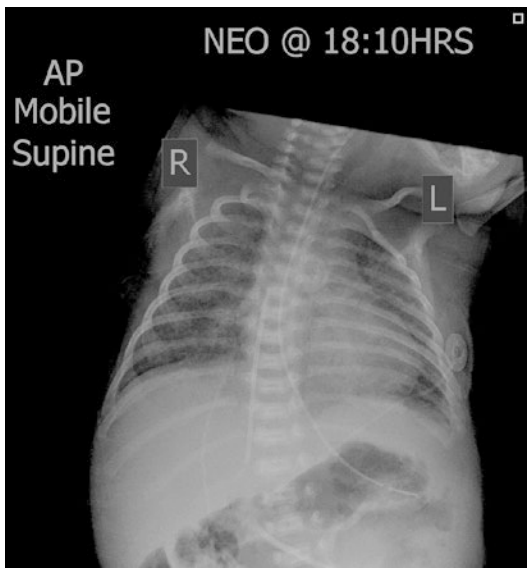

Fig. 9.10 Radiograph showing distal catheter embolus with the retained fragment free-floating in the right heart chambers following an unsuccessful attempt at removal. Such procedures should not be left to the surgical novice. This line was subsequently successfully snared and removed transfemorally in the cardiac catheter suite

9.3.6.4 Anatomical Variations

Variations in venous anatomy can trap the unwary. The most common of these is the left sided SVC. This structure drains into the coronary sinus and therefore a catheter tip lying in close relation to this structure should not be accepted. Occasionally manipulation of the catheter allows it to be directed through the innominate vein to the right SVC, but if this is not possible the attempt should be abandoned or the catheter left abnormally short as a temporizing measure.

Abnormalities of the inferior vena cava may result in dominant azygous or hemi-azygous systems. Neonates with congenital cardiac abnormalities may have significant abnormalities of venous drainage, and care needs to be taken not to encroach on the territory of the cardiac surgeon with respect to future cardiac surgical reconstruction.

9.3.6.5 Catheter Migration

There has been considerable debate about what constitutes an acceptable catheter tip position and consensus is by no means complete. The traditional approach has been to aim for a catheter tip position in the SVC. However, there is a body of expert opinion that emphasises improved performance and durability of a catheter if its tip is within the upper right atrium [20]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend a position in the lower third of the SVC, in a junctional position, or in the upper portion of the right atrium [19]. However, in a neonate the evidence probably supports a distal SVC tip position for PICC lines. Strictly applied this latter definition of acceptability leaves very little margin for error and probably results in many of these lines being left "short". Open insertions of central lines allow for greater control of final tip positions. Although the ideal tip position under such circumstances would be distal SVC or "junctional", many surgeons (including the author) would accept a proximal atrial position. Clearly what is "ideal" is not always possible, and for the individual

neonate a sub-optimal position may occasionally have to be accepted.

Significant migration of the catheter tip either proximally or distally has been described even when a satisfactory tip position has been documented at initial insertion. Distal migration of an upper extremity line can be the cause of arrhythmia, tricuspid valve vegetations, or pericardial effusion/tamponade. Proximal migration has been described with final line tip locations in the innominate, subclavian or internal jugular veins where occlusive/thrombotic problems are much more common.

9.3.6.6 Extravasation

Although subcutaneous extravasation is relatively common, this complication should be considered in unexplained pleural effusion or ascites. The diagnosis can readily be made by diagnostic tap of the relevant cavity, and removal of the offending catheter resolves the problem. The fatal association of cardiac tamponade with neonatal PICC lines led to the guideline that the tips of these catheters should always be left out with the cardiac silhouette [14].

9.4 Concluding Remarks

Vascular access in the neonate is a challenge to neonatologists, anaesthetists and surgeons alike. In common with other interventions in sick preterm infants, these procedures are associated with considerable morbidity and a significant mortality. The early recognition of complications related to vascular access and the subsequent assessment of management options requires considerable clinical judgement and experience. There remains ample scope for clinical research and technological advances in this field.

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Radiology of Surgical Conditions in the Newborn

10

Alexandra L. Williams, Andrew Healey, and Laurence Abernethy

Abstract

When imaging the newborn baby, concerns of particular importance include temperature regulation, appropriate monitoring, minimising the radiation dose and careful use of contrast agents. Radiography and ultrasound examinations can be performed with portable equipment on the neonatal unit or intensive care unit, but more complex imaging usually requires transfer to the radiology department. It is essential that when newborn babies are transported to the Radiology Department, they are accompanied by suitably qualified personnel, capable of monitoring and managing the sick neonate. Temperature, pulse and oxygen saturation should be monitored. This involves a collaborative model of care, with close liaison between radiologist, neonatal unit and transfer team. Staff should be prepared to interrupt or abandon the procedure immediately if the baby becomes unstable. The utmost care must be taken when handling to ensure that vital lines and tubes are not disturbed or displaced.

Keywords

Radiology • Imaging • Interventional radiology • Newborn surgery

10.1 Care of Neonates Undergoing Radiological Investigations

When imaging the newborn baby, concerns of particular importance include temperature regulation, appropriate monitoring, minimising the radiation dose and careful use of contrast agents. Radiography and ultrasound examinations can be performed with portable equipment on the neonatal unit or intensive care unit, but more complex imaging usually requires transfer to the radiology department. It is essential that when newborn babies are transported to the Radiology Department, they are accompanied by suitably qualified personnel, capable of monitoring and managing the sick neonate. Temperature, pulse and oxygen saturation should be monitored.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_10

This involves a collaborative model of care, with close liaison between radiologist, neonatal unit and transfer team. Staff should be prepared to interrupt or abandon the procedure immediately if the baby becomes unstable. The utmost care must be taken when handling to ensure that vital lines and tubes are not disturbed or displaced.

Neonates have a poor ability to maintain body temperature, and hypothermia can lead to acidosis and surfactant deficiency. Whenever possible the baby should be kept in a temperature-controlled incubator. Only the relevant body part should be exposed, and for the shortest time possible, in order to minimize heat loss. In the radiology department the rooms should be warm. To avoid heat loss in more prolonged procedures, chemical warming blankets can be placed under the baby, or the baby can be covered with a sealed clear plastic wrapping and a warming device used to blow warm air under the wrapping. Staff should check that baby is dry at frequent intervals and the core body temperature should also be monitored. Prolonged procedures without monitoring, with an uncovered baby lying in a pool of cold liquid (urine, contrast media, or skin preparation solution) must be avoided.

The skin of newborn babies is very fragile. Care should be taken to avoid pressure points and hyperextension of limbs. Adhesive drapes should be avoided, as should 2% chlorhexidine skin preparation solution, which may cause chemical burns in premature infants.

10.2 Radiation Dose

The newborn baby, like the fetus, is particularly sensitive to the effects of ionising radiation and is at greatest risk of radiation-induced disease. It is essential that when considering exposing a neonate to ionising radiation the ALARA principle is adhered i.e. that every effort is made to ensure that exposure to ionising radiation is kept "As Low As Reasonably Achievable". This relies on careful consideration by the requesting clinician, close collaboration between radiologist and clinician, and meticulous technique on the part of the radiologist and radiographer. Digital pulsed screening with low pulse rates, and removal of the anti-scatter grid, help to reduce the absorbed radiation dose. Screening times should be kept as short as possible. The most effective means of reducing radiation exposure is simple: no examination involving exposure to X-rays should be performed unless it is clinically justified. Whenever appropriate, ultrasound should be used in preference to fluoroscopy and computed tomography (CT).

Contrast may be used intravenously in computed tomography and magnetic resonance imaging, and during fluoroscopy to assess hollow organs and lines and tubes. In the past, the use of contrast media in small children was associated with high risk. Neonates are vulnerable to the smallest fluid shifts and careful consideration to fluid-balance is necessary when administering IV or intra-luminal contrast agents.

If ionic, high osmolar contrast media are used for gastrointestinal contrast studies, there is a risk of massive fluid shift into the bowel, which can rapidly deplete extracellular fluid and result in circulatory collapse. If non-ionic contrast is given by mouth, there is a risk of pulmonary oedema if aspiration occurs. The use of non-ionic low osmolar contrast agents has reduced (but not completely eradicated) the risks associated with the use of contrast.

There are some special indications for using hyperosmolar water-soluble contrast media, such as sodium meglumine amidotrizoate (Gastrografin, Bayer Schering Pharma AG, Berlin), in the gastrointestinal tract in infants, although any use of these agents is potentially hazardous and should only be attempted by experts, after careful consideration of the risks and benefits. These indications include suspected meconium ileus and meconium plug syndrome, in which enemas performed with hyperosmolar contrast can have a therapeutic effect by drawing fluid into the bowel, lubricating and emulsifying the colonic content, and stimulating colonic motility. When used for these indications, Gastrografin is usually diluted 1:2 or 1:3 with saline or water. Even when diluted, hyperosmolar contrast agents may cause rapid fluid shifts, and so must be used with great care in small infants. Dehydration should be corrected before the procedure is commenced, an intravenous fluid infusion should be running, and careful monitoring should be performed during and after the

procedure. Gastrografin may also have a beneficial effect when administered orally to older infants with cystic fibrosis and distal intestinal obstruction syndrome [1].

When iodinated contrast media are administered intravenously, for example for contrast-enhanced CT, special care must be taken because of the immature renal function of neonates. The dose should be carefully calculated on the basis of body weight and the iodine content of the contrast medium, in accordance with the manufacturer's recommendations.

MRI contrast agents containing gadolinium should be used with caution in neonates and young infants, because of immature renal function and the possible risk of nephrogenic systemic fibrosis (NSF). The most stable macrocyclic chelates are generally considered to be safest. Children at risk for renal impairment (for example, those with known medical renal disease or urinary tract structural abnormalities) should be identified and screened. Gadolinium contrast agents should be avoided in acute kidney injury or chronic kidney disease with eGFR <30 mL/min/1.73 m^2. The current recommendation for neonates and infants is that only one dose should be given during an examination, and should not be repeated within 7 days.

10.3 Imaging Modalities

A wide range of modalities are used for neonatal imaging, each of which has a role to play in the care of the surgical neonate. Close collaboration and timely discourse between clinician and radiologist ensures optimum information is obtained from the correct examination with the least radiation exposure and with minimal stress to the sick neonate.

10.3.1 Ultrasound

Ultrasound is ideally suited to the examination of neonates and young infants. Ultrasound examination is painless and non-invasive, and involves no exposure to harmful ionising radiation. With patience, diagnostic images can be obtained even with a restless child. The plane of imaging is infinitely variable and can be adapted to the anatomical location of the lesion. Colour Doppler is uniquely valuable in allowing assessment of blood flow in real time; making it immediately apparent whether a fluid-filled structure is cystic or vascular. In paediatric ultrasound it is helpful to have a range of transducers with different sizes and footprints. Ultrasound is readily accessible and portable, can be used with relative ease on a sick neonate in an incubator, and is often the initial investigation of choice. Inexpensive portable ultrasound devices are now widely available. However, ultrasound does have limitations. It is highly operator dependent. Little information is given on the function of the organ, though ultrasound of the bowel can offer information regarding peristalsis. The field of view of ultrasound is limited in some anatomical locations, as ultrasound has limited penetration of bone and cannot penetrate air. Although ultrasound equipment is relatively inexpensive, neonatal ultrasound can be resource intensive, as successful examination of a restless baby may be time-consuming and requires considerable expertise. Scrupulous attention to hygiene is necessary to minimise the risk of transmission of infection between patients, particularly when using portable ultrasound. Ultrasound transducers should be cleaned and disinfected between examinations, using an approved proprietary broad-spectrum surface disinfectant; in addition, hand washing between examinations should never be forgotten.

10.3.2 Plain Radiography

Although a range of more complex imaging modalities are available, the plain radiograph still has an important role as it is widely available, and can be performed rapidly and with portable equipment. Chest and abdominal radiographs are the first line of investigation in many neonatal surgical conditions, and can often provide the diagnosis without further imaging. Plain radiography provides anatomical information in two dimensions and gives information regarding the components of a substance, whether fat, gas, calcium and bone. Abdominal radiographs provide information

about bowel obstruction, the presence of free or intra-mural gas, and the location of masses or presence of abnormal calcification. However, plain radiography offers no dynamic or functional information and provides only a snapshot of one moment in time.

It is essential that exposure factors are optimized and the beam is well collimated to ensure a minimal dose to the neonate. Radiography in the sick neonate is usually performed in the supine position, particularly if being performed with the baby in the incubator, with decubitus films if there is concern regarding pneumoperitoneum. Care must be taken to ensure drips and lines are not disturbed.

10.3.3 Fluoroscopy

Fluoroscopy is essentially real time radiography, which often involves the use of contrast media to allow visualization of a hollow organ. Contrast can be given orally, rectally, intra-vesically, intra-arterially or intravenously, via stomata and into tubes and lines to assess patency and position. Optimum use of pulsed fluoroscopy and last image capture ensure the exposure to ionizing radiation is kept to a minimum.

10.3.4 Computed Tomography (CT)

CT offers cross sectional demonstration of anatomy, providing visualisation of anatomical details in the axial plane. These images can be reconstructed into sagittal and coronal planes and 3D reformats. Computed tomography is an accessible, rapid test but requires transfer of the sick or ventilated neonate to the radiology department. The use of contrast material may be necessary, particularly for imaging the chest and abdomen. In the neonate, with little body fat, the tissue contrast is poor, making interpretation more challenging than in the older child. Every effort should be made to keep the radiation dose as low as possible, by "right-sizing" the imaging parameters: kV, mAs, slice thickness, and area of coverage should all be individualized. There is no justification for using preset adult CT parameters, which deliver an unacceptably high radiation dose.

10.3.5 Magnetic Resonance Imaging (MRI)

The greatest benefit of MRI is that it does not involve the use of ionising radiation. Using a powerful magnetic field and radiofrequency electromagnetic impulses, MRI produces detailed anatomic or functional images in any plane, with high contrast resolution, providing information about the composition of the tissue being imaged. To date, no long-term adverse effects of MRI have been found at the field strengths routinely used in clinical practice, so long as all safety procedures are rigorously followed. Hearing protection is essential. Issues include the frequently remote location of MR scanners and the need to transport a neonate to the scanner, and poor access to the child while in the scanner. There are difficulties ensuring adequate monitoring and minimising movement during lengthy scans. In neonates the "feed and wrap" technique reduces movement and often avoids the need for sedation or general anaesthetic.

10.3.6 Radio-Isotopes

Nuclear medicine provides information on the pathophysiology of an organ with the injection or ingestion or radiopharmaceuticals. This is of limited use in the investigation of the very sick or ventilated neonate but still has a place (examples—hepatobiliary imaging with Tc^{99m} HIDA for suspected biliary atresia, renal imaging with Tc^{99m} MAG-3 for obstructive uropathy, abdominal scanning with Tc^{99m} pertechnetate for Meckel's diverticulum, thyroid scanning with Tc^{99m} pertechnetate or I^{123} in congenital hypothyroidism, I^{123} meta-iodobenzylguanidine (MIBG) in suspected neuroblastoma, fluoroDOPA PET CT in congenital hypoglycaemia of infancy). Anatomical resolution is relatively poor, but radio-isotope imaging in these situations can provide valuable functional information that is not obtained with other modalities.

10.3.7 Interventional Radiology

Interventional radiology is the application of minimally invasive diagnostic and therapeutic techniques under image guidance, often utilizing ultrasound guided modified Seldinger needle puncture technique, and fluoroscopic guided flexible preshaped wires and catheters together coaxially to perform therapy. CT and MRI can also be utilized for guidance [2]. Vascular access can be obtained by the interventional radiologist under ultrasound and fluoroscopic guidance.

Gastrostomy is often performed surgically in the neonate at the same time as a definitive surgical correction of bowel anomalies; however percutaneous gastrostomy can be performed in certain situations. If abdominal surgery is not imminently planned but gastric feeding is required a direct percutaneous puncture of the stomach using ultrasound or fluoroscopic guidance can be performed. Ultrasound guidance can be useful if a tracheo-oesophageal fistula is present not allowing endoscopic access or fluoroscopic contrast instillation via NG tube.

Percutaneous drainage of any viscus, abscess or fluid collection (ascites, pleural or pericardial effusion) can be performed under ultrasound guidance (Fig. 10.1). Percutaneous core biopsy,

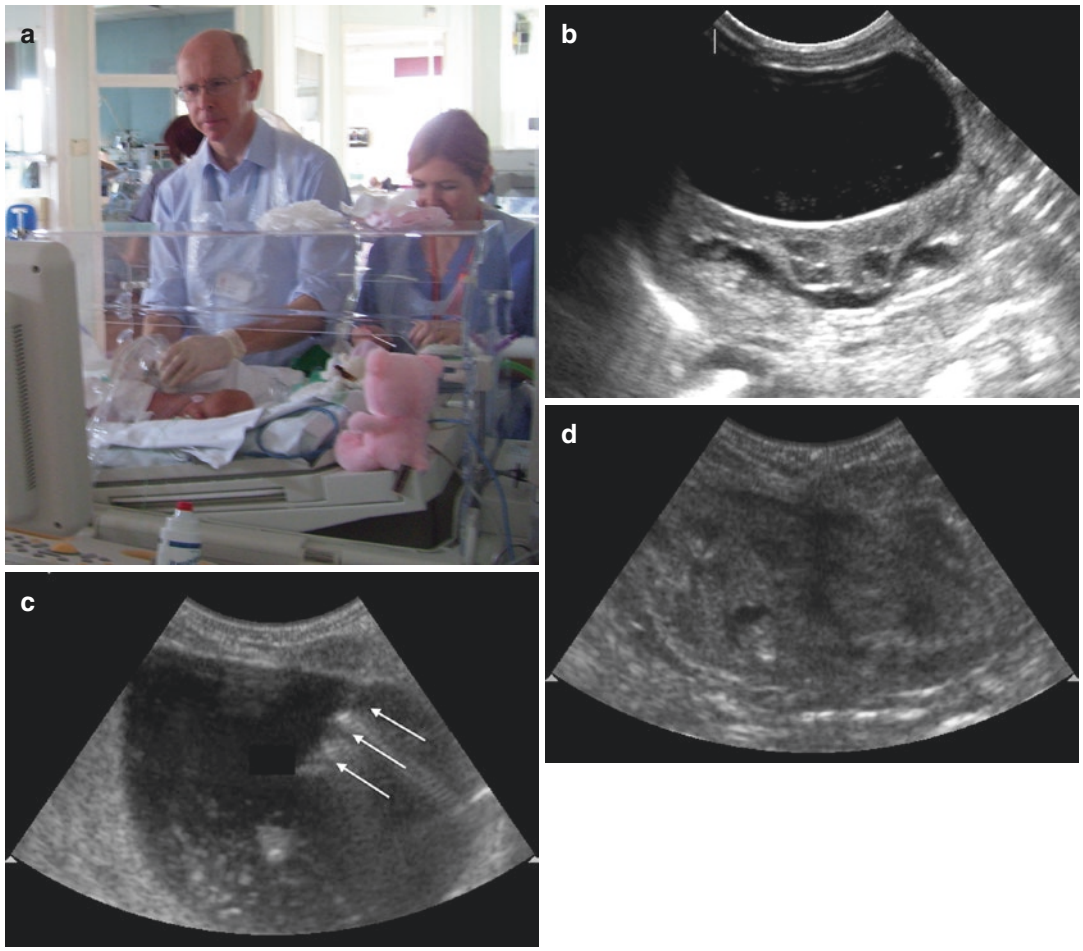


Fig. 10.1 Interventional procedures in the neonate. (**a**) Percutaneous aspiration of a perinephric collection under ultrasound guidance, performed on a premature baby on a neonatal unit. (**b**) Ultrasound image showing perinephric collection. (**c**) The needle path can be seen from the skin surface into the collection (*arrows*). (**d**) Minimal residual perinephric fluid following aspiration

usually performed under real time ultrasound guidance, is an extremely safe and effective way to obtain a tissue diagnosis allowing definitive surgical intervention. Foreign bodies can be recovered using image guidance and a snare device.

10.4 Positioning of Lines, Tubes and Catheters

Newborn babies with surgical conditions often require intensive medical care and the placement of multiple lines, tubes, and catheters. In small babies the correct placement of tubes and catheters may require considerable skill, and there is little latitude for error. Inappropriate placement may be dangerous. Plain radiographs and ultrasound are valuable for confirming the course and location of these devices, but accurate interpretation may be challenging and requires knowledge and experience of the wide range of appearances of malposition and potential complications.

In the newborn baby, the umbilical vein and artery provide an accessible route for the placement of catheters for therapy and monitoring. Correct placement may be challenging and should always be checked with radiographs of the chest and abdomen. The preferred location of the tip of an umbilical venous catheter (UVC) is at the junction between the inferior vena cava and the right atrium. If not advanced far enough, the tip of the UVC may lie in the umbilical vein or its recess, below its confluence with the left portal vein. Fluids infused via a UVC in this position will be delivered directly to the liver through the portal venous system. Oestreich (2010) [3] has demonstrated that a little air is frequently visible in the umbilical vein or portal venous system following UVC insertion; this is not in itself harmful, but may be recognised on the initial placement radiograph, and is helpful in assessing the position of the UVC.

The correctly positioned UVC should pass through the umbilical vein and its confluence with the left portal vein into the ductus venosus, which normally obliterates a few days after birth. The ductus venosus joins one of the hepatic veins to drain into the inferior vena cava just below the right atrium. It is, however, possible for the malpositioned UVC to enter the left portal vein, or to pass to the right into the right portal vein or the main portal vein, from where is possible for it to pass into the splenic vein or superior mesenteric vein. UVC placement in these positions carries a risk of inducing portal vein thrombosis. If advanced too far the UVC may pass into the right atrium, right ventricle and pulmonary artery, or through a patent foramen ovale into the left atrium. Cardiac tamponade, pulmonary embolism and lung abscess are among the possible complications. UVC malposition in a hepatic vein can cause segmental liver infarction [4] (Fig. 10.2).

The umbilical artery can be used for arterial access during the first 5–7 days of life, but it is rarely used after 7–10 days. An umbilical artery catheter (UAC) provides direct access to the arterial blood supply and allows continuous measurement of arterial blood pressure, arterial blood gas sampling, and intravascular access for fluids, medications, and exchange transfusion when other routes are not available. On radiographs, the correctly positioned UAC should be seen entering the umbilical cord and passing inferiorly to the internal iliac artery, then turning cephalad to enter the aorta and proceeding in a straight line to the left of the vertebral column. Its tip should lie above the diaphragm between levels of the T6 and T9 vertebrae. This position is above the origins of the coeliac axis (T12), the superior mesenteric artery (T12-L1), and the renal arteries (L1) (Fig. 10.2).

10.4.1 Nasogastric Tubes

The correct position should be assessed on a plain film; a position of the tip below the level of the diaphragm should be confirmed prior to use to avoid potentially catastrophic complications of feed or medications infused into the lungs. Careful evaluation of the course of tubes and lines is also required, for example an abnormal course of the NG tube can be due to mass effect from mediastinal pathology (Fig. 10.3).

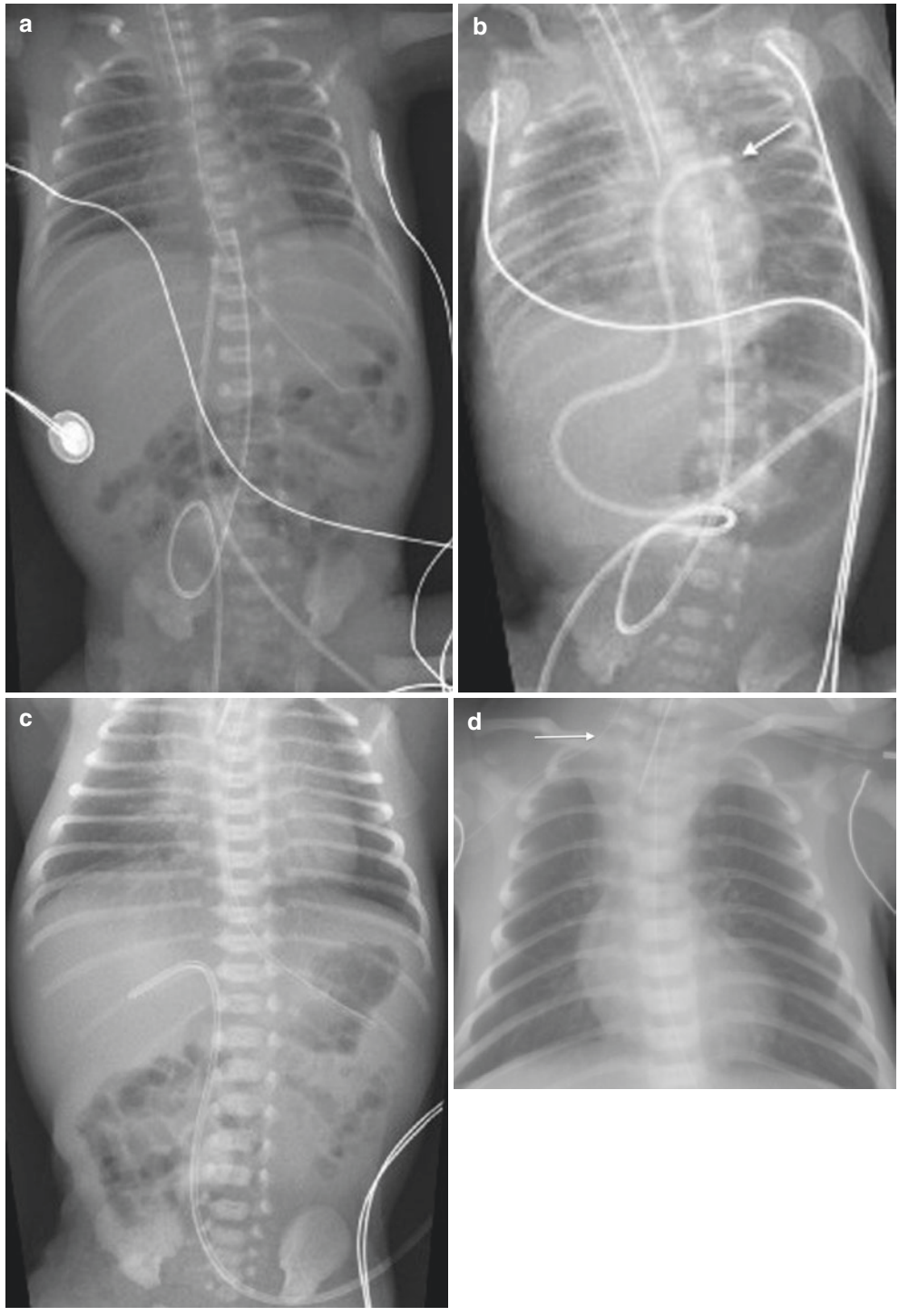


Fig. 10.2 Normal and abnormal positions of vascular access lines. (**a**) Chest and abdominal radiograph shows normal positions of umbilical arterial catheter (UAC) and umbilical venous catheter (UVC). The endotracheal tube and nasogastric tube are also in a satisfactory position. (**b**) Misplaced UVC with its tip in the pulmonary vasculature. (**c**) UVC projected over the liver and coursing to the right, which suggests that the tip lies in the right portal vein. (**d**) Malpositioned right PICC line seen passing cranially into the internal jugular vein

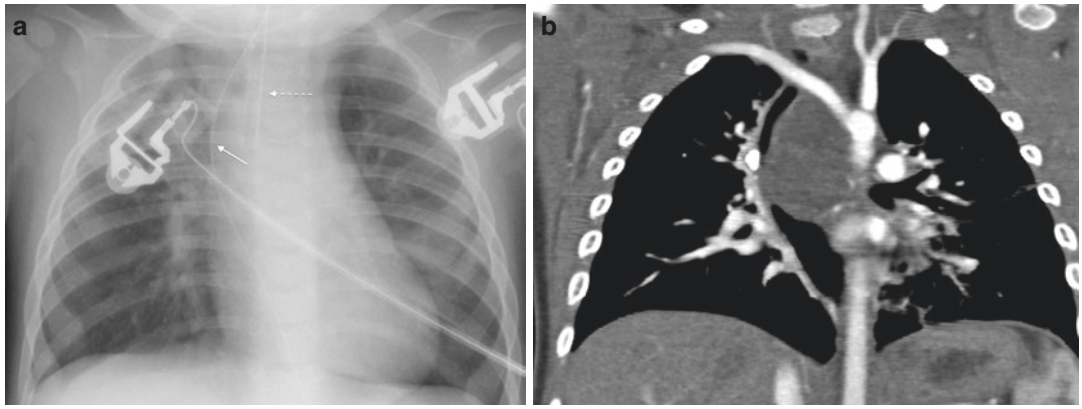


Fig. 10.3 Abnormal course of the NG tube. (**a**) Deviation of the NG tube suggesting mass effect. (**b**) CT confirms the presence of a mediastinal mass

10.4.2 Endotracheal Tubes

The correct position for the tip should be above the carina and below the thoracic inlet. An endotracheal tube, which has been advanced into a main bronchus, will cause hyperinflation of the ipsilateral lung and collapse of the contralateral lung (Fig. 10.4).

10.5 The Neonate with Jaundice

Neonatal jaundice is common, occurring in 60% of full term and 80% of preterm infants [5]. In the first 2 weeks of life this is usually due to an accumulation of unconjugated bilirubin, resulting from immaturity of the conjugating enzyme glucuronyl transferase. This is commonly known as physiological jaundice of the neonatal period and peaks at day 5–7. Persistence of jaundice beyond 2 weeks is abnormal and merits investigation.

Biochemical analysis will determine whether bilirubinaemia is unconjugated or conjugated. Prompt investigation of a conjugated hyperbilirubinaemia is required. Causes include both medical and surgical pathologies. Imaging plays an important part in differentiating intrahepatic from extrahepatic causes of persisting neonatal jaundice and can further clarify pathology in extrahepatic causes. Diagnosis of intrahepatic causes relies heavily on laboratory tests, however imaging does play a vital role in providing complementary information in neonates with complex syndromes as a cause of the jaundice, and with ultrasound guided liver biopsy which ensures a higher diagnostic yield with reduced complication rates (Fig. 10.5).

The three main causes of neonatal jaundice are biliary atresia, hepatitis and choledochal cyst.

The first line imaging investigation in a neonate with persistent conjugated hyperbilirubinaemia is ultrasound. Ultrasound is independent of liver function and can differentiate obstructive causes such as choledochal cyst, bile plug syndrome or stone disease from non-obstructive causes. Features of biliary atresia may be demonstrated and in addition, ultrasound of the abdomen may detect more unusual unsuspected causes of jaundice such as adrenal haemorrhage.

Ultrasound provides exquisite anatomical delineation of the liver, allowing an assessment of size and echotexture. The gallbladder and biliary tree can be evaluated and the whole abdomen can be imaged to look for associated findings such as ascites.

HIDA scan involves the intravenous injection of a Technetium 99 m labelled tracer, which is taken up by the normal liver, excreted in the biliary tree and accumulated in the gallbladder, eventually appearing in the bowel.

MRCP has replaced the traditional ERCP in many clinical situations. This offers detailed anatomical imaging of the biliary tree, and provides further information about the other upper

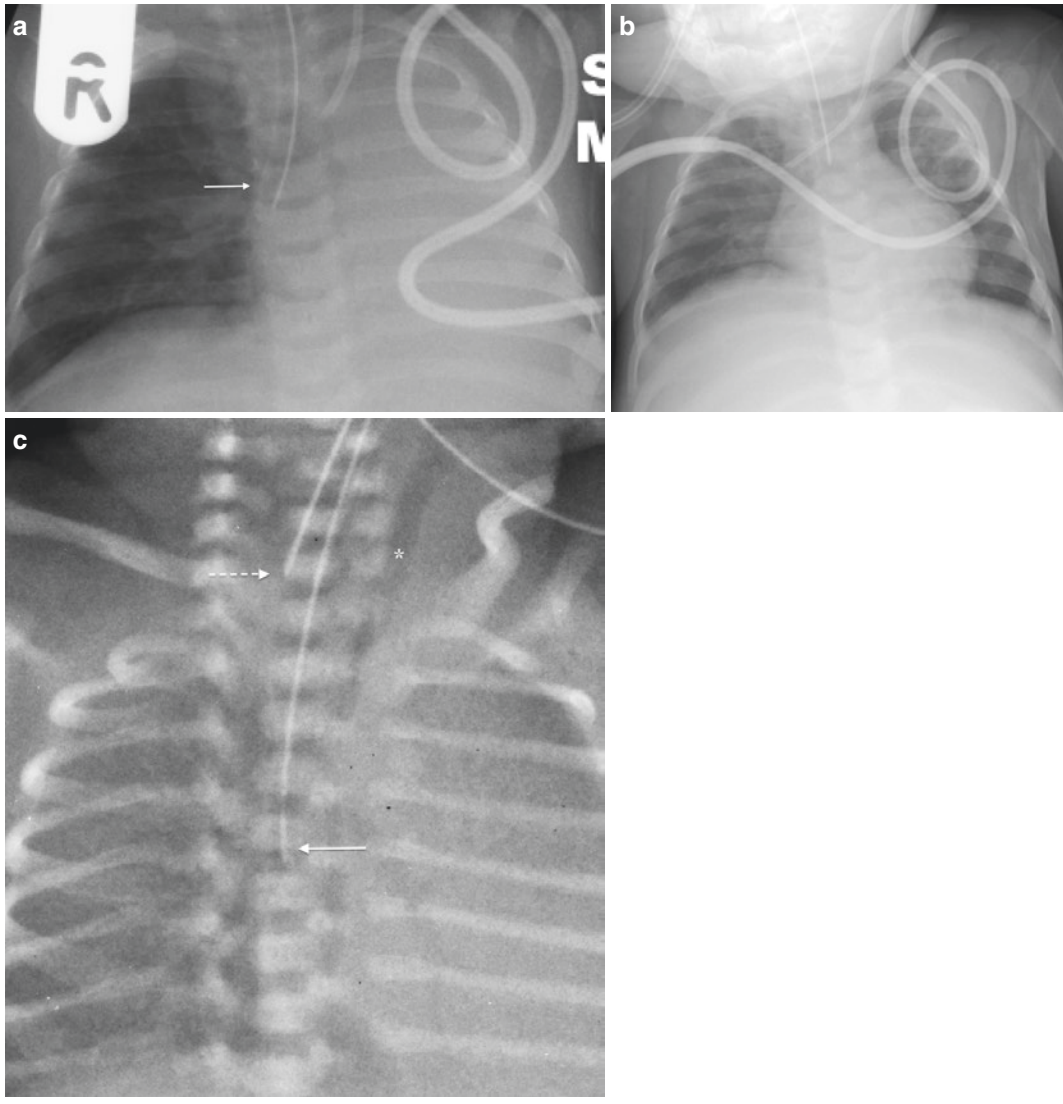


Fig. 10.4 Abnormal position of the endotracheal tube. (**a**) Chest radiograph demonstrates malpositioned ET tube with the tip in the right main bronchus. There is resulting left lung collapse with leftward mediastinal shift and complete opacification of the left hemithorax. Note also the mediastinal and intercostal drains and upper mediastinal clips. Repositioning of the tube results in re-expansion of the lung (**b**). In (**c**) a nasogastric tube is seen in the mid-oesophagus, and an ET tube is noted lying adjacent to this in the upper oesophagus. Air can be seen in the trachea (*)

abdominal organs. It does not involve ionizing radiation and is non-invasive and therefore does not harbour the risks of ERCP such as pancreatitis. ERCP still has a role where therapeutic procedures are to be performed or where the information gained from MRCP is inadequate, however this technique is used much less commonly in children, particularly in neonates, than in adult practice.

10.5.1 Biliary Atresia and Neonatal Hepatitis

Prompt diagnosis of biliary atresia permits early surgery, avoiding early irreversible cirrhosis and the need for transplantation. The main differential for biliary atresia is neonatal hepatitis. Many imaging features of these conditions overlap and there are no specific diagnostic imaging features

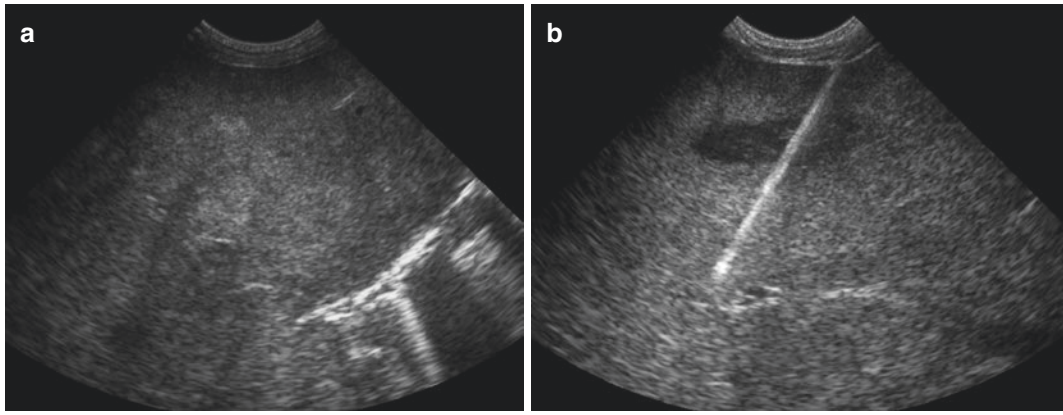


Fig. 10.5 Neuroblastoma with liver metastases. Ultrasound image (**a**) showing diffuse heterogeneity of the liver in a patient with neuroblastoma. (**b**) Percutaneous biopsy under ultrasound guidance. The needle track is visible as a hyperechoic linear focus

of neonatal hepatitis or biliary atresia. Ultrasound findings common to both conditions include enlargement of the liver with increased echogenicity and no evidence of intra-hepatic bile duct dilatation. An absent or small gallbladder occurs in 20–25% cases of atresia [6] and it has been noted that there is no variation in length following a meal in those with atretic gallbladders [6, 7]. However, a small gallbladder may also be seen in severe hepatitis due to reduced bile production and storage. A lack of visualization of the CBD with ultrasound is not diagnostic of biliary atresia.

A more specific finding in biliary atresia is the triangular cord sign, which represents the fibrous remnant of the hepatic duct junction. This is seen as an echogenic structure anterosuperior to the portal vein (Fig. 10.6). This sign is thought to be highly sensitive and specific for biliary atresia [8]. Ultrasound may also show evidence of liver failure, such as ascites, reversal of portal venous flow and splenomegaly. In addition, biliary atresia is associated with polysplenia syndrome in 10–20% [9], which may also be revealed on ultrasound. Correlation with any existing plain radiographs is necessary to identify associated vertebral and rib segmentation anomalies, typical of Alagille syndrome (arteriohepatic dysplasia), in which the ultrasound findings are similar to those of isolated biliary atresia.

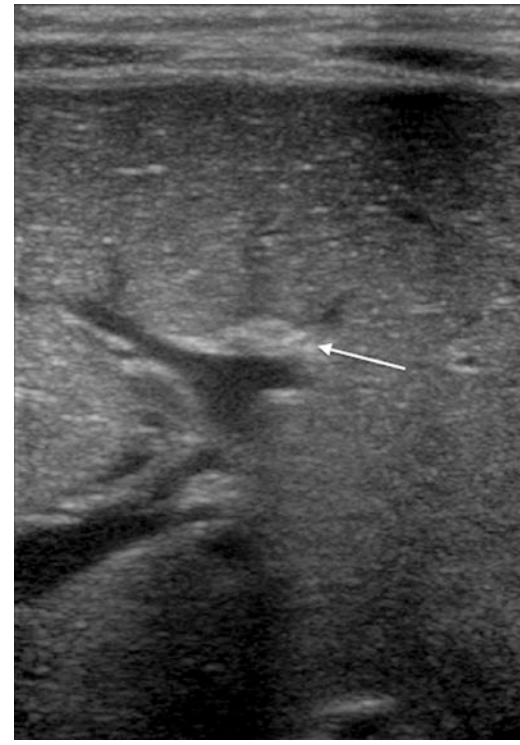


Fig. 10.6 Biliary atresia. High resolution ultrasound of the liver demonstrates a triangular echogenic area (*arrow*) anterior to the portal vein at the porta hepatis. This represents the fibrous remnant of the obliterated extra-hepatic ducts and is known as the triangular cord sign

If biliary atresia is suspected or cannot be excluded on the basis of ultrasound, a HIDA scan is performed. Absence of tracer in the

gallbladder at 24 h suggests biliary atresia, however this appearance may also be seen in severe cases of neonatal jaundice due to poor hepatocellular function. Enhancing liver function with phenobarbitone may help encourage production and excretion of tracer into the small intestine in neonates with hepatitis (Fig. 10.7).

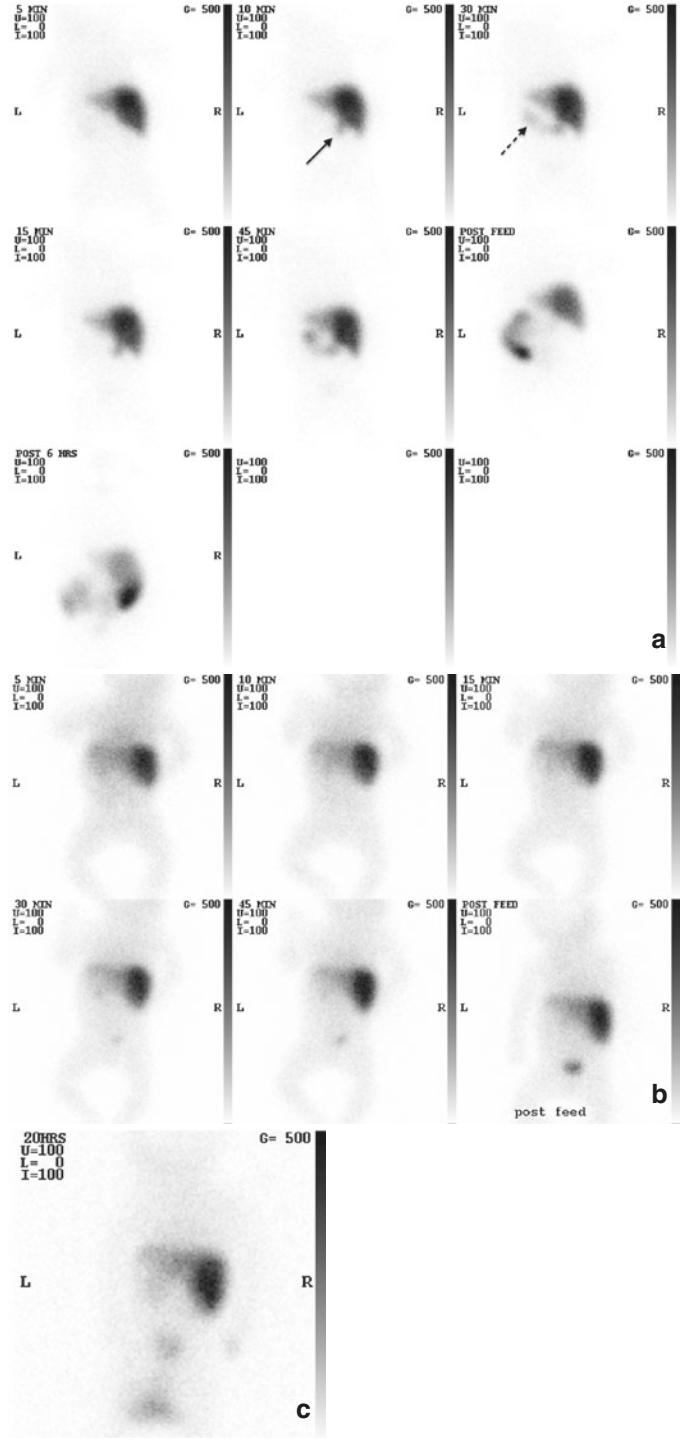


Fig. 10.7 HIDA scan. (**a**) Normal. Note initial accumulation of tracer in the liver. There is progressive passage of radioisotope into the gallbladder at 10 min (*arrow*) and thereafter into the bowel (*broken arrow*), particularly post feed. (**b**) Biliary atresia. Note the persistent tracer accumulation in the liver, lack or radioisotope in the biliary tree or gastrointestinal tract, high background activity and urinary excretion. The appearances are unchanged on the 20 h post injection acquisition (**c**)

MR cholangiography uses the signal from the fluid in the biliary tree to produce images, and is therefore useful in delineating the extrahepatic biliary tree. Identification of the extrahepatic biliary tree excludes biliary atresia. Other pathologies such as choledochal cysts can be excluded.

Rarely percutaneous cholangiography and ERCP may be required to demonstrate biliary atresia, and can also be used to demonstrate the level of the atresia. For a definitive diagnosis ultrasound guided percutaneous biopsy may be necessary.

10.5.2 Choledochal Cysts

Choledochal cysts are thought to originate from an inherent weakness in the biliary tree during development. They may be found incidentally on antenatal screening, or may present in the neonatal period with jaundice or an abdominal mass. Rarely, choledochal cysts may rupture and resulting in an acute presentation with biliary peritonitis.

Ultrasound typically shows an anechoic, thin walled, cystic lesion, in a subhepatic or periportal location, seen separate to the gallbladder and communicating with the biliary tree. No internal blood flow is seen with colour Doppler ultrasound. Secondary intrahepatic duct dilatation and complications such as cholelithiasis may be seen. There is a recognised association with biliary atresia [10]. This diagnosis is important to make in conjunction with that of choledochal cyst as the surgical management will differ.

HIDA scan may also be used to aid in the diagnosis of choledochal cysts, particularly if communication with the biliary tree cannot be established, as this helps to differentiate from a parenchymal liver cyst. On occasion, however, choledochal cysts fail to accumulate tracer and may be missed [5]. MRCP is the definitive investigation of choice to further delineate the anatomy of the biliary tree in cases of obstructive jaundice; however PTC or ERCP still play a role in the diagnosis of difficult cases and in managing the complications.

10.5.3 Inspissated Bile and Cholelithiasis

Risk factors include prematurity, sepsis, dehydration, intestinal atresia, neonates receiving total parenteral nutrition, those with cystic fibrosis and those on medications such as furosemide. An ultrasound demonstrating a dilated gallbladder and biliary tree filled with echogenic sludge in a neonate with jaundice is highly suggestive of inspissated bile syndrome. This is usually managed medically without further imaging. Persistent inspissated bile can be flushed out of the biliary tree following percutaneous transhepatic cholangiography and insertion of a drainage catheter (Fig. 10.8).

Bile pigment gallstones occur quite frequently in the neonatal period and are often an incidental finding on abdominal ultrasound scans performed for other reasons. They usually resolve spontaneously, but may rarely cause obstruction. On ultrasound, intra and extra-hepatic bile duct dilatation may be seen, with an obstructing echogenic focus causing posterior acoustic shadowing.

10.5.4 Spontaneous Perforation of the Bile Ducts

This rare cause of neonatal jaundice usually occurs at the confluence of the common hepatic and cystic duct, and is thought to be due to a congenital weakness in the wall of the ducts or due to a distal obstruction. Ultrasound may show a complex loculated subhepatic collection or ascites. On HIDA scans, tracer may be seen in the peritoneum allowing the diagnosis to be confirmed.

10.6 The Neonate with Failure to Feed/Inability to Pass NG Tube

10.6.1 Choanal Atresia

Unilateral choanal atresia will often have a delayed diagnosis, and there should be a high index of suspicion if an NG tube cannot be passed via one of the nostrils. Bilateral atresia presents

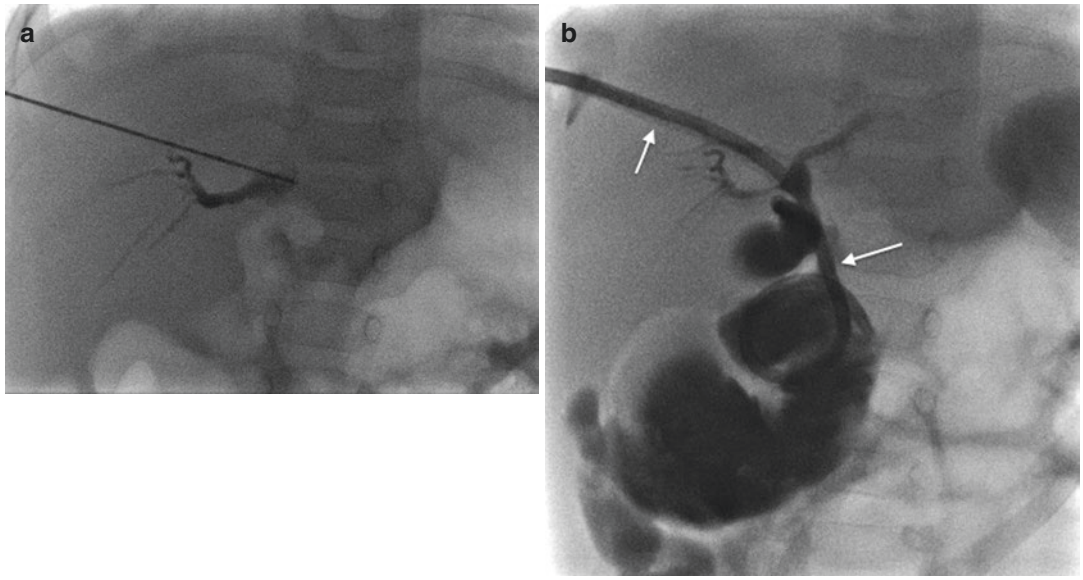


Fig. 10.8 Percutaneous transhepatic cholangiography and drainage. (**a**) contrast injected via the initial puncture needle outlines the right hepatic duct and branches, confirming position. Using Seldinger technique a guidewire is passed through the needle, and a pigtail drainage catheter (*arrows*) is then passed over the guidewire (**b**)

with gasping while feeding. Computed tomography (CT) of the paranasal sinuses will confirm unilateral or bilateral choanal atresia, and distinguish between membranous and bony atresia.

10.6.2 Oesophageal Atresia and Tracheo-Oesophageal Fistula

The neonate with oesophageal atresia (OA) usually presents in the immediate post partum period with respiratory distress, cyanosis, excessive secretions and failure to feed, although maternal polyhydramnios may raise the suspicion in utero. Failed attempts to advance an NG tube are suggestive of an oesophageal obstruction. A plain radiograph with a NG tube in situ can offer a great wealth of information (Fig. 10.9).

Often a pouch-like gas filled radiolucency can be seen in the neck, and if attempts at inserting an NG or Replogle tube have been made, the tip will be seen high in the neck or curled back on itself. In most cases of OA a co-existing trachea-oesophageal fistula (TOF) is confirmed by the presence of bowel gas, In oesophageal atresia, without distal fistula, there will be an absence of bowel gas. However, the absence of bowel gas does not completely exclude the presence of a TOF. Vertebral segmentation anomalies and cardiomegaly point to the diagnosis of the VACTER syndrome/association. Down's syndrome is associated with oesophageal atresia and tracheo-oesophageal fistula, and also with duodenal atresia, which may co-exist (Fig. 10.10).

The less common H-type tracheo-oesophageal fistula may be demonstrated on a conventional contrast swallow, but is often a difficult and elusive diagnosis, requiring a prone tube oesophagogram, sometimes supplemented by endoscopy of trachea and oesophagus. The oesophagogram is performed using non-ionic hypo-osmolar contrast agent. Using lateral imaging contrast is injected via the NG tube with the patient in the prone position and the tube is slowly withdrawn to the pharynx, in order that flow of contrast will be directed into any patent fistula (Fig. 10.11). Care must be taken to ensure that any contrast seen in the lungs or trachea is via a definite fistula and not aspiration from the pharynx. It is argued by some that a tube oesophagogram is not required following a normal contrast oesophagram [11].

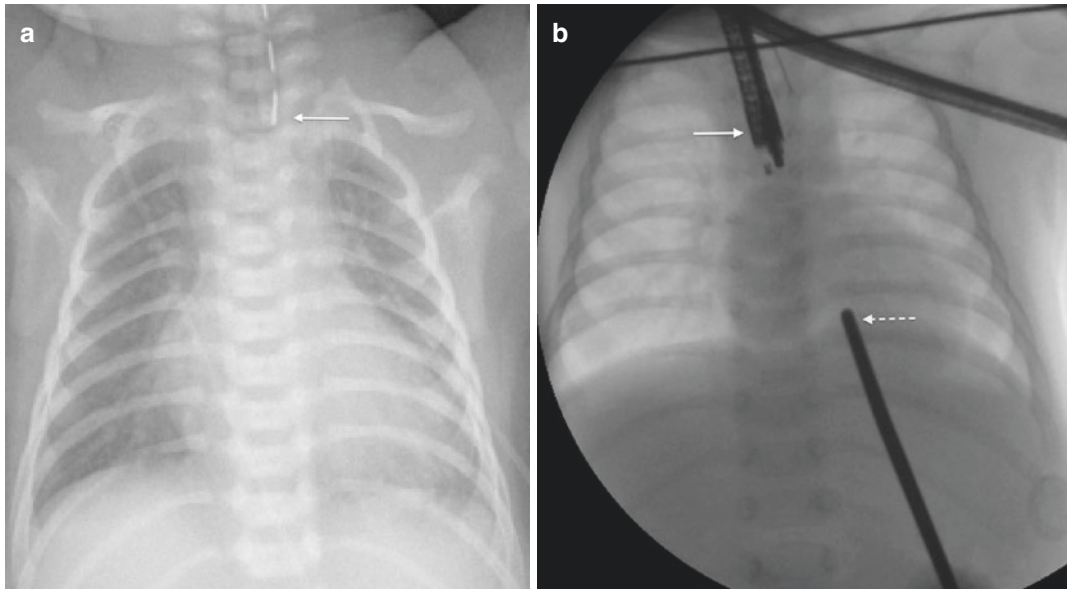


Fig. 10.9 Oesophageal atresia. (**a**) Radiograph of the chest and abdomen demonstrates a Replogle tube in the lower cervical oesophagus (*arrow*) and a paucity of abdominal bowel gas. (**b**) Selected fluoroscopy image from a gap assessment shows an endoscope in the proximal atretic oesophagus (*arrow*) and a Hagars dilator in the distal oesophagus (*broken arrow*)

Further imaging with ultrasound of the abdomen and pelvis and usually also the head and spine may be helpful to exclude further associated anomalies. Oesophageal atresia and tracheo-oesophageal fistula are often associated with tracheomalacia. CT of the thorax supplemented by bronchography and bronchoscopy can be used to assess the airways dynamically during spontaneous respiration.

Postoperative problems following repair of tracheo-oesophageal fistula may require imaging, the most common being stricturing of the oesophagus at the anastomosis site. This can be evaluated with an upper GI contrast study, and treated by balloon dilatation under fluoroscopic or endoscopic guidance [12] (Fig. 10.12).

10.7 The Neonate with Vomiting or Suspected Gastro-Oesophageal Reflux

The appropriate imaging pathway in the investigation of the neonate with vomiting depends upon the patient's age and clinical history. Vomiting in the early neonatal period is likely to be due to a congenital abnormality, whereas vomiting that develops later is likely to be due to an acquired pathology. A good clinical history regarding the nature of the vomit helps to localize the site of pathology. Non-bilious vomiting signifies gastric outflow obstruction, which early in the neonatal period could be due to a high atresia, such as pyloric or proximal duodenal atresia. A history of projectile non-bilious vomiting later in the neonatal period is suggestive of hypertrophic pyloric stenosis. Bilious vomiting indicates obstruction beyond the level of the first part of the duodenum. Faeculant vomiting in combination with abdominal distension suggests a distal obstruction or ileus, which will be dealt with later. Gastro-oesophageal reflux may present with vomiting/possiting, and may also be suspected in children with feeding difficulties, recurrent chest infection, apnoeic episodes or abnormal movement of head and neck resembling spasmodic torticollis (Sandifer syndrome).

In the vomiting neonate a plain abdominal radiograph as a first line investigation will help to direct further investigations. The characteristic

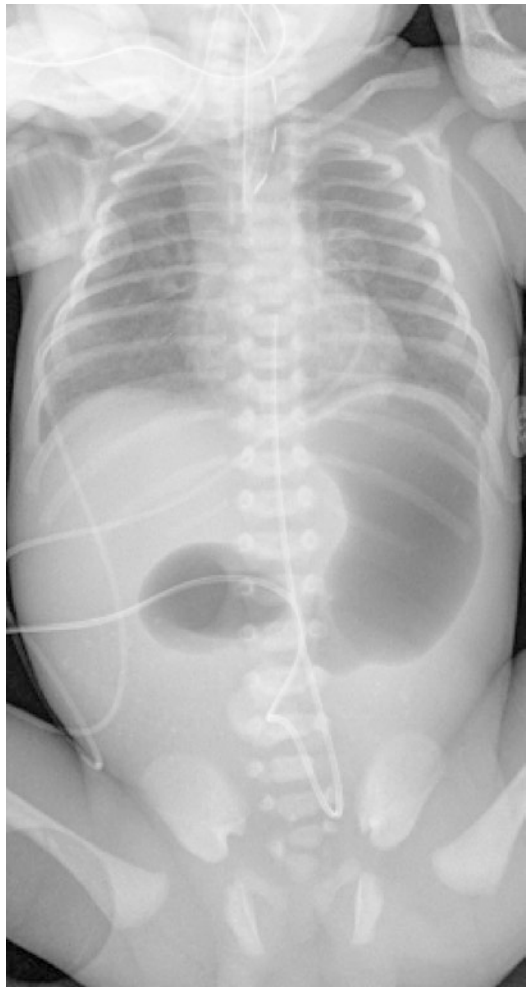


Fig. 10.10 Oesophageal and duodenal atresia. Plain supine chest and abdomen radiographs of this intubated neonate shows a Replogle tube terminating in the lower cervical oesophagus consistent with an oesophageal atresia. A "double bubble" sign in the abdomen due to dilatation of the stomach and duodenum is consistent with duodenual atresia. The presence of bowel gas with oesophageal atresia also confirms the presence of a tracheo-oesophgeal fistula. Note the sacral dysgenesis. Fine speckled calcifications can be seen in the abdomen, consistent with intra-uterine perforation and calcified meconium. An umbilical artery catheter is seen in a suitable position

appearance of some pathologies can give a definitive diagnosis without further imaging, differentiating for example duodenal atresia from jejunal atresia or a more distal obstruction.

Few loops of dilated bowel suggest a high obstruction, whereas multiple loops suggest a distal pathology. Care should be taken very early on in life, as bowel gas can take up to 24 h to reach the rectum in a normal neonate. Also frequent vomiting or the presence of a nasogastric tube with frequent aspirations may mask the typical appearances of, for example, the double bubble sign of duodenal atresia. Augmentation with the introduction of air via a gastric tube, following aspiration of the stomach, may provide the necessary contrast to reach a diagnosis.

An upper gastrointestinal (GI) contrast study is the next investigation of choice in suspected high obstruction. This is usually performed with water-soluble contrast media rather than barium, to minimise the risk of contrast impaction, and allow early surgery without the risk of peritoneal contamination with barium, iso-osmolar contrast is preferred to minimise the risk of contrast aspiration. Following a control film to demonstrate the bowel gas pattern and position of the NG tube, contrast is administered via the gastric tube into the stomach. Careful subsequent imaging allows the outflow from the stomach and caliber of the duodenum to be assessed, and the position of the duodeno-jejunal flexure to be demonstrated and documented. The lateral position shows the normal reversed C configuration to the position of the proximal duodenum, followed by its course superiorly to reach the level of the pylorus. The supine view demonstrates the duodenuo-jejunal (DJ) flexure at the level of the pylorus and to the left of the left sided pedicles of the vertebral bodies. The jejunal loops can then be seen, which normally should lie to the left of the midline (Fig. 10.13a).

10.7.1 Malrotation

Malrotation of the bowel may lead to midgut volvulus, which is a life threatening event and therefore any paediatric patient should have the position of the DJ flexure correctly documented as part of an upper GI contrast study. More than 90% of cases of malrotation and midgut volvulus occur within the first 3 months of life, with 40% occurring in the first 10 days.

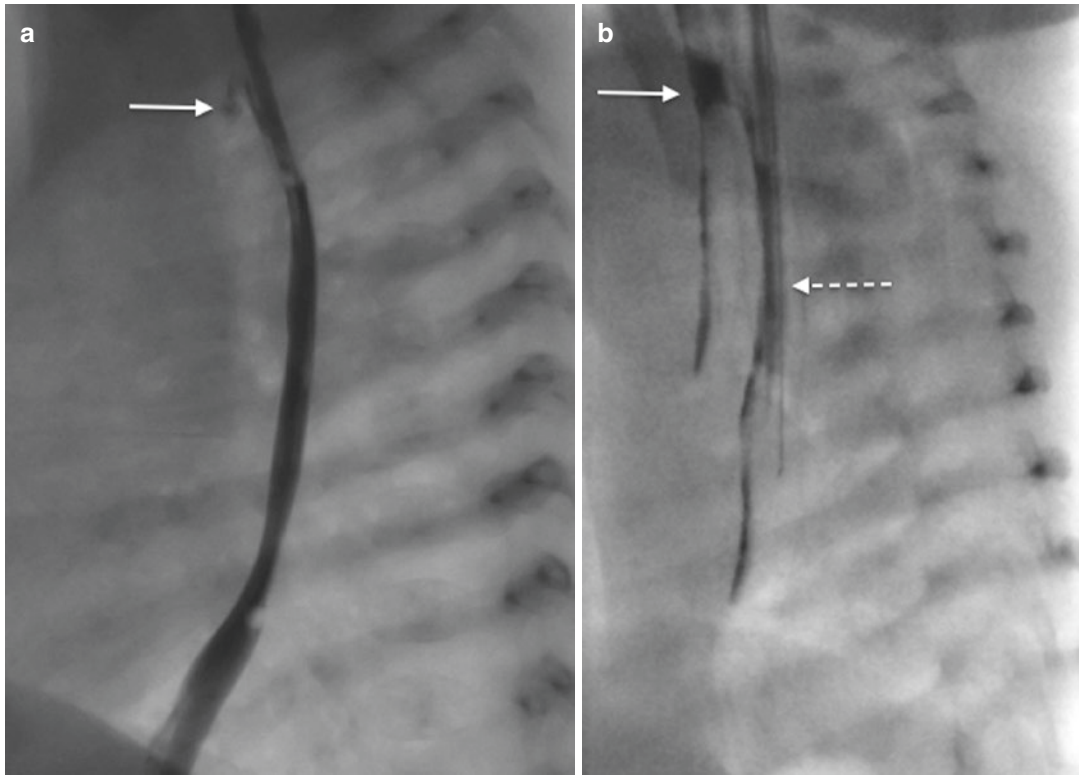


Fig. 10.11 H-type tracheo-oesophageal fistula. Prone tube oesophagogram. In (**a**) there is a tube within the oesophagus and a trace of contrast (*arrow*) is seen passing anteriorly suggesting a fistula. In (**b**) contrast is clearly seen entering the trachea (*arrow*) from the intubated oesophagus (*broken arrow*) in keeping with a fistula

Malrotation does not have any specific plain film features, however distension of the stomach and duodenum and presence of jejunal loops to the right of the midline should raise suspicion in the vomiting neonate. A normal abdominal radiograph does not exclude the diagnosis of malrotation and an upper GI contrast study is mandatory in a neonate with bilious vomiting.

The upper GI series remains the reference standard for the investigation of malrotation and volvulus [13]. The sensitivity of the upper GI series in the diagnosis of malrotation has been shown to be between 93 and 100% [14]. In malrotation, the duodenum is seen to pass anteriorly and inferolaterally to the right, and jejunal loops are seen on the right side of the abdomen (Fig. 10.13b, c). Care must be taken, as a distended gas filled stomach or proximal duodenum can displace the normal position of the DJ flexure, and the appearances of malrotation in small neonates may be subtle. Careful positioning of the patient in the supine view is required to ensure the spine is straight and the visible inferior ribs are symmetrical, and that any abnormality of the position of the DJ flexure is true. Delayed imaging in cases of uncertainty will demonstrate the position of the caecum, which in 80% of patients with malrotation lies high and near the midline, therefore helping to confirm or dismiss the diagnosis of malrotation [13, 15]. In volvulus, a dilated stomach and proximal duodenum are present, and a "corkscrew" appearance to the distal duodenum and jejunum may be seen (Fig. 10.14). Delayed imaging in cases of concern will demonstrate the position of the caecum, and help to confirm or dismiss the diagnosis of malrotation.

In the neonate with suspected malrotation, ultrasound can elegantly demonstrate the abnor-

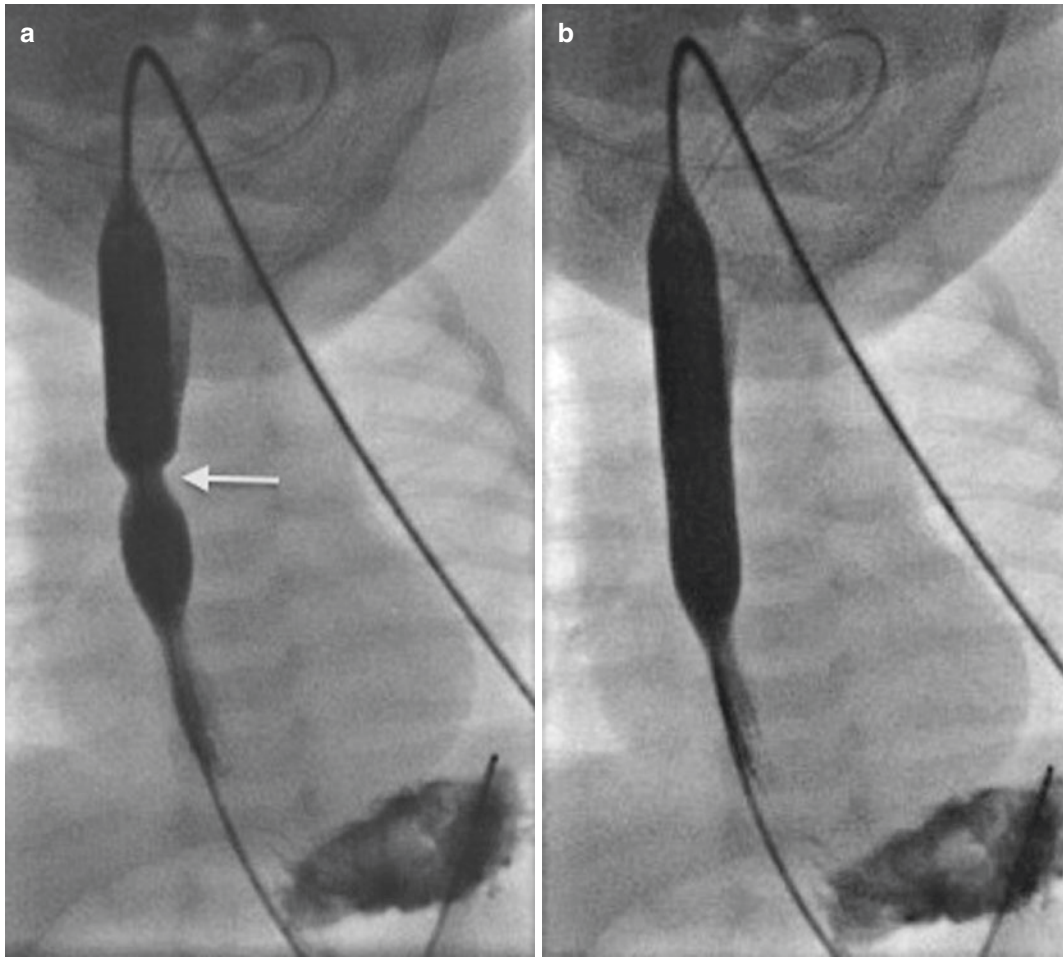


Fig. 10.12 Oesophageal stricture. AP views from fluoroscopically guided balloon dilatation of a mid-oesophageal stricture in a neonate post tracheo-oesophageal fistula repair. In (**a**) waisting of the contrast filled balloon is seen at the site of stricture (*arrow*). In (**b**) the balloon is fully inflated and no waisting is present

mal relationship of the SMA and SMV, with the vein lying to the left of the artery, and may show swirling of the SMV in a clockwise direction around the loops of volved bowel (Fig. 10.15). This investigation however has low sensitivity and specificity compared to the UGI study, as up to 29% cases of malrotation have a normal relationship of the SMA and SMV [16, 17]. In addition, such neonates are often very sick and ultrasound can be very time demanding and would need supplementing further with a contrast study, therefore upper GI contrast study remains the gold standard imaging test of choice in such cases.

10.7.2 Gastro-Oesophageal Reflux

Ultrasound can be used to diagnose gastro-oesophageal reflux. The scan is performed with the baby lying supine, turned slightly to the right side, following a feed. The gastro-oesophageal junction can usually be clearly visualised in the longitudinal plane, and reflux of fluid into the lower oesophagus can be demonstrated. However, identification of structural oesophageal abnormalities such as strictures is difficult.

Gastro-oesophageal reflux as a cause of vomiting may also be demonstrated during the upper

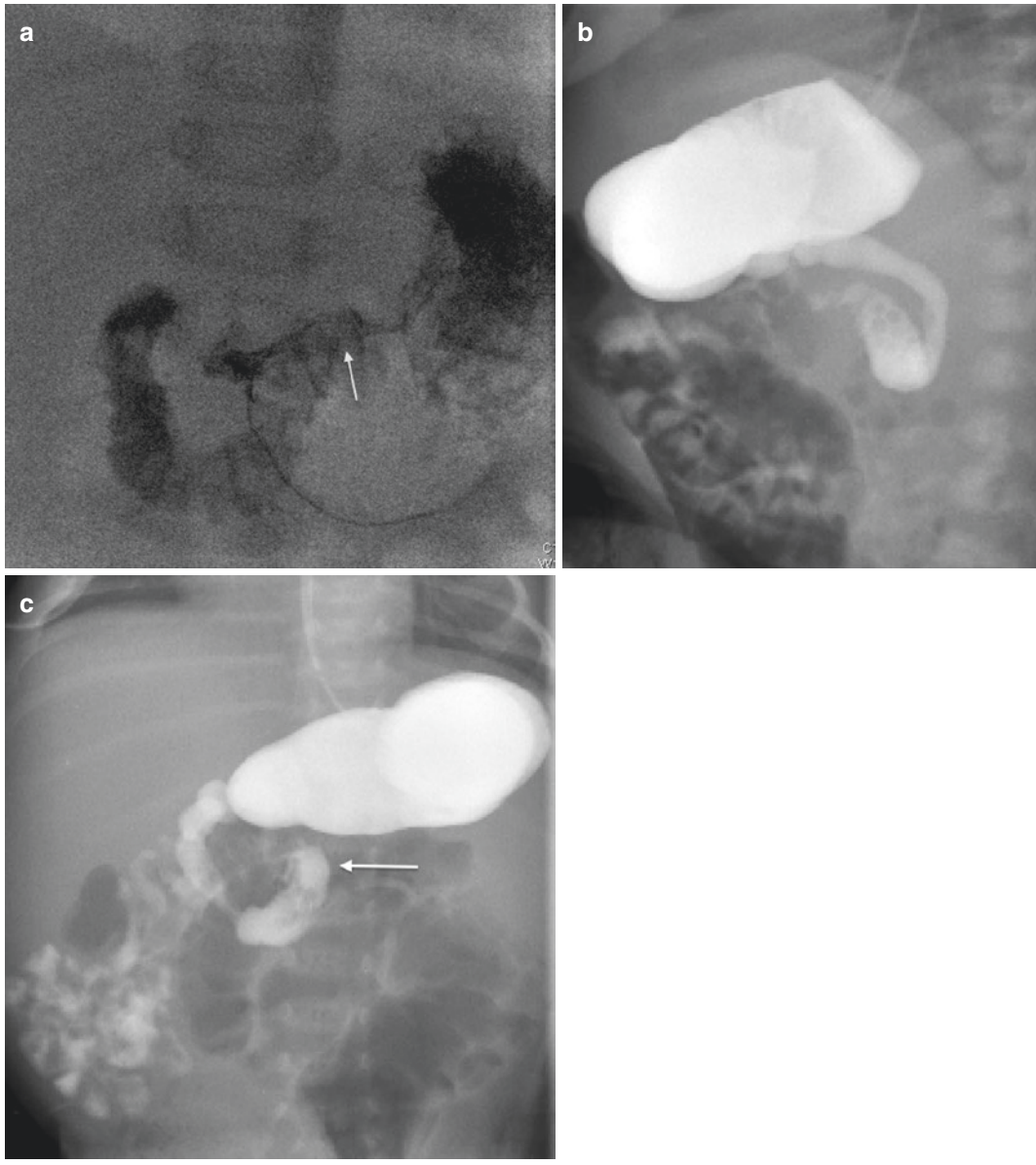


Fig. 10.13 (**a**) Normal upper GI contrast study. Note the normal anatomical position of the duodenojejunal junction at the level of the pylorus to the left of the spine (*arrow*). (**b**, **c**) Malrotation. Lateral oblique images demonstrate an apparently normal appearance, with the duodenum passing posteriorly, inferiorly and superiorly in a c-shape configuration. AP image however demonstrates failure of the third part of the duodenum to cross the midline and the duodenojejunal junction (*arrow*) is seen to the right of midline, below the level of the pylorus. Proximal jejunal loops lie in the right side of the abdomen

GI study, however the upper GI study is usually used to exclude abnormal anatomy or complications of chronic reflux, such as an oesophageal stricture.

Other diagnostic techniques are often used to identify gastro-oesophageal reflux and exclude any other pathology including endoscopy and pH monitoring. An isotope milk scan can often be

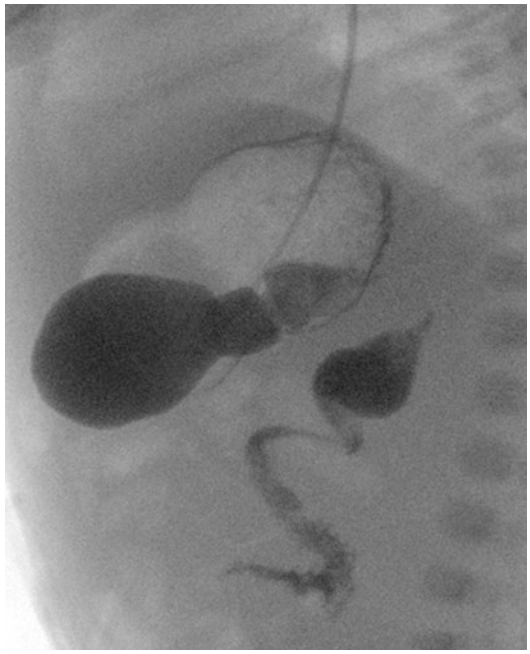


Fig. 10.14 Malrotation and volvulus. Lateral image from an upper GI contrast study demonstrates a corkscrew appearance of the duodenum and proximal jejunum, indicating a volvulus

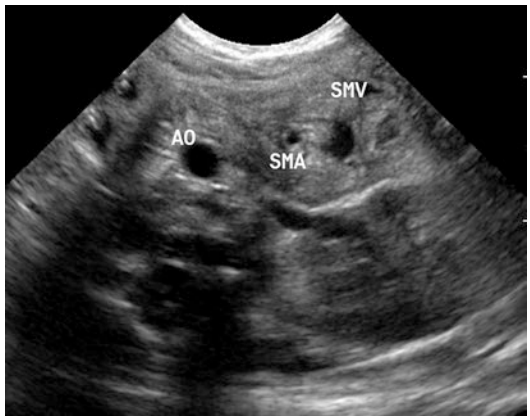


Fig. 10.15 Malrotation. Grey scale transverse ultrasound of the upper abdomen reveals abnormal relationship of the mesenteric vessels, with the SMV to the left of the SMA

useful. This involves the oral administration of Technetium 99 m labeled sulphur colloid with milk to the fasting infant. Imaging of the stomach and oesophagus with the infant supine is then performed over an hour. Images of the lungs may be acquired towards the end of the study, to look for evidence of aspiration of activity into the lungs (Fig. 10.16).

10.7.3 Atresias and Stenoses of the Foregut and Midgut

Absence of gas, on plain radiography, beyond the stomach in a neonate with antenatal polyhydramnios is consistent with a pyloric atresia. Incomplete stenosis is suggested by disproportionally large gas filled stomach relative to the distal bowel. Gastric volvulus may be diagnosed on upper GI study. Filling defects due to gastric bezoars may be seen, typically in premature infants receiving antacids or incorrectly mixed formula feeds. More rarely, a gastric teratoma may be seen on UGI contrast, again as a calcified mass on plain film/control film and as filing defect following contrast. These are often massive, calcified tumours, and are more common in male infants.

In the older neonate, particularly children between 3 and 6 weeks of life with non-bilious projectile vomiting, ultrasound is the primary investigation of choice to confirm the presence of a hypertrophic pyloric stenosis. The pylorus is visualized with a high-resolution linear probe, in longitudinal and transverse planes, and measurements of the pyloric muscle taken. A length of ≥14 mm and single wall thickness of >4 mm is diagnostic of pyloric stenosis [18] (Fig. 10.17). Ultrasound also allows real time demonstration of lack of passage of stomach contents through the pylorus into the duodenum. Pyloric stenosis is an evolving acquired condition, and in equivocal cases, where the measurements are borderline, a repeat scan within a few days is indicated.

10.7.4 Small Bowel Atresia

In duodenal atresia a characteristic “double bubble” may be seen (Fig. 10.18). These neonates usually have bilious vomiting, as the obstruction

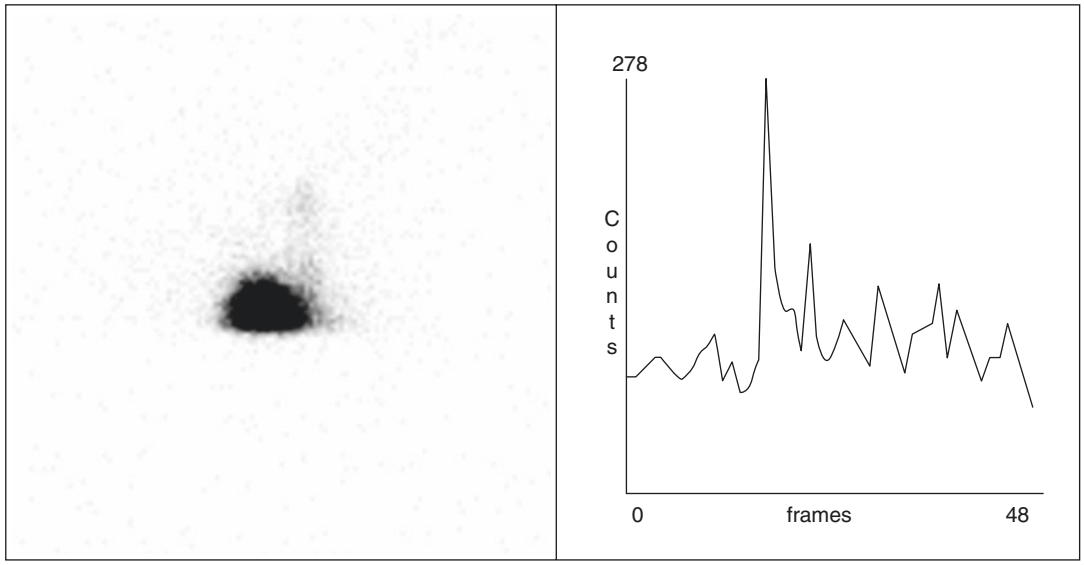


Fig. 10.16 Gastro-oesophageal reflux. Technecium 99 m labeled sulphur colloid milk study. Summation image demonstrates increased tracer extending cranially from the stomach into the oesophagus. Graph of activity against time shows a peak consistent with reflux

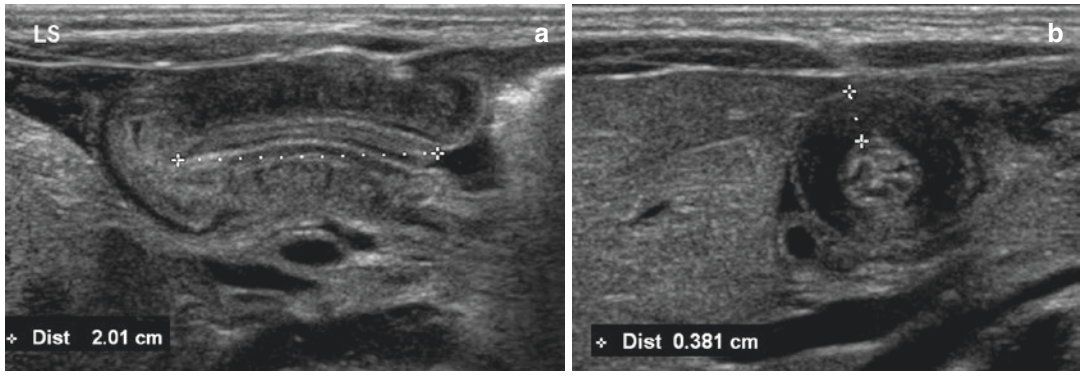


Fig. 10.17 Pyloric stenosis. (**a**) Longitudinal and (**b**) transverse ultrasound images of the pylorus show a thickened elongated pyloric muscle with channel length of 20 mm and individual muscle wall thickness measuring 4 mm, diagnostic of hypertrophic pyloric stenosis

occurs below the level of the Ampulla of Vater, but more proximal obstructions can occur resulting in non-bilious vomiting. The plain film may often clinch the diagnosis and may also provide ancillary information e.g. 11 sets of ribs may be present in the neonate with associated Down's syndrome.

Duodenal stenosis, however, may be of varying severity and distal gas may be seen. In such cases, an upper GI contrast study is required. A windsock deformity suggests the presence of a web (Fig. 10.19). Annular pancreas may mimic the plain film appearances of duodenal atresia or stenosis depending on the degree of duodenal obstruction (Fig. 10.20).

Jejunal atresia usually presents with bilious vomiting and abdominal distension, possibly with antenatal diagnosis. Plain film will show markedly distended proximal loops of small bowel, sometimes seen as the "triple-bubble sign" with an absence of distal gas. The proximal bowel may be grossly dilated.

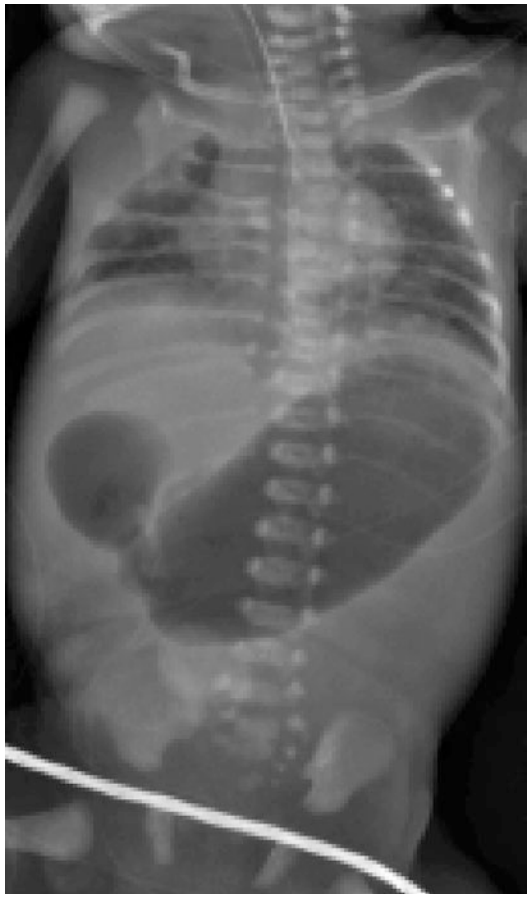


Fig. 10.18 Duodenal atresia. Supine radiograph demonstrates the classic "double bubble" sign and paucity of distal bowel gas. Note also the abnormal sacral segmentation

The plain film, particularly in the left decubitus position (left side down) may be helpful demonstrating free gas outlining the edge of the liver related to bowel perforation and there may be evidence of meconium peritonitis such as peritoneal calcification or a mass containing calcification resulting from meconium pseudocyst formation.

Other causes of high neonatal obstruction, such as duplication cysts, can be demonstrated with ultrasound, and may even have been diagnosed antenatally. Intussusception is rare in the neonatal age group; when it occurs, there is a high likelihood of a pathological lead point such as a Meckel's diverticulum, duplication cyst, polyp or tumour. Ultrasound is the imaging modality of choice to demonstrate intussusception, showing a mass with alternating linear echogenic and hypoechoic areas representing the bowel wall layers of the intussusceptum and intussuscipiens, and invaginated mesenteric fat. Transversely this is seen as alternating concentric rings with a target like appearance (Fig. 10.21). Ultrasound allows the identification of features that make successful or uncomplicated air enema reduction less likely, such as trapped fluid, and may demonstrate features to suggest the need for surgical treatment such as avascular bowel.

Obstruction or displacement of the bowel due to an extrinsic mass can also be demonstrated on a contrast study and may prompt further investigation with ultrasound.

10.8 The Neonate with Abdominal Distention/ Failure to Pass Meconium

A number of different conditions may present with abdominal distension, bilious vomiting, and failure to pass meconium, including Hirshsprung disease, ileal atresia, meconium ileus, meconium plug syndrome, anorectal anomalies, and particularly in premature infants immature left colon, inspissated milk/milk curd obstruction and necrotising enterocolisis (NEC). Radiological investigations can be helpful to differentiate between these possible diagnoses, but in many cases a rectal biopsy is necessary to exclude or make a positive diagnosis of Hirschsprung disease.

Radiological investigation begins with a plain abdominal radiograph, followed in most cases by a water-soluble contrast enema. In the neonate, air should be seen within the rectum by 24 h. In conditions resulting in low obstruction, the abdominal radiograph will normally show nonspecific signs however multiple dilated bowel loops may be evident. It is rarely possible to differentiate between dilated large and small bowel on the plain radiograph in the neonate and small infant. Complications of distal bowel obstruction, such as free gas, calcified peritoneum following meconium peritonitis may be seen. Ancillary findings such as cardiomegaly and

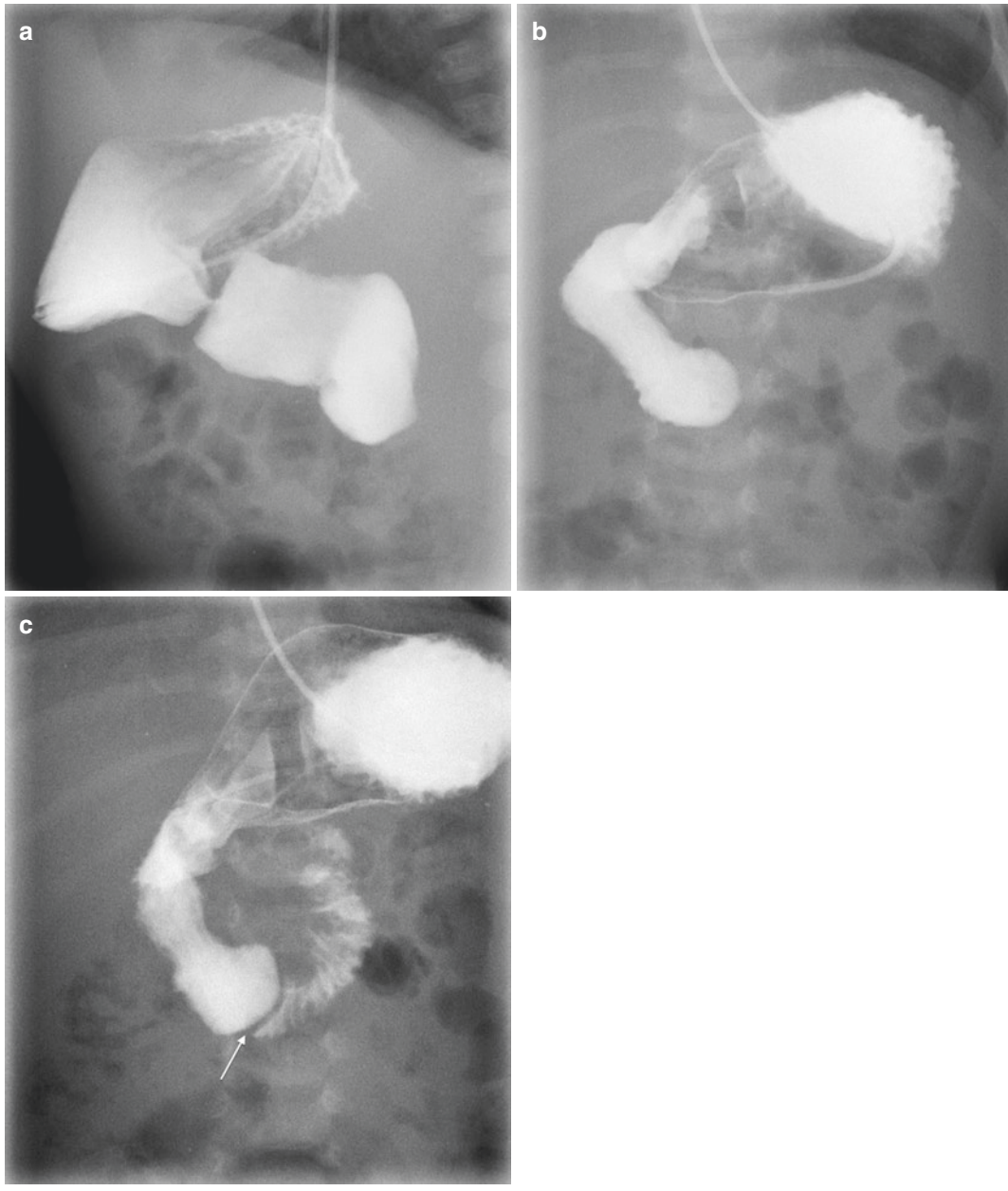


Fig. 10.19 Duodenal web. Water soluble contrast study shows a duodenal stenosis confirmed intraoperatively as being due to a web. Contrast fills the first and second parts of the duodenum which are dilated, with a sharp truncation at the junction between the second and third parts (*arrow*), which has a rounded, bulging appearance. A small amount of contrast passes distally

vertebral segmentation anomalies can also be seen suggesting VACTERL syndrome.

Pneumoperitoneum on the supine abdominal radiograph may appear as a central abdominal lucency, the "air-football sign", visualization of both sides of bowel wall (Rigler sign) or the falciform ligament or umbilical arteries, and the presence of triangular

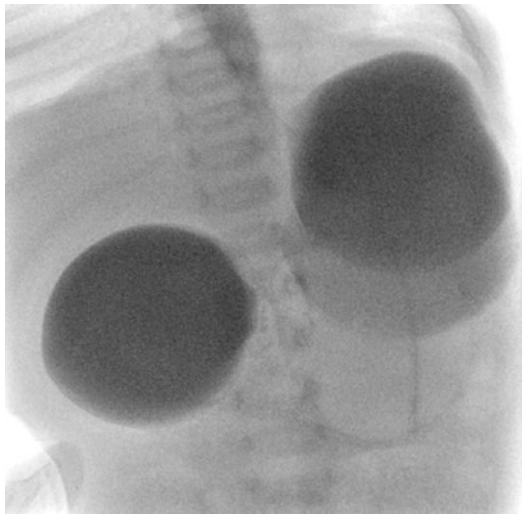


Fig. 10.20 Annular pancreas. Upper GI contrast study demonstrates a markedly distended gas and contrast filled double bubble appearance suggestive of obstruction at the level of the duodenum

shaped pockets of gas in unusual locations. Decubitus radiographs performed in the left lateral position demonstrate the free edge of the liver outlined by gas. In supine neonates too unwell to reposition, the supine horizontal beam lateral radiograph can be used to demonstrate free gas. In neonates with plain film evidence of perforation, further imaging is not usually required (Fig. 10.22).

The next step in the imaging pathway in neonates with distension/failure to pass meconium is a contrast enema, to demonstrate whether the colon is normal, dilated, or small in calibre. Contrast enema in neonates is usually performed with a low-osmolar, non-ionic, contrast medium, which is diluted to avoid significant fluid shifts in sick neonates. The rectum is screened laterally. This may show a small amount of gas in a partially collapsed spasmodic rectum indicative of Hirschsprung disease. A small caliber soft tipped catheter (a 6 French catheter is ideal) is inserted into the rectum and contrast is instilled with the patient in the left lateral position. The normal rectum has the largest diameter of the left side of the colon, and has a larger calibre than the adjacent sigmoid on contrast study.

Movement of the neonate during the procedure helps to opacify the entire colon to the caecum. Reflux into the appendix, small bowel and ideally into proximal dilated bowel is required to ensure a complete study.

Ultrasound can sometimes be used successfully to determine the level of obstruction. Dilated loops can be distinguished from collapsed loops. Dilated fluid filled small bowel proximal to an atresia can be distinguished from the meconium filled loops due to meconium ileus. It may also be possible on ultrasound to distinguish ileal loops from colon [19].

10.8.1 Hirschsprung Disease

Hirschsprung disease is failure of ganglion migration to the full extent of the bowel. Ganglion migration occurs proximal to distal so the rectum is always involved, but a variable amount of more proximal bowel may also be involved. The aganglionic segment results in a failure of relaxation of that segment and therefore a functional obstruction results.

In Hirschsprung disease non-specific signs of distal bowel obstruction may be seen on the plain abdominal radiograph, with gas-filled, dilated bowel loops throughout the abdomen and paucity of gas in the rectum. Intraluminal meconium, pneumotosis, and free intraperitoneal gas or meconium peritonitis following a perforation, usually caecal, may be seen (Fig. 10.23).

A contrast enema typically shows that the rectum has a smaller caliber than the sigmoid colon, with a zone of transition to dilated proximal colon. The rectosigmoid ratio, which is a measurement of the diameter of the rectum divided by that of the sigmoid colon, is of particular use in the diagnosis of Hirschsprung Disease. In normal individuals, where the rectum is larger than the colon, the rectosigmoid ratio is >1. A ratio of <1, i.e. a rectum that is of smaller calibre than the sigmoid, is suggestive of Hirschsprung disease. The rectum may show an irregular pattern of contraction, with a serrated or corrugated appearance. The position of

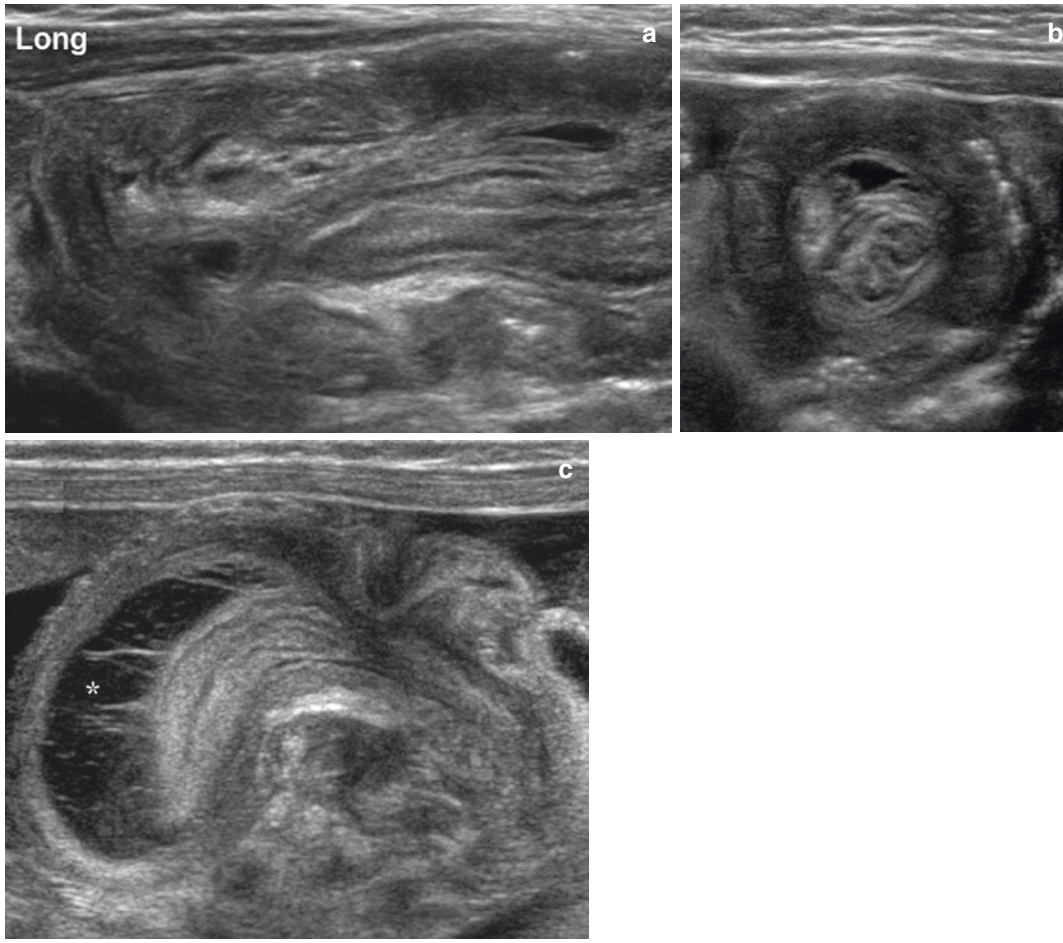


Fig. 10.21 Intussusception. Longitudinal (**a**) and transverse (**b**) ultrasound images demonstrate the typical ultrasound appearance of intususception. In transverse section, alternating rings of hypo and hyperechogencity are seen representing the intussusceptum and mesenteric fat within the intussuscipiens. (**c**) transverse ultrasound image in a neonate with intussusception. A loculated collection of fluid (*) is visible in the intussusceptum, found intraoperatively to be a duplication cyst representing a pathological lead point

the zone of transition is variable. However, in some cases the zone of transition is not easy to demonstrate, and the apparent position of the zone of transition on contrast enema is not a reliable indicator of the true extent of the aganglionic segment as determined by histopathology. Short segment aganglionosis, affecting only the distal rectum, is particularly difficult to diagnose on contrast enema and may only be excluded completely by rectal biopsy; total colonic Hirshsprung disease also presents particular diagnostic difficulties, as there may be a microcolon, or the colon may appear uniformly normal in calibre.

10.8.2 Unused Colon

The unused colon is a spectrum of abnormalities that result in a variable but continuous length of small caliber colon from rectum more proximally. This can be as a result of proximal atresia, luminal stenosis or luminal obstruction, but can also be due to immaturity, particularly in prematurity.

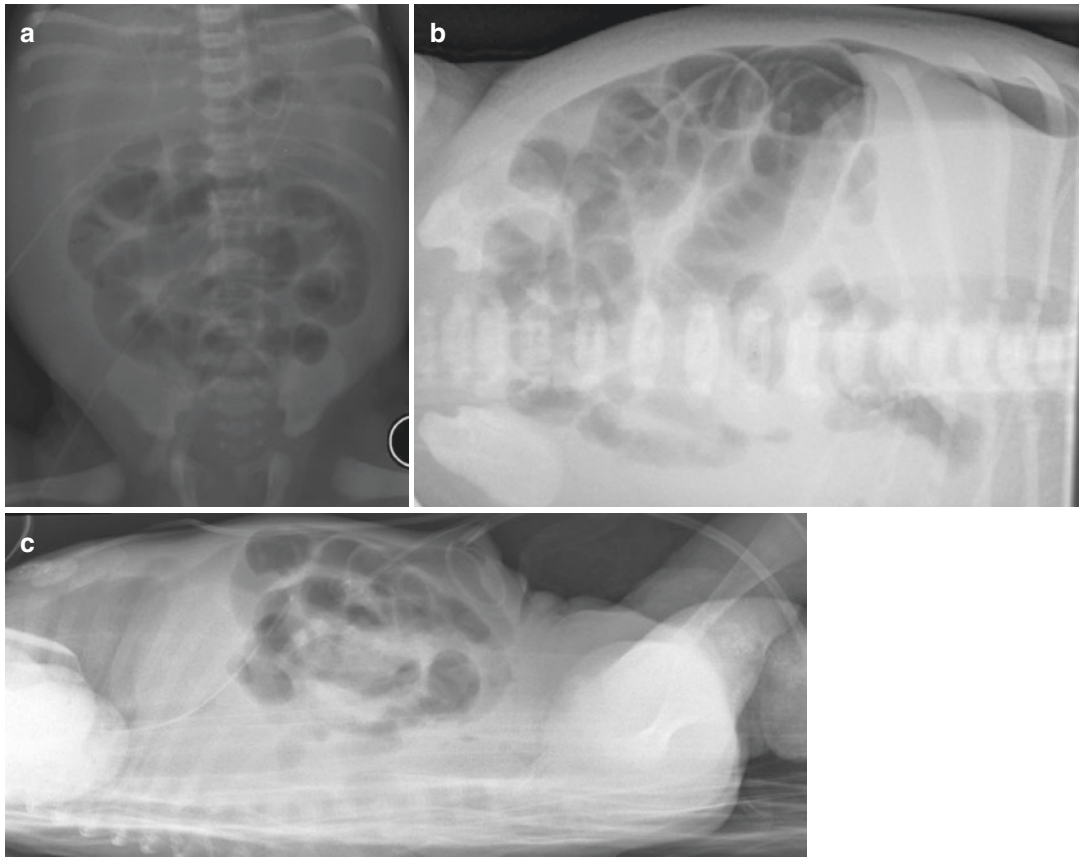


Fig. 10.22 Pneumoperitoneum secondary to perforated meconium ileus. (**a**) Supine radiograph in a neonate with abdominal distension shows central lucency consistent with the "football sign" of pneumoperitoneum, and multiple gas filled dilated loops of bowel. (**b**) Lateral decubitus film demonstrates the free gas over the liver surface. (**c**) Supine lateral shoot through film shows triangular lucency under the anterior abdominal wall consistent with pneumoperitoneum

10.8.3 Distal Small Bowel Atresia

Distal jejunal and ileal atresias may present with distension and failure to pass meconium. 15% of small bowel atresias affect the proximal ileum and 35% affect the distal ileum. Small bowel atresias can be associated with meconium ileus and Hirschsprung disease [20]. The plain abdominal radiograph may reveal evidence of bowel dilatation, pneumatosis, perforation or meconium peritonitis with peritoneal calcifications. Contrast enema typically shows a microcolon (Fig. 10.24). The more the colon is utilized the larger its calibre, therefore the more proximal the small bowel atresia (or obstruction), the less marked the reduction in caliber of the colon as the bowel distal to the atresia utilizes the colon and therefore increases its caliber [21].

10.8.4 Meconium Plug Syndrome

A small left colon, often to the level of the splenic flexure, with multiple long filling defects, is suggestive of meconium plug syndrome, also known as immature or small left colon sydrome. Long segment Hirschsprung disease is a rare but important differential in such cases. In meconium plug syndrome,

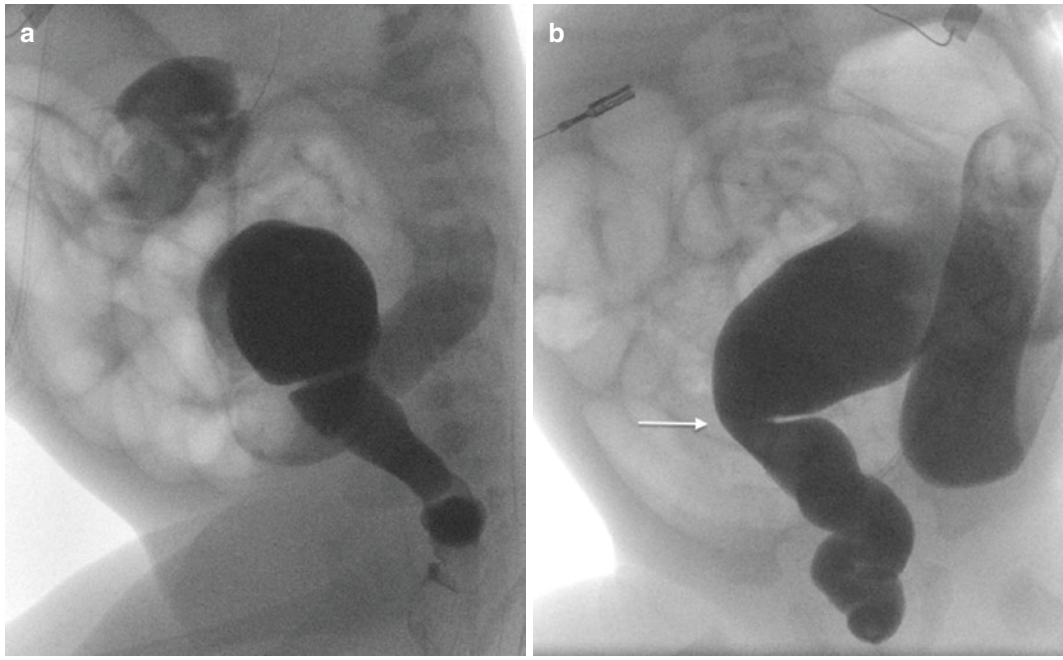


Fig. 10.23 Hirschsprung disease. Lateral and AP views from a water soluble contrast enema demonstrate a contrast filled rectum and sigmoid colon. Note the caliber change at the distal rectum and resulting reversal of the normal rectosigmoid

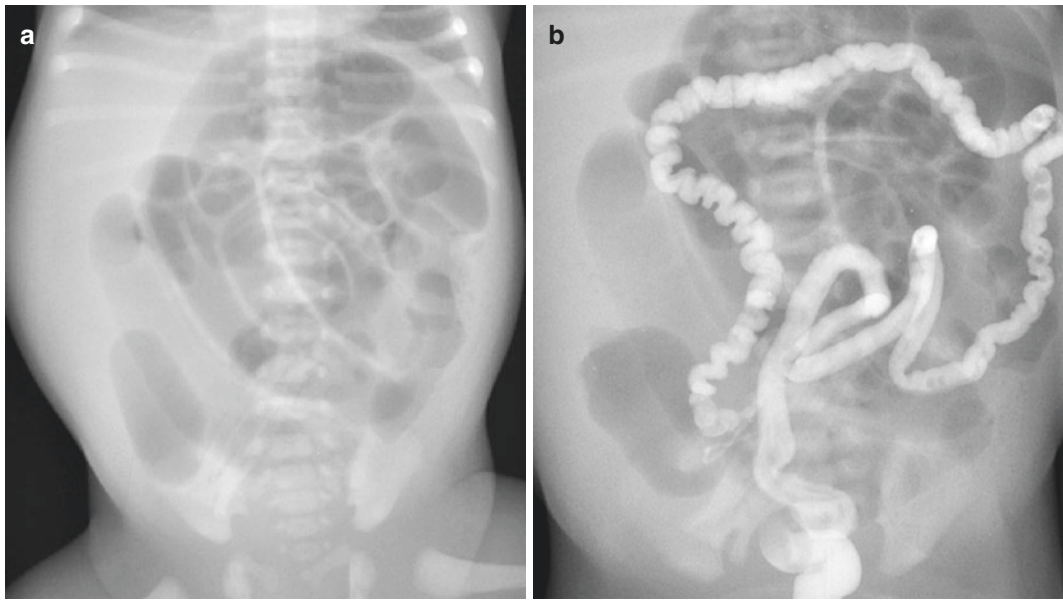


Fig. 10.24 Ileal atresia. (**a**) Plain abdominal radiograph demonstrates multiple dilated bowel loops consistent with a distal bowel obstruction. (**b**) Water soluble contrast enema demonstrates a microcolon

mechanical loosening of the meconium often occurs with therapeutic passage of the meconium plugs during or after the contrast enema with improvement in the degree of abdominal distention and a slow return to normal bowel function (Fig. 10.25).

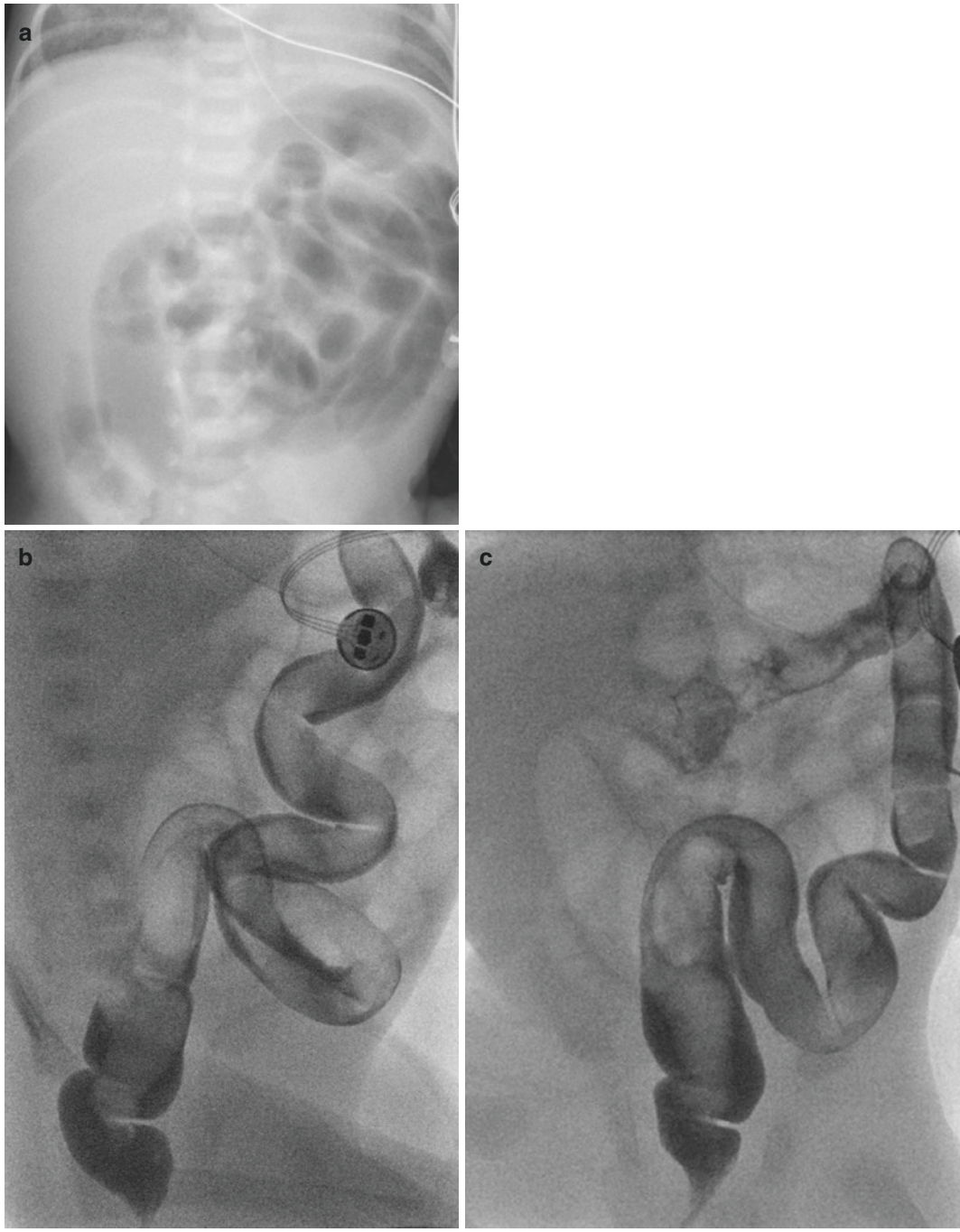


Fig. 10.25 Meconium ileus. 2 day old with known cystic fibrosis and abdominal distension and failure to pass meconium. The control film (**a**) demonstrates multiple distended air filled loops of bowel consistent with a distal bowel obstruction. Contrast enema images (**b** and **c**) demonstrate multiple filing defects consistent with meconium plugs in the left hemicolon and rectosigmoid. Note the normal rectosigmoid ratios

10.8.5 Meconium Ileus

Meconium ileus is usually a manifestation of cystic fibrosis, but it can occur in neonates with pancreatic abnormalities such as pancreatic atresia or pancreatic duct stenosis, and rarely in infants with no apparent underlying abnormality. In meconium ileus, the distal small bowel is obstructed by thick, tenacious meconium. This may be complicated by ileal atresia or stenosis,

perforation and meconium peritonitis, and volvulus. On plain film the bowel loops may vary in size and a "soap bubble" appearance may be seen in the distal bowel loops due to the presence of meconium. In male neonates with perforation and meconium peritonitis, scrotal calcification due to a patent processus vaginalis may be seen.

The contrast enema demonstrates a microcolon with meconium pellets in the collapsed distal ileum and dilated proximal small bowel loops. An enema using a hyperosmolar water-soluble contrast, sodium meglumine amidotrizoate (Gastrografin, Bayer Schering Pharma AG, Berlin) can be used therapeutically for reduction of the obstruction in meconium ileus and meconium plug syndrome; this procedure can be repeated as necessary and may help to avoid surgery in some cases [22]. Hyperosmolar contrast has a therapeutic effect by drawing fluid into the bowel, lubricating and emulsifying the colonic content, and stimulating colonic motility. When used for this purpose in a neonate, Gastrografin is usually diluted 1:2 or 1:3 with saline or water. Even when diluted, hyperosmolar contrast agents may cause rapid fluid shifts, and so should be used only by experts, after careful consideration of the balance of risks and benefits. Dehydration should be corrected before the procedure is commenced, an intravenous fluid infusion should be running, and careful monitoring should be performed during and after the procedure.

10.8.6 Colonic Atresia

Colonic atresias usually occur proximally [21]. There is a recognised association between Hirshsprung disease, particularly short segment, and colonic atresia [23]. The colon distal to the atresia will be small in calibre. In a stenosis if contrast does pass proximally this can be seen to dilute into the dilated fluid filled proximal segment, indicating the site of pathology.

A contrast enema may be indicated following upper GI contrast in patients with suspected multiple intestinal atresia syndrome. Air and contrast in the upper GI study will only pass to the proximal atresia. A contrast enema will usually show a microcolon, but may help to identify the level of the most distal atresia.

10.8.7 Anorectal Malformations

Anorectal anomalies result from the failure of descent and separation of the genitourinary system and the hindgut during the second trimester. Clinically these present with failure to pass meconium, distension and an imperforate anus. In patients with suspected anorectal malformations, plain supine radiograph demonstrates multiple dilated bowel loops suggesting a low obstruction. If there has been mixing of meconium and urine due to a fistulous connection between bowel and urinary tract, calcified intraluminal meconium may be seen. A radiopaque marker of a known length at the area of the obliterated anus is useful to assess the distance between anus and rectum in order to plan surgery. Lateral or prone radiographs are sometimes useful as air within the rectum proximal to the obstruction provides contrast.

However they may not be reliable in demonstrating the level of atresia. Air may not have reached the rectum before 24 h after birth, and the presence of impacted meconium or muscle spasm may give the incorrect impression of a high atresia (Fig. 10.26a, b).

Air may also outline the presence of a fistula. Ancillary findings such as vertebral anomalies, abnormal renal outlines and cardiomegaly would support the diagnosis of VACTERL syndrome.

Contrast studies in infants with anorectal malformations are useful to identify the presence of fistulae. In high anorectal malformations, where the rectum terminates above the levator, fistulae between the GI and GU tract are common. Low malformations in males are associated with fistulae to the prostatic urethra or bladder, whereas in females the fistula is to the proximal urethra. Low fistulae are associated with a perineal or distal vaginal fistula. A MCUG is used to help identify any fistula, particularly in those with a high atresia. Following initial diversion surgery, injection of contrast under a little pressure via a catheter in the stoma may outline the fistula (Fig. 10.26c).

Ultrasound is required in patients with anorectal malformations to exclude urogenital anomalies such as horseshoe kidney, renal agenesis or hypoplasia, and ultrasound of the brain and spine is used to exclude other developmental anomalies. Ultrasound in cases of obstruction with perforation

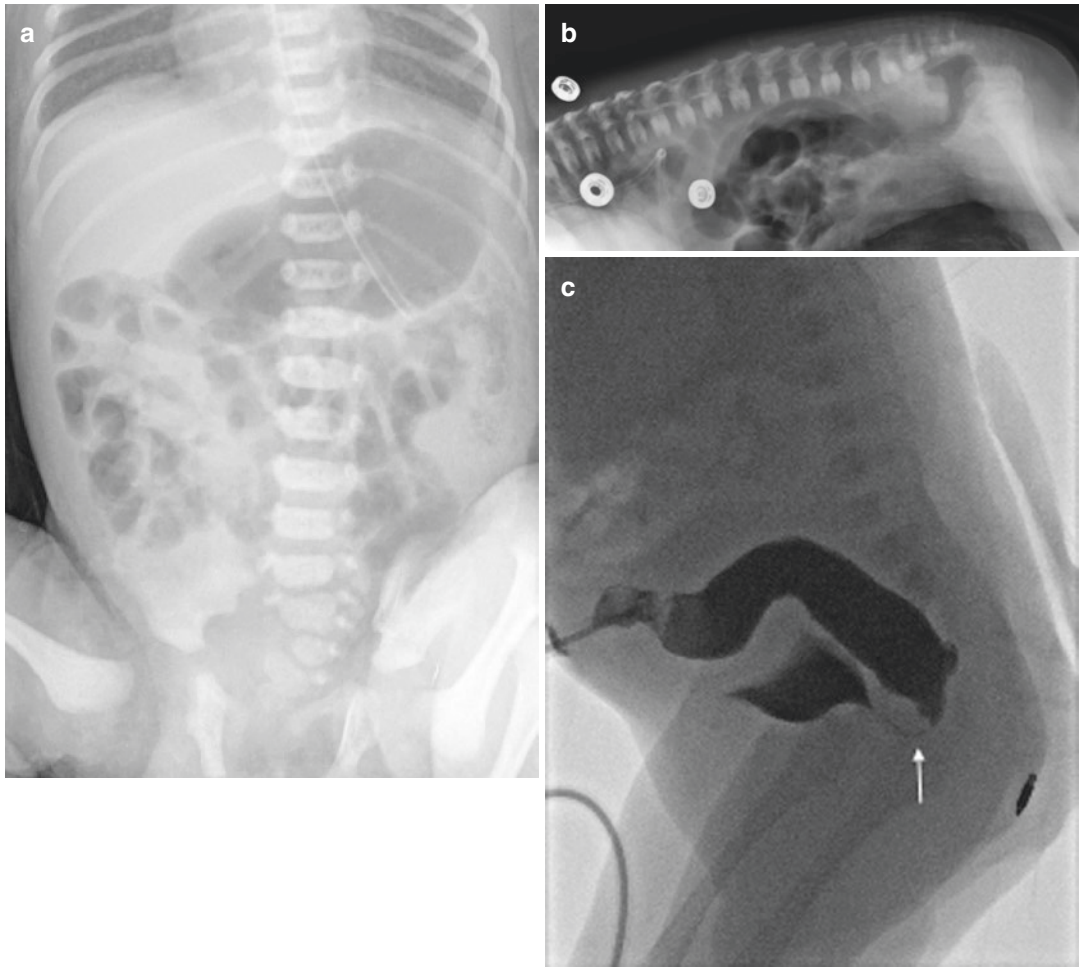


Fig. 10.26 Imperforate anus. Plain film (**a**) demonstrates gas filled bowel loops and paucity of gas in the rectum. Dysgenesis of the sacrum is noted. Prone cross table beam lateral radiograph with buttocks up (**b**) shows air in the non-dependant rectum at the level of obstruction. Selected lateral image from a post-operative water soluble distal loopogram (**c**) shows contrast filling the distal sigmoid and blind ending rectum. The radio-opaque marker placed on the skin helps to demonstrate the anal region and distance between the skin and blind end of the rectum. Contrast can be seen filling the bladder via a recto-urethral fistula (*arrow*)

and meconium peritonitis may demonstrate large peritoneal pseudocysts in neonates with meconium peritonitis.

10.8.8 Necrotising Enterocolitis (NEC)

NEC usually manifests in first 2 weeks of life and can present with vomiting, diarrhoea or more generalised features such as shock and/or sepsis. Clinical signs include distension and abdominal wall erythema. Imaging findings may precede clinical findings, therefore suggesting the diagnosis, and complications may be detected on imaging. Overall mortality of this condition is between 20 and 40%, rising to more than 60% in very low birth weight preterm infants with perforation [24]. Early detection of ischaemic or necrotic loops prior to perforation may improve outcome therefore imaging plays an important role of management [25].

During the acute stages of NEC, the main imaging modalities used are plain radiography and ultrasound. A system developed by Bell et al. (1978) [26] incorporates findings on plain radiograph with historical and clinical data to stage neonates with NEC and thus plan further management. Despite imaging advances since this time, the plain radiograph remains the imaging modality of choice in neonates with suspected NEC [27] however ultrasound is an increasingly valuable tool in NEC with the advantages of providing real time images of abdominal structures, particularly of the bowel.

The bowel gas pattern may be non-specific in neonates with NEC, and bowel distension itself is non-specific and may be seen in normal neonates, those intolerant of feeding, or neonates with ileus resulting from other pathologies. However, alteration of the normal bowel gas pattern is often the earliest, and maybe the only, imaging finding in NEC. Loss of the normal neonatal mosaic configuration of the bowel loops, and loop dilatation with rounded or elongated loops, usually due to ileus, may be seen. A persistent static dilated loop may be present on serial images, and is concerning for necrosis. In distended neonates with little bowel gas on the plain film, ultrasound is useful to determine whether there are fluid filled loops.

Intramural pneumatosis, although not specific for NEC, is most commonly seen in neonates with this condition. It is thought that in the clinical setting of NEC, the presence of intramural gas is diagnostic. The amount of gas is not thought to correlate with severity. On plain film pneumatosis is usually seen in the right iliac fossa, as it involves the distal small bowel and colon most frequently. Curvilinear lucencies may be seen, representing gas in the subserosa. This is best appreciated when seen circumferentially around en face bowel loops. Bubbly lucencies are thought to be due to gas within the submucosa. The bubbly appearance of NEC can be very similar to formed faeces, however formed faeces is not usually present until several days after normal oral intake/feeding has been established. Intramural gas on ultrasound is visible as hyperechoic foci in the bowel wall, which can result in a granular appearance. If seen in the non-dependant bowel wall this can be confused with intraluminal gas and therefore visualization of the dependant portion of the bowel wall is ideal. Differentiation from calcification may also be difficult, though there is usually more defined posterior acoustic shadowing with calcification (Fig. 10.27a, b).

Dissection of intramural gas into the lymphatics and mesenteric venous axis results in portal venous gas, which is present in up to 30% of patients with NEC. Portal venous gas is frequently seen following umbilical vein catheterization and (unlike in adults) is not a serious prognostic sign. On the plain abdominal radiograph, portal venous gas is seen as branching linear lucencies in the right upper quadrant, and is differentiated from gas in the biliary tree by its distribution, as gas in the biliary tree is more central, and by the clinical scenario, as biliary tree gas is rare in the neonate. Ultrasound elegantly demonstrates portal venous gas as multiple mobile hyperechoic foci within the vessels. This finding used to be infrequently seen and so was valuable to confirm the presence of NEC, however the excellent high resolution real time imaging obtained with modern ultrasound machines means that it is now a much more common finding, not only in NEC, but for example after insertion of umbilical venous catheters, and this has therefore diminished its usefulness (Fig. 10.27c, d).

Perforation may occur with resulting free gas. This is the only imaging finding requiring surgical intervention. Plain radiography is the modality of choice for the detection of free gas (Fig. 10.27e, f) In neonates with clinical deterioration but no evidence of perforation on the plain abdominal radiograph, lateral decubitus or horizontal beam (cross table) lateral radiographs are useful, particularly in very sick babies requiring minimal handling.

Ultrasound may detect free gas in the abdominal cavity, and unlike plain radiography clearly detects the presence of abdominal fluid, whether intraluminal, free or in a localized collection. Free fluid can be seen in cases of severe NEC, and the presence of internal septations or focal collections makes perforation more likely.

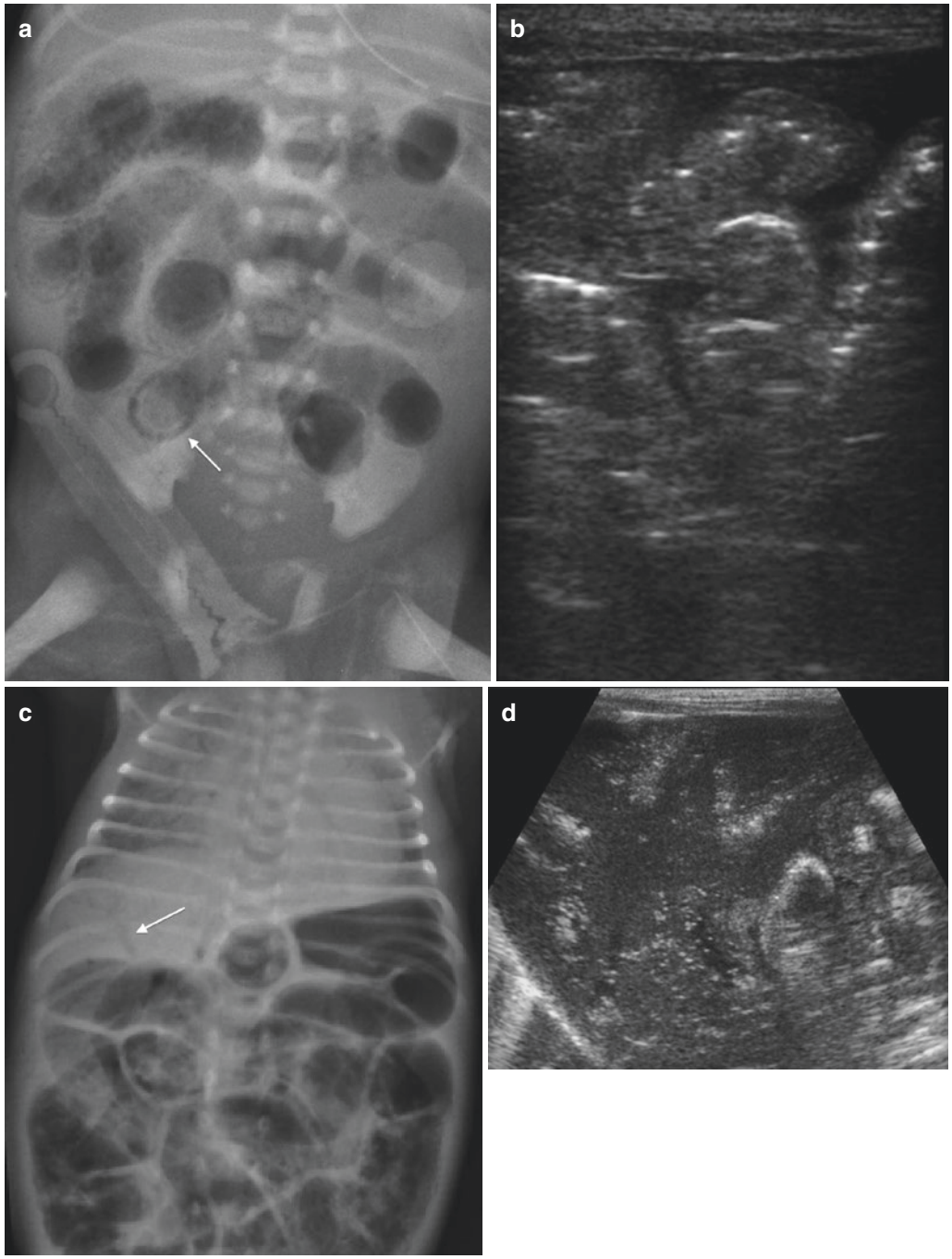
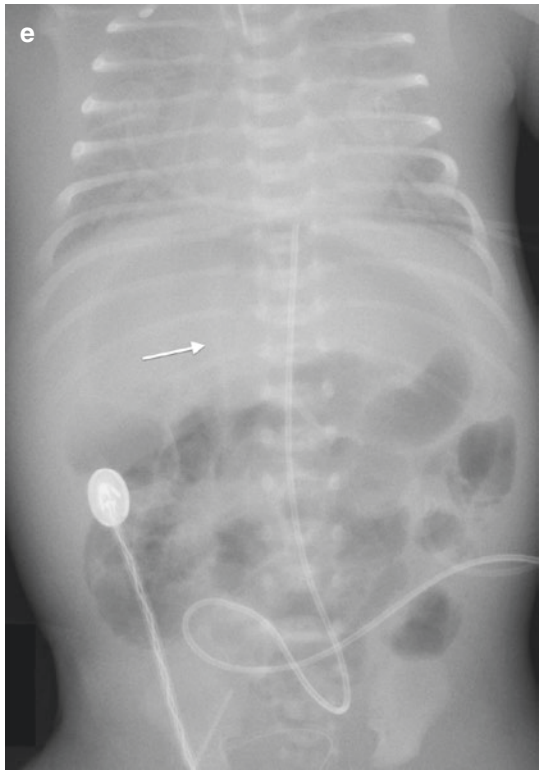


Fig. 10.27 Necrotising enterocolitis (NEC). Radiograph (**a**) in a neonate with NEC demonstrates bubbly and circumferential lucencies (*arrow*) related to the bowel wall consistent with extensive pneumotosis. US images (**b**) demonstrates circumferential hyperechoic foci in dependant and non-dependant positions within the bowel wall consistent with intramural air. Supine radiograph (**c**) in this premature neonate shows generalised asymmetrical bowel loop dilatation. Branching lucencies are seen in the right upper quadrant (*arrow*) extending to the periphery consistent with portal venous gas. Longitudinal ultrasound image of the liver (**d**) demonstrates multiple linear hyperechoic foci within the parenchyma, corresponding to air within the portal veins. On dynamic imaging these are seen as mobile foci within the vessels. Supine radiograph (**e**) shows lucency of the upper abdomen, outlining the falciform ligament (*arrow*), in a neonate with NEC. The appearances are consistent with pneumoperitoneum. Radiograph (**f**) demonstrates Rigler's sign, seen best in the left lower quadrant (*arrow*)



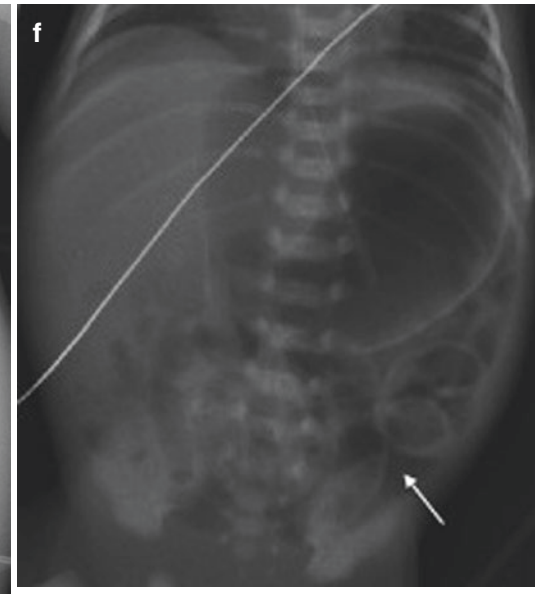


Fig. 10.27 (continued)

Ultrasound is superior to plain radiography in assessing bowel wall thickening, peristalsis and echogenicity and also in the assessment of bowel wall vascularity. Bowel wall hyperaemia is thought to result from vasodilation of mural and mesenteric vessels due to inflammation, and suggests viable inflamed bowel. Absence of flow has been found to correlate with transmural necrosis. Colour Doppler sonography of the bowel wall has been found to be more accurate than clinical examination and plain radiography in the prediction of necrosis in NEC [25]. Ultrasound may therefore be of use in patients with clinically suspected mild NEC with non-specific radiographic features, or in those clinically deteriorating but with no evidence of pneumoperitoneum on plain film.

Contrast studies are often useful in assessing the long-term complications of NEC, which include strictures of involved segments of bowel.

10.9 The Neonate with an Abdominal or Pelvic Mass

Many neonatal abdominal masses are diagnosed antenatally, and these are usually genitourinary (more than 50%) or gastrointestinal in origin. Ultrasound is the initial investigation of choice in neonates with a suspected abdominal mass, with cross sectional imaging to further determine disease site and extent and identify metastatic disease in the case of malignancy. A plain abdominal radiograph may be useful, and may show displacement of bowel loops, or calcification within a soft tissue density which is suggestive of neuroblastoma or hepatoblastoma. Sacral abnormalities may be seen in cases of sacrococcygeal teratoma or other pre-sacral mass, sometimes as part of the Currarino triad.

10.9.1 Renal Masses in the Neonate

10.9.1.1 Hydronephrosis

This is the most common cause of a neonatal mass, and with multicystic dysplastic kidney comprises 40% of all neonatal abdominal masses. The most common cause is ureteropelvic obstruction (Fig. 10.28).

In the full term neonate, a kidney with an AP diameter of the renal pelvis >1 cm on ultrasound is termed hydronephrotic. For premature infants, a useful approximation is 1 mm for each completed month of gestation. Ureteric dilatation may be seen posterior to the bladder, suggesting a distal cause of obstruction at the ureterovesical obstruction or due to posterior uretheral valves, particularly if bilateral. A cystic hypoechoic structure within the bladder at the VUJ is characteristic of a ureterocele. Ureteroceles are associated with duplex systems, which may be detected on ultrasound. A discrepancy in renal length is suggestive, as is the appearance of cortical tissue passing through the medulla. An obstructed upper moiety may be seen, and two ureters may be evident extending from the hila or retrovesically (Fig. 10.29).

A micturating cystourethrogram is performed in those with hydronephrosis to exclude reflux. In the neonate this is performed with antibiotic cover. A small urethral catheter is inserted under aseptic conditions, and water-soluble contrast is instilled into the bladder. Anteroposterior and oblique images of the bladder detect any filling defect or reflux. On voiding, the neonate is turned into the lateral position and the catheter is removed during micturition to give good contrast enhanced views of the urethra, allowing the detection of posterior urethral valves. At the end of the procedure a final image of the abdomen is acquired to ensure there is no late reflux.

Percutaneous nephrostomy is technically challenging in small infants, and requires special expertise and equipment. It is usually reserved for cases of severe bilateral obstruction with renal insufficiency, severely obstructed single kidney with elevated creatinine or for untreatable pyonephrosis (Fig. 10.30).

In the case of neonatal diagnosis of bilateral ureteric reflux, a DMSA scan to look for areas of cortical scarring and relative renal functions is the next step in the imaging pathyway. This is usually delayed until after the neonatal period, to allow maturation of renal function, with the child on prophylactic antibiotic therapy.

10.9.1.2 Multicystic Dysplastic Kidney (MCDK)

This is the second most common abdominal mass in a neonate. Multicystic dysplasia (MCD) is

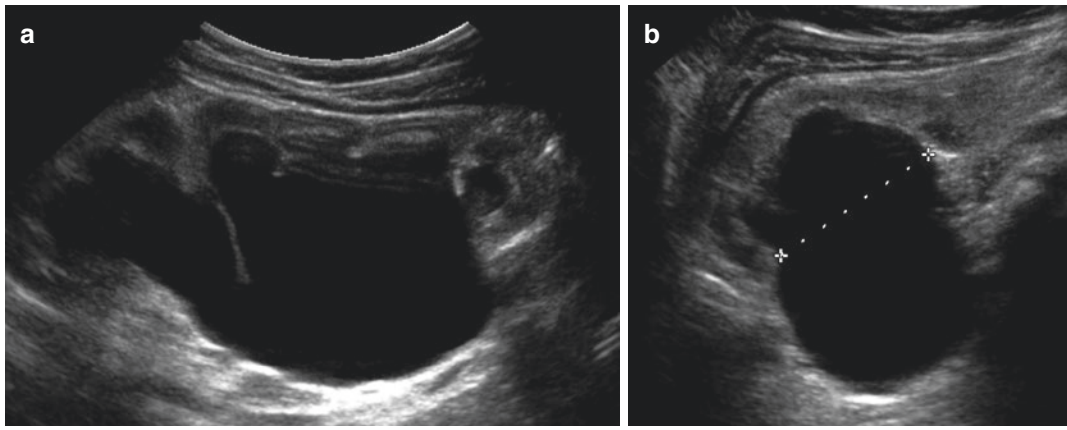


Fig. 10.28 Hydronephrosis. (**a**) Longitudinal and (**b**) transverse ultrasound images of the left kidney show a dilated collecting system with large renal pelvis and blunted calyces. The transverse view allows an accurate AP diameter of the renal pelvis to be obtained, which in this case measured 2.8 cm

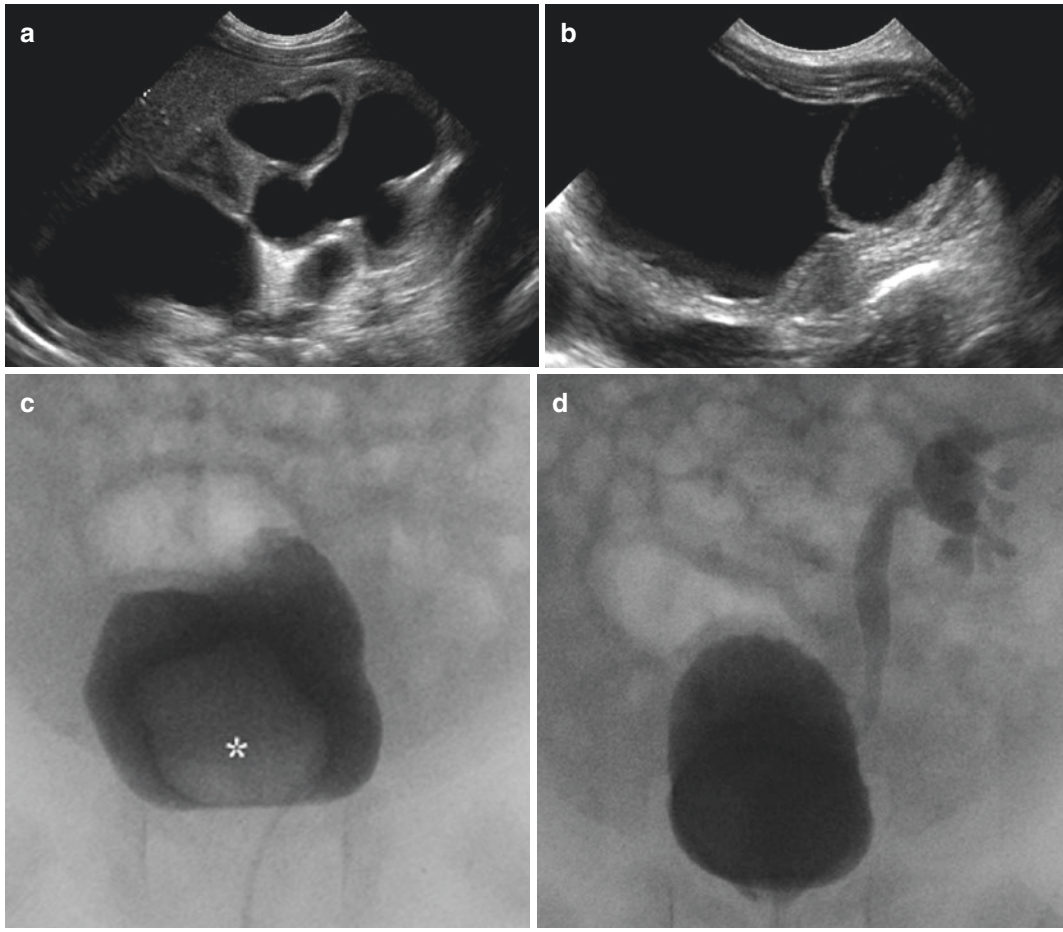


Fig. 10.29 Ultrasound image (**a**) demonstrates an enlarged hydronephrotic duplex kidney, with particular dilatation of the upper moiety. Image (**b**) demonstrates a thin walled cystic structure in the bladder (*), consistent with ureterocoele, shown on MCUG as a filling defect (**c**). Reflux into the lower moiety also demonstrated on MCUG (**d**)

defined as a non-functioning kidney replaced by multiple cysts of varying size and non-functioning dysplastic tissue. There is an abnormal contralateral kidney in up to 40%, usually due to PUJ obstruction or reflux.

On ultrasound there are multiple hypoechoic cysts of varying size which do not communicate with the collecting system, differentiating MCD from a hydronephrotic kidney. Any visible parenchyma is echogenic and the kidney may appear lobulated. The kidney may have involuted and be difficult to visualize (Fig. 10.31). MCD can occur in the upper pole of a duplex kidney. A DMSA scan will confirm absence of functioning renal tissue. Usually these children have serial scans to document growth of the contralateral kidney and ensure involution of the dysplastic kidney. MCUG will assess for contralateral vesicoureteric reflux.

10.9.1.3 Congenital Mesoblastic Nephroma (CMN)

Solid renal lesions occur much less frequently than cystic lesions. Congenital mesoblastic nephroma is the most commonly occurring renal tumour in the first few months of life, and is sometimes diagnosed antenatally. Ultrasound appearances are highly variable, ranging from uniformly solid tumours, to complex solid and cystic lesions with mixed echogenicity. Some lesions appear almost completely cystic. However, most cases presenting

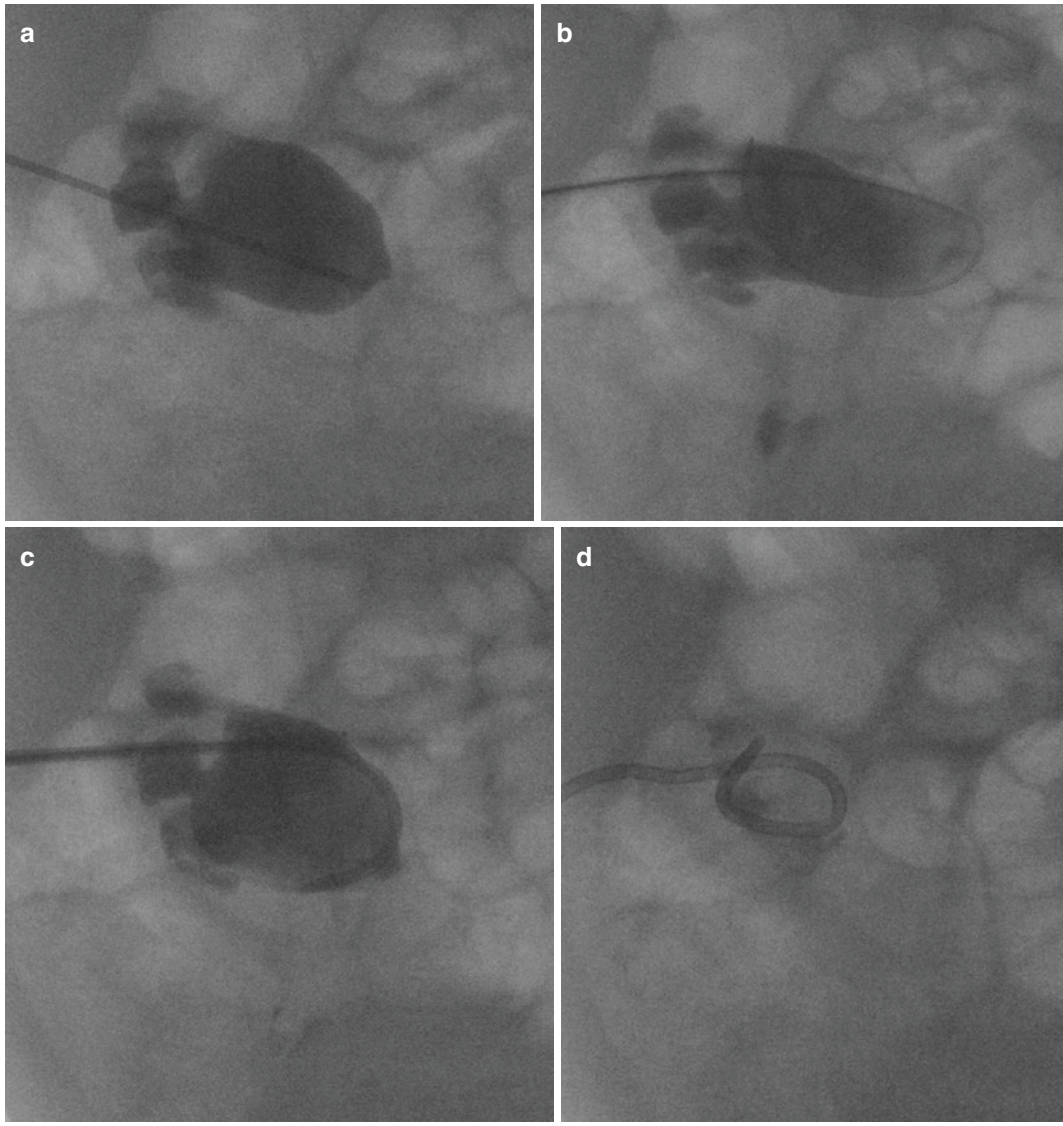


Fig. 10.30 Pyonephrosis in a lower pole moiety. Selected images from percutaneous nephrostomy in a lower moiety pyonephrosis show percutaneous needle puncture into the collecting system (**a**) followed by the introduction of guidewire (**b**) and placement of pigtail catheter (**c** and **d**)

in the neonatal period are the classic variant, which tends to present as a purely solid mass, sometimes showing a characteristic pattern of concentric rings with different echogenicity.

CT typically shows a large, uniform renal mass with minimal, predominantly peripheral enhancement. On MRI, the tumours most often show low signal intensity on T1 weighted images, though there may be areas of T1 hyperintensity if haemorrhage has occurred. T2 weighted images may show varying characteristics [28] (Fig. 10.32).

The differential diagnosis of CMN includes Wilms tumour. This is the most common renal tumour of childhood, but fewer than 2% present at less than 3 months of age. Bilateral tumours are more suggestive of CMN. Wilms tumours are often associated with congenital anomalies or syndromes (Beckwith-Wiedemann, Denys-Drash, and WAGR syndrome-Wilms tumour,

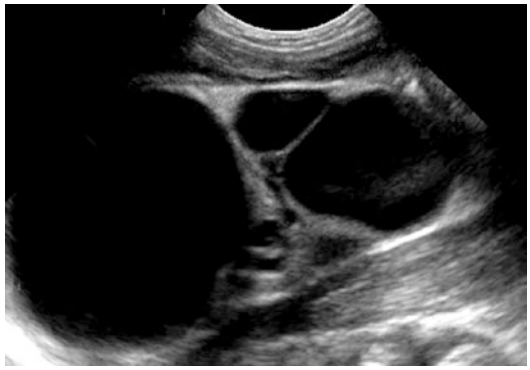


Fig. 10.31 Multicystic dysplastic kidney. Longitudinal ultrasound image demonstrates an enlarged right kidney containing multiple cysts which do not communicate with the collecting system therefore differentiating it from hydronephrosis

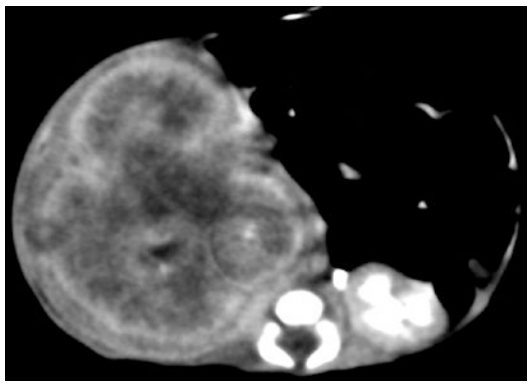


Fig. 10.32 Congenital mesoblastic nephroma. Contrast enhanced CT demonstrates large heterogeneously enhancing solid mass with smooth contours replacing the right kidney

aniridia, genitourinary abnormalities and mental retardation syndromes). Another rare differential is ossifying renal tumour of infancy. This typically presents with haematuria, and is usually at least partly ossified.

10.9.1.4 Renal Vein Thrombosis

Renal vein thrombosis is the most common non-catheter related venous thrombo-embolic event in the neonate [29]. This may present as a renal mass in a sick neonate, usually in association with haematuria or proteinuria. The ultrasound appearances vary with severity and stage of thrombosis. In the early stage, echogenic streaks are seen in the medulla representing interlobular and interlobar thrombus. Subsequently, the kidney enlarges with loss of corticomedullary differentiation. At this stage, bilateral renal vein thrombosis may produce similar appearances to infantile polycystic kidney disease. Thrombus can be hypo or hyperechogenic depending on age, and may appear to distend the vein, and to extend into the IVC. Colour Doppler allows early detection of absence of intrarenal and renal vein flow [30]. Tumour invasion of the renal vein can have a similar appearance. MRI is complementary to ultrasound in demonstrating the extent of the thombus (Fig. 10.33).

10.9.2 Ovarian Cyst

Ovarian cysts are the most common intra-abdominal cystic lesion in the female neonate [31]. Stimulation of the ovary by placental and maternal hormones results in small asymptomatic follicular cysts in up to 80% neonates [32]. Ovarian cysts in the neonate are almost invariably benign, and are only of concern if detected antenatally, if palpable or if complicated.

A simple cyst is seen as an anechoic lesion on ultrasound with thin walls. The visualization of normal adjacent ovarian tissue or a daughter cyst increases the diagnostic certainty. Serial ultrasound follow up should show a gradual reduction in size, as maternal circulating hormones begin to wane. While small ovarian lesions are seen in the adnexa on imaging, large cysts or those with long pedicles commonly extend out of the small neonatal pelvis and may be detected as an entirely intra-abdominal mass [33]. Ultrasound may confirm the cystic nature of the mass but may not be able to identify its origin. Unless a normal ovary is identifiable on one side, the side of the pathology may be difficult to determine, as lesions may appear midline on imaging or may be visible on the contralateral side of the pelvis due to the presence of a pedicle.

Complicated torted or haemorrhagic cysts can have complex ultrasound appearance, with fluid-debris levels, internal septae. A more homogenous solid looking lesion with absence of internal colour flow may be seen. MR will

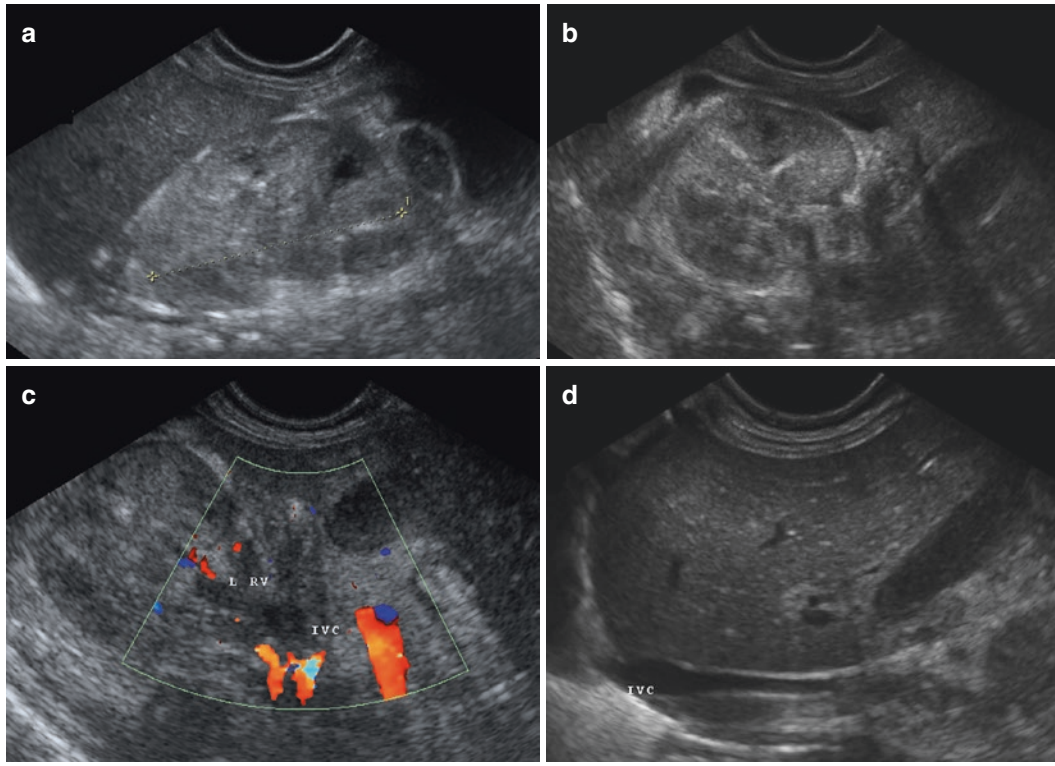


Fig. 10.33 Renal vein thrombosis. Longitudinal and transverse ultrasound images (**a** and **b**) show an enlarged hyperechoic kidney with loss of the normal corticomedullary differentiation. Colour Doppler image (**c**) shows absence of flow in the renal vein. Thrombus is also noted in the IVC (**d**)

locate the lesion and will characterize its contents whether cystic or containing mixed blood products. A haemorrhagic cyst is thought to occur due to torsion, and these are usually excised (Fig. 10.34).

Another cause of abdominoplevic masses in the female neonate is hydrocolpos, a fluid filled distended vagina or hydrometrocolpos, fluid filled distended vagina and uterus. This usually results from vaginal or cervical stenosis, hypoplasia or agenesis, contrary to those presenting in adolescents which are usually due to an imperforate hymen. This condition is usually diagnosed following clinical examination and ultrasound, and has also been diagnosed on antenatal ultrasound and MR [34]. Ultrasound of the renal tract will identify hydroureteronephrosis due to the pelvic mass, and will exclude or confirm any associated congenital renal abnormalities.

10.9.3 Duplication Cysts

GI masses are the second most common site of origin of the neonatal abdominal mass. Most gastrointestinal masses in the neonate are enteric duplication cysts, which represent part of the spectrum of mesenteric and omental cysts. These are usually diagnosed with ultrasound, and are often detected prenatally.

Duplication cysts occur anywhere along the alimentary tract but 75% are intra-abdominal, usually in the distal ileal/ileocaecal region. They are typically cystic and do not communicate with the bowel lumen, though can be tubular and communicate with the lumen therefore filling with gas. The most common mode of presentation is with obstruction, but can also present with a mass, intususception, failure to thrive or rarely haemorrhage due to ectopic gastric or pancreatic mucosa.

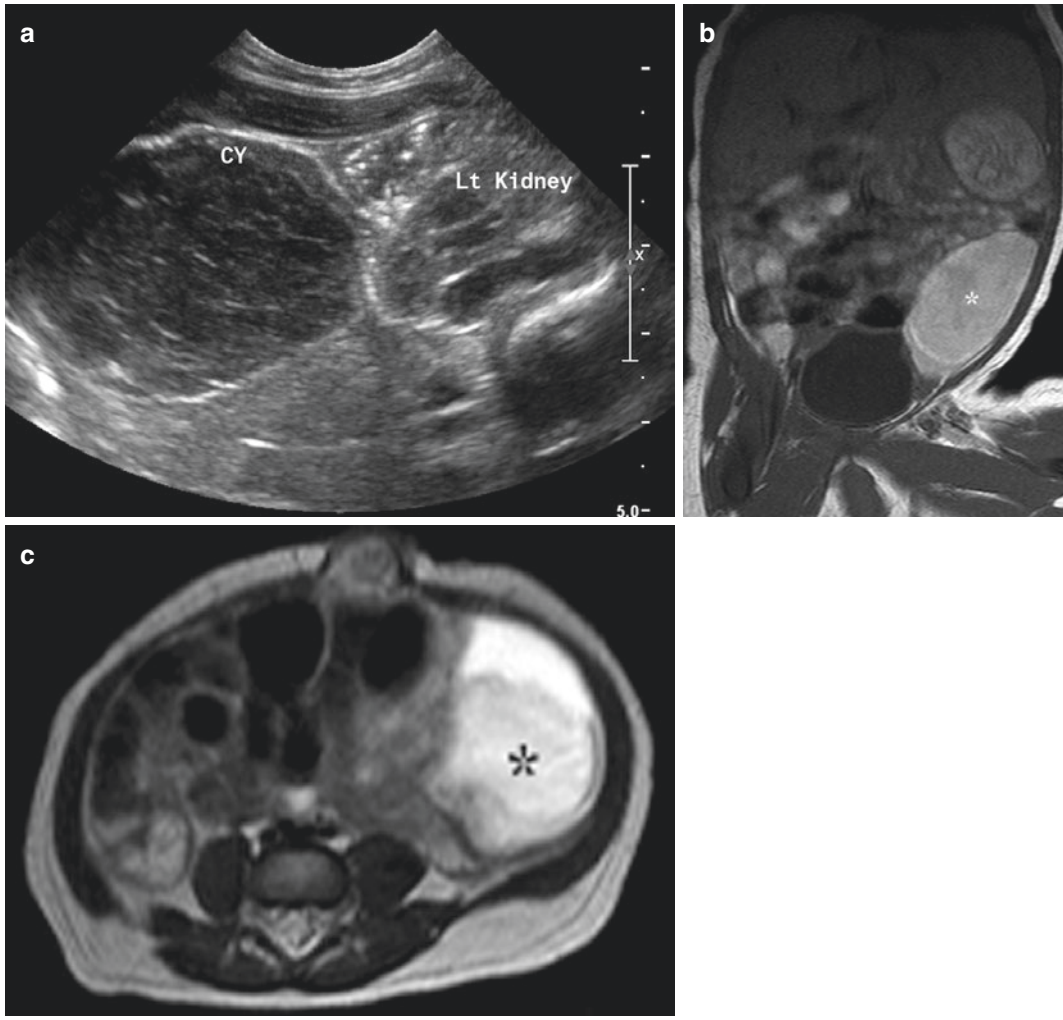


Fig. 10.34 Torsion of ovarian cyst. US image (**a**) (annotated) in a 4 day old female with an antenatal abdominal mass, shows a complex mass in the left flank (cy), inferior to the lower pole of the kidney, which has cystic and solid components. Coronal and axial MR images (**b** and **c**) show a complex lesion (*) in the left lower abdomen which is of intermediate intensity on T1, with high and intermediate intensity contents on T2 and no fat suppression, indicating haemorrhage

Ultrasound demonstrates a cystic lesion most often located in the lower abdomen that is intimately associated with the bowel. In 50% cases this has characteristic double-layered appearance or "rim sign", considered virtually diagnostic. This comprises an echogenic inner mucosal layer and hypoechoic outer muscle layer [35] (Fig. 10.35). Peristalsis of the cyst wall has also been described [36]. The cystic lumen often contains debris, either mucosal slough or old blood. Ultrasound diagnosis may not be achieved in the case of a gas-filled cyst which communicates with the bowel. These may be suspected on the plain radiograph appearances and contrast studies may show a filling defect due to an adjacent duplication cyst, or a cystic structure that fills with contrast in the case of a communicating duplication cyst. MR can be used to confirm the diagnosis if there is uncertainty and in midline lesions as it is useful to exclude any intraspinal extension in the case of possible neuroenteric cysts.

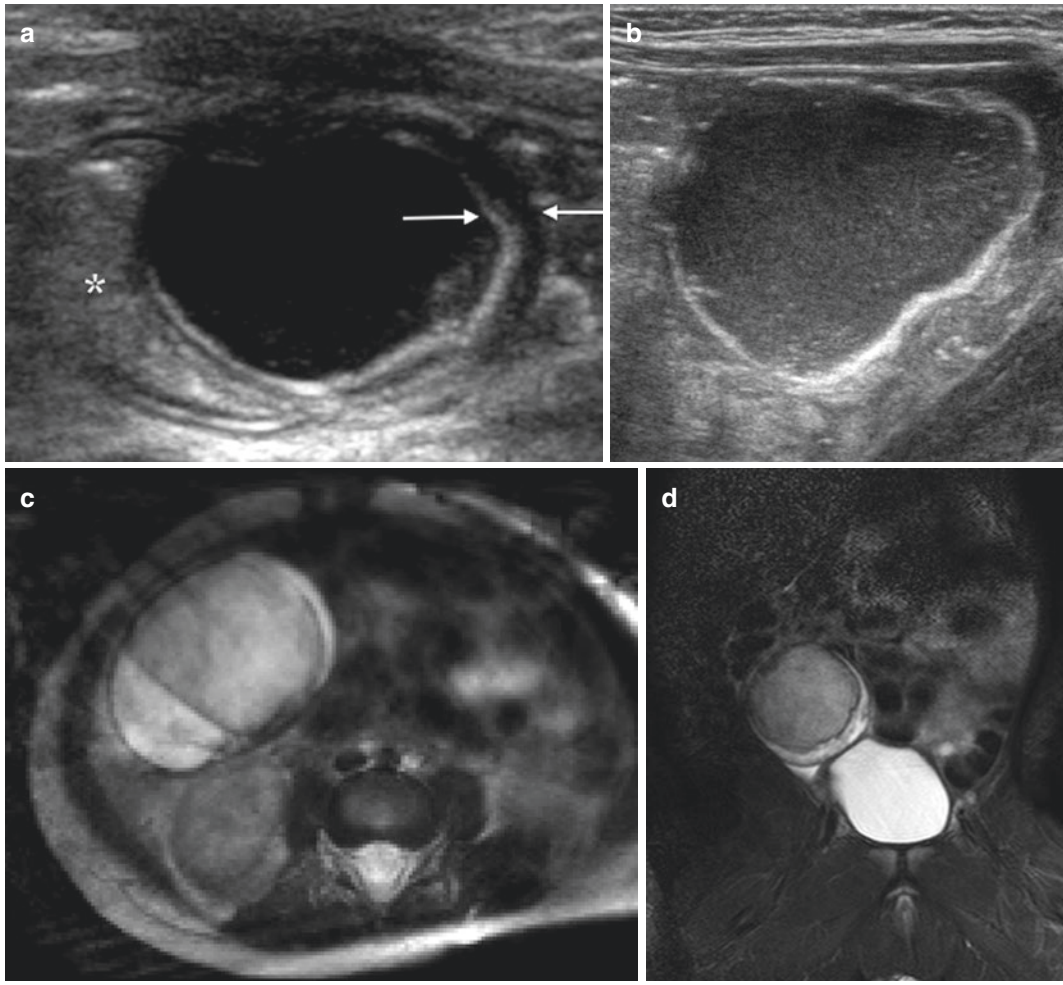


Fig. 10.35 Duplication cyst. Ultrasound image (**a**) demonstrates a cystic structure with a inner hyperechoic and outer hypoechoic wall, consistent with the characteristic "double layered" appearance (*arrows*). The intimate association with the adjacent bowel (*) is illustrated. Ultrasound and MR images (**b**–**d**) in another case show a cystic lesion on ultrasound, with a crenated appearance to the inner aspect of the wall, best seen on the STIR sequence (**d**)

In the more unusual case of haemorrhage, ectopic gastric mucosa may be detected via the use of a Technecium 99 m nuclear medicine scan.

10.9.4 Meconium Pseudocyst

Meconium psuedocyst results from intrauterine bowel perforation and resulting meconium peritonitis. Persistent communication between the perforation, usually caused by ileus, atresia or volvulus, and peritoneal cavity results in a pseudocyst. This may present with distension in the neonate, a palpable mass or may be discovered during imaging of neonates with suspected obstruction. On plain radiograph peritoneal calcification is diagnostic of meconium peritonitis in the neonate, and the pseudocyst usually contains calcifications from exuded meconium. Ultrasound reveals a cyst with thick echogenic possibly calcified walls and echogenic debris filled cyst content (Fig. 10.36).

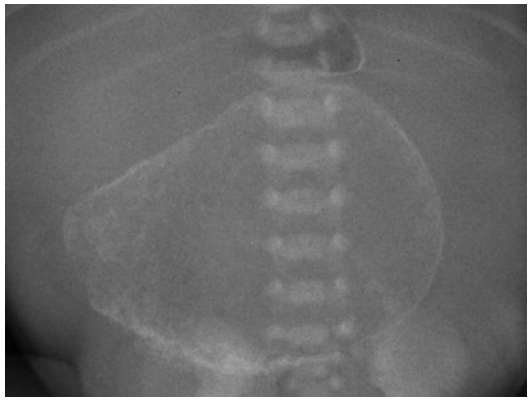


Fig. 10.36 Meconium pseudocyst. Plain abdominal radiograph demonstrates finely calcified ovoid abdominal mass

10.9.5 Adrenal Masses

The best modality for imaging the neonatal adrenal is ultrasound. The normal adrenal has a hypoechoic cortex with an echogenic medulla in a layered configuration and a varying shape, usually described as "y", "v", "z" shaped (Fig. 10.37). The normal adrenal can be up to 3 cm in length and up to 0.3 cm thick. The use of colour flow doppler helps determine internal vascularity of a mass or cystic appearing lesion. The most common reason for adrenal enlargement in the newborn is adrenal haemorrhage, and the most common adrenal mass lesion is neuroblastoma.

Adrenal haemorrhage may occur as a result of birth trauma, usually in term or large for gestational age babies. It may be suspected due to anaemia, jaundice or adrenal insufficiency. Usually this is unilateral, occurring most frequently on the right but is bilateral in 10%. Acute adrenal haemorrhage is seen on ultrasound as echogenic and mass like, but avascular on colour flow Doppler, differentiating it from the highly vascular neuroblastoma mass. Doppler can also be used to assess the renal vain and exclude thrombosis, which is a recognized associated with adrenal haemorrhage [30]. Sub-acutely, adrenal haemorrhage can have a mixed echogenicity and chronically can even be cystic. Usually adrenal haemorrhage resolves and is often found incidentally. Acutely if there is doubt over the diagnosis, or if on sequential scans the lesion is seen to enlarge, MR may be performed, which shows the classic appearance of imaging blood products. A T2 weighted gradient echo sequence produces the characteristic "blooming artefact" caused by the presence of haemosiderin (Fig. 10.38). Chronically after haemorrhage the adrenal gland may calcify. This can lead to confusion as neuroblastomas often contain calcification.

Adrenal cysts may be seen as the late sequelae of haemorrhage, or in association with Beckwith Weiderman syndrome. Bilateral adrenal gland enlargement, with a cerebriform appearance of the gland contour is suggestive of congenital adrenal hyperplasia (CAH).

10.10 Neoplasms in the Neonate

10.10.1 Neuroblastoma

Neuroblastoma is the most common extracranial solid neoplasm in children. It is rare in neonates but is still the most common malignancy in the first week of life. Fortunately there is a better prognosis in children diagnosed before the age of 2 years. It most commonly arises in the adrenal gland but can be found anywhere along the sympathetic chain. Imaging findings should be interpreted in conjunction with bone marrow aspirate and urinary catecholamines.

An abdominal radiograph may reveal stippled calcification, seen in 30% cases, within a soft tissue density. A careful search for bone metastases may reveal lucent, sclerotic or mixed density lesions. Normal structures may also be displaced by the mass.

On ultrasound the appearances are those of a heterogenous increased echogenicity mass. Shadowing echogenicities may be seen representing calcification and there may be evidence of internal low attenuation representing haemorrhage and necrosis. Careful assessment of the liver is required for evidence of metastases and of the IVC and renal veins for intravascular extension of the tumour. In neonates, neuroblastoma can present with associated skin, liver and bone marrow metastasis (Stage 4S), but has a relatively good prognosis.

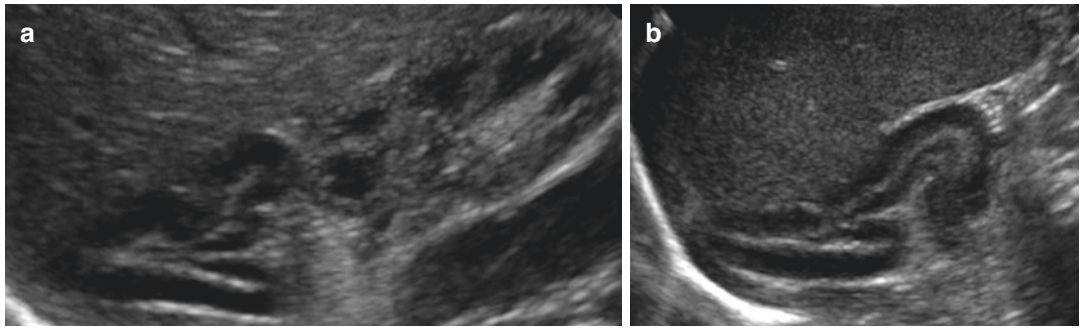


Fig. 10.37 Normal adrenals. Ultrasound appearance of (**a**) right and (**b**) left adrenal glands. Note the layering appearance due to the thick hypoechoic cortex and echogenic central medullary portion

CT further evaluates the origin of the lesion and often has characteristic findings of a large adrenal mass with low attenuation areas of necrosis and haemorhage as well as internal calcification (85%). The mass can often be seen to cross the midline and encase rather than displace vessels. Metastases may also be identified on CT. An MIBG (I^{123} metaiodobenzylguanidine) scan can assess the extent of disease and identify metastases, as tissues with high catecholamine production avidly take up MIBG. The primary tumour will also be visualized. MIBG is highly sensitive and specific for neuroblastoma, concentrating in >90% of tumours. FDG-PET may also have a role in staging high-risk neuroblastoma, but it is less sensitive than MIBG for bone metastases, and so MIBG remains the recommended modality for whole-body staging in most cases [37]. In those tumours that are not MIBG avid, a technecium 99 m MDP bone scan will be performed. MRI is used to assess the state of the involved vessels, and also to look for frequent intraspinal extension of disease via enlarged foramina (Fig. 10.39).

The major differential diagnosis is Wilms tumour. Calcification is uncommon in Wilms tumour. The tumour tends not to cross the midline and displaces vessels rather than encases them. Wilms may be bilateral and spreads along renal vein and into the IVC, unlike neuroblastoma.

Urinary chatecholamines often confirm the diagnosis. Adrenal hemorrhage may also simulate an adrenal tumour, but in haemorrhage there is absence of internal blood flow and the mass typically reduces in size and resolves over a period of a few weeks.

10.10.2 Liver Tumours

10.10.2.1 Hepatoblastoma

This malignant embryonic hepatic tumour is most common hepatic tumor in infancy. There is a strong association with birthweight; the prevalence of hepatoblastoma is inversely proportional to birth weight, [38] and the tumour is also associated with other syndromes such as Beckwith-Weidermann, Gardener syndrome and FAP. Other GU and GI abnormalities may occur in conjunction. Hepatoblastoma may be suspected antenatally, as 4% of cases are congenital [39].

Usually hepatoblastoma presents as a large, painless, palpable mass in the right upper quadrant. If a plain film has been performed a focus of soft tissue density with internal coarse calcifications may be seen in the right upper quadrant. Displacement of the adjacent bowel may also be noted. Ultrasound however should be the initial investigation of choice. The typical appearances are of a well-defined hyperechoic hypervascular solid mass with heterogenous areas of necrosis, usually in the right lobe of the liver. Internal hypoechoic fibrous septae may be present [40] and a resulting "spoke-wheel appearance" has been described [39]. Internal calcification may cause acoustic shadowing and disease may be multifocal.

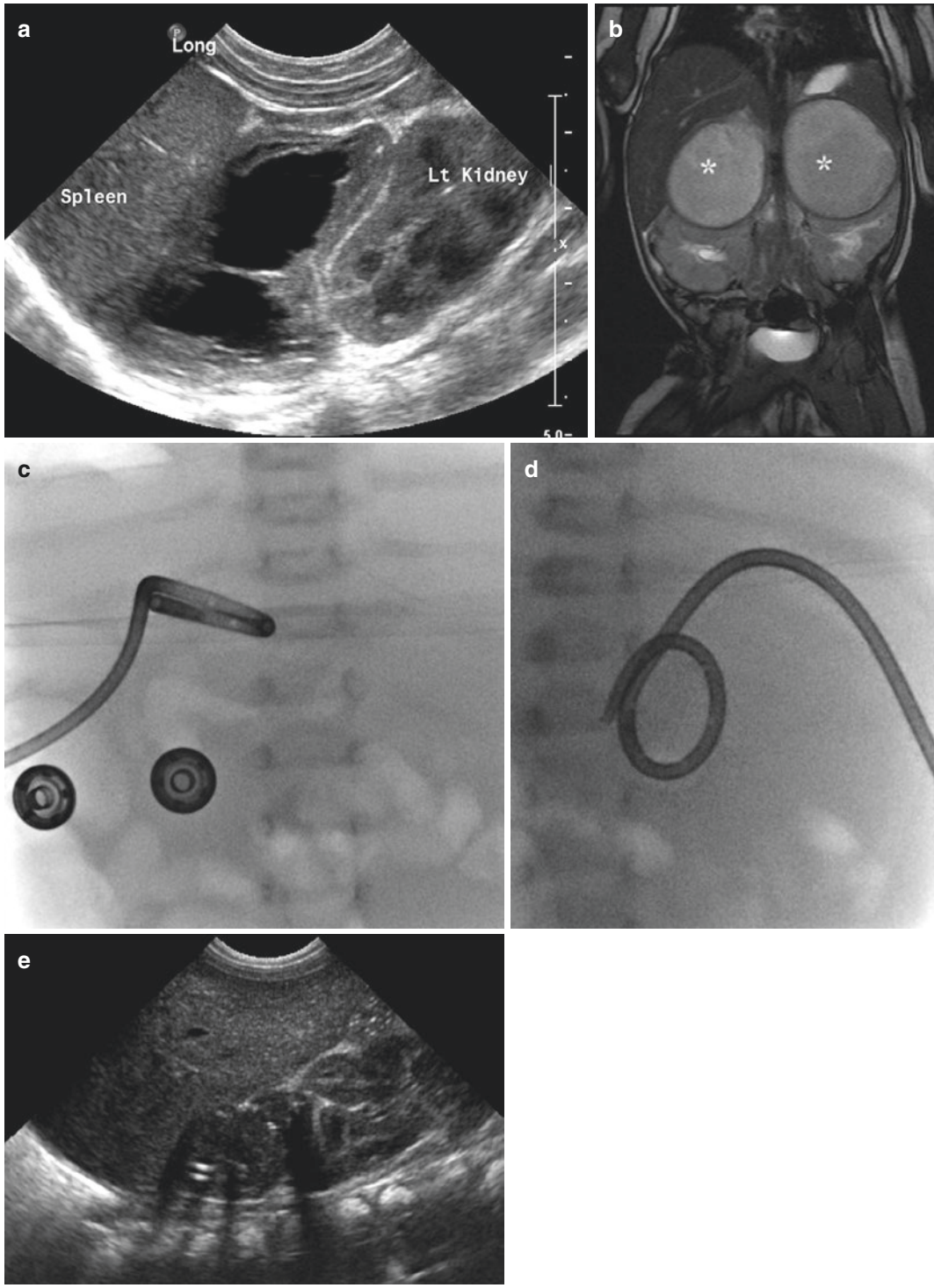


Fig. 10.38 Infected adrenal haematomas. Annotated ultrasound image (**a**) shows irregular thick walled cystic suprarenal mass. Bilateral adrenal collections (**b**–**e**). Single coronal MR image demonstrates large bilateral suprarenal collections (*). Drainage of the bilateral collections with the use of 6F pigtail drainage catheters (**c** and **d**). Ultrasound image (**e**) showing drainage catheter is the right suprarenal collection

Contrast enhanced CT aims to further define the extent of disease and the relationship of the mass to the segmental anatomy of the liver for pre-operative planning. This reveals a large sharply circumscribed mass, which shows low attenuation relative to the liver. Post contrast there is heterogeneous enhancement but the lesion remains hypoattenuating relative to the liver parenchyma. Calcifications are present in 50% [40]. Imaging also aims to identify metastasis, which are commonly to the lungs and periaortic nodes, and less commonly to the brain. If necessary for surgical planning, MR will further characterize the lesion and its extent and relationship to vessels. The mass is low signal on T1 but may have high signal related to haemorrhage, and high signal on T2, again with heterogenous areas dependant on the amount of haemorrhage and necrosis [41, 42]. MR angiography will evaluate the vasculature pre-operatively. AFP levels are

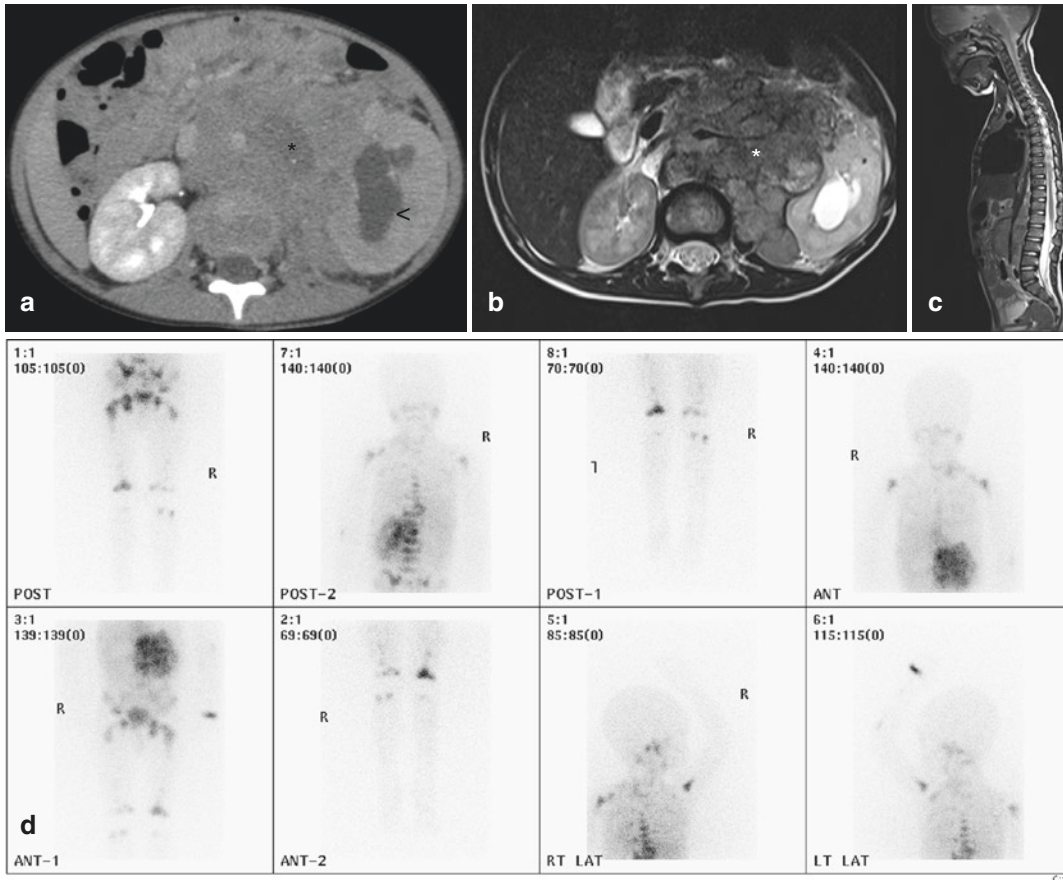


Fig. 10.39 Neuroblastoma. CT demonstrates a large heterogenous retroperitoneal mass (*) containing small calcific foci and low density areas suggestive of necrosis (**a**). Left hydronephrosis also shown (<). Axial and sagittal MR images (**b**, **c**) clealry demonstrate a heterogenous mass (*), encasing the vessels and causing a left hydronephrosis. MIBG scan confirms increased tracer uptake at the site of primary tumour, with more focal areas of uptake in the axial skeleton consistent with bone metastases. Ultrasound image of the pelvis in a more atypical case (**e**) demonstrates a heterogenous presacral mass with internal vascularity. CT (**f**) confirms the mass to be of soft tissue density, and demonstrates internal calcification. Sagittal T2 images further show the heterogeneity of the mass and demonstrate infiltration into the spinal canal via the neural foramina (**g**)

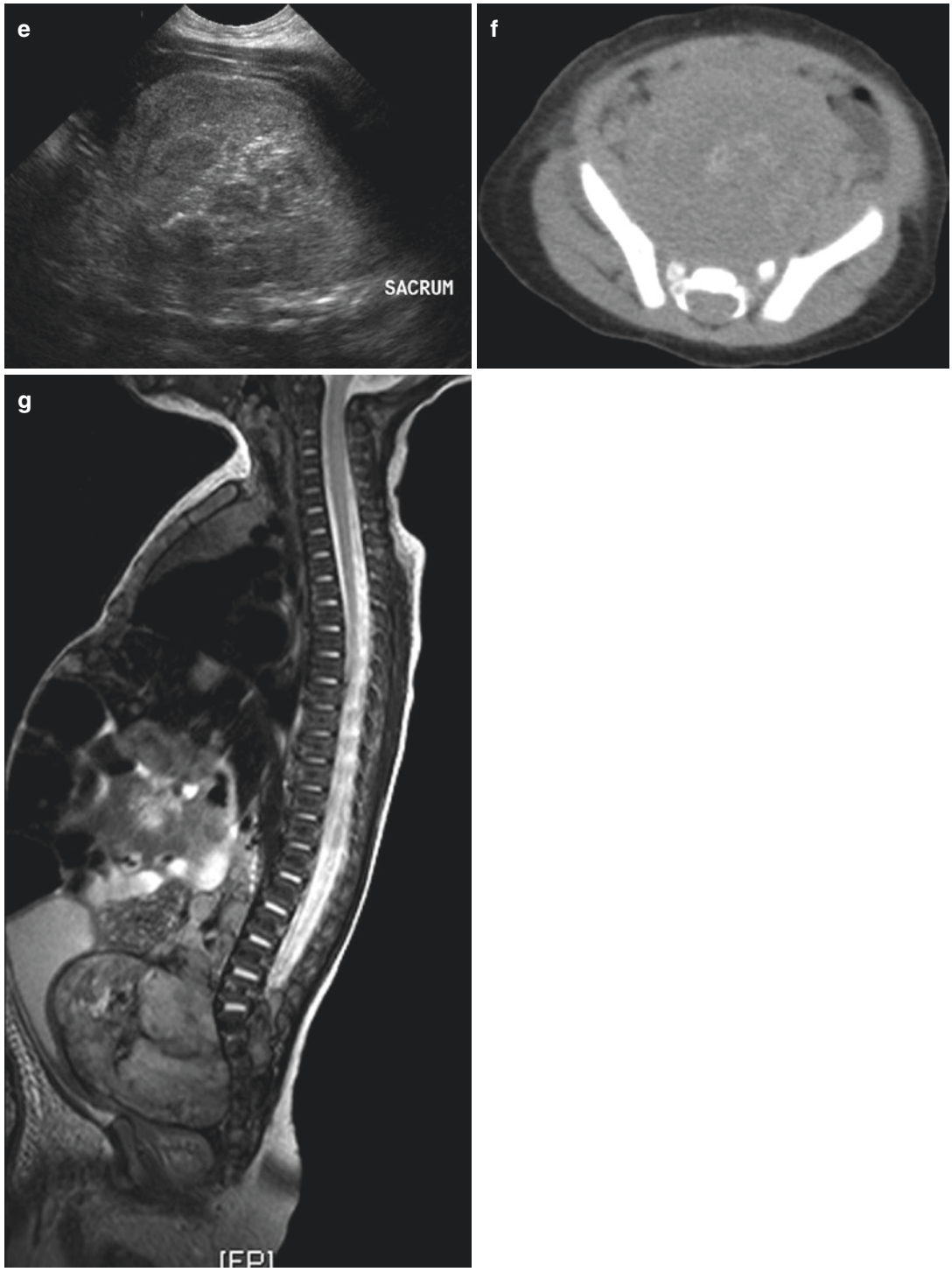


Fig. 10.39 (continued)

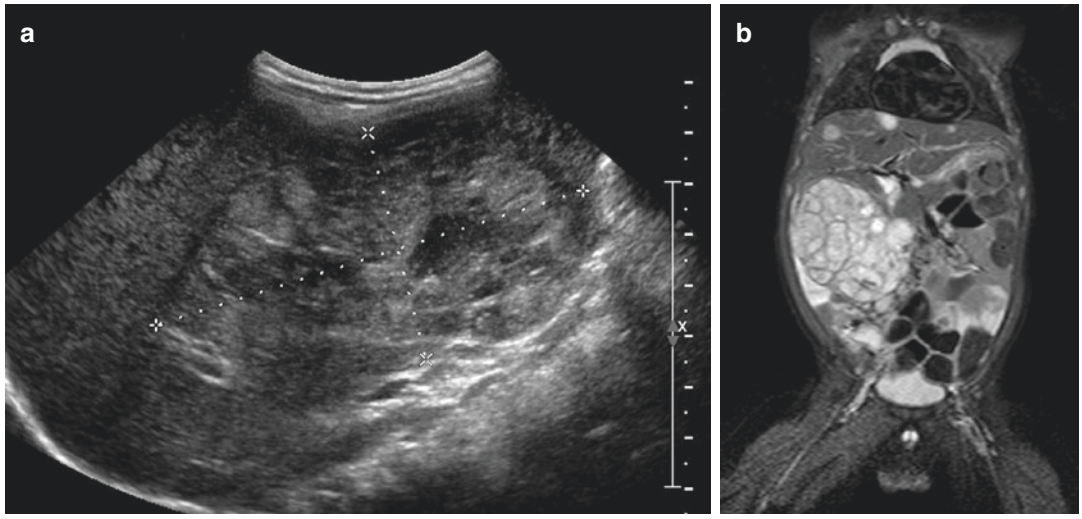


Fig. 10.40 Hepatoblastoma. (**a**) Longitudinal ultrasound image in a baby presenting with increasing lower chest upper abdominal swelling shows a large heterogenous mass involving the right lobe of the liver, marked by calipers. (**b**) Coronal STIR MR image demonstrates a large heterogenous high signal lesion in the liver with further multiple foci of signal abnormality confirming the multifocal nature of the tumour

elevated in >90% (Fig. 10.40). There are no pathognomonic features of liver tumours and correlation of imaging findings, tumour markers and clinical presentation and findings on examination is essential. Biopsy is usually required to confirm the diagnosis.

In the absence of an elevated AFP level, the differential diagnosis of a liver tumour in the neonatal period includes atypical teratoid rhabdoid tumours and benign vascular tumours, including proliferative haemangioma and haemangioendothelioma. Metastatic neuroblastoma is another differential to consider, however these lesions are usually multiple and there is usually a primary suprarenal mass. Mesenchymal hamartomas are predominantly cystic with no associated elevation in serum AFP levels. Hepatocellular carcinoma is rare in infants.

Interventional radiology has a role in chemotherapeutic tumour embolisation and subsequent imaging is directed at assessing the response to surgical/chemotherapy.

10.10.2.2 Hepatic Vascular Tumours

Infantile hepatic haemangioma is the most common benign vascular liver tumour in infancy and the third most common liver tumour in children, after hepatoblastoma and mesenchymal hamartoma. Liver haemangiomas must be distinguished from other vascular lesions such as arteriovenous malformations, and from malignant tumours such as hepatoblastoma and embryonal sarcoma.

Liver haemangiomas can be classified anatomically into three subtypes, dividing them into focal, multifocal, and diffuse lesions [43]. Focal liver haemangiomas are well-defined, solitary, spherical lesions, which are often incidental findings on ultrasound scans performed for other reasons. Multifocal lesions are also typically spherical and well-circumscribed. They sometimes co-exist with multiple cutaneous common infantile (proliferative) haemangiomas. In fact five or more cutaneous infantile haemangiomas necessitates a liver ultrasound for liver evaluation. Many are asymptomatic, but some large focal or multifocal lesions cause high-output cardiac failure because of arteriovenous or portovenous shunting. Diffuse hepatic haemangiomas present with extensive liver involvement, often with marked hepatomegaly, which may lead to abdominal distension, IVC obstruction and respiratory compromise [44]. Rarely, diffuse liver haemangiomas may present with hypothyroidism

secondary to tumour production of iodothyronine deiodinase.

More recently, liver haemangiomas have been classified according to their biological behaviour, in line with haemangiomas occurring elsewhere in the body, into proliferative (common infantile) haemangiomas and congenital haemangiomas [45]. Proliferative haemangiomas characteristically express the GLUT-1 antigen, whereas congenital haemangiomas and other vascular tumours are GLUT-1 negative. Proliferative haemangiomas develop rapidly after birth, undergoing a phase of rapid enlargement, before entering a phase of stabilisation and eventual regression. They appear highly vascular on imaging, with a characteristic pattern of centripetal enhancement on contrast-enhanced CT or MRI. Most congenital haemangiomas occurring in the liver are of the rapidly involuting type (RICH). On MRI or CT, they typically show a thin rim of peripheral enhancement. Rapid involution is typical, often leaving a small residual, sometimes calcified, lesion in a characteristic subdiaphragmatic location.

A plain radiograph may demonstrate hepatomegaly or a right upper quadrant soft tissue density mass. Fine calcification may be seen in upto 16% and in those with high output cardiac failure, cardiomegaly may be noted on a chest film [46].

Ultrasound is the primary imaging modality for diagnosis and follow-up. Focal or multifocal lesions are typically well-defined, spherical lesions with increased echogenicity in comparison with normal liver. The lesions appear highly vascular on colour Doppler (Fig. 10.41). Large feeding arteries and draining veins, collateral vascular supply, evidence of rapid arteriovenous shunting may be demonstrated. In cases with particularly marked arteriovenous shunting, there may be marked enlargement of the coeliac axis, with abrupt narrowing of the descending aorta below its origin. Diffuse liver haemangioma shows heterogeneous echogenicity throughout the liver, with marked hypervascularity on colour Doppler.

CT typically shows well-circumscribed lesions with relatively low attenuation. Following intravenous contrast the lesions show initial nodular enhancement then progressive centripetal fill-in. A central varix and enlarged draining veins may be seen. Calcification is visible in up to 50% of cases, but the calcifications are fine and granular rather than the coarse, chunky calcifications of hepatoblastoma. On MRI, the lesions typically show relatively low signal intensity on T1 weighted images and markedly high signal intensity on T2 weighted images. Flow voids may be seen within the lesion. The characteristic phases of enhancement are well demonstrated on MR without a high radiation exposure.

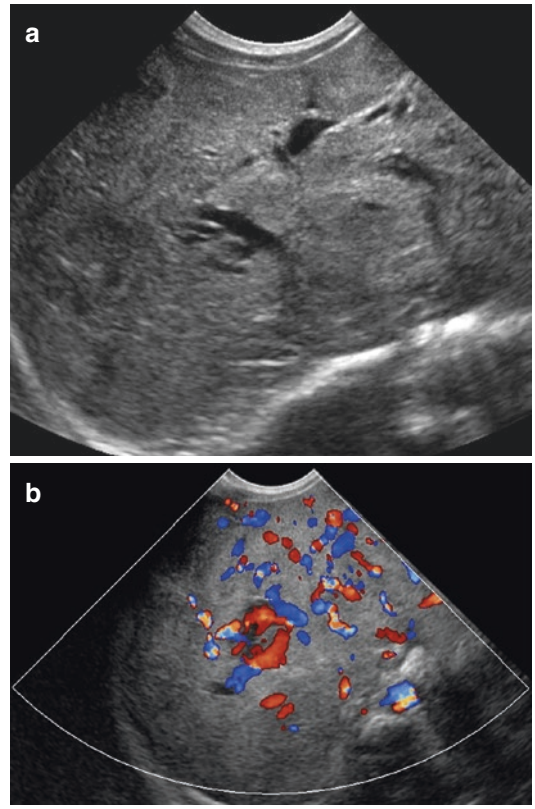


Fig. 10.41 Liver haemangioma. Grey scale and colour Doppler ultrasound images of the liver (**a** and **b**) reveal a heterogenous appearance with multiple areas of increased vascularity

Measurement of alpha-fetoprotein helps to exclude hepatoblastoma, although elevated alpha-fetoprotein must be interpreted with caution in the early neonatal period, and serial measurements may be necessary. AFP is moderately elevated in some infants with liver haemangio-

mas. In cases where the diagnosis is uncertain, percutaneous biopsy may be necessary, but this must be performed with extreme caution because of the risk of haemorrhage. Catheter angiography is generally reserved for cases requiring embolisation for rapid control of cardiac failure.

10.10.2.3 Mesenchymal Hamartoma

This is a benign developmental cystic tumour of the liver, which has a male (2:1) predominance and typically presents in children <2 years. This represents the second most common benign liver mass in children after infantile haemangioendothelioma. The imaging appearances vary from a predominantly cystic, septated mass to a largely solid mass containing few small cysts [47].

On ultrasound the cystic portions are predominantly anechoic, with solid portions and septa within the cysts appearing echogenic. The appearances are thought to be reminiscent of "Swiss cheese". The septae and solid portions are relatively hypovascular on Doppler imaging. Pedunculation of the lesion may make the site of origin difficult to determine with ultrasound. On CT a complex predominantly low attenuation cystic lesion is seen, with internal enhancing sepate/stroma. Haemorrhage and calcification are not usually a feature. The MR appearance of the cystic component is variable on T1 depending on cyst content, and the solid components may be hypointense on T1 and T2 W imaging due to fibrosis. The septae and solid components show mild enhancement post-contrast [48].

The differential diagnosis includes hepatoblastoma and focal infantile haemangioendothelioma. Hepatoblastoma has a more solid appearance on imaging with calcification and an associated marked elevation of the serum AFP. Predominantly solid hamartomas can result in diagnostic difficulty, particularly if the AFP is mildly raised, as the AFP in some hepatoblastomas can be misleadingly low. Differentiating on biopsy can also be difficult and surgery may be required. Haemangioendotheliomas demonstrate calcification in upto 50% of cases and are highly vascular tumours compared with the hypovascular solid components of mensenchymal hamartoma.

10.10.3 Intra-Abdominal Lymphatic Malformation

Lymphatic malformations are proliferations of lymphatic tissue that fail to communicate with the normal lymphatic system. These usually arise from the mesentery, related to the small bowel in 60% and the colon in 40%, but can arise from the omentum or retroperitoneum. They are usually large and present with abdominal mass in the neonate.

Ultrasound appearances are of a large well-defined anechoic cystic structure. This is usually multilocolated with thin septae but can be a single cystic structure. Haemorrhage or infection can result in complex appearances. Cross sectional imaging is useful to delineate the extent in the case of large lesions. CT shows a well-defined fluid filled mass with enhancing septae. The fluid varies in attenuation depending on its chylous or haemorrhagic constituents. MR appearances again are dependant on the nature of the fluid, varying from hypointense on T1 W-imaging and hyperintense on T2-weighted images, to hyperintense on both if the content is fatty or haemorrhagic (Fig. 10.42).

10.10.4 Presacral Masses

The usual presentation of a presacral mass is with an abdominal, pelvic or perineal mass. Pre-sacral masses are often diagnosed in utero during antenatal ultrasound, followed increasingly with fetal MR. A presacral mass may be suspected on the basis of a plain film, which may show displacement of the bowel loops. Care should be taken to assess the presacral space on the initial lateral rectal film of a lower GI study. The most common masses are teratoma and menigocoele, however duplication cyst, dermoid cyst or hamartomas, or a combination of these pathologies, can also occur in the presacral region. MR is the imaging modality of choice, possibly with a limited CT to look for the presence of calcification if the nature of the mass is uncertain.

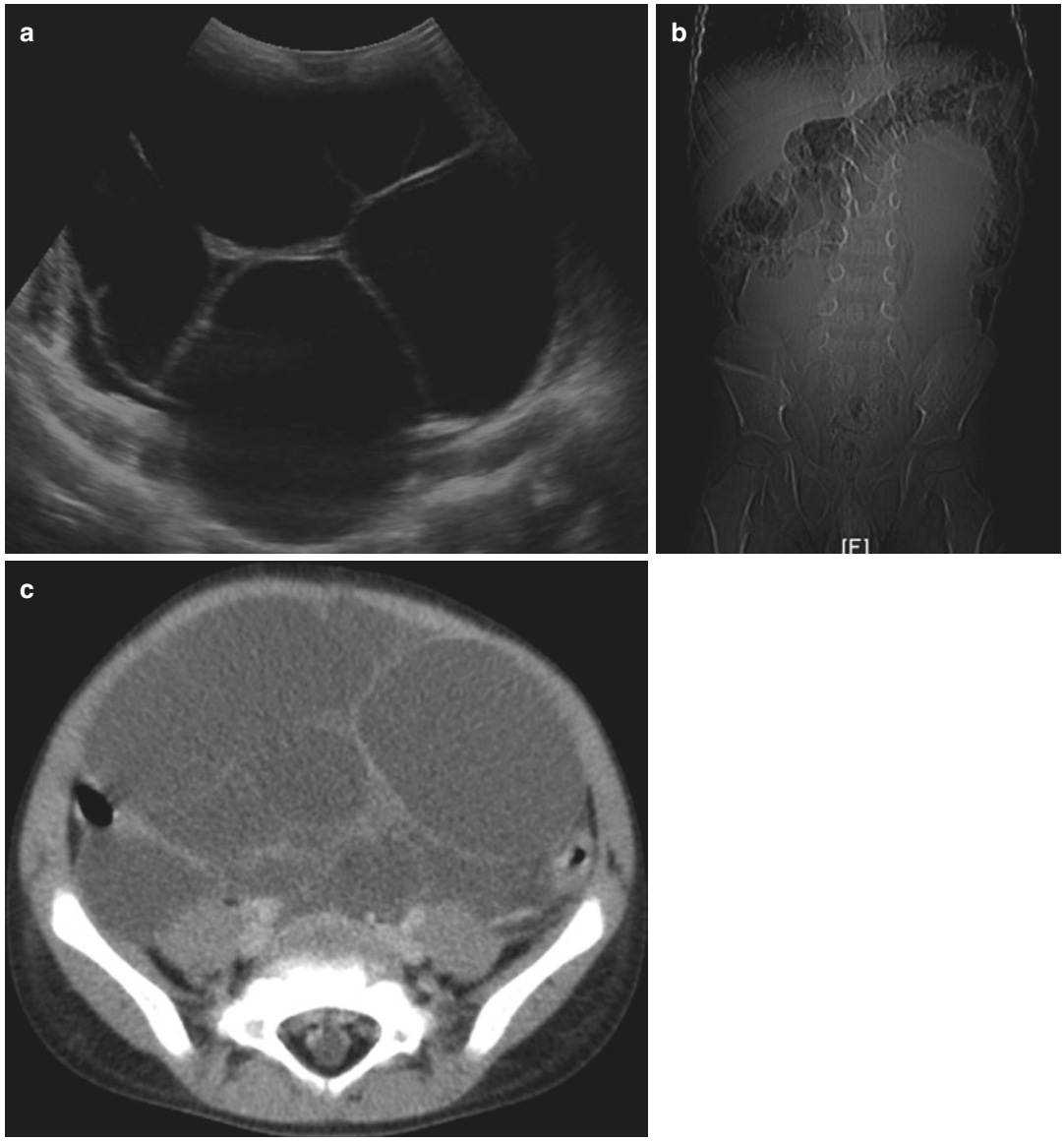


Fig. 10.42 Cystic lymphatic malformation. Ultrasound image (**a**) demonstrates a large multilocular cystic mass in the abdomen. CT scout image (**b**) illustrates the mass effect on the adjacent transverse colon and axial CT (**c**) confirms the cystic nature and the presence of thin septations

10.10.5 Sacrococcygeal Teratoma

Sacrococcygeal teratoma is the most common solid tumour in neonates. The mass may extend into the pelvis and abdomen causing some diagnostic confusion. The characteristics on imaging are determined by the tissue composition and to some extent the degree of malignancy. Benign lesions have well differentiated mature tissues and are predominantly cystic lesions with fat and calcification (in 50%). Calcification is a rare finding in malignant tumours and a predominantly soft tissue mass with haemorrhage and necrosis is more suggestive of a malignant lesion [49].

On plain radiograph, a large soft tissue density mass with internal calcification or low density suggestive of fat may be seen. On contrast studies there may be mass effect with displacement of the rectum, colon, and bladder. Ultrasound is useful in the diagnosis of the mass, showing cystic or solid components and demonstrating internal calcification, but cross sectional imaging is required for surgical planning. CT demonstrates the cystic components, internal calcification and fat and will reveal any metastatic disease or bony involvement- the coccyx is always involved in these lesions. However the exquisite anatomical detail provided by MR determines the internal content of the lesion and the relationship to and invasion of surrounding bony and soft tissue structures (Fig. 10.43).

10.10.6 Anterior Meningocoele

An anterior menigocoele, herniation of a CSF filled dural sac through a vertebral defect or foramina, may present as a presacral/abdominopelvic mass. A plain radiograph or contrast study control film showing spinal abnormalities should raise suspicion. MR is the investigation of choice in these individuals, as the hernial sac and neck are well seen, and the nerve roots and spinal defects are well demonstrated. This usually occurs at the level of the sacrum and is associated with anorectal and genitourinary abnormalities, therefore ultrasound imaging of the abdomen is recommended. In neonates with anorectal malformation and evidence of sacral abnormalities on plain film, the Currarino triad must be

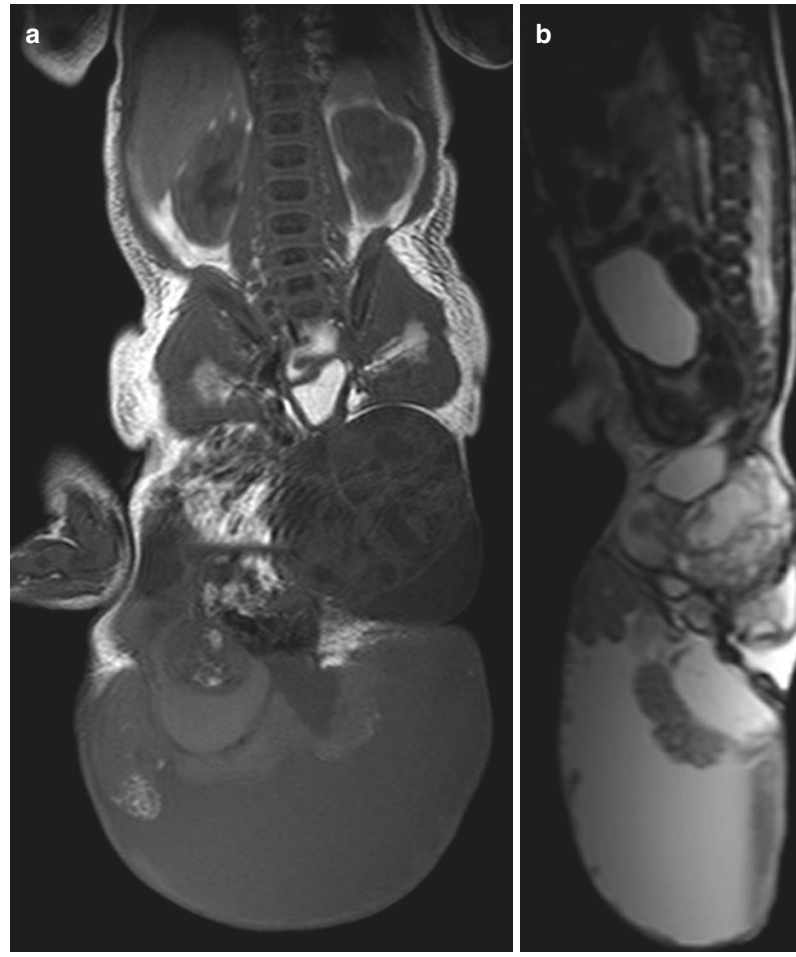


Fig. 10.43 Sacrococcygeal teratoma. (**a**) Coronal T1 W and (**b**) sagittal T2 W MR images show a large complex cystic and solid exophytic tumour arising from the tip of the coccyx

considered, also known as the ASP triad (anorectal malformation, sacrococcygeal defect and presacral mass) [50]. This is a rare syndrome that is autosomal dominant in 50% of cases.

10.10.7 Enteric Cysts

Enteric cysts from the rectum may present as presacral masses. They include duplication cysts and tailgut cysts/retrorectal cystic hamartomas. Duplication cysts of the rectum are rare, and like duplication cysts at other sites they may communicate with the true lumen of the rectum. Ultrasound of the duplication cyst may demonstrate the typical "double wall", which differentiates them from the thin-walled tailgut cyst. Cross sectional imaging further defines the mass, with the contents of the cysts appearing predominantly low on T1 (or high if high mucoid content in the case of tailgut cysts) and high on T2 unless complicated by haemorrhage. Soft tissue enhancement following gadolinium contrast agent is suggestive of malignant degeneration.

10.11 The Neonate with Difficulty in Breathing/Chest Mass

Neonates often present to radiology with a presumptive diagnosis of an intrathoracic problem following antenatal ultrasound diagnosis. Some conditions may be diagnosed antenatally. In these cases abnormalities are usually evident on the neonatal plain film.

Intrathoracic pathologies on plain radiograph that initially appear solid, may later become gas containing. The chest radiograph is used for primary diagnosis and to assess the extent of mass effect and resulting mediastinal shift. It is wise to carefully examine the position of lines and tubes in all neonates, as these may also help to support a diagnosis or raise cause for concern (Fig. 10.44).

Ultrasound can be useful, particularly in the neonate with a dense hemithorax, to differentiate lung consolidation from effusion, to further assess a peripheral intrathoracic or chest wall mass which appears apparently solid on plain radiograph or to investigate a mediastinal mass, as the sternal unfused ossification centres provide multiple acoustic windows which can be accessed in order to visualize the thymus and mediastinum in exquisite detail [51]. Further characterization can be achieved with cross sectional imaging.

10.11.1 Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernias (CDH) are increasingly diagnosed prenatally, and in the neonate imaging is used to differentiate CDH from other masses, to look for associated abnormalities and to aid in the management of complications.

CDH in the neonate can often be reliably diagnosed on plain film (Fig. 10.44). Immediately post partum, the affected hemithorax may be completely opacified, with mass effect and contralateral mediastinal shift. Once air has replaced the fluid in the GI tract, subsequent imaging shows bubbly lucencies in the hemithorax, more frequently on the left, with contralateral mediastinal shift and a paucity of gas in the abdomen. A right sided hernia often contains liver and therefore appears as a density in the thorax. The lung volumes are reduced due to resulting hypoplasia, and truncation of the development of the pulmonary vasculature leads to pulmonary hypertension.

An abnormal course of inserted tubes and lines helps to confirm the diagnosis, and a knowledge of the expected deviations of tubes and lines is required to avoid misinterpreting findings as malposition of apparatus. In a left CDH a nasogastric tube may be seen to deviate away from the side of the hernia in the oesophagus, with the tip either lodging at the GO junction or lying within the hemithorax indicating the hernia content includes the stomach. An umbilical venous catheter may demonstrate rightward deviation, apex leftward angulation or tip position in the portal venous system (Fig. 10.45). In the case of a right CDH, leftward deviation of the NG tube in the medastinum is noted. An umbilical venous catheter may be seen to deviate towards the right following

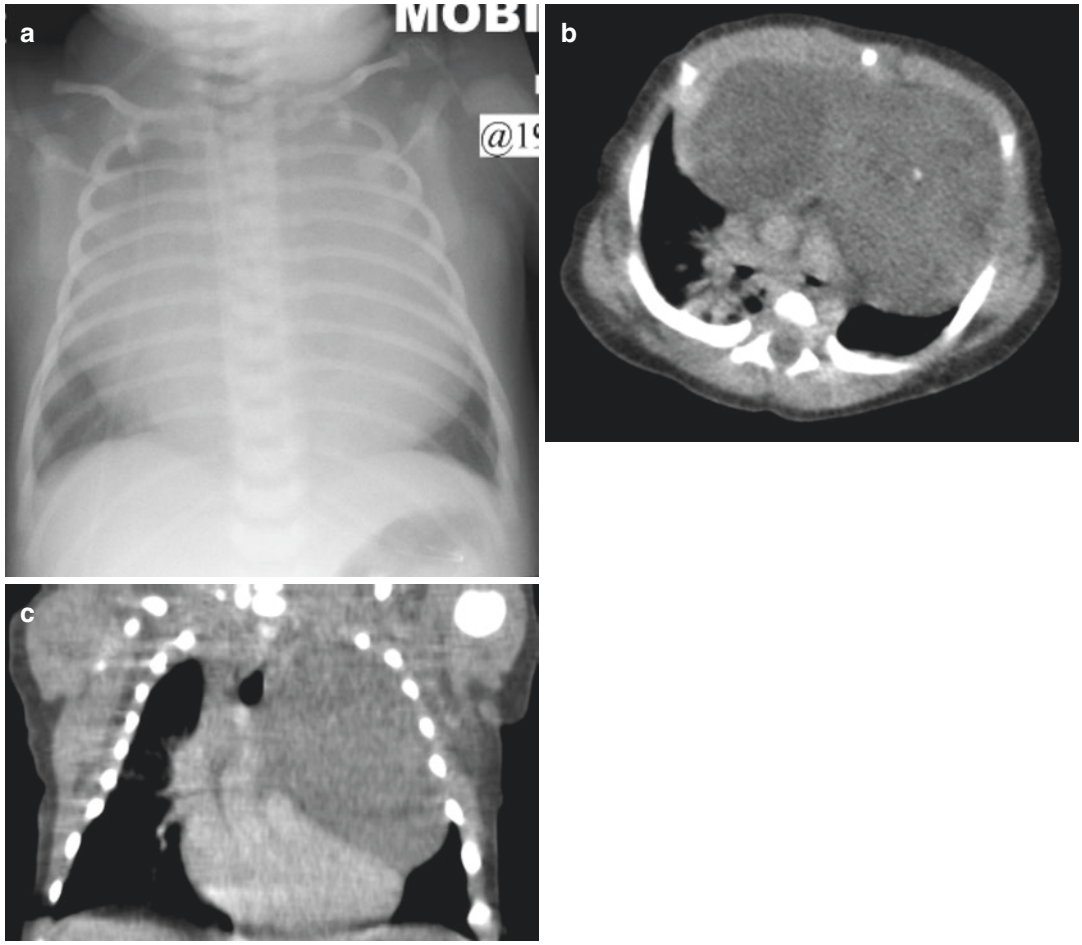


Fig. 10.44 Mediastinal teratoma. Chest radiograph (**a**) demonstrates marked mediastinal widening and a gentle deviation of the NG tube to the right. Axial (**b**) and coronal (**c**) CT demonstrate the large heterogenous anterior mediastinal mass. A small focus of calcification is present on the axial image

the abnormal position of the liver [52]. The plain film is used to confirm the diagnosis however, the amount of aeration of the lungs, the degree of mediastinal shift and the content of the hernia are not thought to predict outcome [53]. When the diagnosis is in doubt, injection of contrast through the NG under fluoroscopic guidance will outline the bowel and confirm the presence of hernia (Fig. 10.46). Cross sectional imaging can provide information about hernia contents and co-exisiting pathologies.

Associated abnormalities are present in between 25 and 50% of patients, including oesophageal atresia, cardiac malformations and GU abnormalities.

10.11.2 Congenital Airway Malformations

Congenital cystic adenomatoid malformation and congenital pulmonary adenomatoid malformations (CCAM/CPAM) are hamartomatous lesions of the lung, thought to occur due to a failure of the pulmonary mesenchyme to progress to normal bronchoalvealar development, with resultant abnormal dilatation and proliferation of the distal bronchioles. A classification system developed by Stocker is based on the size of the gross and microscopic features of the cysts and the resemblance on histology to segments of the developing bronchial tree and airspaces [54].

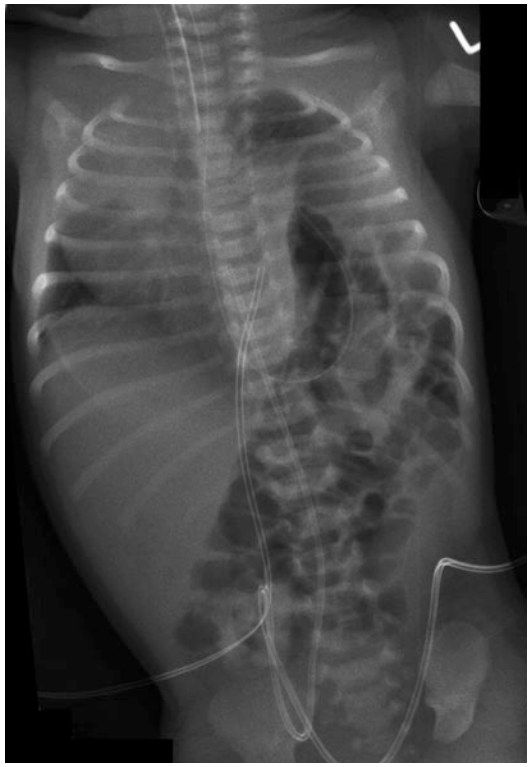


Fig. 10.45 Congenital diaphragmatic hernia. Plain chest and abdominal radiograph demonstrates large left diaphragmatic hernia. Note the course of the NG tube confirming the intrathoracic position of the stomach

Originally describing three types, this has since been extended to five [55]. On imaging, however, only three types can be distinguished: large cyst (Type I), the most common occurring and the most commonly imaged, small cyst (Type II) and microcystic or solid (Type III) [56, 57]. These lesions can have an abnormal communication with the airways and usually have pulmonary supply and drainage, though hybrid lesions can have systemic supply.

CCAMs are often suspected prenatally on ultrasound, the differentials being CHD, sequestration and foregut malformation cysts. The spectrum in utero is variable, and with time lesions may decrease in size relative to the chest. A lesion increasing in size on antenatal ultrasound with progressive mediastinal shift is cause for concern as this may lead to the development of hydrops and fetal demise in utero [58].

Plain film demonstrates variable density depending on the cyst content, number of cysts and mediastinal shift. Cross sectional imaging helps to identify and characterise CCAMs, evaluate mass effect and differentiate CCAM from sequestration.

Type I lesions have one or more large air filled cystic structures. These are often very large and exert mass effect resulting in mediastinal shift and compression of the contralateral lung. As clearance of fetal fluid from the cystic spaces is delayed, a large cyst may initially be seen as a soft tissue density mass which subsequently becomes filled with air. Air fluid levels may be seen. Type II may be seen as an air filled heterogenous multicystic mass or radio-opacity /focus of consolidation. Type III lesions appear solid at imaging due to the presence of microscopic cysts, and may be seen as a persistent area of increased homogenous density/consolidation [59].

Cystic lesions in the neonatal chest have a wide differential, including CDH, bronchogenic cyst, CLE, pulmonary sequestration. CDH can be excluded with the aid of oral contrast if required. Bronchogenic cysts are usually mediastinal (see later). Progressive lung expansion and mediastinal shift, with absence of internal opacities as in CCAM, will be seen with CLE. In the early stages where the abnormal lung is filled with fetal fluid, sequential plain films may reveal the diagnosis (Fig. 10.47).

Ultrasound may reveal echogenic parenchyma in both CCAM and sequestration but colour Doppler can be employed to identify an anomalous vessel thereby differentiating the two [51]. Cross sectional imaging helps to identify lesions seen antenatally, but not visible on plain film, perhaps due to decreasing size, and can further characterize an apparently solid plain film abnormality. Macrocystic CCAMS can have an abnormal systemic arterial supply. These lesions are known as hybrid lesions as they have features of CCAM and BPS [56].

10.11.2.1 Pulmonary Sequestration

A pulmonary sequestration has no communication with the tracheobronchial tree and has a systemic arterial supply, usually from the aorta. Intralobar sequestration is an area of lung tissue

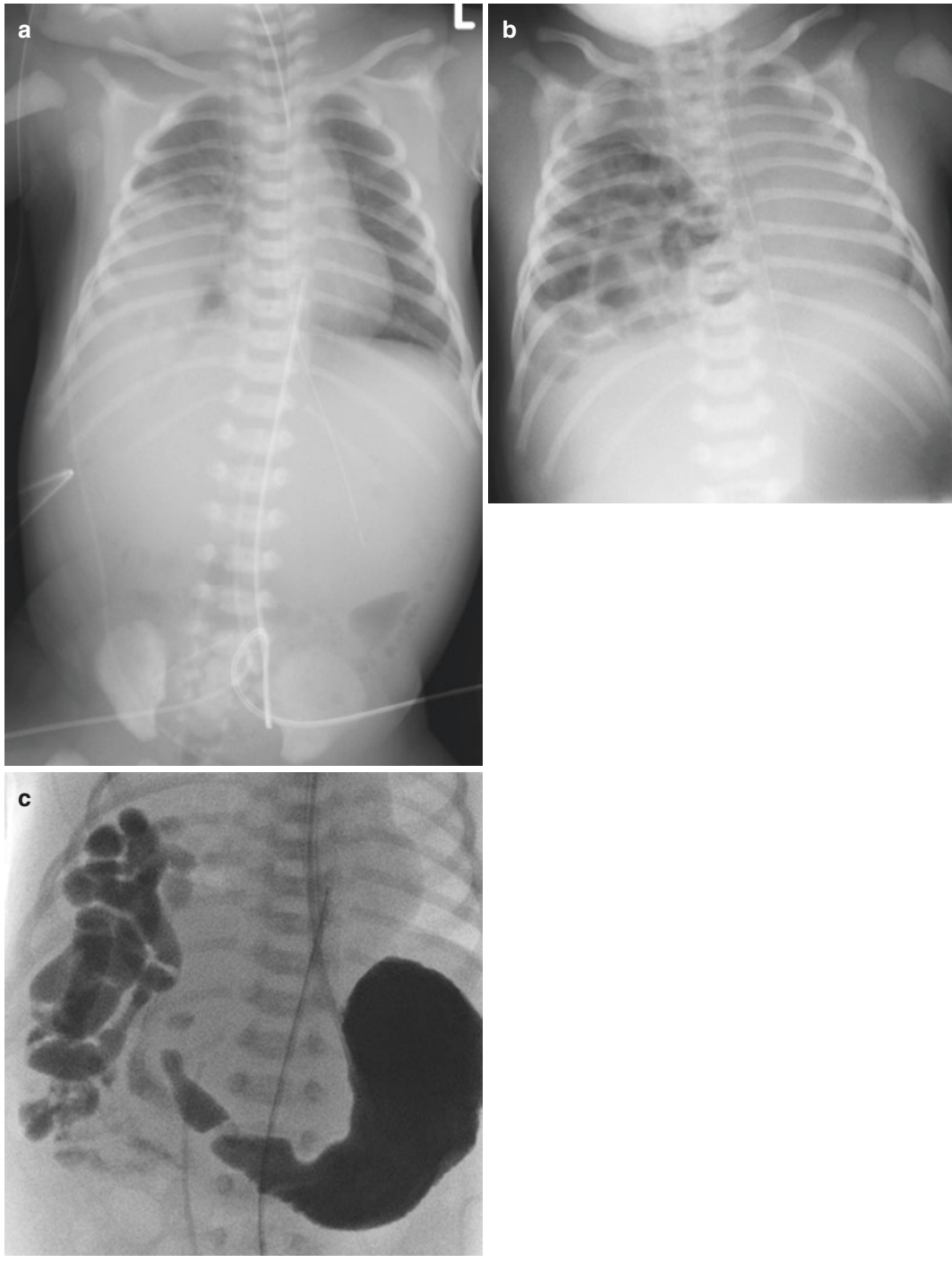


Fig. 10.46 Congenital diaphragmatic hernia. Neonate presenting with respiratory distress. Initial plain film early post delivery (**a**) demonstrates opacity in the right mid and lower zones, with absence of the normal outline of the right hemidiaphragm. The tip of the NG is well below the left hemidiaphragm. Note the low position of the umbilical venous catheter. Film 6 h later (**b**) shows marked mediastinal shift to the left and multiple air filled lucencies in the right hemithorax. The NG tube is displaced to the left in the thorax and the tip is seen to lie in the region of a distended gas filled stomach. Selected image from a water soluble upper GI contrast study (**c**) shows the normally positioned stomach to fill with contrast. The duodenum is seen to pass to the right of midline and contrast is seen in multiple loops of intrathoracic jejunum

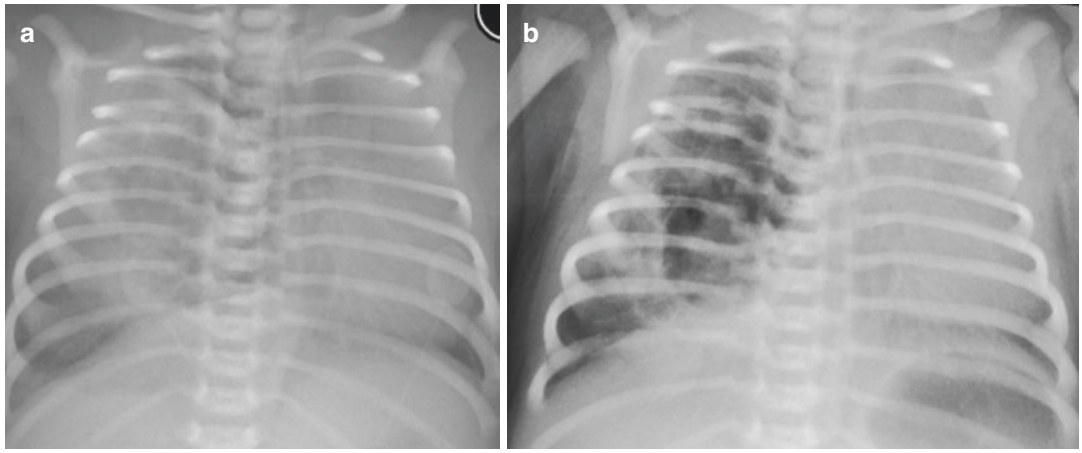


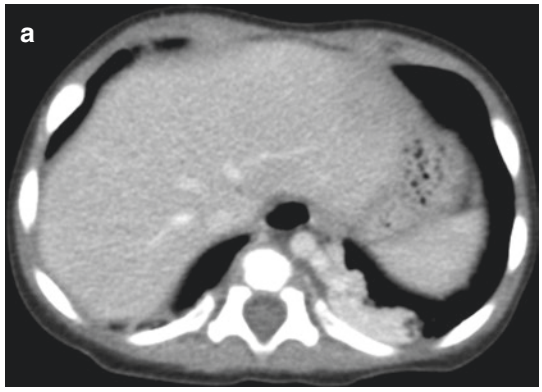
Fig. 10.47 Congenital cystic adenomatoid malformation (CCAM). (**a**) Radiograph taken shortly after birth in a neonate with respiratory distress shows ill defined slightly heterogenous density occupying a large proportion of the right hemithorax. There is evidence of contra-lateral mediastinal shift. (**b**) Radiograph taken at 12 h of life more clearly demonstrates air filled cystic lucencies within the right hemithorax. The hemidiaphragm is clearly seen and the gastric bubble is visible below the left hemidiaphragm

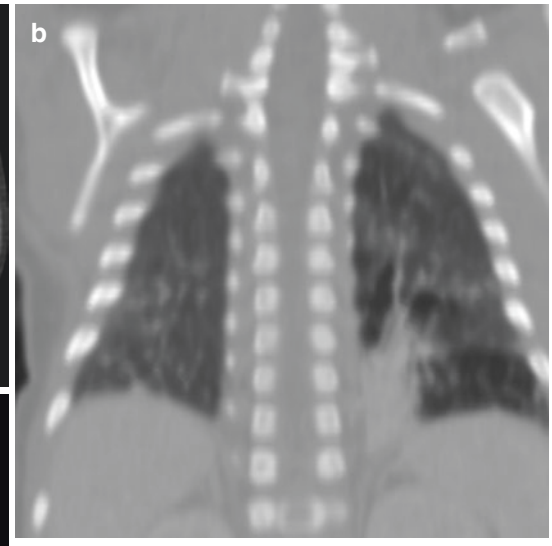
that is contained within the pleural covering of the adjacent lung but does not communicate with the tracheobronchial tree, and has systemic arterial blood supply but normal pulmonary venous drainage. They often present in adults but may be an incidental finding in children. Extralobar sequestration is an area of lung tissue that has its own pleural covering separate to that of the adjacent lung, does not communicate with the tracheobronchial tree and has systemic arterial blood supply and systemic venous drainage. They often present in infancy and may be an incidental finding in neonates. This may be associated with other congenital abnormalities, and can be situated below the diaphragm and mistaken for a neuroblastoma or adrenal haemorrhage [60].

On plain film, sequestrations appear a soft tissue density masses, usually at the lung base. The appearances on ultrasound are of a soft tissue mass, somewhat similar to CCAM, however the differentiating aberrant blood supply may be demonstrated. CT angiography with 3D reconstruction is the preferred imaging modality of choice. This allows identification of the anomalous arterial vessels, thereby differentiating this from a CCAM, and also allows the identification of anomalous veins, which differentiates intra and extra-lobar sequestration and aids surgical planning [59] (Fig. 10.48).

10.11.2.2 Congenital Lobar Emphysema (CLE)

In utero the appearances of CLE are similar to normal lung and therefore this is less frequently diagnosed antenatally relative to the other intrapleural mass lesions [61]. Diagnosis is usually made with plain radiography, performed due to respiratory distress. Usually the upper lobes are involved, most frequently the left. Early films may present some diagnostic difficulty as a dense mass/hemithorax may be seen, due to retention of fetal lung fluid. In time this clears to show the characteristic progressively hyperlucent hyperinflated lobe and its resulting mass effect including adjacent atelactasis, rib space widening, flattened ipsilateral hemidiaphragm and contralateral mediastinal shift. CT may be required to confirm the diagnosis, particularly if more than one lobe is involved, to further define mass effect or for the purpose of preoperative planning. CT demonstrates a hypoattenuated distended lobe, with a relative reduction in the pulmonary vascularity. Adjacent atelectasis may be seen and compression of the adjacent normal lung tissue, and there may be mediastinal shift [59]. On plain film and CT the presence of bronchovascular markings help to differentiate this from a pneumothorax or cyst (Fig. 10.49).





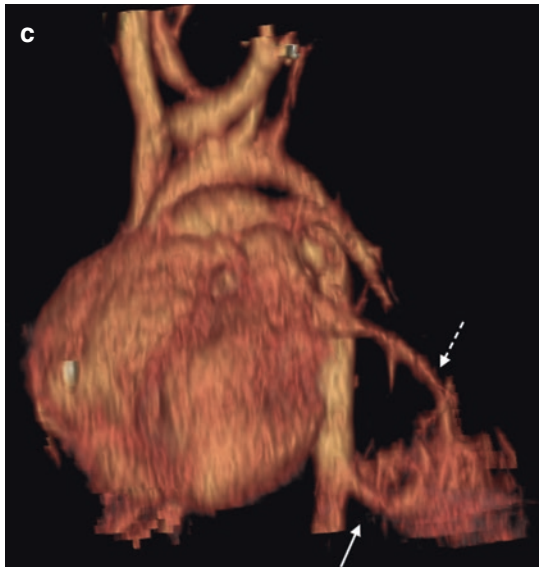


Fig. 10.48 Sequestration. (**a**) Axial and (**b**) coronal reformat CT demonstrate a focus of high attenuation in the postero-basal segment of the left lower lobe, with the impression of vascular communication with the aorta. (**c**) 3D reformat clearly demonstrates feeding artery (*solid arrow*) from the aorta and draining vein (*broken arrow*)

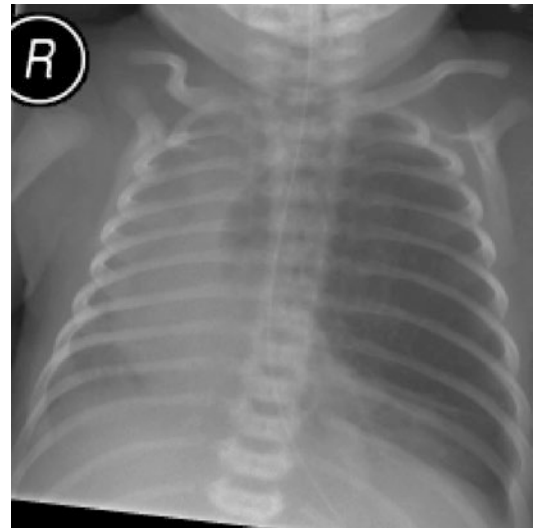


Fig. 10.49 Congenital lobar emphysema. Plain radiograph shows increased lucency and hyperexpansion of the left upper lobe with marked contralateral mediastinal shift

10.11.2.3 Bronchogenic Cysts

Bronchogenic cysts represent part of the spectrum of foregut duplication cysts. They are usually mediastinal in location, most commonly the subcarinal position or in the right paratracheal region. The usual cause for presentation results from pressure effects, though these may be discovered incidentally on the plain radiograph as a mediastinal mass (Fig. 10.3). Cross sectional imaging defines cyst content and extent, and relationship to adjacent structures, aiding surgical planning. They are usually solitary well circumscribed ovoid or spherical lesions, with uniform fluid attenuation. With IV contrast a non or minimally enhancing wall is seen. An air fluid level may be present if there has been infection, which is also suggested by an increase in size and rim enhancement, or if there is some communication with the bronchial tree or GI tract [59].

10.11.2.4 Anomalous Pulmonary Venous Drainage

This can be total, involves pulmonary arterial supply with systemic venous drainage of the lungs or partial, pulmonary arterial inflow with mixed pulmonary venous and some systemic venous drainage.

Scimitar syndrome/pulmonary venolobar syndrome/hypogenetic lung sydrome is a specific type of partial anomalous pulmonary venous return, which is characterized by ipsilateral anomalous pulmonary venous drainage of all or part of the lung into the IVC resulting in a left to right shunt. The anomalous vein usually joins the IVC below the diaphragm, though it can join the hepatic vein, portal vein, coronary sinus or right atrium. There is associated right lung hypoplasia and cardiac dextroposition. Right pulmonary artery abnormalities and systemic arterial supply, and abnormalities of the right bronchial tree may also feature. Post natal plain films may show the curvilinear density in the right lower lobe passing towards the right hemidiaphragm, The scimitar describes the characteristic shape of the draining vein from the right lower lobe to an infra diaphragmatic systemic vein. This is best depicted on contrast enhanced CT. Surgical correction is considered if there is significant left to right shunting.

10.11.2.5 Pulmonary Underdevelopment

Pulmonary agenesis and aplasia have similar imaging characteristics. Post-natally, plain film demonstrates diffuse opacification of the hemithorax and ipsilateral mediastinal shift. CT helps to confirm the absence of lung and pulmonary vasculature. In pulmonary aplasia, a blind ending bronchus will be seen.

Pulmonary hypoplasia is usually seen secondary to a pathology restricting lung growth. The most common cause is congenital diaphragmatic hernia, but other intrathoracic space occupying lesions may be a cause such as CCAM, sequestration, mediastinal mass. On cross sectional imaging, the bronchus and lung are present however the airways and vessels are decreased in number.

10.11.2.6 Pulmonary Artery Sling

This is an anomalous origin of the left pulmonary artery, which arises from the proximal right main pulmonary artery and courses between the trachea and oesophagus, forming a sling around the trachea. This diagnosis may be alluded to on upper GI studies, which reveal oesophageal compression, however multidetector CT with 3D reconstructions is the imaging of choice. Posterior compression of the trachea and anterior compression of the oesophagus are seen occurring at the same level. This anomaly can be associated with other congenital lung and cardiac anomalies.

10.11.2.7 Bronchial Atresia

This is rare and usually found incidentally in adults and it occurs due to obliteration of a segmental, subsegmental or lobar bronchus. Distal airways fill with mucous and the adjacent lung appears a little hyperinflated. The mucous filled bronchus ay be visible on plain film, but is well demonstrated on CT as a dilated tubular opacity with air trapping and decreased vascularity.

10.11.2.8 Tracheo-Bronchomalacia

Tracheal or bronchial malacia is collapse of the major airways on expiration, secondary to absence, immaturity or incompleteness of the cartilage rings of the large airways. It can be rec-

tified with positive end-expiration ventilation, and often requires prolonged ventilation until the airways fully develop. If limited to the trachea aortopexy can be curative.

10.11.3 Chest Wall Masses

Chest wall masses in neonates are rare. None of the malignant conditions of childhood such as Ewing sarcoma/PNET or metastasis from neuroblastoma, leukaemia and lymphoma frequently involve the chest wall of neonates. Benign lesions common in children including fibrous dysplasia, Langerhans cell histiocytosis and haemangioma are also rare in neonates.

Mesenchymal hamartoma of the chest wall is an uncommon benign tumour that most commonly affects infants and may present with a deforming chest wall lesions noted at birth, or as an incidental finding on plain film. These always arise in the rib and comprise of a benign proliferation of skeletal tissue with a prominent cartilaginous component and haemorrhagic cavities. The imaging features are of a large extrapleural partially calcified soft tissue mass arising from one or more ribs, with destruction and distortion of the adjacent thorax. Cross sectional imaging reveals prominent haemorrhagic cystic components, possibly with fluid-fluid levels, and mineralized elements [62] (Fig. 10.50).

Fetus in fetu, or fetiform teratomas may also be detected antenatally, requiring post-natal cross sectional imaging to define the exact nature of the mass and its relationship to adjacent structures (Fig. 10.51).

10.12 The Neonate with a Urinary Tract Infection

The management and imaging pathways of urinary tract infection (UTI) in children are controversial, but there is general consensus about the need for comprehensive investigation of UTI occurring in the neonate. In the UK, there are evidence-based guidelines for the investigation and management of UTI in children [63].

The initial imaging modality of choice is the ultrasound scan. The aim of ultrasound is to confirm underlying developmental anomalies, assess the ureters and upper tracts for hydronephrosis/hydroureteronephrosis and identify any complications such as abscess or pyonephrosis. Standard ultrasound will confirm the number of kidneys, and assess the renal length. The use of high frequency probes in neonates permits a detailed assessment of the kidney including the echogenicity of the cortex relative to the liver and spleen, the corticomedullary differentiation, the degree of dilatation of the collecting system, prominence of the proximal or distal ureters and evidence of urothelial thickening. An assessment of bladder wall thickness is made. This is difficult in the neonate who usually has an empty or partiallly filled bladder, but this should measures <5 mm when collapsed and <3 mm when full. A ureterocoele is easily identified with ultrasound. Colour Doppler is useful to assess the vascularity of the kidney.

Increased length of one or both kidneys, interruption of the central renal sinus and identification of two renal pelves or ureters is suggestive of a duplex system. When duplicated ureters insert separately into the bladder the Weigert-Meyer rule states that the upper pole ureter is the ectopic ureter and its orifice inserts inferomedially in the bladder in relationship to the lower pole normal ureter. As a result the upper pole ureter is susceptible to obstruction, seen as a dilated upper moiety on ultrasound. Careful assessment of the bladder will identify any associated ureterocoele, which is associated with an increased risk of UTI in the neonate [64]. The lower pole ureter is more likely to reflux and an MCUG is therefore performed.

In the context of UTI and reflux, detailed scanning of the cortex and medulla is useful. Debris in the collecting system and bladder may be seen, and thickening of the urothelium is well demonstrated on the high-resolution images achievable in neonates. In a patient with these features and hydronephrosis, not responding to pharmacological management, may need intervention. Focal thinning and

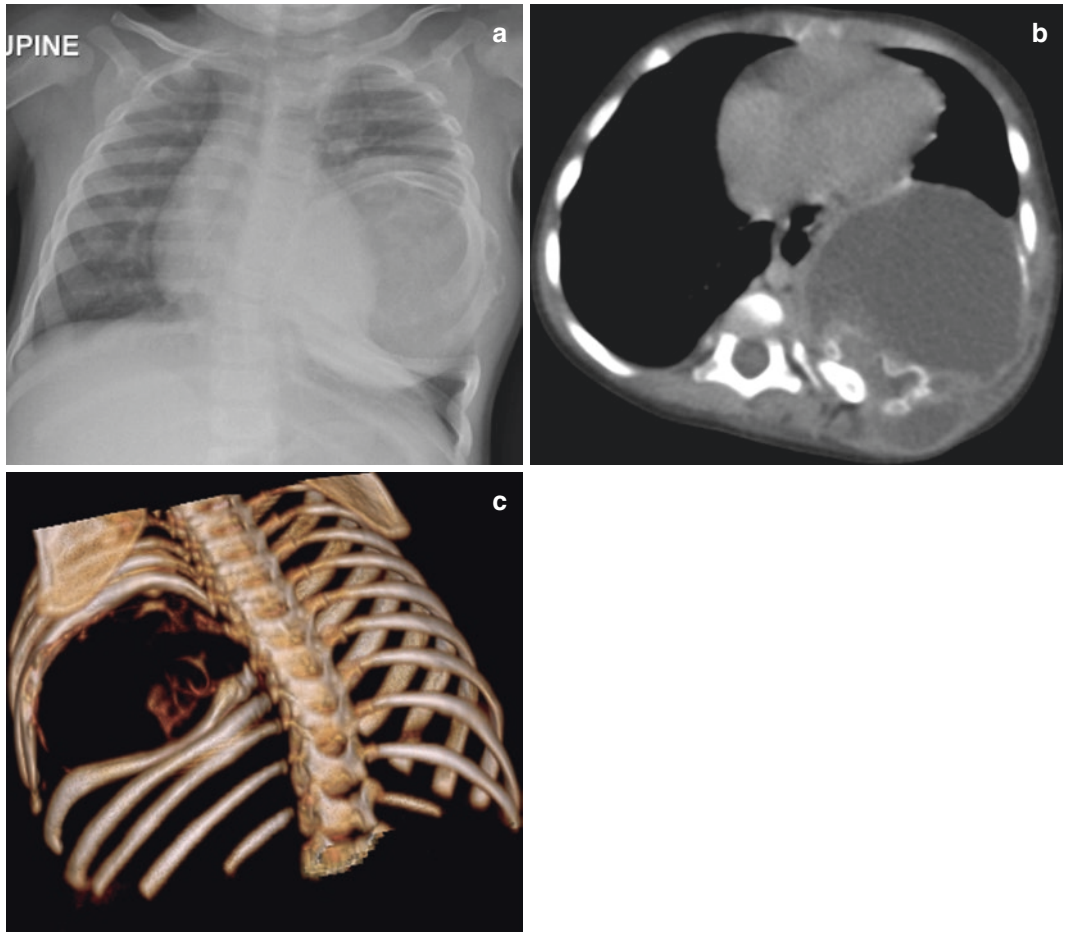


Fig. 10.50 Mesenchymal hamartoma of the chest wall. (**a**) Plain radiograph at presentation demonstrates a large soft tissue density mass involving a left posterior rib with splaying of the adjacent ribs suggesting a slow growing pathology. (**b**) Contrast enhanced axial CT shows a mass with intra and extrapleural components. (**c**) Volume rendered 3D image of the chest wall demonstrates the osseous expansion of the involved rib and splaying of adjacent ribs due to mass effect

adjacent calyceal prominence is in keeping with scarring. A DMSA scan after the neonatal period, when the kidneys have matured, will further evaluate this. In the presence of atypical infection, highly echogenic rounded foci in the collecting system are suggestive of fungal disease (Fig. 10.52).

The MCUG is used in the neonate to identify vesicoureteric reflux (Fig. 10.53), or to exclude bladder outlet obstruction as a cause of hydronephrosis. Following sterile bladder catheterization a control film is obtained to identify the position of the catheter and look for any renal tract calcification. In addition, vertebral, sacral, or other anomalies associated with syndromes such as VACTERL (Vertebral, Anorectal, Cardiac, Esophageal, Renal, Limb) may be seen. The bladder is slowly filled with warmed water-soluble contrast agent. Early bladder views allow the identification of diverticula or ureterocoeles. Oblique views of the full bladder allow a careful search for vesicoureteric reflux. In males, lateral views of the bladder and urethra during micturition are vital in order to exclude or confirm the presence of urethral valves, and a final AP view of the abdomen will identify any remaining contrast within the urinary tract.

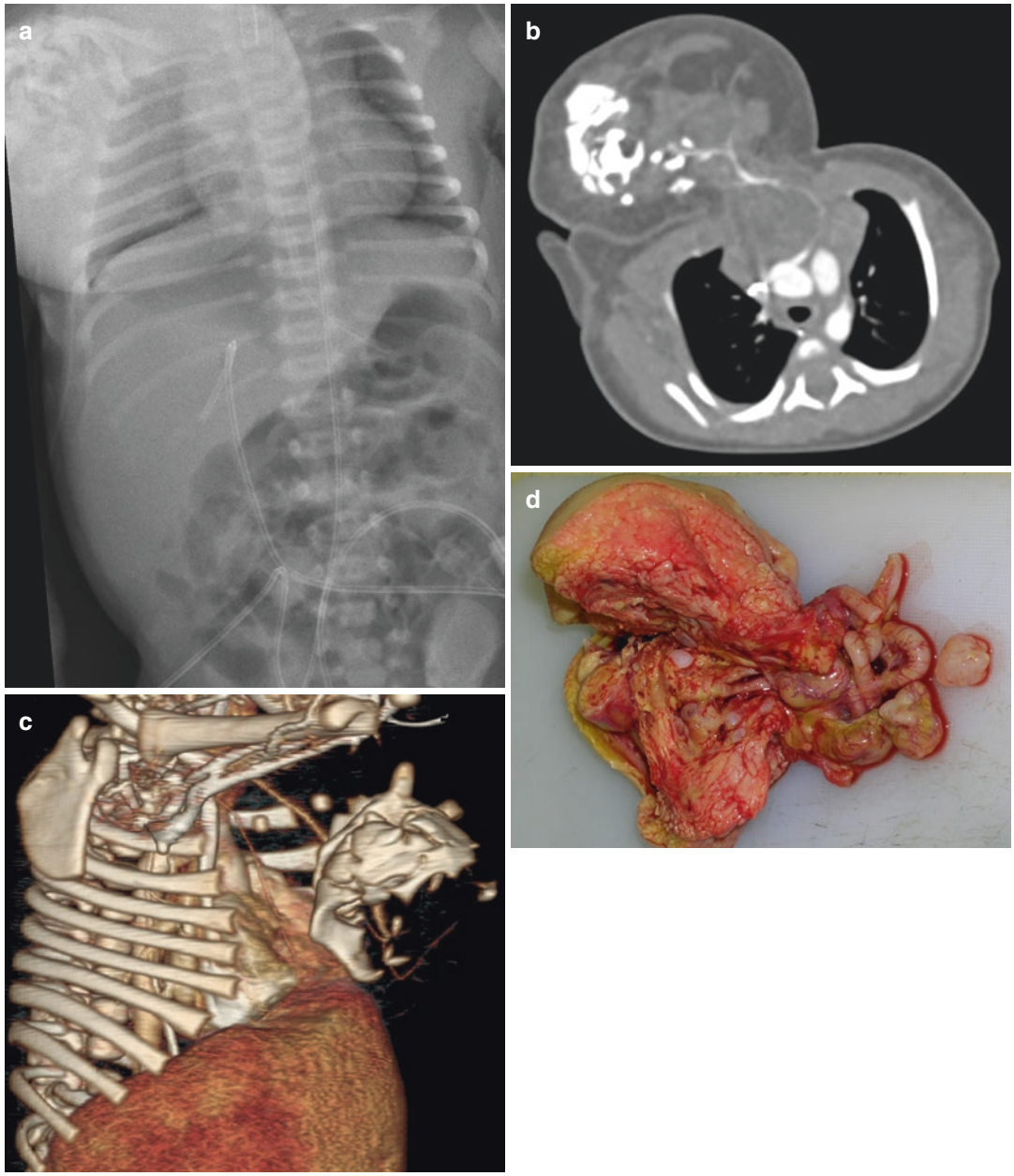


Fig. 10.51 Teratoma of the chest wall. Plain film (**a**) demonstrates a large heterogenous chest wall mass containing some areas of calcific density. Axial contrast enhanced CT (**b**) and volume rendered 3D reformat (**c**) confirms the anterior chest wall mass containing calcific density and demonstrates a feeding vessel from the mediastinum. Gross specimen image (**d**) shows the presence of a fully formed colon. Renal and uterine tissue was also present. The absence of a formed axial skeleton differentiates this fetiform teratoma from a fetus-in-fetu

In children shown to have reflux or atypical/recurrent infections a DMSA scan is performed in conjunction with an ultrasound, to identify areas of scarring. Technecium-99 m dimercaptosuccinic acid (DMSA) binds to the proximal renal tubules and produces an image of functioning renal cortex. Anterior, posterior and oblique views of the kidneys are obtained and relative

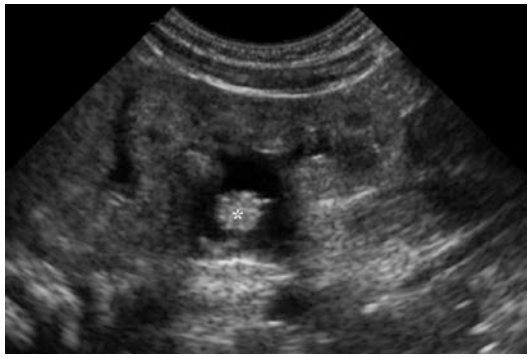


Fig. 10.52 Renal candidiasis. Oblique ultrasound image of the kidney in a neonate with sepsis demonstrates a hyperechoic spherical focus (*) in the collecting system consistent with a fungal ball

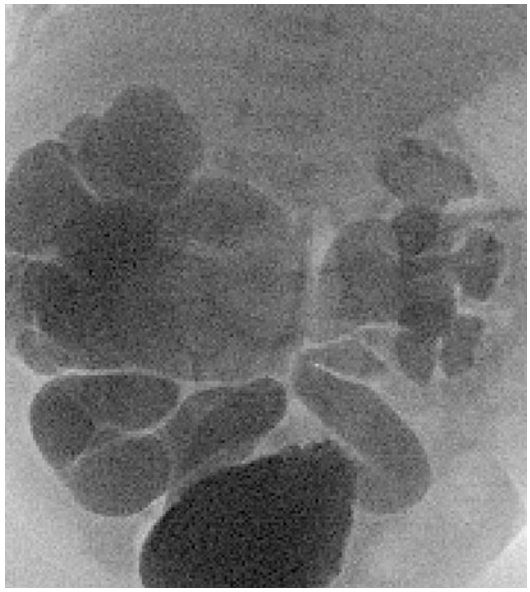


Fig. 10.53 Vesicoureteric reflux. Micturating cystourethrogram shows gross bilateral reflux, more marked on the right, with dilated tortuous ureters, dilated renal pelvises and marked calyceal blunting

renal functions are calculated. No information about the collecting system, ureters or bladder is obtained. Many abnormalities such as cysts, abscesses and non-functioning duplex moieties can have similar appearances. DMSA is usually performed after any acute infection, but is best deferred until after the neonatal period, in order to allow renal function to mature and to avoid false positive results due to recent infection (Fig. 10.54).

10.12.1 Vesico-Ureteric Reflux

Vesico-ureteric reflux is diagnosed on MCUG by the dynamic visualization of retrograde flow of contrast instilled into the bladder into the ureter/collecting system (Fig. 10.54). Reflux is graded according to the international reflux grading system, developed by the International Reflux Study Committee: I Reflux into ureter not reaching the pelvis; II Reflux reaching pelvis but no calyceal blunting; III Mild calyceal blunting; IV Progressive caliceal and ureteral dilatation; V very dilated and tortuous collecting system, intrarenal reflux [65]. The grade of reflux has been shown to have prognostic implications [66]. In the refluxing duplex system usually the ureter of the lower moeity is demonstrated, and a ureterocoele may be demonstrated relating to the site of insertion of the upper moiety. Reflux into ectopic ureters inserting low into the bladder neck will only be seen during voiding. If reflux is demonstrated in the neonate treatment dose of antibiotic followed by prophylaxis is prescribed.

Other techniques such as voiding ultrasonography with ultrasound contrast agents are in use [67]. Although there is no exposure to ionizing radiation, these methods are extremely time and resource intensive.

10.12.2 Obstructive Uropathy/Bladder Outlet Obstruction

Pelvi-ureteric junction obstruction is the most common form of urinary tract obstruction in children, and is now often detected on antenatal ultrasound. This may present as a mass in the neonate (see previous). There is an association with a contralateral MCDK [68].

Ultrasound reveals marked hydronephrosis, with a disproportionally large pelvis compared to the degree of calyceal dilatation. An abrupt caliber change is present at the renal pelvis and there

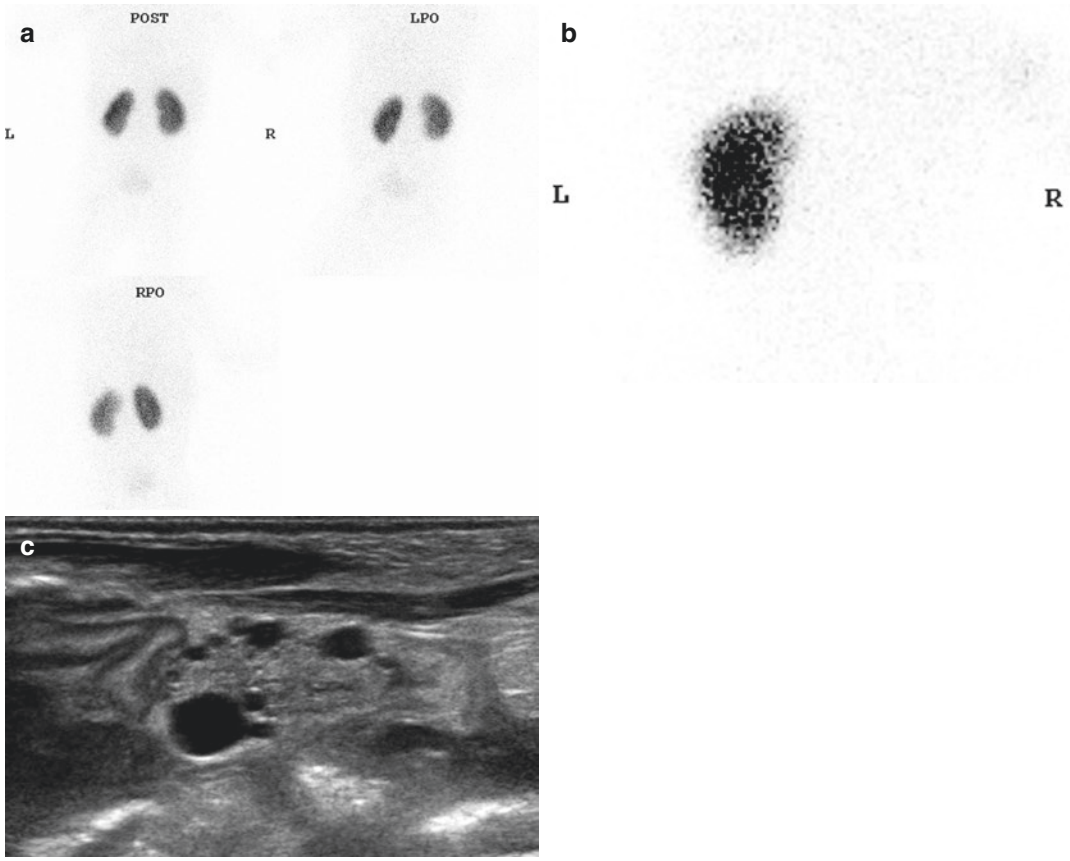


Fig. 10.54 Normal DMSA. (**a**) shows bilateral symmetrical tracer uptake with smooth cortical outline. Abnormal DMSA (**b**) shows absence of tracer uptake in the right kidney in keeping with absence of functioning renal tissue. Ultrasound image (**c**) shows a small multicystic kidney

is a normal calibre ureter downstream (Fig. 10.28). Colour Doppler may be used to identify crossing vessels causing obstruction, however in the neonate this is challenging. A nuclear medicine renal scan using Tc^{99m} MAG-3 is required to assess the degree of obstruction; however, this is usually performed after the neonatal period, to allow renal function to mature. This condition may improve with time and ultrasound is used in the serial follow up of these cases. If infected, or if the contralateral kidney is dysplastic, percutaneous nephrostomy may be required as a temporising measure prior to surgery (Fig. 10.55).

In the case of bilateral hydronephrosis in the male, or a large trabeculated bladder presenting as an abdominal mass, the MCUG is the gold standard imaging modality to exclude or confirm the presence of posterior uretheral valves. Ultrasound may suggest the diagnosis in the presence of a trabeculated thick walled bladder suggesting bladder outlet obstruction, and bilateral hydroureteronephrosis. Ascites may also be present. The condition is now frequently diagnosed antenatally on the basis of these findings and treated in utero. The classical imaging findings on MCUG are an abrupt caliber change of the urethra from the dilated posterior urethra to the small caliber more anterior bulbous urethra. Occasionally the valves themselves may be visible as a filing defect. Care must be taken as the catheter inserted for the procedure may stent the valves and obscure the caliber change, therefore withdrawal of the catheter during micturition is required (Fig. 10.56). The bladder wall may appear trabeculated, and bilateral VUR may also be seen.

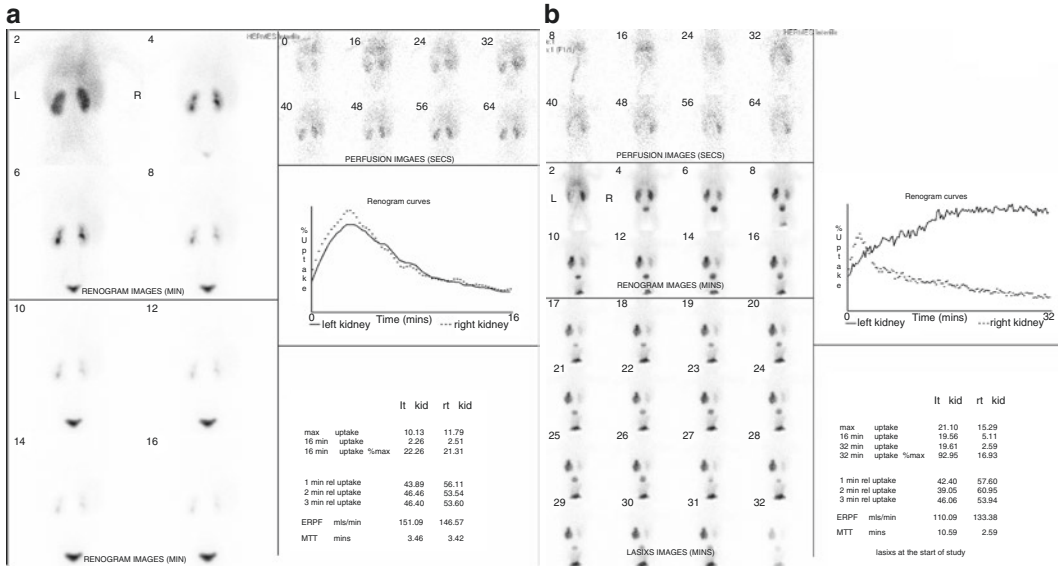


Fig. 10.55 Normal MAG 3 (**a**) shows symmetrical perfusion of the kidneys (top right), prompt bilateral tracer accumulation and excretion (left images), and smooth renogram curves. MAG 3 in PUJO (**b**) demonstrates reduced perfusion to the left kidney, delayed tracer accumulation, and delayed excretion into a dilated renal pelvis. Note the abnormal renogram curve on the left with increasing tracer uptake, compared to the smooth normal curve of the right

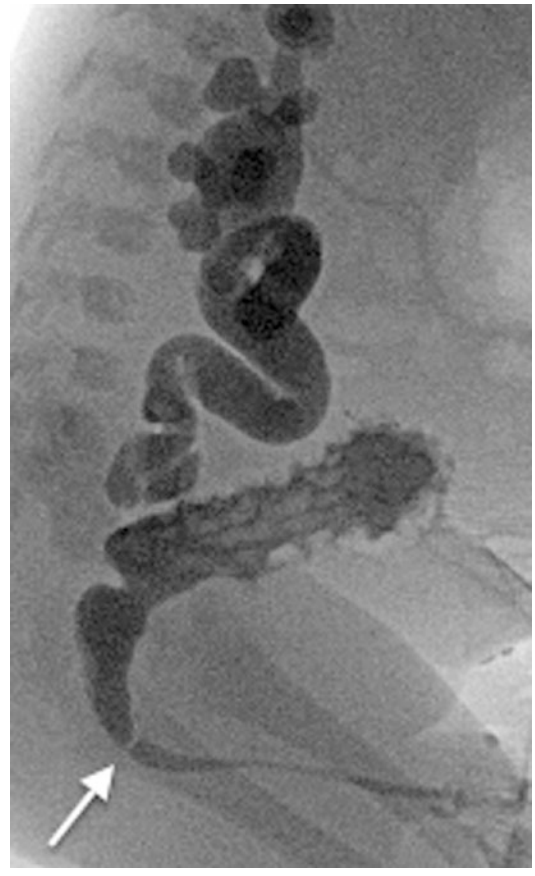


Fig. 10.56 Posterior urethral valves. Selected lateral image from the MCUG demonstrates an enlarged, trabeculated bladder. There is dilatation of the posterior urethra, and a linear filling defect at the point of calibre change consistent with a valve. There is resulting unilateral reflux

10.13 The Neonate with a Scrotal Swelling

Ultrasound with a high frequency linear transducer is the mainstay of imaging the swollen scrotum/inguinal region, with colour Doppler optimized to display low flow velocities in the testis. Power Doppler may also helpful in neonates, as this has higher sensitivity to low blood flow and is independent on the direction of flow, however its usefulness is limited due to increased movement artefact.

The neonate is scanned supine. Each hemiscrotum is scanned in turn in the longitudinal and transverse planes, including each testis and epididymis, and each the spermatic cord which is traced from the scrotum proximally through the inguinal canal. The normal neonatal testis is seen as a well-defined ovoid structure of intermediate echogenicity. A surrounding echogenic line represents the tunica albuginea. An internal hyperechoic line represents the mediastinum testis. The head of the epididymis is seen superiorly as a pyramidal structure of similar echogenicity to the testis, the body and tail are thin and long, extending along the longitudinal axis of the testis. The appendix testis, and the epididymal appendages may also be visible on ultrasound in the neonate. In the longitudinal plane the spermatic cord is seen as a linear hyperechoic structure, running from the inguinal canal to the scrotum.

The common neonatal scrotal pathologies include hydrocoele, hernia and torsion. Trauma, infection and neoplasm (germ cell tumour) are rare at this age. More unusual causes of neonatal scrotal swelling due to intra-abdominal pathology and a patent processus have been reported in the literature and should be considered when clinical and imaging findings are atypical. Neonatal adrenal haemorrhage presenting as a swollen scrotum is rare but well recognized [69] and a mass of calcified meconium may be present in the scrotum in association with meconium peritonitis [70], a condition which has also been described on antenatal ultrasound and in which ultrasound can avoid unnecessary surgical intervention [71]. It follows that any unusual appearances in the scrotum on ultrasound should prompt careful interrogation of the abdomen.

Abdominal radiographs taken for other clinical reasons can reveal scrotal abnormalities. The inguinal regions should be carefully examined on the neonatal plain radiograph as focal lucency over this region is suggestive of an inguinal hernia. Fine curvilinear calcification of the scrotal region can indicate meconium peritonitis. A soft tissue density mass may indicate scrotal haematoma or incarcerated hernia.

10.13.1 Hydrocoeles

In neonates, hydrocoeles are usually congenital due to a patent processus vaginalis. These are well demonstrated on ultrasound as anechoic fluid collections, surrounding the testis, which may extend upto the inguinal canal. A hydrocoele of the cord resulting from closure of the processus above the testis is seen as a fluid collection contained within the spermatic cord. More rarely an abdominoscrotal hydrocele may be encountered visualized on ultrasound as a large inguinoscrotal hydrocoele extending superiorly through the deep inguinal ring into the abdominal cavity (Fig. 10.57).

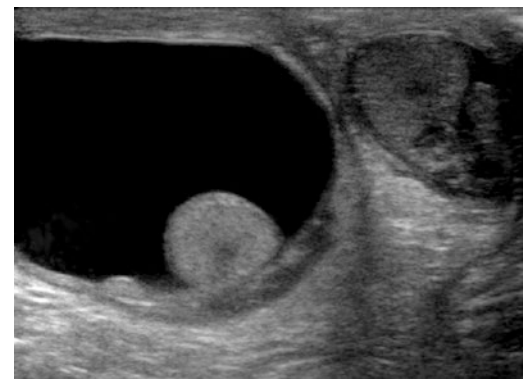


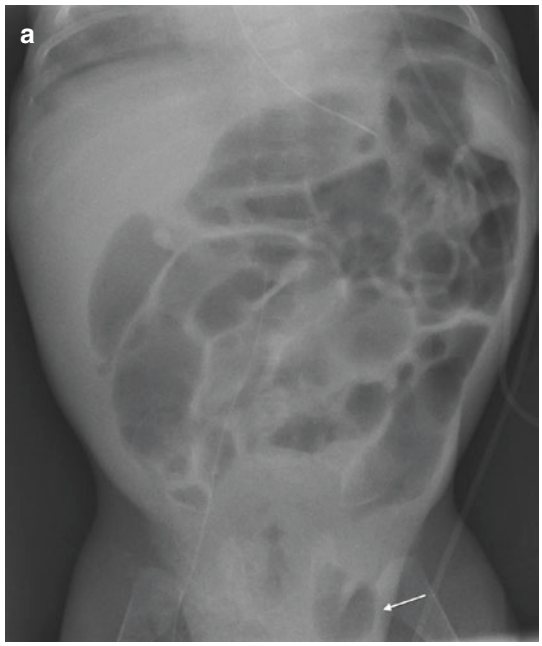
Fig. 10.57 Hydrocoele. Ultrasound demonstrates a right hemiscrotum filled with homogenous hypoechoic fluid consistent with a simple hydrocoele

10.13.2 Hernia

Although usually this diagnosis can be made clinically, ultrasound is helpful in case of the acute scrotum, or where the clinical findings are atypical. On ultrasound, fluid or gas filled bowel loops are seen to fill the hemiscrotum. Peristalsis of the involved loops can be captured. An aperistaltic loop is suggestive of a strangulated hernia and Colour Doppler can be employed to try and assess vascularity of the involved bowel [72]. Highly echogenic omentum may be identified in the scrotum or inguinal canal. There is a high incidence of synchronous and metachronous contralateral inguinal hernias, particularly in neonates and premature infants, and the contralateral side should be interrogated to exclude synchronous inguinal hernia [73]. Careful interrogation of the inguinal regions on the plain film of a neonate with distension and multiple distended loops of bowel may reveal a knuckle of herniated bowel (Fig. 10.58).

10.13.3 Testicular Torsion

Testicular torsion in neonates is usually extravaginal. This is torsion occurring proximal to the attachment of the tunica vaginalis. This often occurs prenatally, presenting as a swollen discoloured hemiscrotum after birth and can be mistaken for haematoma due to birth trauma [74]. Appearances of the testis may be normal, particularly if scanned at the hyperacute stage. In the acute phase marked enlargement of the affected testicle with heterogeneity in echogenicity can be seen. Subtunica fluid may be present. Linear hypoechoic striations extending radially from the mediastinum testis may be present. A twist of the spermatic cord may be evident at the superficial ring, though difficult in neonates. A reactive hydrocoele may be present [75]. Absent or reduced blood flow may be demonstrated with colour Doppler ultrasound, though colour Doppler signals are sometimes difficult to obtain in the neonate and comparison of flow with the unaffected side is required [72]. Increased scrotal wall vascularity on the affected side is also an



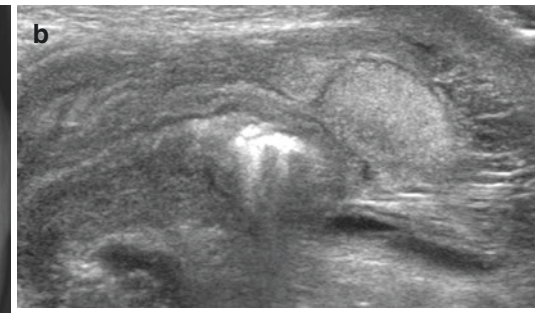


Fig. 10.58 Inguinal hernia. Plain radiograph (**a**) in a neonate with an inguinal mass demonstrates lucency in the left groin at the periphery of the image, consistent with a herniated bowel loop. Ultrasound (**b**) confirms the presence of herniated bowel along the inguinal canal into the left hemiscrotum

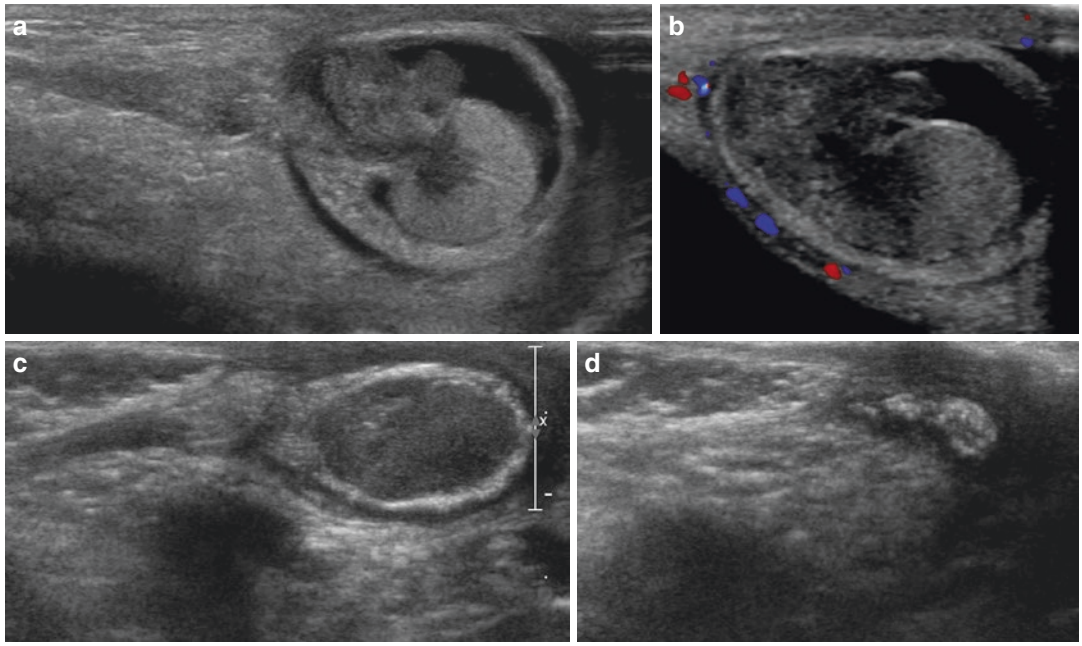


Fig. 10.59 Testicular torsion. Ultrasound images (**a** and **b**) in a neonate with an acutely swollen scrotum reveal an enlarged heterogeonous testis. The mediastinum testis is relatively hypoechoic with radiating striations, whilst the surrounding parenchyma is echogenic. Colour Doppler demonstrates peripheral flow but no flow within the parenchyma of the testis. Another case, image (**c**) shows curvilinear hyperechogenicity of the tunica, suggestive of calcification, and hypoechogenicity of the parenchyma. The appearances are suggestive of a chronic torsion. The contralateral testis in this case was atrophic and heavily calcified (**d**) in keeping with a previous torsion on the contralateral side also

indicator of infarction and necrosis. It is important to note however that some patients with early torsion will have a normal exam, and the presence of Doppler flow cannot exclude intermittent torsion-detorsion (Fig. 10.59a, b).

More chronic or prenatal torsion may be identified by a normal sized heterogeneous testis with peripheral hyperechogenicity, followed by atrophy of the testicle with further peripheral and internal hyperechogencity in keeping with calcification of the tunica albuguinia and testicular parenchyma. A complex hydrocoele is common [74, 75] (Fig. 10.59c, d). Torsion of the testicular appendages is rare in the neonate.

10.13.4 Infection

This is a rare entity in neonates, but conditions such as posterior urethral valves, and imperforate anus predispose the neonate [72]. Usually the epididymal head is involved, appearing enlarged and either hyper or hypoechoic. Similar changes in the testis suggest co-existing orchitis. Increased vascularity is noted.

10.14 Urogenital Anomalies

10.14.1 Congenital Obstruction of the Genital Tract and Cloacal Anomalies

A cloacal malformation should be suspected in a female infant with an imperforate anus, single perineal orifice and normal abdominal wall. Cloacal dysgenesis is associated with other genitourinary malformations including renal agenesis, multicystic dysplastic kidney, and renal ectopia, in addition to other manifestations of VACTERL

(Vertebral, Anorectal, Cardiac, Esophageal, Renal, Limb) syndrome. Early imaging is important to confirm the diagnosis and detect associated anomalies, and should not be delayed. Ultrasound is most useful to demonstrate renal tract obstruction, hydrocolpos and associated genitourinary anomalies. Plain radiography of the abdomen and pelvis may demonstrate bowel obstruction and calcified masses, due to admixture of urine and meconium; abnormal connection with bowel may be indicated by the presence of air within the bladder or vagina. There may also be signs of sacral agenesis and vertebral segmentation anomalies.

10.14.2 Disorders of Sexual Differentiation (DSD)/ Ambiguous Genitalia

Ultrasound imaging is of major importance in the initial assessment of a newborn infant with ambiguous genitalia, to determine the location and morphology of the gonads and whether a uterus is present. Ultrasound is most useful in the early neonatal period, when the persisting effects of maternal hormone stimulation result in relative prominence of the uterus and ovaries, and ovarian follicles may be present, helping to distinguish between ovaries and testes. High resolution ultrasound of the perineum and labial folds may be helpful in identifying the presence and nature of ectopic gonads.

Ultrasound of neonates with ambiguous genitalia requires special expertise, but is generally easier to obtain and provides superior anatomical resolution to MRI, which is limited by the very small size of the key abdominal structures and lack of well defined fat planes.

Ultrasound of the adrenals may also be helpful in the immediate postnatal period, when the adrenals are normally easily visualised. Congenital adrenal hyperplasia is an autosomal recessive disorder in which there is complete or partial deficiency of one of the enzymes involved in the synthesis of steroid hormones. Glucocorticoid deficiency stimulates secretion of adrenocorticotrophic hormone (ACTH) by the anterior pituitary, resulting in adrenal hyperplasia and excessive production of adrenal androgens. Enlargement of the adrenals may be identified on ultrasound in about 50% of cases. The adrenal cortex is enlarged relative to the medulla, and in some cases the enlarged adrenal cortex has a lobulated, convoluted, "cerebriform" appearance.

Genitography may also be used in the early postnatal period. Injection of water soluble contrast into the perineal openings under fluoroscopic control can demonstrate the configuration of the urethra and the presence of any abnormal connection between the genital tract, bladder, and bowel. This may confirm the presence of a vagina and cervix, and help to elucidate more complex malformations, for example by demonstrating the length and configuration of a common channel, such as a urogenital sinus.

10.15 Increasing Head Circumference, Suspected Hydrocephalus and Intracranial Haemorrhage

Cranial ultrasound is usually the first line modality for brain imaging in the neonatal period. The anterior fontanelle provides a window that allows high resolution imaging of the brain to be achieved with suitably designed high frequency, small footprint transducers. Image quality and field of view may be limited by the size of the anterior fontanelle, but in most neonates cranial ultrasound is sufficient to exclude hydrocephalus. Cranial ultrasound can be performed with portable scanners on preterm and unstable babies in the neonatal intensive care unit, and has become routine for monitoring babies at risk of intracranial complications, such as germinal matrix haemorrhage, hypoxic-ischaemic brain injury, and hydrocephalus. Cranial ultrasound can also diagnose major cerebral malformations and vascular abnormalities such as vein of Galen malformations (Fig. 10.60).

Small, portable ultrasound devices are now widely available and can be used successfully by practitioners from many different disciplines, but

appropriate supervised training is essential to achieve competency. A thorough knowledge of the ultrasound appearances of the normal brain in the preterm and term neonate, an understanding of normal variants, and experience of a wide range of pathology are essential for safe practice. Meticulous and careful technique and acquisition and secure storage of standard images are important. Care must be taken with the amount of pressure applied, as bradycardia may be induced by excessive pressure.

MRI provides images of the whole of the brain in multiple planes, with no limitation of the field of view. This makes MRI more sensitive that

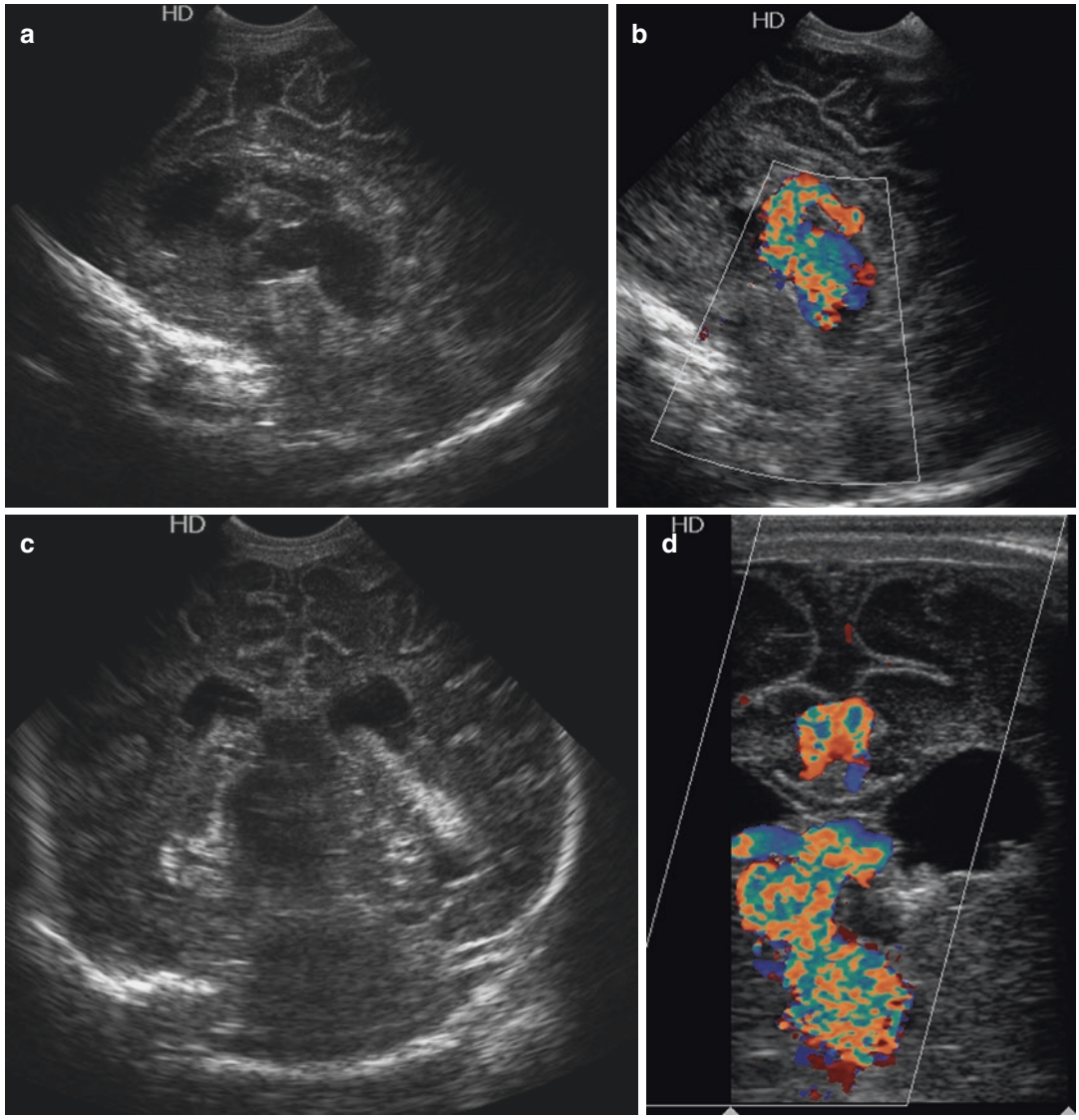


Fig. 10.60 Vein of Galen malformation. (**a**) Grey scale and (**b**) colour Doppler sagittal and coronal (**c** and **d**) ultrasound images demonstrate a hypoechoic structure in the midline which demonstrates marked colour flow. Non-contrast axial CT brain (**e**) demonstrates the highly attenuating markedly dilated vessel and prominent venous sinuses. Single sagittal image from a cerebral angiogram (**f**) demonstrates early filling of the vein of Galen which is dilated, as are the draining falciform, sagittal and straight sinuses. Post procedure radiograph (**g**) demonstrates the embolisation coils in situ

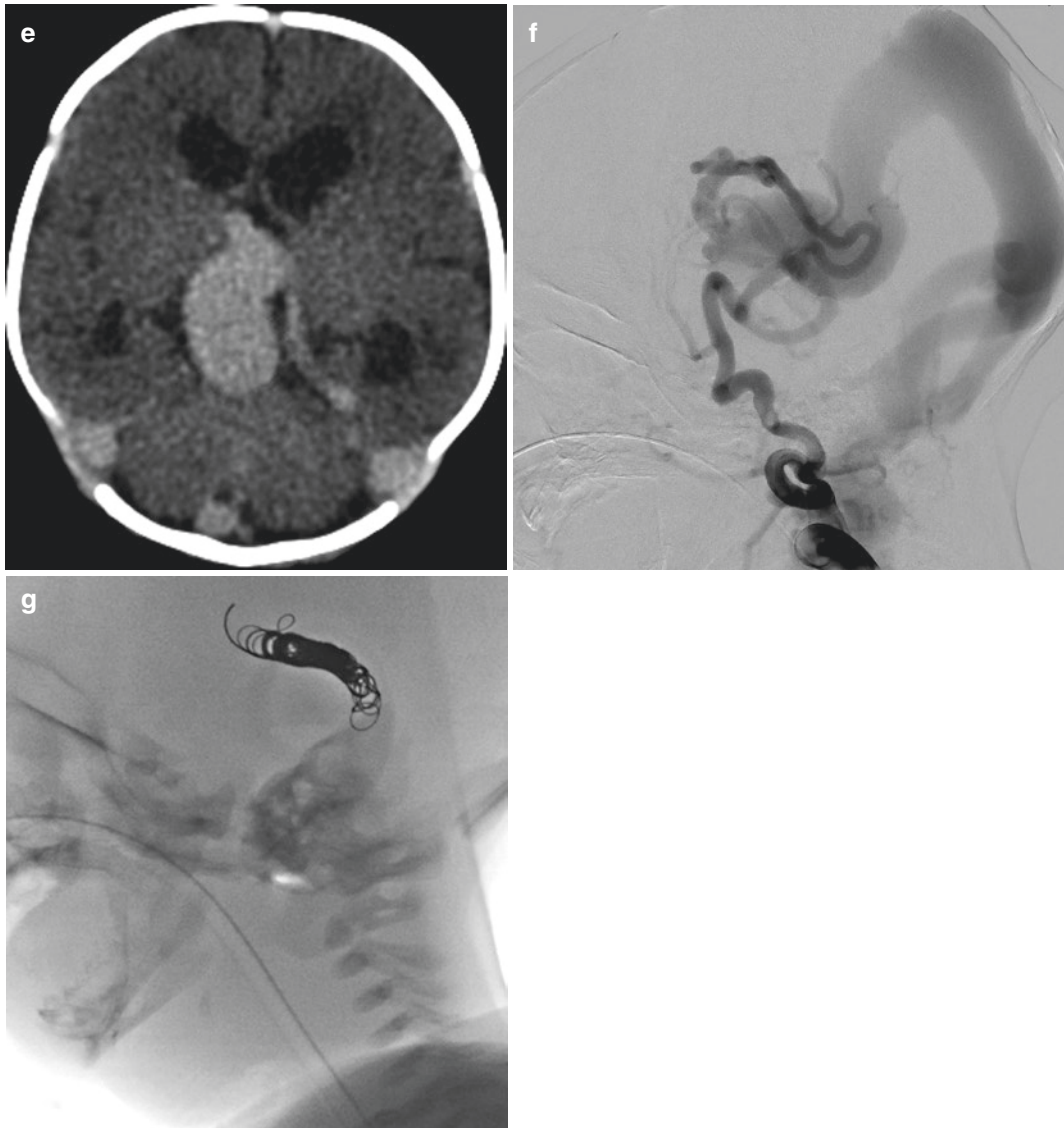


Fig. 10.60 (continued)

ultrasound for demonstrating subdural and extradural collections. High contrast resolution makes MRI more suitable for demonstrating subtle structural abnormalities and hypoxic ischaemic injury to the basal ganglia, thalami and cerebral cortex. MRI is used in preference to CT whenever possible, because of the better contrast resolution, multiplanar capability and avoidance of exposure to ionizing radiation. However, the acquisition time for a CT brain scans is much shorter (30 seconds or less with modern CT scanners), and so CT is sometimes more appropriate for urgent imaging in sick and unstable neonates. Volume CT and MRI scans can be used for image guided neurosurgery such as ventricular shunt insertion for hydrocephalus.

10.16 Suspected Spinal Dysraphism/Sacral Dimple

Isolated sacral dimples and small sacral pits are commonly found in newborn infants. Radiological investigation is usually not necessary for typical

midline sacral dimples lying in a low position, less than 25 mm from the anus [76]. Investigation is necessary for lesions that are large (more than 5 mm), away from the midline, or in a high position (more than 25 mm from the anus), lesions discharging fluid, or those associated with other markers of spinal dysraphism such as a hairy patch or vascular birthmark. Imaging of the spine is also indicated in neonates with imperforate anus and urogenital anomalies.

Ultrasound is the first investigation of choice, supplemented by MRI when ultrasound is abnormal or equivocal, when there are neurological signs, or when there is a discharging lesion. Tethering of the spinal cord can be recognised on ultrasound when the conus of the spinal cord lies below the level of the L2 vertebral body. Thickening of the filum terminale can also be recognised (> 2 mm at the L5-S1 level), and a lipoma or dermoid lesion may be identified within the lumbosacral spinal canal (Fig. 10.61).

In young infants, a high definition ultrasound scan can provide images of the spinal cord and the lumbosacral spinal canal with equal or better spatial resolution than MRI, but once spinal dysraphism or a tethered cord has been diagnosed, MRI can provide visualisation of the whole of the spinal cord, spine, sacrum and paravertebral tissues, to help exclude associated abnormalities such as syringomyelia. MRI is also valuable to evaluate the full extent and complexity of overt spinal dysraphism and dorsal dermal sinuses [77].

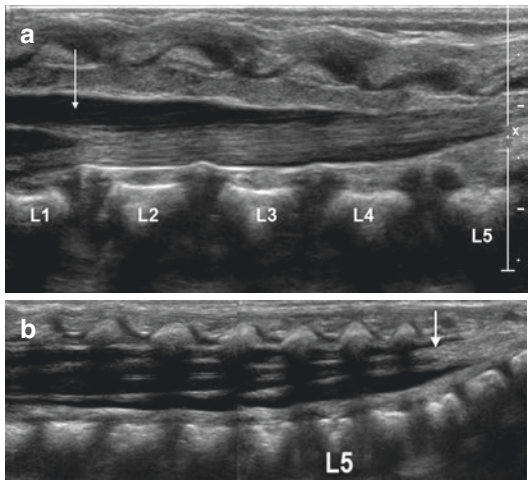


Fig. 10.61 Spinal ultrasound. (**a**) normal spinal ultrasound. Ultrasound images of the normal spine demonstrate cord terminating at a normal level (*arrow*) with a normal appearance to the conus. The nerve roots of the cauda equina are lying dependant in the canal (baby is in the prone position), with no evidence of a thickened filum. (**b**) Tethered cord. Longitudinal ultrasound images of the abnormal spine show a very low lying conus (*arrow*) and hyperechoic canal contents distal to this. The appearances of tethered cord with filar lipoma were confirmed on MR

10.17 The Neonate with a Neck Swelling

Ultrasound is ideally suited to the examination of superficial lesions of the head and neck in infants. As well as characterizing any abnormal structures ultrasound is very effective at confirming the presence of normal neck structures, particularly the thyroid and salivary glands. However, ultrasound is limited in the assessment of deep lesions and some anatomical locations are not easy to visualise. Ultrasound cannot penetrate bone and air, and so ultrasound may fail to demonstrate deep extension of lesions around the skull base, cervical spine, pharynx and trachea. MRI is often complementary to ultrasound in these situations. However, MRI does not offer the same capability for real time imaging that ultrasound can provide; imaging times are relatively long, and the images are easily degraded by movement artifact.

10.17.1 Congenital Cystic Lesions of the Neck

10.17.1.1 Thyroglossal Duct Cysts

The thyroid gland develops in the floor of the primitive pharynx, descending from the tongue through the floor of the mouth, anterior to the developing hyoid bone, to reach its final location in the neck by the seventh week of gestation. The thyroglossal duct connects the gland to the tongue during migration and normally involutes by the end of the tenth week of gestation. The foramen caecum on the tongue is the site of the original

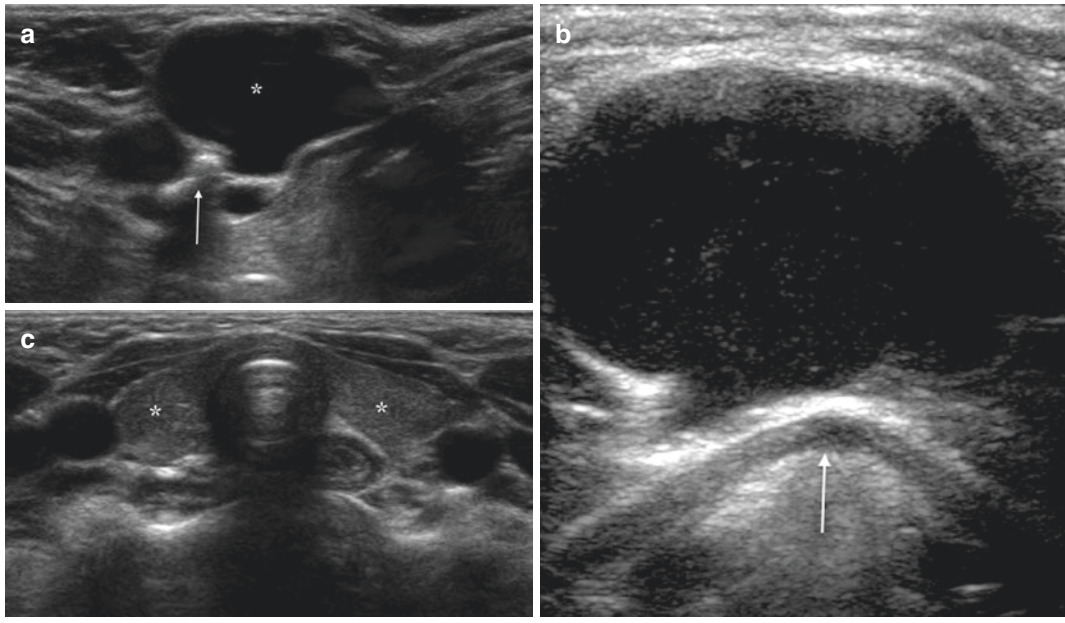


Fig. 10.62 Thyroglossal duct cyst. Longitudinal ultrasound image (**a**) reveals a midline hypoechoic cystic lesion (*), closely related to the hyoid bone (*arrow*), in keeping with a thyroglossal duct cyst. The transverse image (**b**) again confirms the relationship to the hyoid. Ultrasound image (**c**) confirms the presence of a normal thyroid (*), essential to demonstrate to avoid inadvertent excision of a lingual thyroid

opening of the duct. Persistence of any part of the thyroglossal duct may result in a cyst, but can also lead to sinus or fistula formation.

Clinically a thyroglossal duct cyst usually presents as an anterior neck mass in or near the midline. It may become infected and present with acute enlargement. On ultrasound the cyst may appear anechoic, hyperechoic or heterogeneous due to the presence of proteinaceous material (Fig. 10.62). The cyst may be complex, containing septations, and can be very mobile.

10.17.1.2 Lymphatic Malformations

Lymphatic malformations consist of fluid-filled cystic structures, formed from lymphatic vessels which fail to connect with normal drainage pathways. The lesions may be unilocular or multilocular, and there is a wide variation in the size of the individual cysts. Lymphatic malformations may be macrocystic or microcystic. Microcystic lymphatic malformations (previously known as lymphangiomas) consist of multiple tiny cysts within a solid matrix; macrocystic lymphatic malformations (cystic hygromas) may be very large and exert significant mass effect on adjacent structures. Both types may undergo rapid enlargement as a result of haemorrhage or infection.

Lymphatic malformations may occur at any anatomical location except in the central nervous system, but the neck, axilla and mediastinum are the commonest sites. Cervical lymphatic malformations are associated with trisomy syndromes, Turner syndrome, Noonan syndrome, and fetal alcohol syndrome. Soft tissue lymphatic malformations may be associated with overgrowth of adjacent skeletal structures, particularly in the craniofacial region.

Ultrasound in macrocystic lymphatic malformations characteristically reveals large, thin walled, fluid-filled cystic spaces, which may contain internal septations. If there has been recent haemorrhage or infection, mobile echogenic debris may be visible. The cysts may be mobile but are usually not compressible. Colour Doppler typically shows only sparse blood vessels around the walls of the cysts (Fig. 10.63a–c). Microcystic lymphatic malformations are shown to consist of multiple tiny cysts, sometimes at the limit of ultrasound resolution, within a densely echogenic solid

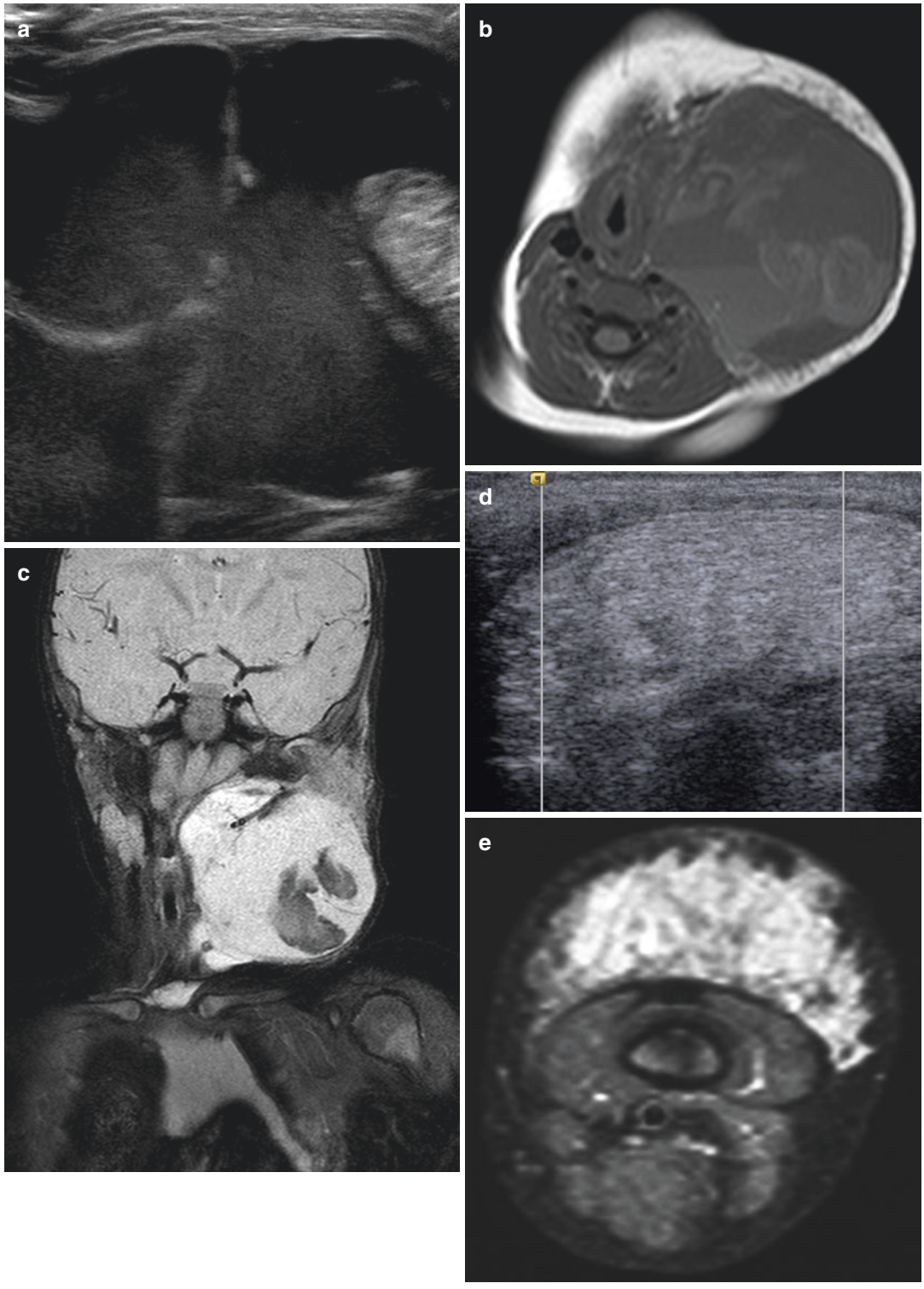


Fig. 10.63 Lymphatic malformations. Macrocystic lesion (**a**–**c**) demonstrates large avascular cystic spaces on ultrasound, with fluid-fluid levels and internal debris noted on the axial T1 and coronal T2 weighted MR images. Microcystic lesion (**d** and **e**) is depicted by a hyperechoic lesion on ultrasound, due to the presence of multiple small echogenic cystic walls, and high signal abnormality on the T2 STIR sequence

matrix. Grey scale ultrasound appearances may be similar to those of a proliferative haemangioma, but colour Doppler shows that a microcystic lymphatic malformation is much less vascular and lacks the high density of small vessels typically seen in a proliferative haemangioma (Fig. 10.63d, e).

MRI is the optimal modality for assessing the deep extension of lymphatic malformations in areas which are not accessible to ultrasound; for example, deep to the carotid and jugular vessels, into the retropharyngeal region and upper mediastinum.

Macrocystic lymphatic malformations can be surgically resected but they can also be effectively treated with sclerotherapy. A sclerosant agent such as doxycycline or sodium tetradecyl sulphate can be injected into the cystic spaces after percutaneous aspiration. Sclerotherapy is not usually performed in the neonatal period, unless the lesion is very large, symptomatic, or causing potentially dangerous compression of vital structures.

10.17.1.3 Branchial Cysts

Branchial cleft anomalies may take the form of cysts, sinuses with an external opening to the skin surface, or fistulae which have both cutaneous and internal openings. Cysts tend to present in older children or young adults, whereas sinuses and fistulae are often noticed in the neonatal period. The abnormalities are bilateral in 2–3% of cases and can be familial.

First branchial cleft abnormalities occur in the region between the external auditory meatus, the parotid gland and the submandibular triangle. They may present clinically with recurrent inflammation in the region of the ear or angle of the mandible. The cyst may be superficial or deep to the parotid gland.

Second branchial cleft anomalies are the commonest, accounting for 90% of all branchial abnormalities. 75% of these are cysts, which are usually located in the anterior triangle of the neck, along the line of the anterior border of the sternomastoid muscle, anterolateral to the internal jugular vein and carotid artery, and lateral to the thyroid. A fistula passes from the tonsillar fossa to the supraclavicular region of the neck, with the ostium lying just above the clavicle. On imaging, a second branchial cleft cyst typically displaces the sternomastoid posteriorly, and its contents may be anechoic, or contain debris (Fig. 10.64).

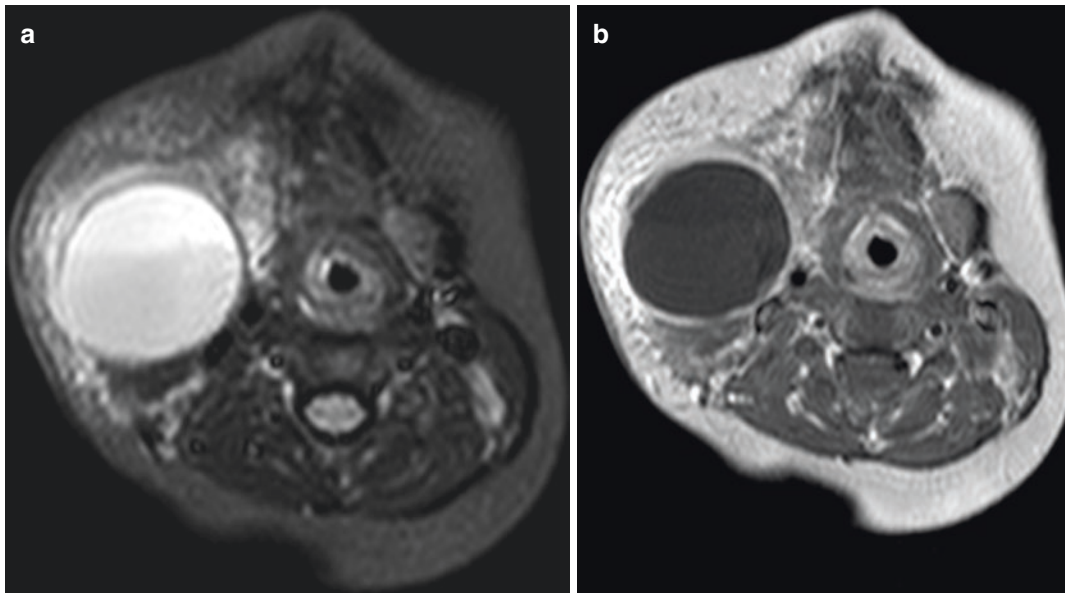


Fig. 10.64 Branchial cleft cyst. Axial T1 post gad and T2 weighted imaging demonstrates a well defined cystic mass with rim enhancement, containing fluid-fluid layers, in the right carotid space, closely related to the sternomastoid muscle

Third and fourth branchial cleft abnormalities are rare. They may present in childhood or adult life and mainly occur on the left side. Third branchial cleft cysts lie posterior to the carotid artery and sternomastoid muscle. In fourth branchial cleft anomalies, only sinuses have been reported; they run a very long course into the mediastinum and are associated with ectopic parathyroid glands and parathyroid adenomas.

10.17.1.4 Dermoid Cysts

Dermoid cysts, which are composed of ectoderm and mesoderm, can be found in the head and neck. Ultrasound of dermoid cysts typically shows a hypoechoic structure with well-defined walls, containing echogenic elements due to the presence of fat or calcification. Cranial lesions often related to cranial sutures (Fig. 10.65). Lateral and medial margins of the orbit are also common sites. Midline cranial lesions in particular require careful investigation to exclude intracranial extension. Ultrasound is valuable in initial assessment but further imaging with CT or MRI is often necessary.

Dermoid cysts also occur in the neck, typically in the midline above the hyoid, but sometimes between the hyoid and the isthmus of the thyroid. Lesions in this location may be difficult to differentiate from thyroglossal cysts, but dermoid cysts tend not to show movement with the tongue. Dermoid cysts can also occur adjacent to or within the thyroid.

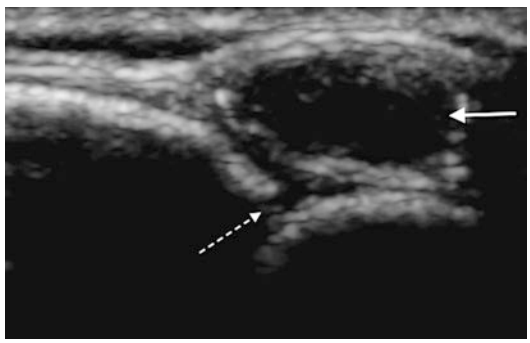


Fig. 10.65 Dermoid cyst. Ultrasound demonstrates a well demarcated focal cystic lesion (*solid arrow*) closely associated with the underlying cranial suture (*broken arrow*)

10.17.1.5 Thymic Cysts

The thymus descends from the third pharyngeal pouch, following which the thymo-pharyngeal duct that normally involutes completely. Remnants of the duct or possibly cystic degeneration may result in the presence of a thymic cyst. Two thirds of these present in the first decade and they usually present as a swelling in the lower third of the neck laterally. Although the cysts are usually unilocular and hypoechoic, they may be mulitilocular and if they bleed can contain echogenic fluid. In 50% of cases there is mediastinal extension and it may be possible to demonstrate continuity with the thymus on ultrasound.

10.17.2 Jugular Varix

Jugular varix (jugular vein ectasia) is a common venous malformation, which presents as a bluish neck swelling in infants due to dilatation of the external or internal jugular vein. It may enlarge alarmingly when the child cries or strains, but is usually of no clinical significance, and becomes less prominent with age. Ultrasound examination is often reassuring, revealing simple dilatation of the jugular vein with turbulent flow, but no evidence of venous obstruction or thrombosis and no other significant vascular abnormality (Fig. 10.66).

10.17.3 Benign Sternomastoid Tumour of Infancy (Fibromatosis Colli)

Benign sternomastoid tumour of infancy is characterised by diffuse or focal enlargement of the sternomastoid muscle, typically first recognised at 2–8 weeks after birth. It is often associated with a history of birth trauma, suggesting that it may be caused by haematoma formation followed by healing with fibrosis. However, associations with hip dysplasia and tibial torsion suggest that some cases may be caused by abnormal fetal position in utero. Shortening of the muscle may cause torticollis. Spontaneous resolution usually occurs over a period of

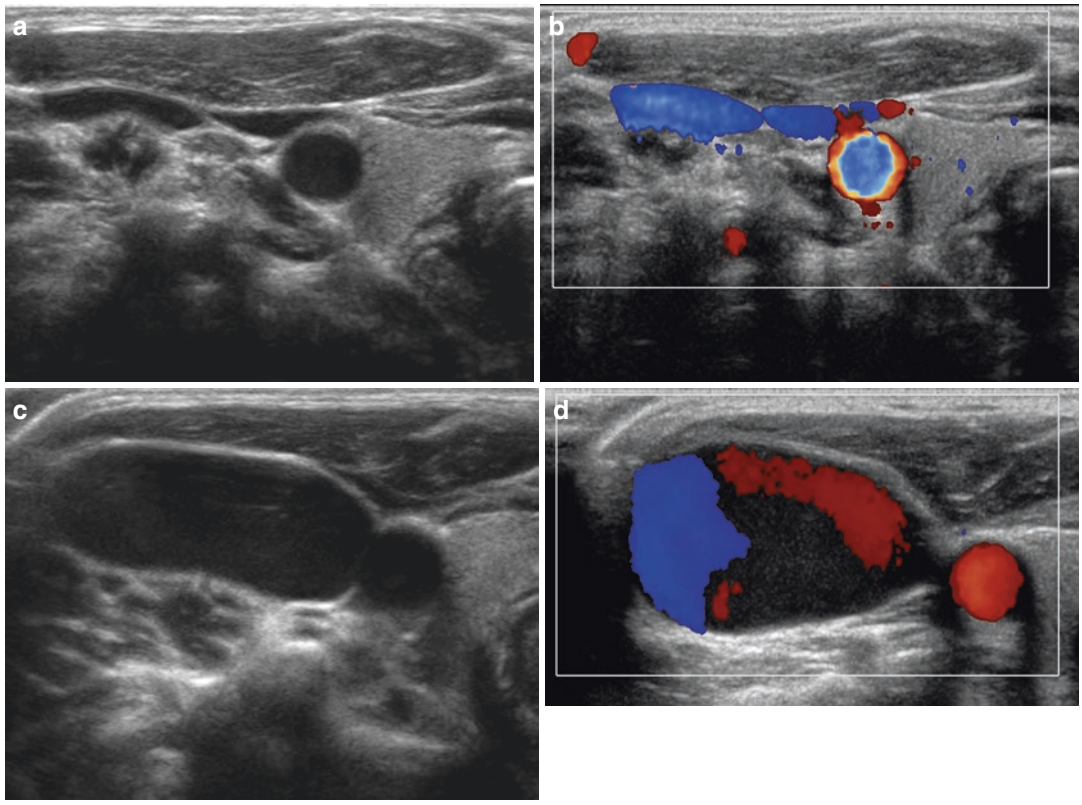


Fig. 10.66 Jugular varix. Grey scale and colour Doppler ultrasound images of the jugular vein (**a**–**d**) demonstrates marked dilatation with Valsalva consistent with varix/ectasia in a child presenting with a neck mass on crying

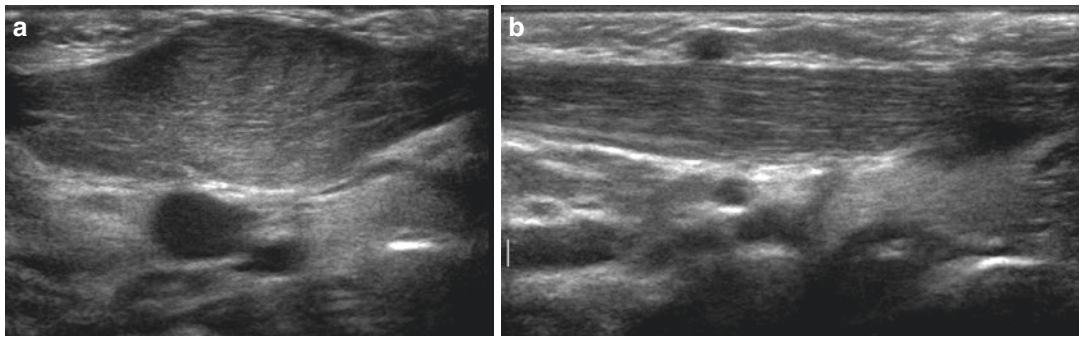


Fig. 10.67 Fibromatosis colli (benign sternomastoid tumour of infancy). Longitudinal grey scale ultrasound image of the sternomastoid shows a smooth fusiform swelling of the muscle belly (**a**), compared with the normal contralateral side (**b**)

4–8 months, and may be helped by physiotherapy, but some cases require surgery for persisting torticollis. Severe, untreated cases may result in strabismus, facial asymmetry and plagiocephaly.

Ultrasound shows a well-defined mass within the belly of the muscle, which is usually isoechoic or slightly hypoechoic in comparison with normal muscle, but may be hyperechoic (Fig. 10.67). Calcification may be visible.

Sometimes there is diffuse enlargement of the whole of the muscle [78].

10.18 The Neonate with a Superficial Vascular Birthmark or Soft Tissue Swelling

10.18.1 Proliferative Haemangiomas (Common Infantile Haemangiomas)

These benign vascular tumours may occur at any site but seem to have a particular predilection for the parotid region. Superficial cutaneous lesions are easily recognised as typical "strawberry naevi", but deeper lesions may cause diagnostic difficulty. Proliferative haemangiomas usually appear shortly after birth, although some cutaneous manifestation may be visible at birth in up to 40% of affected children. These lesions undergo a proliferative phase of rapid growth, becoming raised, bulky but soft, compressible lesions with a characteristic strawberry-red colour. Following a few weeks of proliferation and growth, they typically enter a phase of stabilisition lasting for several months, followed by a phase of involution. The rate of regression is variable; 50% enter the phase of involution by 5 years of age, and 90% by the age of 9 years. The prognosis for cosmetic outcome is not universally favourable; even after involution, some residual abnormality is present in 20–40% of cases, including telangiectasia, increased or decreased pigmentation, thinning of overlying skin and persisting fibrofatty masses.

Proliferative haemangiomas occur more frequently in girls than in boys, and there is a significant association with prematurity. Systemic haemangiomatosis is a condition in which multiple cutaneous and visceral haemangiomas occur; although this condition is rare, it is usually recommended that infants with five or more cutaneous lesions should have an abdominal ultrasound scan to exclude hepatic or splenic lesions.

Haemangiomas usually only require treatment if they cause secondary problems such as airway or vision obstruction or difficulty with feeding. Although eventual stabilisation and regression can be expected, proliferative haemangiomas may cause significant symptoms. Ulceration, bleeding and secondary infection may occur, particularly in peri-oral lesions. Large lesions close to the eye and airway may have disastrous consequences. In the young infant, permanent visual impairment may occur if the eye is occluded for more than 1 week; a large proliferative haemangioma on the eyelid therefore requires urgent investigation and treatment. Similarly, lesions involving the oropharynx, larynx or trachea may rapidly progress to cause airway obstruction, and require prompt intervention. Intra-lesional steroids, systemic steroids or propranolol are effective methods of inducing involution. Surgery is rarely required.

Imaging is not usually necessary for typical cutaneous proliferative haemangiomas, but it can be very valuable in determining the extent of particularly large lesions and those at dangerous sites. If the nature of the lesion is not certain on the basis of its clinical features, ultrasound and colour flow imaging may be helpful in showing a typical appearance of a well defined, solid, echogenic mass which is intensely vascular, containing a high density of small vessels with high blood flow velocity (Fig. 10.68). However, appearances change as the lesion undergoes stabilisation and regression. The lesions become relatively less vascular, and the residual vascular spaces enlarge as the solid components regress. In the past, lesions with these appearances were sometimes described as "cavernous haemangiomas".

Some haemangiomas are present at birth and show differing patterns of biological behaviour; the rapidly involuting congenital haemangioma (RICH) regresses spontaneously, whereas the non-involuting congenital haemangioma (NICH) does not.

Rarer vascular tumours, such as Kaposiform haemangioendotheliomas and tufted haemangiomas are much more serious and may cause a severe coagulation disorder due to platelet consumption (Kasabach-Merritt syndrome). The characteristic clinical features of Kasabach-Merritt Syndrome are an enlarging soft tissue mass associated with a severe systemic bleeding

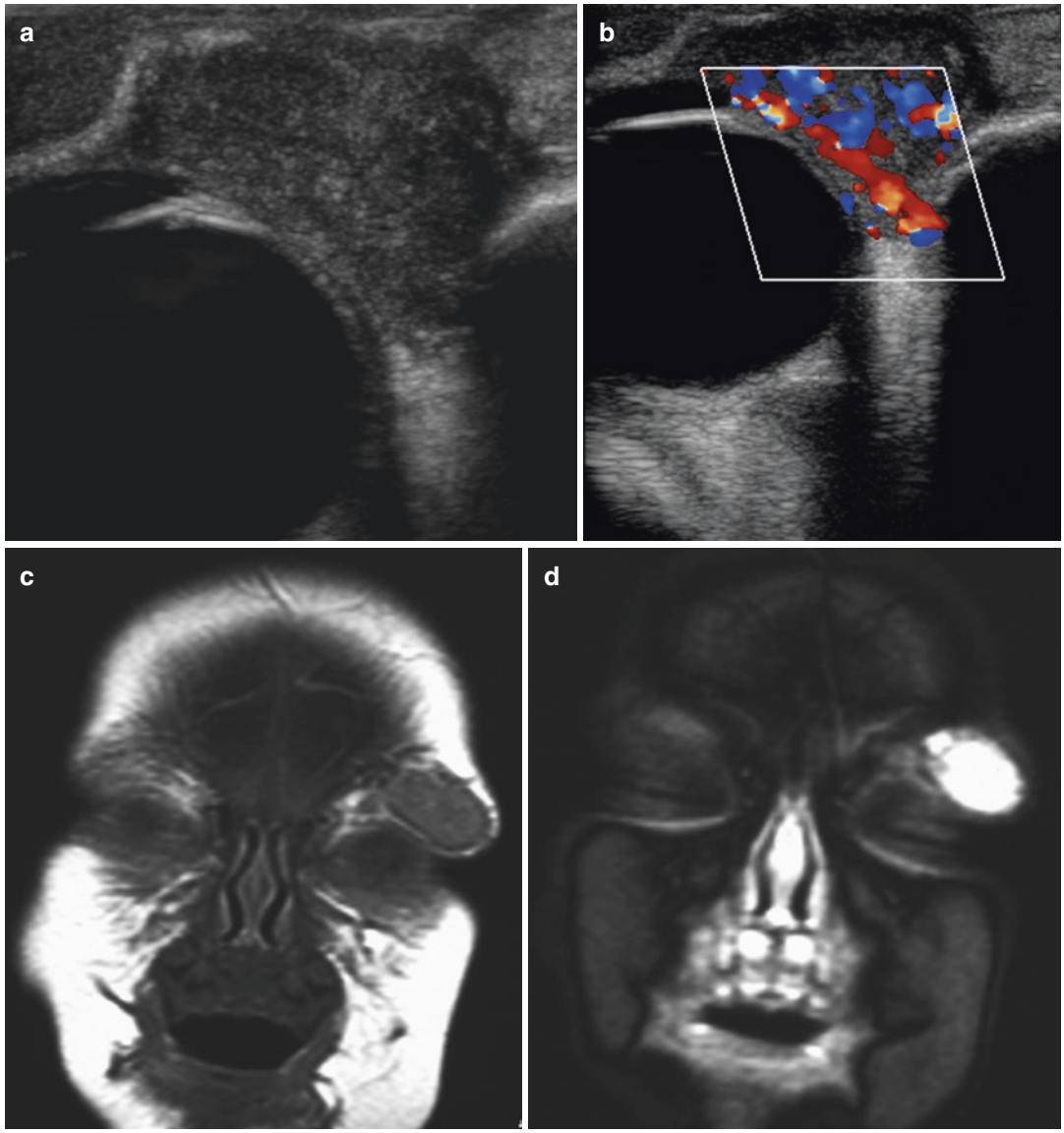


Fig. 10.68 Proliferative haemangioma. Grey scale (**a**) and colour Doppler (**b**) ultrasound demonstrates a highly vascular mass at the lateral aspect of the eyelid extending posteriorly into the orbit. On MR this is of intermediate T1 (**c**) and high signal on the T2 STIR (**d**)

disorder and marked reduction in platelet count, which may be impossible to correct by platelet transfusion (Fig. 10.69). On ultrasound they are seen as ill defined soft tissue masses with variable echogenicity. Calcifications may be present which are never present in infantile/proliferative haemangiomas. MR imaging shows a heterogenous lesion with mainly intermediate or low signal on T1-weighted sequences and high signal on T2-weighted sequences, with subcutaneous stranding. Gradient echo sequences may show signal voids due to the presence of haemosiderin.

These lesions are initially managed medically with platelet transfusion and systemic treatment with steroids or vincristine, but in critical cases with life-threatening platelet consumption, interventional radiology may be life-saving. Embolisation of the tumour can control

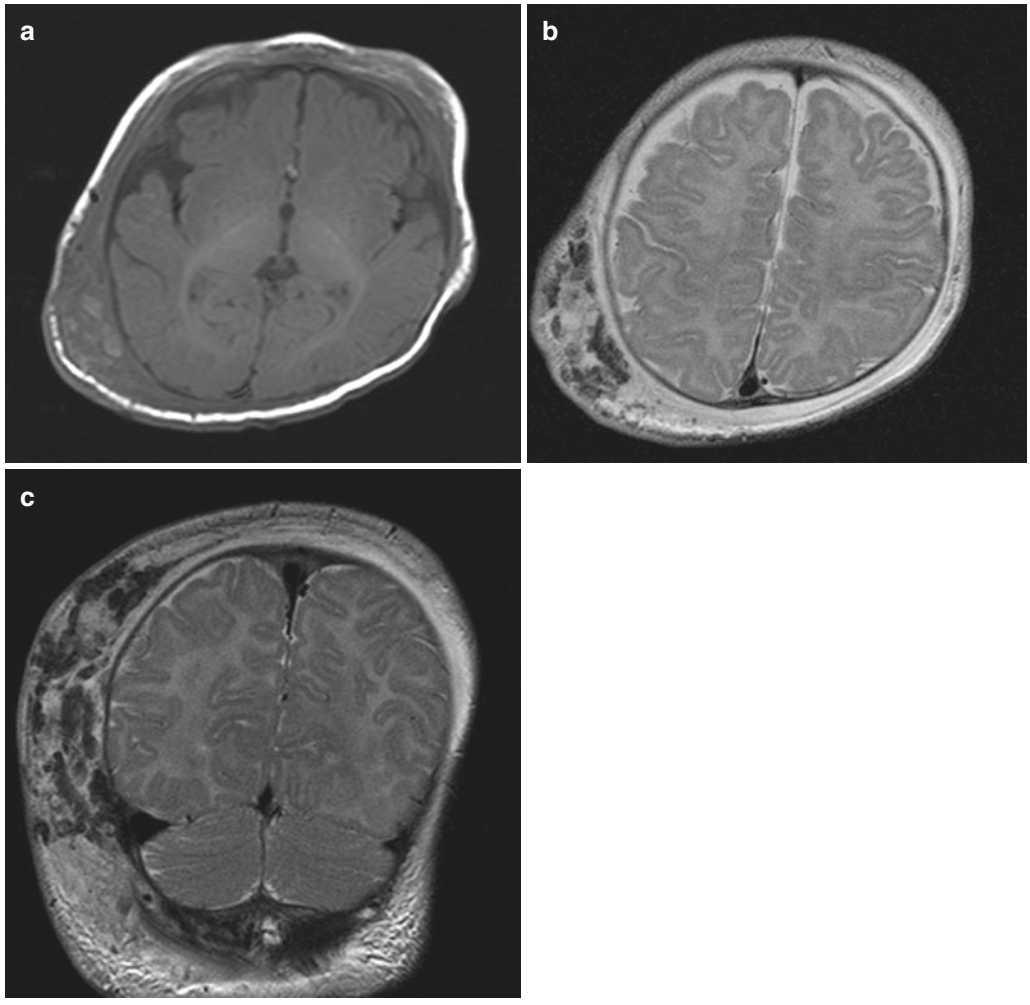


Fig. 10.69 Kaposiform haemangioendothelioma presenting with Kasabach-Merrit syndrome. Axial T1 (**a**) and axial (**b**) and coronal (**c**) T2 weighted images demonstrate extensive heterogenous soft tissue abnormality in the right parieto-occipital area with internal flow voids

platelet consumption acutely and allow time for chemotherapy to take effect.

10.18.2 Vascular Malformations

Venous malformations are congenital hamartomatous lesions, which do not grow by cellular proliferation in the same way as haemangiomas, and do not spontaneously regress. The lesions may become more or less apparent with body habitus, particularly becoming more apparent initially with neonatal weight loss prior to full feeds and then apparent regression with eventual weight gain. Venous malformations are varied and complex; some patients have diffuse malformations involving both deep and superficial systems, whereas others have localised or segmental abnormalities. Localised, superficial lesions have characteristic clinical features; they are bluish in colour, and there is no local increase in skin temperature. They are easily compressible and typically increase in size on Valsalva manoeuvre. However, deeper lesions are impossible to assess fully on clinical criteria alone, and are often much more extensive than initially expected.

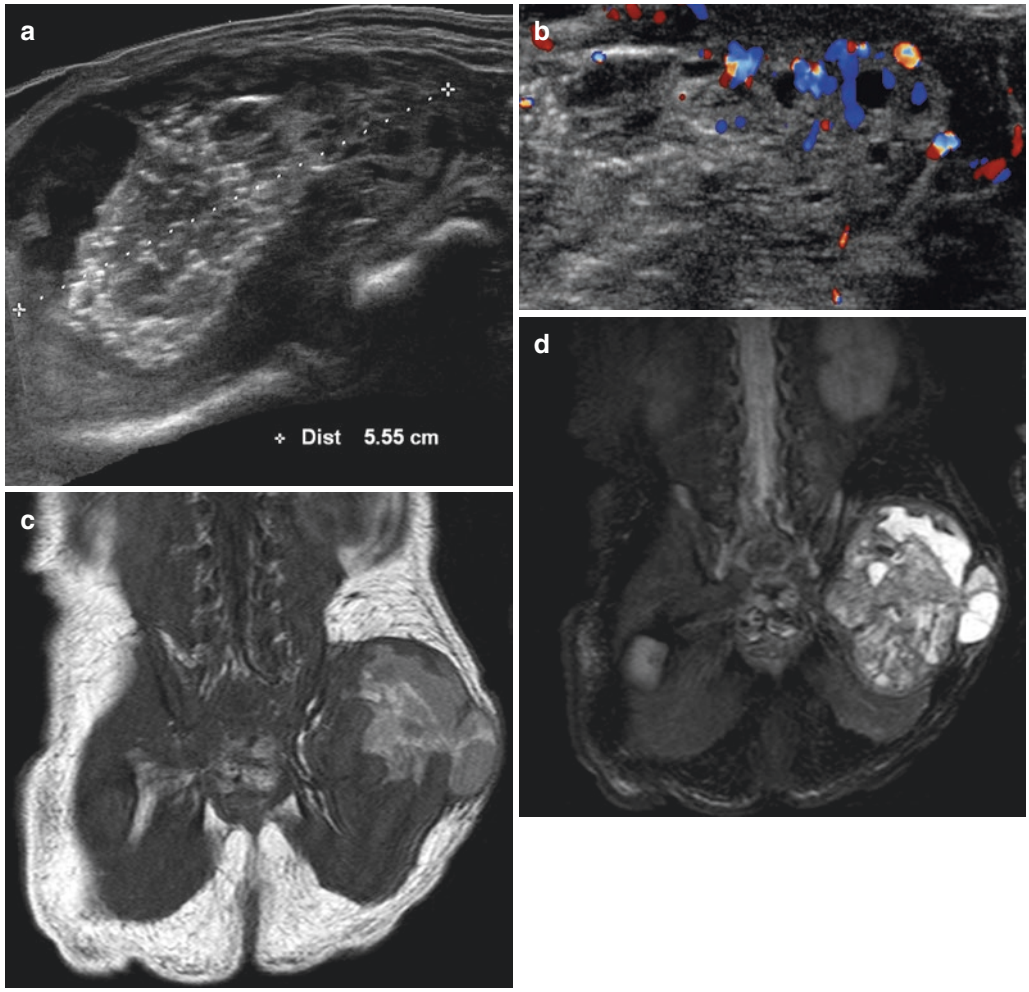


Fig. 10.70 Venolymphatic malformation. Neonate presenting with buttock swelling increasing in size. Panoramic grey scale (**a**) and colour Doppler ultrasound images (**b**) show heterogenous mass within the soft tissues, marked with calipers, with cystic spaces and vascular elements. T1 (**c**) and T2 fat suppressed (**d**) coronal MR images demonstrate a heterogenous partly solid partly cystic soft tissue mass

Grey scale ultrasound reveals the vascular spaces as hypoechoic structures. Varicosities, stenoses, complex interconnecting channels and venous lakes are typical. Colour flow imaging shows slow, turbulent flow within dilated, compressible vascular spaces (Fig. 10.70). Colour Doppler US shows that these lesions consist mainly of dilated vascular spaces and the spectral waveform is consistent with a low flow, low pressure lesion. Phleboliths may be seen on plain film or on ultrasound, and are typical of venous malformations.

Arteriovenous malformations are also hamartomatous, consisting of a network of abnormal vascular channels comprising both feeding arteries and draining veins. Clinically, high flow vascular malformations present as a soft tissue mass with cutaneous discolouration, locally increased temperature and palpable arterial pulsation. Arteriovenous malformations tend to be present at birth, and to grow in parallel with the growth of the child, although some lesions manifest unpredictable, aggressive growth. However, arteriovenous malformations may progressively enlarge as a result of increasing blood flow and arteriovenous shunting. Skin ulceration and uncontrollable haemorrhage may occur, and large lesions may result in high-output cardiac failure.

Ultrasound is helpful in confirming the vascular nature of the lesion and demonstrating high velocity blood flow.

Vascular malformations rarely require treatment in the neonatal period, unless control of serious complications is necessary. Venous malformations can be treated with percutaneous sclerotherapy, under imaging guidance. Sclerotherapy is often effective in controlling symptoms, and can be performed as frequently as is required. Arteriovenous malformations can be extremely difficult to treat effectively. Trans-arterial embolisation may be necessary to control haemorrhage or cardiac failure.

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Anaesthesia for Neonatal Surgery

11

Richard E. Sarginson and Sanaulla K. Syed

Abstract

Neonatal anaesthesia has evolved considerably over the last two decades. New agents and techniques have been widely adopted by paediatric anaesthetists, allowing a renewed emphasis on minimizing, or avoiding, periods of post-operative ventilation and sedation.

The newer drugs include remifentanil, an "ultra-short" acting opioid, the local anaesthetic agent levo-bupivacaine, the volatile anaesthetic agent, desflurane, and sugammadex, a relaxant reversal agent. There is also a better understanding of the pharmacology of the more established drugs.

Techniques include a variety of local and regional blocks, often aided by better needles and ultrasound imaging. Ultrasound guidance has also enabled more accurate and rapid vascular access. A number of devices and instruments have enlarged the repertoire of airway management techniques available to paediatric anaesthetists, including the laryngeal mask airway, micro-cuff endotracheal tubes and small fibre-optic bronchoscopes. Forced air warming devices have proved effective in preventing hypothermia.

Keywords

Anaesthesia • Pharmacology • Newborn surgery

11.1 Introduction

Neonatal anaesthesia has evolved considerably over the last two decades [1, 2]. New agents and techniques have been widely adopted by paediatric anaesthetists, allowing a renewed emphasis on minimizing, or avoiding, periods of post-operative ventilation and sedation.

The newer drugs include remifentanil, an "ultra-short" acting opioid, the local anaesthetic agent levo-bupivacaine, the volatile anaesthetic agent,

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_11

desflurane, and sugammadex, a relaxant reversal agent. There is also a better understanding of the pharmacology of the more established drugs [3].

Techniques include a variety of local and regional blocks, often aided by better needles and ultrasound imaging. Ultrasound guidance has also enabled more accurate and rapid vascular access. A number of devices and instruments have enlarged the repertoire of airway management techniques available to paediatric anaesthetists, including the laryngeal mask airway, micro-cuff endotracheal tubes and small fibre-optic bronchoscopes. Forced air warming devices have proved effective in preventing hypothermia [2].

Overall, the survival rates of surgical neonates have continued to improve. However, there are also some clouds on the horizon. Concerns have been raised about the possible occurrence of neural toxicity induced by anaesthesic agents in human neonates. Larger cohorts of paediatric anaesthetists and intensivists are now employed in most institutions, following changes in medical working practices. Individual clinicians may face difficulty in acquiring and maintaining sufficient exposure to rare conditions and technical procedures. Continuity of care is affected by shift working patterns, particularly amongst trainees.

The dramatic improvements in neonatal care of recent decades have also resulted in difficult ethical dilemmas, particularly the wisdom of the treatment of severely malformed or damaged babies. There can also be crises in the availability of neonatal surgical beds in any particular regional centre during conditions of peak demand.

We aim to provide a current perspective of neonatal anesthesia for a largely surgical readership in this chapter. Neonatal anatomy and physiology are covered in detail elsewhere in this volume. We start by reviewing the available drugs and techniques for general and regional anaesthesia. We look at some general aspects of perioperative management of neonates, including vascular access. The anaesthetic management of number of specific conditions is then considered, particularly those situations where close cooperation is needed between the surgeon and anaesthetist. We focus our attention mainly on conditions in the domain of "general" paediatric surgery. However, we also consider the impact of co-existing congenital heart disease or airway abnormalities found in a proportion of babies with congenital defects such as diaphragmatic hernia, oesophageal atresia, exompahalos or craniofacial syndromes. Finally, we discuss some current controversies and ethical questions in our field.

11.2 History

Specialist neonatal anaesthesia evolved in the post war period in large regional paediatric centers with neonatal surgical units. The local configurations varied, depending on the location of maternity and neonatal paediatric units. In Liverpool, by the late 1960s, Stead and Nightingale could report institutional figures for 3000 neonatal operations over a 20-year period, during which only ten *intra-operative* deaths had occurred [4]. These results were based on a technique originally described by Jackson Rees [5, 6], incorporating intubation, muscle relaxation with D-tubocurarine, controlled ventilation by hand using a T-piece and the use of nitrous oxide ± halothane and morphine. Emphasis was also placed on maintenance of temperature, careful fluid management and close clinical monitoring, using an amplified oesphageal stethoscope, brachial blood pressure and clinical assessment of the quality of the pulse, heart sounds and perfusion. Regional techniques and analgesia regimens received rather less attention until the 1980s. Babies capable of resuming spontaneous respiration were subsequently managed on the neonatal surgical unit and babies requiring ventilation either went to the Paediatric Intensive Care Unit (PICU) or were returned to Neonatal Intensive Care Unit (NICU) in a Womens Hospital 3 miles away. Remarkable progress was made with a limited repertoire of drugs and monitoring equipment and a high level of clinical observation and experience.

The majority of neonates still require general anaesthesia for surgical procedures, including intubation, muscle relaxation and artificial ventilation. Some lower limb and groin operations can

be performed under spinal or caudal block. The need for pre or post-operative ventilation remains a consideration in the choice of technique. The timing of some procedures needs careful thought and discussion. In the following section we survey of the pharmacology of the common anaesthetic drugs now used in neonates.

11.3 Pharmacology in the Neonate

The population defined as "neonates" encompasses babies varying in weight from 500 g to 5 kg and 24–44 weeks post conceptual age (PCA). Postnatal age (PNA) varies from a few hours to 20 weeks. The "ex premie" infant of greater than 44 weeks PCA, with various persisting morbidities, is often included in "neonatal" pharmacological studies, trials and discussions.

Consequently, anaesthetists are faced with a heterogeneous "neonatal" group, with considerable variation in body habitus, organ function maturation, congenital malformation and disease processes, all of which may affect the pharmacodynamics and pharmacokinetics of anaesthetic drugs.

11.4 General and Developmental Pharmacology

Pharmacodynamics (PD) is the science of the dose response relationship in the body [3, 7]. This is often described in terms of the blood concentration required to achieve a target effect. Although this relationship is reasonably well established for some drugs, such as muscle relaxants, it remains poorly understood for many other anaesthetic agents. In part, this is due to the problem of understanding and measuring the desired theraputic effects of particular anaesthetic agents. For example, general anaesthetics, such as propofol or volatile agents, are used to induce "unconsciousness", a state that is difficult to define or measure in neonates. Many general anaesthetic agents are less effective for other desirable effects, such as providing analgesia or obtunding the stress response. Other agents, such as opioids or regional blocks, are used in combination with general anaesthetic agents to achieve these aims. This is often referred to as balanced anaesthesia. Anaesthetic drugs and combinations also have side effects, such as inducing hypotension, which also have PD aspects [3].

Pharmacokinetic (PK) theory is used to describe and predict the effects of processes, such as plasma protein binding, metabolism and renal elimination, on the time course of the blood concentration of a drug in the body. Typically, this involves the use of somewhat abstract compartment models. The aim is to determine the various components of the model in particular patient populations. These include the volume of distribution, clearance and various rate constants. For neonates, adjustment of PK models is needed in relation to size and the maturation of physiological functions, such as glomerular filtration rate (GFR). Fat free mass may be a better measure of size than total body weight for predicting GFR and drug clearance [3]. The relationship between postmenstrual age (PMA) and GFR has been well described [8]. The maturation of the clearance of drugs such as morphine and paracetamol can be estimated with reasonable accuracy from the PMA [7].

11.5 Allometric Scaling

Several theorists have attempted to interpret the available data relating size to metabolic rate, typically measured by oxygen consumption [9]. Rubner (1883) found that the metabolic rate depended on the surface to volume ratio, $M^{2/3}$, where M is the body mass. Kleiber (1932) reported that basal metabolic rate scaled with $M^{3/4}$ in mammals over a wide range of size. West and colleagues sought to explain a universal ¾ "power" scaling law on the basis of a model where the energy costs of vascular transport are minimized. However, doubt has recently been cast on the concept of such a

universal scaling law [10, 11]. It appears that the exponent value for M ranges between 2/3 and >3/4, depending on the species and the size range under study and the metabolic conditions. Many drug-dosing calculations are currently based on surface area calculations. Allometric scaling theory may be useful in predicting variables such as oxygen consumption and GFR. It remains to be seen which scaling model will best explain specific drug PD and PK data in relation to size.

11.6 Pharmacogenetics and Pharmacogenomics

Pharmacogenetics is defined as the study of genetic variations which give rise to different responses to drugs between individuals. Examples from anaesthesia include the rare variant of pseudocholinesterase that results in the prolonged action of suxamethonium and the variant in ryanodine receptors associated with malignant hyperthermia. Although some patients will have a family history of the relevant condition, few neonates will have undergone tests, an exception being the long QT syndromes.

Pharmacogenomics is wider in scope, incorporating genome-wide studies to identify pathophysiological processes invoving many genes. Most work in this field has been concerned with the profiling and detection of disease. Developmental pharmacogenomic studies explain some of the inter-individual variation in many drugs metabolized by Cytochrome P450 enzymes [7, 12].

11.7 Inhalational Agents

Volatile inhalational agents continue to have a prominent place in neonatal anaesthesia [13]. The use of nitrous oxide has waned over the last 20 years. Sevoflurane has replaced Halothane as the main inhalational induction agent. It has more of the desirable characteristics of an ideal agent, being relatively non-irritant in the airway, potent due to a high lipid-gas solubility, and rapidly absorbed and eliminated due to the low blood gas solubility (Table 11.1). The other commonly used volatile agents, at least for maintenance of anaesthesia, are Isoflurane and Desflurane [14, 15].

Neonates have a higher alveolar ventilation and lower functional residual capacity than older children and adults. They also have a higher cardiac output and greater perfusion of vessel rich tissues, all factors leading to a more rapid wash in of inhalational anaesthetics in early life. The minimal anaesthetic concentration (MAC) is used to describe anaesthetic vapour potency. This is the concentration at which half of the subjects will move in response to a surgical stimulus. The MAC for Halothane, Isoflurane and Desflurane is low in premature neonates, peaks at 1–6 months and then gradually falls as age increases. A different pattern has been found for Sevoflurane, with neonates having MAC values more similar to infants. During the maintenance phase of anaesthesia, inhalational agents will commonly be used in combination with either an opioid or regional block, which both reduce the MAC value. In

Table 11.1 Physicochemical properties of Inhalational anaesthetics

	Halothane	Isoflurane	Sevoflurane	Desflurane	Xenon
BP (°C)	50.2	48.5	58.5	23.5	−108
MAC (%) in O_2	0.89	1.52	3.3	9.16	71
MAC (%) in N_2O	0.36	0.92	2.5	7.33	NA
B-G	2.4	1.4	0.75	0.45	0.14
O-G	224	98	80	29	1.9
Odour	Non irritant	Irritant	Non irritant	Pungent	0dourless
% Metabolised	20	0.2	3.5	0.02	<0.01

BP boiling point, °C; *MAC* minimum alveolar anaesthetic concentration; *B-G* blood-gas partition coefficient; *O-G* oil-gas partition coefficient

practice, there is considerable variation in the response to volatile agents and a degree of dose titration is necessary at various stages of surgery.

11.8 Nitrous Oxide

Nitrous oxide (N_2O) has analgesic properties but is insufficient by itself to guarantee lack of awareness during anaesthesia, particularly where muscle relaxation removes motor responses from the patient. N_2O also displaces nitrogen from enclosed airspaces, which can result in gas volume expansion of trapped air in the gut, peritoneum, emphasematous lobes or venous air emboli. It also inhibits vitamin B_{12} synthesis, which can result in anaemia and possibly polyneuropathy if it is administered repeatedly or for long time periods. It is still used by some anaesthetists as a carrier gas, which reduces the MAC values of volatile agents. It is also has a role, typically in the form of "Entonox" (a 50:50 O_2-N_2O mixture), for procedural analgesia, for example during chest drain removal.

Although nitrous oxide had a major role during the development of neonatal anaesthesia, the short acting potent opioid, remifentanil, has largely replaced it for major neonatal surgery. In common with many developments in the evolution of anaesthetic practice, no large scale randomized controlled trial (RCT), with appropriate outcome measures, has been done to test the claimed advantages of remifentanil over nitrous oxide. N_2O is implicated in the occurrence of neuro-toxicity in neonatal experimental rats and monkeys. It is likely that its use may drop further, although it probably will continue to have a niche for smoothing gas induction and procedural sedation.

Xenon has low blood gas solubility and can be used for anaesthesia with minimal cardiovascular side effects, albeit with a MAC value of 70% in adult volunteers. It is expensive and is under investigation for neuroprotection in asphyxiated infants.

11.9 Intravenous Agents

A number of drugs are used for the induction and maintenance of anaesthesia, sedation during mechanical ventilation on PICU and "procedural" sedation [16]. From a historical perspective, thiopentone has been largely replaced by propofol. Ketamine has undergone a recent re-evaluation and renaissance, particularly as an analgesic agent in subanaesthetic doses. Intravenous agents, for example propofol, midazolam, ketamine or dexmedetomidine can be used for maintenance of anaesthesia as an altenative to volatile agents, although this is not a common approach in neonates.

11.9.1 Thiopentone

Thiopentone is a highly lipid soluble barbiturate derivative, with a rapid onset of action. The initial offset and recovery after a bolus dose is largely governed by redistribution. Metabolism in the liver is capacity limited and the relevant enzymes become saturated during thiopentone infusions, resulting in very slow elimination. The effective induction dose in neonates (ED50) is in the region of 3 mg/kg, less than in older infants (Table 11.2). Thiopentone has anticonvulsive properties and is effective in reducing intracranial pressure and cerebral oxygen consumption. Thiopentone use in babies has waned relative to propofol or sevoflurane induction, probably due to the better recovery profiles for the latter agents. However, there are circumstances where it should still be considered, particularly in babies with neurological conditions resulting in seizures or raised intracranial pressure.

Table 11.2 Effective dose definitions

• ED_{50}: dose at which 50% of the population or sample manifests a given effect
• ED_{90}: dose at which 90% of the population or sample manifests a given effect
• ED_{max}: dose at which maximal response to a given drug is reached

11.9.2 Propofol

Propofol is an alkylated phenol, which is soluble in lipid but not water. It has a large volume of distribution, rapid redistribution and rapid elimination. The prompt offset and recovery, together with a low incidence of nausea and vomiting, have made propofol the main agent for intravenous induction and total intravenous anaesthesia in paediatric outpatient surgery. It is formulated in an oil-water emulsion. It can induce significant degrees of hypotension, mainly due to vasodilation, and a period of apnoea after a standard induction dose. The volume of distribution and clearance of propofol are both reduced in neonates, where postmenstrual and postnatal ages are predictors of clearance maturation [17]. It should be used with caution or avoided in hypovolaemic or septic babies, patients with ventricular dysfunction and patients with raised intracranial pressure. In the neonatal ICU setting, there is a recent report of significant hypotension, poorly responsive to fluids, associated with a low dose of propofol (1 mg/kg) used to facilitate endotracheal intubation for surfactant administration in preterm infants of 30 weeks PCA [18]. This has been contested by another group who used 2 mg/kg after atropine administration in a similar group of premature babies [19].

11.9.3 The Propofol Infusion Syndrome

Propofol infusions in children have been associated with a severe illness characterized by lactic acidosis, lipaemic serum, cardiac arrhythmias and failure, multi-organ dysfunction and rhabdomyolysis. Some cases have been fatal, particularly where the problem was not recognized and treated early by stopping the drug and starting haemofiltration. The aetiology is poorly understood but appears to involve impaired fatty acid oxidation [20]. A number of case reports were collated by Bray [21] and subsequently propofol was withdrawn as a sedative agent in neonatal and paediatric intensive care. Most cases occurred where doses of ≥4 mg/kg/h were used for >24 h, although there are sporadic reports of an earlier onset [22]. The use of propofol is largely confined to induction of anaesthesia in neonates, although a case could be made for low dose infusions in combination with remifentanil for limited periods. Further research is needed.

11.9.4 Ketamine

Ketamine is a very lipid soluble N-methyl-D-aspartate glutamate (NMDA) receptor antagonist. The role of ketamine in paediatric anaesthesia and analgesia is still under active investigation [23]. The standard formulation is a racemic mixture of the S+ and R− enantiomers. There is also a S+ ketamine formulation, which has twice the analgesic potency of the mixture and is shorter acting. Ketamine produces a state of "dissociative" anaesthesia and, in contrast to other intravenous anaesthetic agents, analgesia. Ketamine is metabolized in the liver to produce norketamine, which has about a third of the potency of ketamine. Further metabolism results in water-soluble substances excreted by the kidney. Elimination is prolonged in neonates due to immature liver metabolism and renal function.

Ketamine has sympathomimetic and bronchodilator activity. Induction doses of 1–2 mg/kg do not result in hypotension in otherwise healthy patients, although it does have a dose dependent negative inotropic effect on the myocardium.

It can be given intramuscularly (IM) at 4–5 times the intravenous dose. The IM onset of action is within 5 min, in contrast to 1 min IV. The status of ketamine in neonates is a little uncertain. It can be used for induction in cardiovascularly unstable patients and is also used by infusion for analgesia, ICU sedation and as a component of intravenous anaesthesia. It has been used in combination with propofol or dexmedetomidine. The preservative free formulation has also been used as an adjunct to local anaesthetics in the epidural space, typically in "single shot" caudal blocks. However, concerns about potential spinal cord and brain neural toxicity may limit its use in the neonatal population.

11.9.5 Midazolam

Midazolam is a relatively short acting benzodiazepine compared with diazepam and lorazepam. It has dose dependent hypnotic, amnesic and anticonvulsant properties. Midazolam is not used alone as an "anaesthetic" agent but may be used to supplement an opioid during intravenous anaesthesia and is used for intensive care sedation. It is also extensively used in PICU as part of sedation regimens for children and infants undergoing mechanical ventilation. The maturation of midazolam clearance lags somewhat behind the maturation of glomerular filtration rate in the first few months of life [24]. There are a number of concerns about midazolam in neonates, particularly preterm infants [25]. It has been associated with lack of sedation and even seizures, together with poorer neurological outcomes in sedation trials in neonatal intensive care units [26]. This seems to be related to the functional maturation of γ-aminobutyric acid type A ($GABA_A$) receptors, the site of action of benzodiazepines, in early life. The use of midazolam should probably be restricted to the short term or avoided in neonates pending further research.

11.9.6 Alpha-2-Adrenergic Agonists

Clonidine and dexmedetomidine are α-2 agonists with a spectrum of useful sedative and analgesic properties, together with limited cardiovascular and respiratory side effects. Dexmedetomidine is pure α-2 agonist with a shorter adult elimination half-life (2–3 h) than clonidine (12–24 h). However, clearance in neonates is approximately one third of that in adults, which implies that infusion rates to maintain a target effect site concentration should be reduced in the newborn population [27]. Dexmedatomidine is only approved by the FDA for ICU sedation of adults for less than 24 h and is not licenced in the UK. There has been a recent proliferation of "off label" paediatric studies but neonatal data is limited to phase 2/3 studies. It has been used as a sole drug for sedation or in combination with a variety of agents, including ketamine and opioids, as a component of intravenous anaesthesia. Other potential indications include premedication, sedation for procedures such as radiology scans and treatment of sedation withdrawal phenomena [28, 29]. Clonidine has been used as an analgesic adjunct to local anaesthetics in epidural or caudal "single shot" injections or infusions. It has also been used as a PICU sedative agent and to treat opioid withdrawal symptoms. Data on both drugs for various possible neonatal indications is limited and further research is necessary.

11.9.7 Muscle Relaxants

Muscle relaxants are used to enable endotracheal intubation, to maintain muscle relaxation during major surgery in body cavities and occasionally to control severe laryngospasm. Their use has been a major enabling factor in the development of many surgical techniques.

Knowledge of neonatal responses to muscle relaxants is necessary for their effective use in this age group [30]. Acetylcholine receptors (AChRs) cluster to form primitive motor-end plates on muscle fibres from 9 to16 weeks post conceptual age (PCA). The number of nerve terminals is reduced during the second trimester. The neuromuscular junction (NMJ) then matures and continues to grow for the first year of life. The high extracellular fluid (ECF) volume in neonates increases in the volume of distribution for muscle relaxants.

Succinylcholine (suxamethonium) is the only depolarizing neuromuscular blocking agent in clinical use. The rapid onset and short duration of action are unique and desirable features, particularly for emergency cases. Elimination depends on hydrolysis by plasma cholinesterase. Infants require 2–3 mg/kg of succinylcholine to produce reliable conditions for intubation [31]. The increased dose requirement of succinylcholine in younger patients is mainly due to its rapid distribution in the ECF. A deficiency in plasma cholinesterase may result in prolonged neuromuscular block ("sux apnoea") but this is a relatively rare occurrence. Although infants aged less than 6 months have only half the plasma cholinesterase

activity of adults, this does not prolong the effect of succinylcholine.

There is an ongoing debate about the use of succinylcholine. The recent development of sugammadex provides an alternative means of limiting the duration of aminosteroidal nondepolarizing block, albeit currently an expensive one [32].

The clinically available non-depolarizing neuromuscular blocking relaxants (NDR) can be classified into benzylquinolinium or aminosteroidal compounds. Although neonates and infants are more sensitive to NDRs than adults, in terms of requiring a lower plasma concentration to produce a given effect, this is offset by an increased volume of distribution and dose does not vary significantly with age. The increased sensitivity of the neuromuscular junction of the human neonate and infant to NDRs is the result of reduced acetylcholine release from immature motor nerves. Fewer neonatal NMJ receptors need to be occupied to produce block. The effect site compartment concentration of muscle relaxants is less in neonates than older age groups. Different muscle groups have different response curves. The diaphragm requires a greater dose of relaxant to attain a similar degree of relaxation as the adductor pollicis, which is commonly used for monitoring.

11.9.8 Atracurium

Atracurium is a bisquaternary benzylquinolinium diester with an intermediate duration of action. Atracurium is eliminated mainly by Hofmann elimination, a spontaneous fragmentation of the molecule at normal body pH and temperature, which is independent of renal or hepatic function. The ED95 of atracurium was found to be significantly lower in neonates and infants than in children. After 0.5 mg/kg atracurium, 95% depression of twitch occurs more rapidly in neonates than in children (0.9 min vs. 1.4 min), while recovery to 10% of the control twitch height is also more rapid (22.7 vs. 28.6 min). The predictable recovery and lack of accumulation with repeat doses or an infusion of atracurium has made this drug the standard NDR in our neonatal practice over the last two decades.

11.9.9 Vecuronium and Rocuronium

These drugs are popular in situations of cardiovascular instability, due to their virtual absence of side effects. There is also likely to be renewed interest in these agents because their neuromuscular block effects can be rapidly reversed by Sugammadex, even from profound levels of block.

Vecuronium is a monoquaternary aminosteroid relaxant. The ED95 of vecuronium is significantly lower, and the duration of action considerably longer, in neonates than in children aged 3–10 years.

Rocuronium is an analogue of vecuronium with a more rapid onset of action. The ED95 of rocuronium is also lower, and the duration of action longer, in infants than in children. Clinically relevant doses of rocuronium produce a negligible increase in heart rate, with no change in arterial blood pressure.

Other NDMRs have been used in infants, including mivacurium and rapacuronium, but we have no experience of these drugs in our hospital.

11.10 Reversal Agents

Spontaneous recovery from neuromuscular block (NMB) is gradual and shows considerable variation between individuals. The exact time course for onset, duration and recovery in an individual patient is unpredictable and can only be measured by monitoring the clinical response. Residual degrees of block, despite apparent clinical recovery in diaphragm function, can be associated with morbidity, for example upper airway obstruction or aspiration pneumonitis. Atracurium has the most predictable offset of the available NDRs in neonates.

11.10.1 Neostigmine

Neostigmine has been the standard “reversal” agent for non-depolarizing muscle relaxants

for decades. It acts by inhibiting acetylcholinesterase at two binding sites. Acetylcholine levels remain elevated until neostigmine is hydrolysed. However, it has side effects at muscarinic ACh receptors, including bradycardia, hypotension, bronchospasm, increased salivation and gastrointestinal smooth muscle contraction. An anti-muscurinic drug, either atropine or glycopyrrolate, is given with neostigmine to counteract the muscarinic side effects. These drugs also have side effects, such as tachycardia and dry mouth, and "balancing" the muscarinic and anti-muscurinic effects can prove difficult.

Infants show a more rapid recovery from NMB than older children and adolescents when given standard neostigmine doses and there is evidence that lower doses in mg/kg terms are needed to reverse similar degrees of block [33].

11.10.2 Sugammadex

Sugammadex is a relatively new drug, with a "doughnut" shaped molecular structure. It encapsulates molecules of the aminosteroid relaxants, rocuronium and vecuronium, inactivating them. Sugammadex, 2 mg/kg, was sufficient to inactivate a moderate degree of rocuronium induced NMJ block in children [34]. Furthermore, the rate of recovery was rapid, with a narrow range of variation (1.2 ± 0.3 min). This is considerably faster than neostigmine and without any significant side effects. Higher doses of sugammadex (up to 16 mg/kg) can be used to reverse more profound degrees of block. One implication of this is that a rapidly induced neuromuscular block with a large dose of rocuronium can be reversed within a similar time period to the offset of suxamethonium in emergency situations. However, there are a few caveats restricting the current use of sugammadex. There is limited reported clinical experience in the neonatal age group. It is expensive and only inactivates rocuronium and vecuronium. However, the advantages of this drug are such that it is likely to become widely used for aminosteroid NMR reversal unless some unsuspected adverse effect is discovered.

11.11 Opioids and Other Analgesics

The control of pain is a crucial aspect of neonatal anaesthesia and post-operative care [35]. The studies of Anand and colleagues in the late 1980s emphasized the role of effective analgesia on the outcome of major neonatal surgery [36–39]. Opioids have been studied in a number of neonatal settings, ranging from analgesia in post-operative babies breathing spontaneously to procedural pain relief in babies with varying levels of respiratory support in neonatal intensive care units. There is still no consensus on optimal "multimodal" analgesic & sedation regimens, particularly in the neonatal ICU [40].

The main opioids used in our practice are fentanyl, morphine and remifentanil. In recent years, the unique properties of remifentanil have had a major impact on the intraoperative analgesic management of the neonatal surgical population.

11.11.1 Morphine

Morphine is widely used for post-operative analgesia and intensive care sedation. The onset of action in the central nervous system is approximately 5 min, with peak effect at 15 min. The clearance of morphine and its metabolites is prolonged in neonates, the half-life being longest in the preterm infants (9.0 ± 3.4 h) reducing to 6.5 ± 2.8 h at term and 2.0 ± 1.8 h beyond 11 days PNA [37]. The volume of distribution appears to be reasonably constant over early life. Morphine is frequently delivered by a loading dose, followed by an infusion and boluses in a nurse controlled analgesia (NCA) regimen (Table 11.3).

Table 11.3 Intravenous morphine infusion in neonates for postoperative pain relief

Programme	Background	Bolus	Lockout
NCA	0.5 mL/h	0.5 mL	60 min

Dose and programme information
Weight (kg) × 0.2 mg morphine made up to 20 mL in normal saline 10 μg/kg/mL
NCA nurse controlled analgesia
From Acute Pain management guidelines, Alder Hey Children's Hospital

There is considerable inter-individual and intra-individual variation over time in dose requirements during the neonatal period. Consequently, morphine dose guidelines need to be adjusted to account for post conceptual and postnatal age. The pharmacodynamic study of the effects and side effects of morphine and other opioids is difficult in neonates. There seems to be wide range of blood concentrations associated with therapeutic effect, particularly in ventilated pre-term neonates. The effectiveness of morphine in controlling the response to invasive procedures such as endotracheal tube suctioning in ventilated neonates has been questioned [38].

11.11.2 Fentanyl

Fentanyl is a very potent synthetic μ-opioid with high lipid solubility and a more rapid onset of action than morphine. It became popular for the intra-operative management of infants undergoing major surgery, including cardiac surgery, in the 1980s [41, 42]. It is associated with cardiovascular stability and enables the co-administration of lower concentrations of intra-operative volatile or intravenous agent. Fentanyl has also been used for analgesia and sedation in ventilated neonates [43, 44]. Tolerance and withdrawal phenomena both seem to occur within a week, in common with other opioids. However, the dose of fentanyl required for stable intraoperative haemodynamics, control of pulmonary hypertension and blunting of the stress response (≥10 μg/kg) causes profound respiratory depression and will commit the infant to period of post-operative ventilation. In some cases, ventilation is required for non-pharmacological reasons but in other cases can be avoided by the use of alternatives such as remifentanil.

11.11.3 Remifentanil

Remifentanil is a very potent ultra-short acting μ-opioid. It was introduced into clinical practice in 1996, although it only became available in most paediatric institutions somewhat later. It is hydrolysed by non-specific plasma and tissue esterases and its elimination is effectively independent of hepatic and renal function. Esterase function appears to be mature at birth and allometry alone is sufficient to model remifentanil PKs across the paediatric age range [45]. Although remifentanil is not licenced for neonates, many anaesthetists have adopted it as the opioid of choice for intra-operative use in this group [46]. Neonates, including premature babies, tolerate a bolus dose of 1 μg/kg, followed by an infusion in the range 0.1—0.25 μg/kg/min. Higher infusion rates have also been reported. To some extent, the dose rate depends on the doses of other anaesthetic agents used simultaneously, for example sevoflurane, nitrous oxide or propofol [47, 48]. We use a dilution of 10 μg/mL attached to a dedicated line to give remifentanil. The line must be flushed prior to extubation to avoid subsequent inadvertent administration.

Remifentanil has had a major impact on our approach to neonatal anaesthesia in recent years, allowing greater flexibility in timing of regional block procedures and more babies to be extubated at the end of surgery or earlier in intensive care. However, no large scale randomized controlled trials comparing remifentanil-based anaesthetic techniques with other opioid regimens have been done in the neonatal surgical population. There are some smaller trials in babies undergoing procedures in neonatal intensive care, where the rapid dose adjustment and recovery characteristics of remifentanil are very attractive [49, 50].

Other opioids such as sufentanil and alfentanil are also available in some hospitals.

11.11.4 Codeine and Tramadol

Codeine and tramadol are used for mild to moderate pain in children. Codeine is an opioid with a lower affinity for μ-receptors than morphine. It is partially metabolized to morphine by the CYP2D6 enzyme, which is subject to polymorphisms [51]. The maturation of this enzyme is important to the analgesic effect of codeine [52].

In older patients, the analgesic effectiveness of codeine is enhanced by co-administration of paracetamol. The very limited data on neonatal codeine pharmacodynamics and kinetics, together with the unpredictable metabolism of codeine to morphine, suggests that it has little place in neonates.

Tramadol is a synthetic phenyl-piperidine analog of codeine and is a racemic mixture of two enantiomers. The M1 metabolite has a higher affinity for opioid receptors and a longer duration of action. The developmental pharmacology of this drug is complex. M1 formation develops more rapidly with age due to liver enzyme maturation than does GFR dependent elimination in the kidney [53]. A recent trial of tramadol versus fentanyl for near term neonates undergoing gastro-intestinal surgery showed similar postoperative efficacy for both drugs with no specific advantage for tramadol over fentanyl in terms of time to extubation or establishment of feeds [54]. Further research is needed to establish the analgesic role of tramadol in the neonatal population.

11.11.5 Paracetamol

Paracetamol is a mainstay for treatment of mild to moderate pain and has been extensively studied in neonates. Most studies have focused on the pharmacokinetic, rather than pharmacodynamic aspects of paracetamol treatment. An intravenous preparation is now available which enables more extensive peri-operative use. It is currently not recommended for babies with a postconceptual age (PCA) of <32 weeks [55]. The recommended dose is 10 mg/kg 6 hourly between 32 and 44 weeks PCA [56]. An alternative 'Stockholm protocol' is 7.5 mg/kg 6 hourly between 33 and 36 weeks and 7.5 mg/kg 8 hourly between 28 and 32 weeks PCA [57]. Pain services in most institutions have published guidelines based on these studies. It is crucially important to avoid dosing errors with intravenous paracetamol because of the risk of liver damage from overdose. The main risks are double dosing (between wards and theatres) and ten times errors.

11.11.6 Non-Steroidal Anti-Inflammatory Agents (NSAIDS)

These drugs are widely used in paediatric surgery as part of multi-modal analgesic regimens, particularly for "day case" ambulatory patients. The commonly used agents are Ibuprofen and Diclofenac, the latter being available as a suppository as well as an oral preparation. Currently, NSAIDS are not recommended for babies under 3 months of age, not least due to a potential impact on glomerular filtration rate [35].

11.11.7 Local Anaesthetics

The local anaesthetics (LAs) currently in use are all amino amides. These agents are extensively bound to plasma proteins, including alpha-1 acid glycoprotein (AAG) and albumin. Neonatal AAG levels are low, reaching adult levels by 1 year [58]. Clearance of LAs is lower in neonates, maturing between 3 and 8 months [59]. The potential for local anaesthetic toxicity is higher in neonates than older children. Great care is needed in the handling of these drugs around small babies. We recommend drawing up the correct dose of the local anaesthetic just prior to use and immediately discarding any surplus.

The longer acting local anaesthetics, bupivacaine, levobupivacaine and ropivacaine, are used for most regional and neuraxial blocks in children. Bupivacaine is a racemic mixture. The S-enantiomer, levobupivacaine, is mainly used now because it is less toxic to the heart. However, the maximum recommended dose is 2 mg/kg, the same as bupivacaine, with a maximum infusion rate of 0.2 mg/kg/h. The onset of action of these agents is slower than lidocaine. The optimum concentration depends on the indication and site. Most "single shot" injections are given as 0.25% and infusions as 0.1–0.125% solutions. 0.5% bupivacaine, levobupivacaine or rocuronium is used for spinal anaesthesia, in a dose of 1 mg/kg [60]. There is scope for further investigation of the volume and concentration the local anaesthetic for various neonatal blocks in relation to

the effectiveness and duration of analgesia [61]. Infusions are usually stopped by 48 h to avoid excessive accumulation. A number of adjunct agents have been combined with local anaesthetics to either reduce absorption or augment and prolong the effect. These include adrenaline, clonidine, ketamine and opioids. However, there is concern about the potential neurotoxocity of such mixtures and these adjunct drugs are not licenced for spinal or epidural use in the neonatal population.

11.11.8 Topical Local Analgesia

Various topical preparations of local anaesthetics are available for application to skin. The most extensively studied are the "eutectic mixture" cream of lidocaine and prilocaine (EMLA) and tetracaine (Ametop) [62]. Their status in neonates is uncertain due to absence of a licence in this age group and a limited number of studies. However, the balance of risk favours their use, providing care is taken with dose. For example, a small dose application to the area over the sacrococcygeal membrane is useful for "awake" caudal blocks. There is a risk of methaemoglobinaemia if excessive prilocaine is absorbed in small prematures. Oral sucrose (25%) also has an impact on pain responses and has been compared with topical local anaesthetic creams [63].

Lidocaine can be applied to mucosal surfaces in spray or nebulized format for airway endoscopies and is safe provided accurate doses are applied. Local infiltration of either lidocaine or longer acting agents is somewhat under-utilised for other "minor" procedures, such as line, drain or catheter insertion.

11.12 Regional Analgesia Techniques

Several studies have shown that regional anaesthetic techniques provide good intra-operative conditions and post-operative pain relief in neonatal patients but other outcomes, such as PICU and hospital stays, morbidity or resumption of bowel function have been less studied [64]. Epidural analgesia attenuates the neuroendocrine stress response after major abdominal surgery in infants to a greater degree than systemic morphine [65].

Two national prospective audits in French speaking countries [66, 67] and one in the UK [68] show that regional anaesthetic techniques have a reasonably good safety record in neonatal patients.

Some adverse incidents in the original French study were associated with suboptimal equipment. Suitable regional anaesthesia equipment for infants is now widely available. The recent French study [67] shows a sixfold higher complication rate for central blocks, compared with peripheral blocks, in the whole paediatric population. In the neonatal subgroups, the majority of the blocks were caudals, lumbar epidurals, infraorbital, ilioinguinal and rectus sheath blocks. Other blocks, such as thoracic epidurals, sciatic or brachial plexus were rarely performed. When reporting complication rates or estimating risks, the denominator for individual blocks is important. The "risk-benefit" profile for paravertebral or transabdominis plane blocks remains to be established.

Ultrasound (US) is an important aid in regional anaesthesia. Improvements in technology have enabled high-resolution US images of nerves and surrounding structures which can be helpful in performing neuraxial blocks in neonates, whose spines are still ossifying (Fig. 11.1).

The anatomy of the spinal column and epidural space can be viewed prior to performing an epidural. Needles can be inserted in to the epidural space under real time imaging or using a trajectory estimated from imaging. The insertion of catheters and the distribution of fluid injectate can also be visualized by ultrasound during general anaesthesia (Fig. 11.2). However, such techniques require considerable resources and expertise. There is a recent pro-con debate about the place of regional vs systemic analgesia for neonatal surgery published in the journal, Pediatric Anesthesia [69]. The choice of technique currently depends as much on the available facilities, the expertise of the individual anaesthetist and the institutional culture as on clear-cut evidence of the major outcome benefits of any particular technique. Furthermore, the advent of

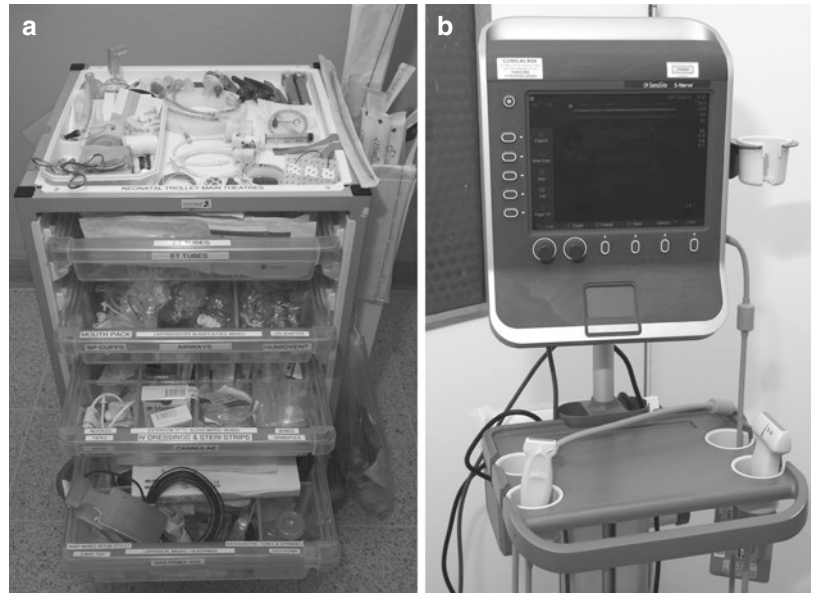

Fig. 11.1 *Left*—neonatal anaesthetic equipment cart which can be wheeled to the operating table at the time of induction. *Right*—the Sonosite "S Nerve" ultrasound device

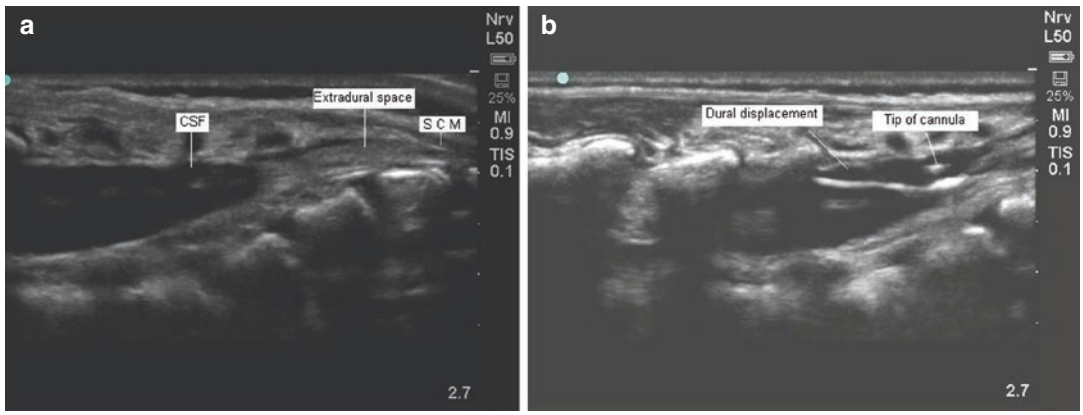

Fig. 11.2 Caudal space ultrasound images in a term neonate. Top image (**a**) shows the dural sac terminating at L4. *CSF* cerebrospinal fluid; *SCM* sacro-coccygeal membrane. Bottom image (**b**) shows the tip of a cannula inserted into the caudal extradural space through the SCM. The start of a bolus injection of local anaesthetic displaces the dura anteriorly. Images obtained from the Sonosite S-Nerve machine. Depth of field = 2.7 cm

remifentanil and ultrasound guided blocks such as the paravertebral and transabdominis plane (TAP) blocks has increased the range of options for both intra-operative and post-operative management.

11.12.1 Caudal Blockade

The long established "single shot" caudal block is well suited to the neonate [70]. It is now possible to visualise the injection and spread of local anaesthetics in the caudal space with ultrasound imaging (Fig. 11.2) [71]. The block can be used for almost all surgical interventions below the level of the umbilicus, most commonly inguinal hernia repair. The "awake" caudal technique is a useful alternative to general or spinal anaesthesia in premature infants [72]. A recent comparison between spinal and caudal anaesthesia was reported in 575 preterm amd ex-preterm infants undergoing herniotomy. There was a higher overall success rate in

the caudal group, with fewer babies needing additional sedation or conversion to general anaesthesia and fewer attempts at caudal compared with spinal puncture [73].

11.12.2 Epidural Catheters Inserted Via the Caudal Route

Epidural catheters can be threaded to the appropriate segmental level via a caudal cannula inserted through the sacral hiatus, a technique described in a large case series by Busoni [70]. However, the position of the catheter had to be either estimated or identified by X-ray, with contrast. The use of ultrasound to visualize the catheter position was first reported by Chawathe [74], where a radiologist scanned the study patients during first 24 h. The use of portable ultrasound by the anaesthetist to assess the catheter position in the operating theatre has since been described [75].

11.12.3 Epidural Blockade

Bösenberg and colleagues originally showed a reduction in the post-operative ventilation rate for babies undergoing tracheo-oesophageal fistula repair by using epidural analgesia [76]. Similar results are achievable for major abdominal surgery. Epidural analgesia may also be associated with earlier resumption of peristalsis in small babies, although the evidence for this is limited at present [77]. The tip of the epidural catheter needs to lie at the appropriate dermatomal level for the surgery. This can be achieved by direct epidural puncture or threading the catheter up from the caudal or lumbar regions.

The neonatal subgroup in a large prospective safety of 10,000 epidural blocks [68] had 6 complications in 529 epidural blocks, significantly higher than in the older age groups. However, most complications were due to drug errors or systemic toxicity and none were due to catheter insertion. There are sporadic reports of serious complications elsewhere, leading to continuing debate about safety of the technique [69].

Recently, Willschke et al. have described an ultrasound-guided approach to epidural blockade in neonates and infants [78].

11.12.4 Transversus Abdominis Plane Block

The transversus abdominis plane (TAP) block has been recently described and offers an alternative to epidural block, at least in the early post–operative period [79]. There are small case series of TAP blocks for lower abdominal operations and stoma formation in neonates [80, 81]. A single injection can provide effective blockade of the thoracolumbar spinal nerves innervating the abdominal wall. The needle-tip position and injection should be monitored by real time ultrasound in neonates because of the proximity of intra-abdominal organs to the injection site (Fig. 11.3). The duration of action of the TAP block is an open question and more studies are needed to establish its place in neonatal anaesthesia. There is some preliminary evidence that this block in neonates may considerably reduce post-operative analgesia doses [82].

11.12.5 Rectus Sheath Block

Rectus sheath block (RSB) is a simple procedure that can be performed using either a landmark technique or under ultrasound guidance [83]. 25 G styletted neonatal spinal needles are useful for this block because the resistance of the anterior and posterior rectus fascia is easily felt. Bilateral blocks can be used for peri-umbilical incisions, such as those used for laparoscopy, pyloric stenosis or primary closure of gastroschisis. Unilateral RSB can also be used for other procedures where the rectus muscle is incised, such as ventriculo-peritoneal shunt insertion or gastrostomy.

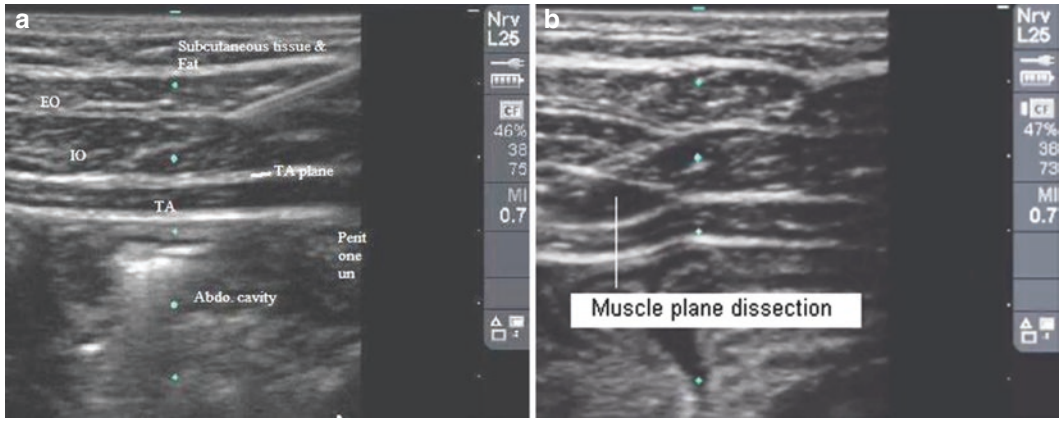

Fig. 11.3 Transversus abdominis (TA) plane anatomy and block in a term neonate. Top image (**a**) shows the layers of the left lateral abdominal wall at umbilical level. Left side of the image is lateral. Needle seen approaching the TA plane. *EO* external oblique; *IO* internal oblique; *TA* transversus abdominis. Bottom image (**b**) shows local anaesthetic being injected into the TA plane, causing plane "dissection"

11.12.6 Ilio-Inguinal Block

This technique is widely used to provide analgesia for pediatric inguinal hernia repair under general anaesthesia. The accuracy of needle placement is improved by ultrasound (US) guidance [84], particularly in the thin abdominal wall muscle layers of the neonatal population. The ilio-inguinal and ilio-hypogastric nerves are usually easily visualized between internal oblique and tansversus abdominis near the iliac crest, where the muscles thicken. A medial to lateral "in plane" needle direction, using US guidance, reduces the risk of peritoneal puncture.

11.12.7 Spinals

Premature infants are at risk of postoperative apnoeic and desaturation episodes up to 60 weeks PCA [85]. Recent concerns about the potential for general anaesthetic neurotoxicity in neonatal animals and the increasing survival rates in extremely premature babies with bronchopulmonary dysplasia have provoked a renewed interest in unsupplemented ("awake") spinal anaesthesia. Although spinal anaesthesia for inguinal hernia repair reduces the risk of post-operative apnoea in comparison with general anaesthesia, there is debate over the magnitude and significance of this effect. A Cochrane meta-analysis of the 4 available RCTs in 2003 [86] did not demonstrate a major advantage but some patients had additional sedation in the spinal group and the numbers were relatively small (108 infants). This report and the evidence that newer volatile anaesthetic agents, sevoflurane and desflurane, are associated with a lower rate of post-operative apnoea than that previously reported for halothane [87, 88] influenced many anaesthetists to continue with general anaesthesia for this group.

The success rate of spinal block was 97.4% in 1554 infants treated over three decades in the Vermont Infant Spinal registry [89]. However, failure rates are higher in less experienced hands and this technique has a significant "learning curve", with higher failure rates described in smaller series [90, 91]. An alternative approach is to use "awake" caudal blocks.

Spinal blocks have shorter durations of action in neonates in comparison to older children and adults. This is due to a larger cerebrospinal fluid volume and turnover rate. Using a variety of spinal local anaesthetic agent formulations, various studies have reported durations of action between 46 and 128 min. The most comprehensive information comes from Frawley and colleagues, who

report durations between 85 and 87.5 min for 1 mg/kg of Ropivacaine and Levobupivacaine respectively [60, 85].

Complications during infant spinal anaesthesia are rare. Intravascular injection was the only reported complication in the 506 spinal anaesthetics considered in the French language study of paediatric regional anaesthesia [66]. Spinal anaesthesia has a sedative effect on most infants. This seems to be related to the reduction in afferent signals to the reticular activating system [92].

The dermatomal spread of hyperbaric local anaesthetics depends on the position of infants. Inadvertently high blocks have been reported but not epidural haematoma formation. Easley and Tobias reported aseptic meningitis in an infant after spinal anaesthesia [93].

11.12.8 Paravertebral Block (PVB)

The paravertebral space (PVS) is situated in the angle between the transverse process and the vertebral body and runs craniocaudally alongside the entire length of the vertebral column. In the thoracic region, adjacent levels of the PVS communicate with each other, but at the lumbar level, individual segments are separated by the origins of the psoas muscle [94].

PVB has been used in children since 1992, when two different techniques were described. Lönnqvist used a percutaneous catheter technique [95] and Sabanathan placed a catheter surgically during thoracotomy [96]. In children, the main indication for PVB is unilateral thoracic and abdominal surgery. However, placement of two paravertebral catheters during bilateral thoracotomy or sternotomy has also been described.

Ultrasound can used to locate the transverse process and the parietal pleura. Neonates need accurate placement of the needle into the smaller paravertebral space. Experience with this block continues to grow [97].

Most paediatric studies are extended case series, limiting formal comparison with other analgesic techniques [98, 99]. In children, it has been shown that PVB can produce extended postoperative analgesia lasting >12 h, exceeding the expected duration of the local anaesthetic. PVB may also produce pre-emptive analgesia [100].

Paravertebral block should be avoided in sepsis and empyema and used with caution in babies with coagulopathy.

11.13 Vascular Access

Peripheral venous access is the mainstay for the delivery of fluids and drugs to babies [101]. The saphenous veins at the ankle and scalp veins are particularly reliable for volume transfusion. “Long lines” (peripherally inserted central venous catheters) can be inserted into the SVC from forearm, antecubital or scalp veins, taking care to position the tip above the pericardial reflection [102]. The Vygon 22 G 20 cm lines are particularly useful because the guidewire can be passed through a 24 G cannula. In chubby infants, veins can be visualized with a small ultrasound probe.

Central venous access is important in many infants undergoing major surgery. The need for this depends on a number of factors, including the adequacy of peripheral access, the anticipated need for parenteral nutrition, the urgency of surgery and the estimated risks and benefits. For example we would place a central line in a baby with gastroschisis for TPN. SVC pressure and oxygen saturation measurements help to judge if the baby will tolerate primary closure. However, we rarely place a central line during tracheo-oesophageal fistula repair, provided adequate peripheral access has been obtained.

The options for central lines include percutaneous insertion in the internal jugular (IJV), subclavian or femoral vein, tunnelled surgical placement of a “Broviac” type line or a percutaneous PICC line. Ultrasound imaging is invaluable for vein location and needle guidance during percutaneous techniques. There are a large number of potential complications associated with central lines, some of which can be fatal.

Arterial access is valuable for continuous blood pressure monitoring and blood gas sampling. Continuous blood gas electrodes are also available but are not in widespread use. However, there are risks attached to the use of arterial lines, including limb ischaemia, flush emboli, inadvertent arterial drug administration and insertion time. Cold light transillumination devices and small ultrasound probes help the accurate location of neonatal arteries.

11.13.1 Pre-Operative Assessment and Preparation

Neonatal anaesthesia is often required under circumstances of considerable urgency. Furthermore, babies with acute conditions are often transferred from district hospitals or specialist neonatal units to the neonatal surgical centre. Many regional neonatal surgical centres are not co-located with maternity units or their associated neonatal ICUs. Good communication between teams is vital.

Surgery is rarely so urgent to preclude the adequate anaesthetic assessment of a baby. The maternal and perinatal history should be reviewed and the baby examined. Relevant maternal information includes the drug history, any pregnancy related illnesses such as pre-eclampsia or diabetes and chronic maternal illness. The birth history should include the mode of delivery, APGAR scores, any resuscitation or birth trauma, medications, feeds and fluids administered. The baby's vital signs, hydration state and breathing pattern should be observed. The airway and cardiorespiratory system should be assessed. Radiographs, echocardiograms, fluid therapy and current medication should be reviewed. Many babies will come from another hospital with a detailed referral letter but sometimes a telephone conversation with the relevant neonatologist will also be required.

The surgeon and anaesthetist should discuss the proposed surgery, any further consultations, investigations, and the availability of blood products. A cardiac assessment will be needed in neonatal conditions associated with congenital heart disease or babies showing signs of cardiac failure, unexplained hypoxaemia, murmurs, abnormal pulses or chest X-ray abnormalities. A plan for post-operative care should be discussed and the parents interviewed and given the opportunity to ask questions and discuss concerns. In many instances, discussions with family members will occur on several occasions, taking into account factors such as instrumental delivery, transfer between hospitals, tiredness and emotional turmoil.

11.13.2 Intra-Operative Management

11.13.2.1 Induction of Anaesthesia

Anaesthesia is generally induced in the operating theatre. It is important to assemble and check the appropriate equipment, drugs and fluids for an individual baby before inducing anaesthesia (Table 11.4) (Fig. 11.4). Some babies will be transferred to the theatre from an intensive care unit, already intubated and ventilated.

Induction of anaesthesia can be done by inhalation of a volatile agent, typically sevofurane, or intravenous injection. The intravenous options are

Table 11.4 Checks before anaesthetising a neonate

• Pre-operative huddle with surgeon and theatre team (WHO guidelines)
• Warm theatre environment and elimination of distractions
• Anaesthetic equipment checked and appropriate for the particular patient
• Labelled drugs drawn at required dosage for the particular patient
• Meticulous care during preparation of IV infusion drips, avoiding air entrainment
• Blood and blood products in close proximity if required for the given surgery
• Non-invasive monitoring in place before induction of the patient
• Spatial awareness about the position of monitors and venous access on the patient
• Provision of anaesthetic care by single team if possible
• Post-operative care plan discussed, including ICU bed if necessary

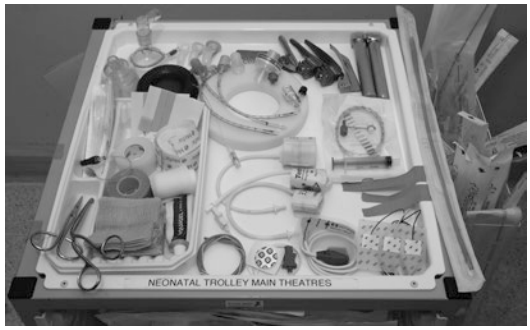

Fig. 11.4 Top surface of a neonatal cart—equipment prepared for a term baby

propofol, thiopentone, ketamine or midazolam, sometimes in combination with an opioid.

11.13.2.2 Intubation

Experienced neonatal anaesthetists typically undertake intubation after the induction of anaesthesia and the administration of a muscle relaxant [103]. Neonatologists typically use a variety of sedative agents, without relaxants, or awake intubation. In the vast majority of cases, a standard neonatal laryngoscope and careful head positioning are used for intubation.

The size, type and fixation of the endotracheal tube are critical. A variety of tubes are available. They are labeled by the internal diameter in mm but the external diameter can vary, depending on the material and manufacturer. The size range of tubes manufactured is illogical because the increments are in the diameter rather than the cross sectional area. However, if departments keep a range of tubes from different manufacturers, small increments in external diameter are possible.

Although formulae exist for the size and length of tube for different ages, there are significant variations in the diameter and length of the trachea. Experienced anaesthetists "custom" fit a tube with a small leak at 12–15 cm lung inflation pressure.

Recently, paediatric tubes with microcuffs have become available, which allow control of the leak in situations of changing compliance. The jury is still out on the pros and cons of cuffed versus uncuffed tubes [104]. Glottic and subglottic damage still occurs from endotracheal tube placement in neonates. The placement of an excessively large tube, which causes ischaemic damage of the laryngeal and subglottic mucosa, is usually responsible. This may result in post-extubation glottic and suglottic oedema, granulations, cyst formation and fibrosis. The subsequent onset of inspiratory stridor and intercostal recession typically occurs when half of more of the subglottic orifice has been lost. Holzki and colleagues recently published a unique long-term study of this problem [105]. Dexamethasone is a valuable treatment for early extubation stridor and can be considered prophylactically for patients who have been intubated long term, for example preterm infants.

A different approach may be necessary in some circumstances. "Difficult intubation" refers to the situation where the laryngeal inlet cannot be visualized using a traditional laryngoscope [106]. Most of these cases are predictable from the pre-operative assessment, for example babies with micrognathic syndromes such as Treacher-Collins, Goldenhar, or the Pierre Robin sequence. Other rare conditions include congenital fusion of the jaws, laryngeal atresia and various masses that impinge on the airway, e.g. cystic hygromas.

There are also situations where the larynx is easily visualized by conventional laryngoscopy but anatomical abnormalities below the larynx can impede the passage of a tube, for example congenital or acquired subglottic stenosis and long segment distal tracheal stenosis (funnel trachea).

Various techniques are available. It is wise to preserve the baby's spontaneous respiration, where possible, until the airway has been visualized and secured. A nasopharyngeal airway can be valuable during the gaseous induction of a micrognathic infant with a volatile agent, typically Sevoflurane. A size 1 Laryngeal mask airway (LMA) can be placed in most cases and is a useful conduit for a fibre-optic bronchoscope (FOB). Gas exchange and anaesthesia can be maintained through the LMA during attempts to intubate, which can either be done by loading a tube over a 2.2 mm FOB or by passing a guidewire into the trachea through a larger FOB with a suction channel placed just above the laryngeal

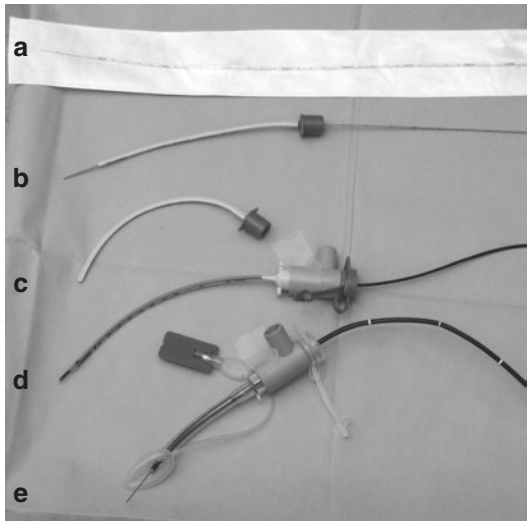

Fig. 11.5 Difficult intubation equipment. (**a**) Tube exchange catheter; (**b**) 2.0 mm internal diameter ETT and bougie; (**c**) 3.0 mm internal diameter endotracheal tube (ETT); (**d**) 2.2 Fiber-optic bronchoscope with connector port and ETT; (**e**) 3.6 Fiber-optic bronchoscope with guide-wire through suction channel and size 1 laryngeal mask airway

inlet. A tube exchange catheter is then threaded over the guidewire after withdrawing the FOB. A tube can then be inserted over the exchange catheter following removal of the LMA. Figure 11.5 shows some of the available equipment. Other devices are available for difficult intubation in some institutions, such the Bonfils and Brambrink video laryngoscopes.

11.13.2.3 The Role of Rapid Sequence Induction

Rapid sequence induction (RSI) is used in older children and adults to reduce the risk of aspiration of gastric contents into the lungs in the emergency situation, with a potentially full stomach. The main elements of this technique are pre-oxygenation using 100% oxygen via a facemask prior to intravenous induction, the use of a rapid onset muscle relaxant, cricoid pressure delivered by an assistant and intubation without mask ventilation of the lungs.

This technique is less practical in small infants and neonates. Pre-oxygenation is less effective due to their high metabolic rate and low functional residual lung volume. Babies may also struggle and it can be difficult to apply effective cricoid pressure without distorting the trachea, which can lead to difficulties in intubation. An alternative is to empty the stomach via a nasogastric tube, careful gaseous induction with sevoflurane and 100% oxygen and gentle mask ventilation after administration of a non depolarizing relaxant, with or without carefully applied cricoid pressure [107].

11.13.2.4 Maintenance of Anaesthesia and Analgesia

This is usually achieved by a combination of a volatile agent and either an opioid or regional block technique. The availability of the short-acting agents desflurane and remifentanil have enabled rapidly titrated anaesthesia and the prospect of rapid recovery after intense intra-operative analgesia. The intra-operative use of remifentanil also allows the option of performing blocks at the end of surgery, rather than at the beginning. This approach may be useful when the extent of surgery is unpredictable or needs to be expedited when the bowel is compromised or there is stomach or airspace distension.

If a baby is very small or has poor lung compliance and a neonatal ventilator is used intra-operatively, some form of total intravenous anaesthesia may be required. Otherwise, maintenance is usually continued with a volatile agent, combined with an opioid or regional blockade.

11.13.2.5 Ventilation

There are a number of options for ventilating the lungs of neonates during surgery [108, 109]. The traditional method is hand ventilation using a T piece [5], which is generally still used during induction and intubation. There are also advantages to hand ventilation during thoracic surgery, where changes in compliance or kinking of large airways during lung retraction can be rapidly appreciated. There may be more subtle advantages to hand ventilation, including maintaining close contact with the patient and inevitably providing “biologically variable ventilation”, which may have a role in preventing atelectasis [110, 111]. This fascinating topic awaits further investigation in the neonatal population.

Fig. 11.6 Surgery on 720 g preterm baby ventilated with Dräger Babylog 800 neonatal ventilator

Mechanical ventilation, using a neonatal ventilator or an oscillator, can offer advantages to the patient in some conditions. The lungs are particularly susceptible to overdistension and ventilator induced lung injury during CDH repair or surgery on premature babies with RDS or other forms of acute lung injury (Fig. 11.6). Lung protective ventilation methods, with limited tidal volumes and permissive hypercapnia may be beneficial to such babies.

The third option is ventilation using a modern circle system and anaesthetic ventilator but this option is questionable in small prematures or infants with poor compliance. It is wise to have a T piece available at all stages of neonatal anaesthesia, irrespective of the form of ventilation selected.

11.13.2.6 Temperature

Neonates are vulnerable to hypothermia, which is associated with diverse adverse peri-operative outcomes, including delayed recovery, increased infection risk, increased blood loss and impaired peripheral perfusion [112]. In most circumstances, active measures are necessary to maintain near normothermia. General measures to minimize heat losses include raising the air temperature while a baby is exposed, minimizing the time out of an incubator, warming fluids and humidifying inspired gases. The availability of infant forced air-warming devices has had a major impact on our practice [113]. Temperature monitoring is mandatory, usually by an oesphageal probe, which is carefully placed into the mid-oesophagus. Rapid changes of temperature can occur when body cavities are closed and vigilance is necessary to avoid overheating.

Occasionally, babies who are being treated with theraputic hypothermia for a brain injury after asphyxia or a cardiorespiratory arrest appear for surgery.

11.13.2.7 Humidification

Humidification of inspired gases is achieved either by using a heated water bath humidifier in the inspiratory limb of the breathing circuit or the use of a heat and moisture exchange humidifier (HME) attached to the endotracheal tube. The latter can be combined with a bacterial filter but the issue of excessive dead space can become a problem in small babies. The efficiency of various HMEs in the neonatal population is not well evaluated.

11.13.2.8 Fluids and Electrolytes

Fluid and electrolyte therapy has to be judged in the individual surgical neonate, depending on the clinical circumstances [114]. Well infants, undergoing elective surgery, are very different to sick babies with large fluid deficits, capillary leak and ongoing losses. Starvation times for elective cases are 2 h after clear fluids and 4 h after milk.

During surgery, fluid administration can be divided into “maintenance” and “theraputic” infusions. Maintenance fluid refers to sufficient water, electrolytes and glucose to maintain normal intravascular tonicity and glycaemia, whilst avoiding hyper- or hypo- natraemia and glycaemia. This can generally be achieved by an infusion of a dextrose-electrolyte solution from a syringe pump. On occasions, parenteral nutrition will be in progress and the infusion rate may need to be adjusted to avoid hyperglycaemia (see below). The exact composition of the fluid depends on the age and size of the baby. A small, premature newborn undergoing major surgery will often need 10% dextrose in a balanced salt solution given at 3–4 mL/kg/h. Older infants, born near term and undergoing minor

surgery will need less or no glucose. Rather than placing over-reliance on protocol driven fluid regimens, it is important to assess the clinical response to fluid administration and measure electrolytes and glucose values at appropriate intervals.

Theraputic fluid refers to those fluids administered to replace fluid losses, blood loss and to achieve goal directed therapy. The goals may be to compensate for hypotension due to anaesthetic drugs, capillary leak in sepsis and ongoing gastrointestinal losses. The goals may include superior vena caval oxygen saturation $\geq$ 70% in addition to maintaining blood pressure, tissue perfusion and urine flow, although this approach has not been extensively evaluated in infants. A variety of isotonic crystalloids and colloids are used for this purpose. There is little evidence to support any particular crystalloid, colloid or combination. Boluyt [115] recommended normal saline in an evidence-based guideline. However, large volumes of this fluid produce a dose dependent hyperchloraemic acidosis and many anaesthetists believe that there is sufficient evidence from studies in older age groups to use balanced solutions such as Hartmann's solution or Plasmalyte [116]. Colloids include gelatin solutions or 4.5% albumin. More clinical trials are needed in this field.

The authors administer intravascular volume therapy manually by using a burrette, syringe and three-way tap distal to a fluid warmer. This has the advantage that precise fluid volumes can be given at variable rates, in contast to maintenance fluid, where a volumetric pump can be used.

11.13.2.9 Blood Products

A significant proportion of surgical neonates will need peri-operative transfusion of one or more blood products—red cells, platelets, fresh frozen plasma (FFP) and cryoprecipitate [117]. Occasionally, massive transfusion is required during extensive surgery for necrotizing enterocolitis (NEC) or the excision of large tumours, such as sacro-coccygeal teratoma. However, in many other procedures, blood loss is minimal. Blood volume estimates are 80–90 mL/kg in term and 90–100 mL/kg in preterm infants. The haemoglobin (Hb) value of neonates varies considerably, partly depending on local placental transfusion practice. The anaesthetist should consider a transfusion threshold and an allowable blood loss. Guidelines in this area are largely based on expert opinion. Haemoglobin thresholds range from 12 g/dL for acute blood loss in the first 24 hrs postnatally to 7 g/dL for older stable babies who have adapted to lower levels of haemoglobin. Fresh frozen plasma and cryoprecipitate may be required to treat coagulopathy and low fibrinogen levels associated with sepsis or large volume transfusion.

11.13.2.10 Glucose and Nutrition

Good nutrition is vital in the neonatal period [118]. Neonates have high metabolic rates, grow rapidly and have limited nonprotein energy reserves, particularly low birth weight preterm infants. Whenever possible, enteral feeding is preferable and should be interrupted for no more than 4 h prior to surgery and be re-established as soon as possible. Where enteral feeding is delayed or disrupted by abdominal pathology or acute illness, parenteral nutrition, and the means to deliver it, should be established early. During anaesthesia, energy requirements are at the resting energy expenditure (REE) level, in the range of 40–70 kcal/kg/day. Considerable variations have been reported in the REE of term and preterm infants. Allowing for growth in addition to REE, values of 100–120 kcal/kg/day in term surgical babies and 110–160 kcal/kg/day in preterms are described. The stress response of surgical trauma or critical illness appears to have little effect on energy requirements with only a modest increase in the first 24 h after surgery. Pierro and colleagues [118] recommend not exceeding 18g/kg/day glucose in TPN to avoid net fat synthesis and increased CO_2 production. Where babies already established on TPN come to theatre, the infusion rate may need to be reduced to avoid hyperglycaemia or hyponatraemia.

The majority of babies will not be on TPN. A reasonable estimate of the intra-operative glucose requirement is 120–150 mg/kg/h for a term baby. This value is likely to be higher in preterm

and growth retarded infants, infants of diabetic mothers and babies with Beckwith-Wiedemann syndrome. If a neonate requires a higher than expected glucose concentration to maintain normoglycaemia, the possibility of an insulinoma should be considered [119].

11.13.2.11 Monitoring

Basic monitoring should be attached to infants before the induction of anaesthesia. This includes ECG, oxygen saturation and non-invasive blood pressure. Depending on the surgical condition and pathophysiological state of the baby, more invasive minitoring may be established after induction. This might include the insertion of an arterial line or a central venous line, which enable continuous pressure monitoring and sampling of arterial or central venous blood gases. End tidal carbon dioxide (ET-CO_2) monitoring is established at the time of intubation. The difference between the arterial and ET-CO_2 tensions depends on the siting of the ET monitoring tube, which should be as close as possible to the endotracheal tube.

Suitable alarm limits should be set on the anaesthetic machine and monitor screens.

11.13.2.12 Unexpected Events

A large number of untoward intra-operative events are possible and experienced surgical and anaesthetic teams will aim to minimize the risk of their occurrence. This is is promoted by a culture of mutual respect, dialogue, regular audit and critical incident reviews. Clinically, there are common patterns of presentation of intra-operative problems, such as a fall in oxygen saturation, acute changes in lung compliance or airway resistance, hypotension, hypertension, tachycardia or bradycardia. The differential diagnosis is extensive for many of these signs. Relatively common problems are summarized in (Table 11.5). For example, hypotension during a laparotomy may be due to hypovolaemia, haemorrhage, sepsis or anaesthetic drug induced vasodilatation. During a thoracotomy, distortion of the great veins due to retraction is another possible cause for hypotension. Hypertension could be due to inadequate anaesthesia or occasionally an undiagnosed coarctation of the aorta or a renal problem.

Table 11.5 Some possible intra-operative complications in an anaesthetized neonate

A. Respiratory complications
1. Dislodgment or disconnection of the endotracheal tube
2. Endotracheal tube obstruction or kinking
3. Endo-bronchial intubation
4. Pneumothorax or mediastinal air-leak
5. Pulmonary haemorrhage
6. Pulmonary or lobar collapse and atelectasis
7. Restriction of chest by pressure from drapes, retractors or hands
B. Circulatory complications
1. Hypotension
2. Tachycardia or bradycardia
3. Systemic or pulmonary hypertension
4. Venous air embolism
C. Miscellaneous
1. Hypothermia or hyperthermia
2. Low urine output
3. Coagulopathy
4. Failure of anaesthetic or monitoring equipment

11.13.3 Post-Operative Care

Before committing a baby to surgery, the surgical, anaesthetic and neonatal staff should discuss a post-operative care plan. In most instances, the post-operative care location and the timing of extubation will depend on the anaesthetic techniques chosen. Babies will generally be kept intubated and ventilated if they are admitted to a PICU or NICU. The transfer arrangements depend on the local circumstances. Transport is a potentially hazardous process, requiring care and adequate monitoring. The team responsible for the subsequent care of the baby should receive a detailed handover.

Babies deemed suitable for early extubation will usually be cared for in a theatre recovery room. They should be placed in a suitable thermal environment and the have ECG, blood pressure, pulse oximetry and apnoea monitoring

established. Transfer to a neonatal surgical unit should only occur when the anaesthetist and recovery nurse are satisfied that the vital signs are stable, respiration is adequate, and analgesia is satisfactory. Post-operative orders for observation, fluid management, feeding, analgesia, antiemetic drugs and antibiotics should be agreed and completed. It is unwise to prescribe fluids for more than 12–24 h because losses may be unpredictable and the fluid status of infants needs frequent review.

Skilled care by experienced neonatal surgical nurses is very important for a successful outcome [120]. Most institutions also have a specialist pain service to advise upon, audit and troubleshoot regional block and opioid infusions, together with the wider aspects of pain management. However, we would encourage anaesthetists to follow up babies in the post-operative period.

11.14 Specific Conditions

11.14.1 Congenital Diaphragmatic Hernia (CDH)

The majority of CDH cases are now diagnosed antenatally. There is a spectrum of severity, particularly in the degree of lung hypoplasia and the presence or absence of associated cardiac lesions. It is generally accepted that surgery is rarely urgent and steps should be taken to stabilize and optimize the baby's condition on an intensive care unit before undertaking operation. These infants are very susceptible to ventilator induced lung injury. Improvements in survival rates have been related to "gentle" ventilation regimens that limit tidal volumes and peak distending pressures with an acceptance of a degree of permissive hypercapnia [121–123]. High frequency oscillatory ventilation (HFOV) has been used both as a "rescue" technique for infants failing on conventional mechanical ventilation (CMV) and as a primary mode of ventilation [124] (Fig. 11.7). There is a place for ECMO in a small group of infants who have shown evidence of sufficient lung capacity after initial

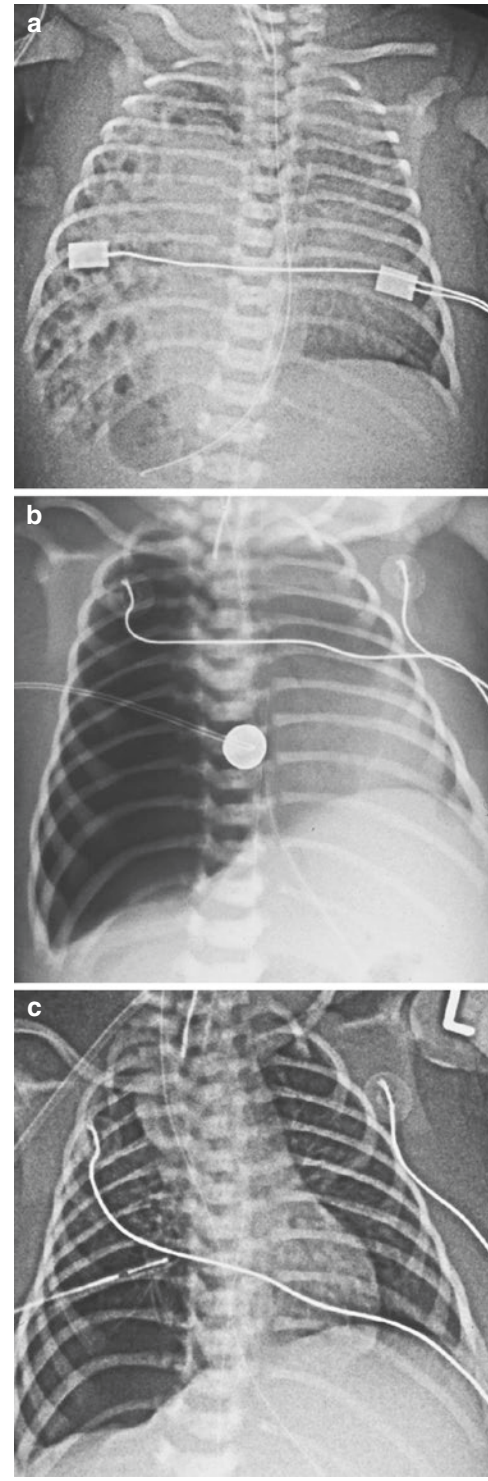

Fig. 11.7 Right sided CDH (**a**). The patient developed a tension pneumothorax postoperatively on conventional ventilation (**b**) and was successfully managed with high frequency oscillatory ventilation (**c**)

resuscitation but subsequently deteriorate. Diaphragm repairs can be carried out during HFOV or ECMO.

Whether repairs are undertaken in theatre or on the ICU depends on the local circumstances. If a baby is stable on either CMV or HFOV and meets the criteria for repair, it is advisable to continue the ventilation mode during repair and use an opioid-muscle relaxant technique of anaesthesia. The lung mechanics may deteriorate to varying degrees with the return of herniated viscera to the abdomen, due to elevation of the unaffected diaphragm. On occasions, patch closure of either the abdomen or diaphragm may be required. Some babies with CDH can be considered for epidural of paravertebral blocks if their lung mechanics are good enough for a trial of early weaning.

CDH babies who have undergone foetal endoscopic tracheal occlusion (FETO) are beginning to appear in some units [125]. This procedure can result in tracheo-malacia, which may be severe enough to require stenting.

11.14.2 Oesophageal Atresia and Tracheo-Oesophageal Fistula (OA/TOF)

Infants with OA/TOF are often born with other features in the VACTERL cluster of abnormalities and need a detailed pre-operative clinical evaluation, looking for evidence of congenital heart disease, chromosomal abnormality, other gastro-intestinal atresias and renal and bony malformations. It is particularly important to establish whether a duct dependent cardiac lesion is present.

There are a number of classifications of variants of OA/TOF [126, 127]. In oesophageal atresia with distal tracheo-oesphageal fistula, the fistula site on the posterior tracheal wall ranges from the mid-trachea to carina and is occasionally in a bronchus [128]. Most OA/TOF babies present breathing spontaneously and the diagnosis is based on the coiling of a nasogastric tube in the upper pouch, together with distal bowel gas, in a baby who chokes with feeding attempts (Fig. 11.8).

A small number of infants require resuscitation and are transferred after intubation and ventilation. This can be a difficult situation, with gaseous distension of the bowel, compromised ventilation and the risk of aspiration. The priority is to control the fistula. A 2 or 3F Fogarty catheter can be placed in the fistula as a temporizing measure but surgical ligation is urgent, even if oesphageal repair has to be delayed due to poor intra-operative tolerance of lung retraction.

Various approaches to the induction of anaesthesia of OA/TOF infants have been described. In our institution, babies usually undergo a gaseous induction with sevoflurane, followed either by muscle relaxation and intubation or placement of a size 1 laryngeal mask airway (LMA) after gaseous induction if the baby has adequate spontaneous respiration. The trachea is then examined with an Olympus 2.2 fibre-optic bronchoscope (FOB) through the endotracheal tube or LMA. The identification of the rare upper pouch fistula may be easier with the LMA method [Atz 06] (Fig. 11.9).

The tube is carefully positioned in relation to the fistula. We believe direct vision of the fistula site is important for subsequent surgical and anaesthetic management (Fig. 11.9). It is particularly important to avoid displacement of the ETT into a carinal fistula orifice [129]. The endotracheal tube should be initially sited above a carinal fistula, with the option of advancing it into the left main bronchus if abdominal distension is a problem. Alternatively, a Fogarty catheter can be placed under direct vision to control a carinal fistula prior to ligation [130], although this has not been necessary in most cases in our experience.

A group in Zurich reported 47 cases of fibre-optic assisted TOF repair, without any major problems due to gastric hyperinflation despite intermittent advancement of the thin FOB via the ETT into the fistulae [131]. The passage of a FOB or guidewire can be useful to aid the surgical identification of and the approach to a lower tracheal or high H fistula. However, there is a risk

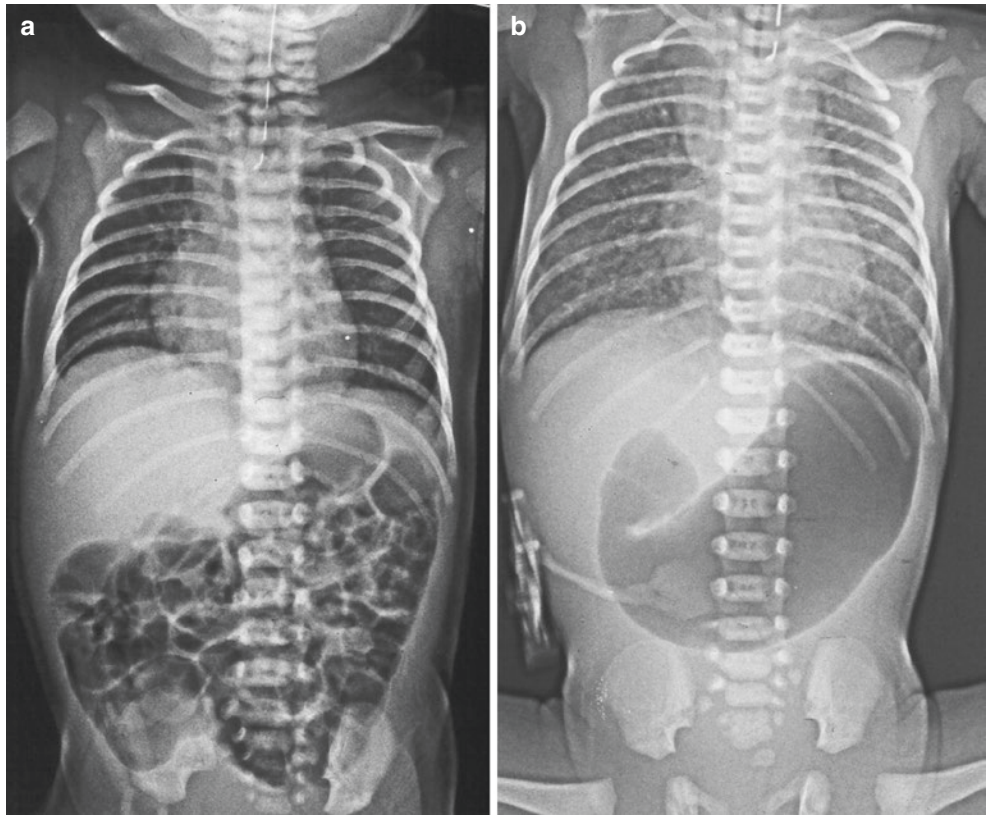

Fig. 11.8 Pre-operative radiographs in babies with oesophageal atresia and tracheo-oesophageal fistula. The case on the right also had duodenal and ano-rectal atresias

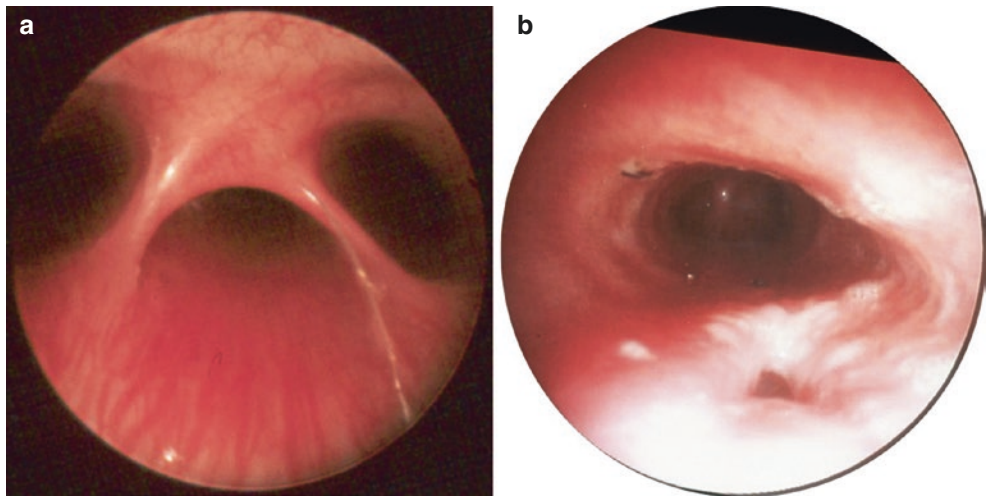

Fig. 11.9 Bronchoscopic images of a carinal fistula (*left*) and an "H" fistula (*right*). The "H" fistula is high on the posterior tracheal wall and is easily missed

that gastric fluid may reflux through a fistula into the trachea during FOB manipulations.

The tube can sometimes be advanced beyond a midtracheal fistula and it may help to orientate the bevel orifice away from the fistula. Another option is to use a microcuff tube to occlude a midtracheal of high fistula.

Once the baby is positioned for thoracotomy, we arrange the drapes so that we can rapidly access the tube, which is cut long and can be repositioned with the aid of the FOB if necessary. Suctioning may also be required intra-operatively.

A few babies may be too small or ill to allow these manoevres. The anaesthetist and surgeon have to agree on a feasible plan of action in the individual case.

In some institutions, tracheo-oesophageal fistulae are repaired using thoracoscopic techniques, in which case the endotracheal tube may need to be advanced into the left main bronchus to allow endoscopic instrumentation and single lung ventilation. This can be accomplished either by direct vision using a FOB or by using fluoroscopic control [132]. The alternative is to site a bronchial blocker in the right main bronchus (see below—thoracic problems).

We advocate hand ventilation using a T piece during dissection and repair of the oesophagus to detect changes in compliance and resistance during lung retraction. Good communication between the anaesthetist and surgeon is vital.

Analgesic options for oesophageal atresia repair are either systemic opioids (e.g. remifentanil intra-operatively followed by morphine) or an epidural or paravertebral block. These techniques enable early extubation. If a baby is to be ventilated in the early post-operative period, intra-operative fentanyl (10–20 μgm/kg) is well tolerated.

11.14.3 Airway, Thoracic and Respiratory Problems

A number of relatively rare disorders affecting the tracheo-bronchial tree and the lungs require surgery in the neonatal period [133]. Many of these babies will present with obvious symptoms and a reasonably certain pre-operative diagnosis. However, in some babies, the onset of symptoms can be more subtle and insidious and in some cases the problem may co-exist with a more obvious congenital disorder, typically congenital heart disease. Cases of congenital subglottic stenosis, long segment lower tracheal stenosis (funnel trachea) and "H" tracheo-oesophageal fistula can present in this way. Stenoses of the trachea can be quite narrow before obvious symptoms become apparent. Difficulties in passing a normal sized tube through the stenosed segment during anaesthesia may trigger the diagnosis, which is made by a combination of airway endoscopy, bronchography and CT imaging. Urgent referral to a centre specializing in slide tracheoplasty is required for severe long segment tracheal stenosis.

Space-occupying congenital lesions of the lung include cystic pulmonary adenoid malformation (CPAM), congenital lobar emphysema (CLE) and sequestered lobes. These conditions may present with obvious respiratory distress or be asymptomatic at birth. The surgical approach to these lesions may be by open thoracotomy or thoracoscopy [134]. Although many thoracic operations can be accomplished using two lung anaesthesia and lung retraction or delivery of a lesion through the incision, some situations are better managed with single lung ventilation. This is much more difficult in neonates than adults or older children and requires the accurate placement of a tube into the mainstem bronchus on the opposite side to surgery or the use of a blocking device in the main bronchus of the operative side. There are problems associated with both approaches. Placement of a tube into either of the bronchi can be accomplished with a small 2.2 FOB, which will pass through a 3.0 mm ETT. A blocker is placed outside the ETT to allow FOB visualization. 2 or 3F Fogarty catheters, pulmonary artery catheters or Cook 5F Arndt catheters (in larger infants) have all been described for this purpose, although none are ideal. A detailed discussion of this subject can be found in Tobias [133]. When possible, the use of a combination intra-operative remifentanil, a low concentration of volatile agent and a regional technique such as epidural or paravertebral block will enable early extubation [135].

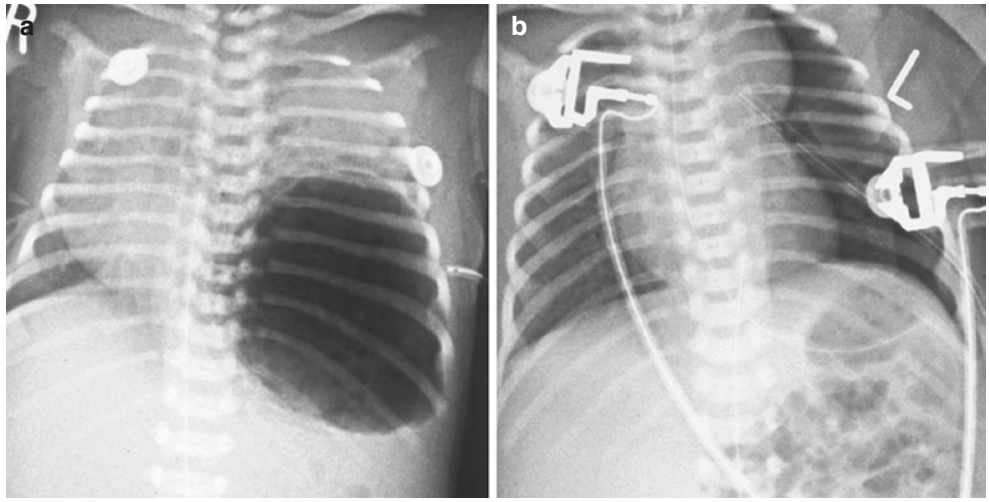

Fig. 11.10 Pre-operative radiograph of left sided cystic pulmonary adenoid malformation (**a**). An attempt to place a chest drain at the referring hospital was unsuccessful! Post operative film (**b**) with the baby established on high frequency oscillatory ventilation

In principle, there is an argument for preserving spontaneous respiration during the early phases of anaesthesia until isolation of a hyper-inflated lobe or segment has been achieved. However, in practice some babies are already in respiratory failure and ventilated when they present for surgery. In this situation, high frequency oscillatory ventilation can be effective when gas exchange is inadequate on conventional ventilation (Fig. 11.10).

11.14.4 Abdominal Wall Defects

The major defects are gastroschisis and exomphalos, with the incidence of gastroschisis increasing in recent decades. Many cases are diagnosed antenatally.

Gastroschisis is generally an isolated problem, without other major congenital malformations other than small bowel atresias, although the authors have encountered occasional exceptions. Babies with this condition tend to be small for dates and are susceptible to hypothermia and fluid depletion. Although there are a number of strategies for surgical treatment, the aim in our institution currently is to achieve a primary closure as soon as is reasonably possible. This can be achieved in 70–80% of cases. Close co-operation between surgeon and anaesthetist is necessary during attempts at primary closure. Various approaches to judging the impact of primary closure on lung mechanics, the circulation and abdominal pressure have been described, including measuring bladder pressure and changes in CVP and SVC oxygen saturation. Although placement of an arterial line, central line and blocks is desirable, the state of the bowel should be closely observed during any anaesthetic interventions.

Many of these babies are admitted to an ICU postoperatively for ventilation. Selected cases can be rapidly weaned and extubated if a sequence of remifentanil and regional blockade is used, for example caudal catheter epidural, rectus sheath or TAP blocks. Some can be extubated in theatre but will need to be closely observed for signs of respiratory compromise [136].

Exomphalos presents similar problems to gastroschisis, although fluid losses are not as severe if the sac is intact. They may also have concomitant congenital heart disease. Very large defects are likely to need staged closure, which can be often deferred in the neonatal period.

11.14.5 Bowel Obstructions

Neonates can present with a wide spectrum of congenital and acquired gut obstructions in the neonatal period [137]. The more common condi-

tions include intestinal atresias (which may be multiple), malrotation, meconium ileus and pyloric stenosis. Meconium ileus can be a presenting feature of cystic fibrosis. Duodenal atresia can be associated with Down's syndrome. The anaesthetic management of this group has been transformed in recent years by the use of intra-opreative remifentanil and the post-operative use of caudal epidural catheters or transabdominis plane (TAP) blocks, supplemented by low dose opioid regimens and intravenous paracetamol. This is a field of ongoing study in our department.

Most infants in this group can be extubated in theatre and returned to the neonatal surgical unit breathing spontaneously, unless they have perforated bowel and extensive peritonitis with signs of sepsis,. Sicker babies with signs of septic shock generally need more invasive monitoring and intensive care, including a period of ventilatory support.

11.14.6 Coexistent Congenital Heart Defects

A small group of babies may need abdominal or thoracic operations prior to correction of heart defects, such as hypolastic left heart syndrome (HLHS), transposition of the great arteries, truncus arteriosus, tetralogy of Fallot or atrio-ventricular septal defect (AVSD). Examples would include repair of oesophageal atresia and laparotomy for NEC, duodenal atresia, imperforate anus or Hirschprung's disease. A proportion of these babies will be ventilated in an ICU prior to surgery. An anaesthetic technique based on opioids, supplemented by low concentrations of isoflurane or midazolam is well tolerated [138]. Arterial and central venous monitoring is advisable. There is a strong argument for these cases to be transferred to a hospital with a cardiac service, with the involvement of a specialist paediatric cardiac anaesthetist if time allows.

Duct dependent lesions are managed with prostoglandin E1. The adequacy of the duct should be assessed prior to transfer to theatre and the continuity of the infusion assured during the operative period.

11.14.7 Persistent Pulmonary Hypertension of the Newborn (PPHN)

During birth, the circulation undergoes a transition from the fetal to the neonatal circulation. The key events are a dramatic fall in the pulmonary vascular resistance (PVR) with a simultaneous increase in pulmonary blood flow as the lungs expand, a rise in the systemic vascular resistance and closure of the fetal shunts at the foramen ovale and ductus arteriosus [139]. A major part of this process occurs over a few minutes during birth. However, after an initially rapid fall in PVR, there is a slower decline over days and the closure of the duct may take hours or days. Various physiological and pathological processes can delay or reverse the decline of PVR, including hypoxia, hypercarbia, acidosis, asphyxia, meconium aspiration, pulmonary hyoplasia, congenital heart disease and acute abdominal episodes. PPHN can present in the neonatal peri-operatve period. If right atrial, ventricular or pulmonary artery pressures rise to systemic levels or higher, right to left shunting may occur at the foramen ovale or ductus arteriosus, which does not close fully for 2–3 weeks.

Treatment includes measures to improve oxygenation, control hypercarbia and acidosis, good analgesia and the use of inhaled nitric oxide (iNO), high frequency oscillatory ventilation (HFOV) and inotropic support in the more severe cases [140, 141]. Occasionally extracorporeal membrane oxygenation (ECMO) is required in cases refractory to conventional treatment. Expert echocardiography is needed to establish the diagnosis and assess the response to treatment.

11.14.8 Prematurity and the NICU Graduate

Premature babies present a number of challenges, depending on the degree of prematurity and low weight [142, 143]. Some operations are required urgently (e.g. for perforated NEC), whereas other procedures can often be deferred until the infant grows to a reasonable size, when surgery and anaesthesia carry lower risks and morbidity (e.g.

repair of most inguinal hernias or V-P shunt insertion).

Premature infants are at increased risk of developing a wide range of conditions, including intraventricular haemorrage, periventricular leukomalacia, hydrocephalus, necrotising enterocolitis (NEC), respiratory distress syndrome (RDS) and chronic lung disease, patent ductus arteriosus (PDA), retinopathy, metabolic bone disease, inguinal hernia and episodes of infection and sepsis. Great care is needed in the anaesthetic management of these infants. Avoidance of hyperoxia, overdistension of the lungs, and excessive deadspace are important considerations during anaesthesia. We recommend the use of a neonatal ventilator and humidification system in theatre is for the smaller babies (<2 kg). A T piece circuit should also be available. Other important considerations are the provision of adequate venous access, fluid, electrolyte and glucose administration and temperature control.

11.14.9 Necrotising Enterocolitis (NEC)

NEC remains a difficult problem, which still carries a high morbidity and mortality. Babies with this condition are often very small, with compromised ventilation and unstable haemodynamics. NEC is also associated with severe congenital heart defects, such as hypoplastic left heart syndrome (HLHS), where splanchnic perfusion may be precarious. The optimal surgical management is still a subject of debate and trial [144, 145]. During surgery, large volumes of fluid and blood products may be needed. It is particularly difficult to assess volume status intra-operatively. Most babies will require periods of TPN post-operatively. Although a long line into a central vein can be used for inotropes and glucose administration, they are not suitable for sampling or rapid fluid administration. A Broviac line placed into the superior vena cava (SVC) is particularly valuable prior to laparotomy and enables intermittent monitoring of SVC oxygen saturation ($S_{vc}O_2$) and reliable delivery of blood products. Aiming for $S_{vc}O_2$ value of ≥70% been shown to improve outcome in the early goal directed resuscitation of adults and children with sepsis. Trials of this approach or the use of cerebral near infrared spectroscopy to guide resuscitation are anticipated in premature neonates with NEC. An arterial line is desirable but may be difficult to place.

At the completion of surgery, it is wise to admit small preterm babies who have undergone extensive surgery for NEC to the PICU for a period of observation and cardiorespiratory support, prior to transfer, if the neonatal ICU is in a separate hospital.

11.15 Minimally Invasive Surgery

Laparoscopic and thorascopic approaches have emerged in recent years for a number of neonatal conditions, although currently this approach is more common in older infants and children outside a few pioneering centres. Ponsky and Rothenberg recently described 649 cases in babies under 5 kg undergoing 43 different laparoscopic or thoracoscopic procedures [146]. The commoner procedures were fundoplication, pyloromyotomy, PDA ligation, oesphageal atresia/tracheo-oesphageal fistula repair and colonic pull through. Low complication and conversion to open surgery rates were reported, together with impressive operating times. Most publications in this field do not describe anaesthetic management in detail and most case series are not confined to neonates. Kalfa et al. [147] described eight anaesthetic incidents in 49 neonates undergoing 50 laparoscopic or thoracoscopic procedues over a 10-year period. Three required temporary or definitive interruption of CO_2 insufflation due to the 02 saturation dropping below 70%. Risk factors for anaesthetic incidents included low preoperative temperature, high variation of end tidal CO_2, thoracic insufflation, a high oxygen or a vascular expansion requirement at the start of insufflation and surgical time > 100 min. A further multicentre report [148] described similar findings. It appears that these procedures are successful if experienced teams use instruments and

insufflation equipment designed for small infants, with low open conversion rates. When single lung ventilation is used for thoracic cases, a degree of permissive hypercapnia is well tolerated [149]. However, much larger series are needed to assess the risk of potentially catastrophic events such as gas embolism.

11.16 Controversies and Ethics

11.16.1 Neonatal Anaesthetic Neurotoxocity

This is currently a difficult and controversial issue, with a rapidly expanding literature. Several anaesthetic agents have been shown to cause abnormal neural apoptosis in neonatal rodents and some primate species, including volatile agents, barbiturates, benzodiazepines and ketamine. The peak vulnerability is around 1 week of postnatal age and also involves suppression of neurogenesis and synaptogenesis. The effects are related to the dose and duration of exposure to the drug. The degree of damage is more pronounced with combinations of agents.

The occurrence of this problem in humans is unknown. No large-scale prospective studies of children exposed to neonatal anaesthesia or ICU sedation have been completed, with detailed assessments of long-term neuro-developmental outcomes. Many premature and term infants undergoing surgery and anaesthesia also have conditions which may influence neurological outcome. Readers are referred to recent editorials and reviews on the subject [150–152]. Various clinical studies are underway to investigate this issue but it is likely to be several years before good data is available. A large Danish epidemiological study did not demonstrate any deficit in academic performance at 15–16 years in 2689 adolescents who had undergone hernia repair as babies [153]. However, anaesthetic exposure for hernia repair is relatively short lived in contrast to major surgery and ICU sedation.

Until this issue is better understood, we believe surgical, anaesthetic and intensive care departments can adopt some precautionary principles. Some operations can reasonably be delayed to a later age on risk—benefit grounds, for example cultural circumcision. Anaesthetists can adjust their practice to minimize the dose exposure of babies to the agents or combinations of agents currently associated with neurotoxicity in experimental animals. For example, the use of remifentanil and regional techniques can reduce the cumulative dose exposure to volatile anaesthetics intra-operatively and to sedative drugs on ICU. Benzodiazepines can largely be avoided if post-operative ventilation periods are shortened or eliminated. Individual doctors and departments have to weigh up the available evidence and make decisions under conditions of considerable uncertainty.

11.16.2 Evidence

In recent years, a large number of evidence-based medicine (EBM) guidelines have appeared, based on the grading of the quality and quantity of evidence [154, 155]. Recommendations or guidelines for treatment should take into account the importance of the outcomes under consideration and the quality of the evidence supporting interventions aimed at various outcomes. Relevant outcomes can range from mortality, quality of survival and organ function to costs such as operation times, equipment investments, intensive care and neonatal unit stays.

Well-executed, registered, randomized controlled trials (RCTs) are seen as the best form of evidence. In the fields of neonatal surgery, anaesthesia and intensive care, such evidence is often scanty and much current practice is based on case series, personal or institutional experience and expert opinion. There are a large number of reasons for this, some of which are understated by the more assertive advocates of the EBM approach.

Many neonatal conditions are rare and exhibit considerable variation in phenotype. Anaesthetic drugs, fluids and ventilation are generally titrated

to the condition of the individual patient, generating several problems in trial design if inflexible treatment regimens are investigated [156]. Many drugs are being used "off label" in this population, with a consequent lack of basic pharmacological data [157]. If the current best treatment is used for the control arm of an RCT and the treatment is reasonably effective, a large, costly trial of patients will be needed to determine the advantages or otherwise for a new treatment. Furthermore, important outcomes, such as long-term neurological function, are more difficult to measure than short-term physiological or pharmaco-kinetic data. There may be rare but potentially devastating outcomes or side effects that will only be picked up in large studies. Examples include the propofol infusion syndrome and the debate over the value of epidural versus systemic opioid analgesia in the neonatal surgical population [69]. The skill and experience of anaesthetists undertaking procedures such as spinal, epidural or paravertebral blocks, inevitably varies. Consequently, the risk of devastating complications, such as paraplegia, is difficult to quantify. The effectiveness and risk of regional procedures in a large multicentre study may vary more between centres and individual practitioners than a comparative intravenous analgesia method, such as titrated opioid therapy.

11.16.3 Treatment of Multiple Congenital Defects

A small number of babies present with multiple major congenital defects, typically congenital heart disease and either oesphageal atresia or diaphragmatic hernia. Some combinations of defects may present only once or twice in an individual surgeon's or anaesthetist's career. An early multidisciplinary case conference is important in such cases. Decisions need to be made about the sequence of treatment, whether treatment can be reasonably be undertaken locally and in some instances whether prolonged complex treatment in the face of a poor overall prognosis is justified.

There are also difficult decisions to be made over the management of extremely premature babies of borderline survivability [158]. These decisions are generally in the domain of the neonatologist and surgeon, with anaesthetists being asked to perform a more technical role. However, experienced neonatal anaesthetists are aware of clinical situations where aggressive treatment is very unlikely to result in a favourable outcome. The ethical dilemmas involved should not be avoided, despite the potential for differing opinions, debate and conflict.

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Intensive Care and the Surgical Neonate

12

Francis A. Potter

Abstract

This chapter examines the role of the Intensive Care Unit in the management of the surgical neonate. It discusses some of the techniques that are used and looks at the requirements of some specific neonatal conditions.

Keywords

Intensive care and the Surgical Neonate • Ventilation • Newborn surgery

In the context of the surgical neonate, Intensive Care is concerned with the support of potentially failing or failed systems so as to allow treatment of the acute problem–usually by some form of operation. It may be needed pre-operatively to prepare the infant for surgery but it is more commonly required after the surgical insult.

The hallmark of intensive care has been mechanical ventilation of the lungs and this remains the case today. Other modalities of system support: inotropes and vasoactive drugs for the cardiovascular system, acute renal replacement with haemofiltration or peritoneal dialysis are also generally available in paediatric intensive care, but some technologies such as extracorporeal membrane oxygenation (ECMO) remain confined to a few centres.

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The organization of delivery of this care varies both within and between countries. Within the UK there are broadly two models of care: patients being cared for as part of a unit looking after (surgical) neonates only–usually with a small number of ventilator cots; or with surgical neonates receiving care alongside other, older, paediatric intensive care patients.

The overall pattern of surgical treatment will also both influence and be influenced by the availability of intensive care—for example using regional anaesthesia to try to avoid post-operative ventilation, timing of surgery for diaphragmatic hernia repair, use of silos for staged repair of abdominal wall defects.

Intensive Care for the surgical neonate contains elements of medical neonatal care of the premature infant: support for the immature respiratory system, obtaining good enough nutrition to allow satisfactory early growth and development, and elements of paediatric intensive care-which itself derives much of its technique and technology from its adult counterpart.

P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_12

Most of what is done is done on the basis of extension or extrapolation from other practice. Faced with a particular problem in an individual infant, evidence from large multicentre trials, performed on cohorts of similar patients (both similar to each other and similar to the patient in question) is, generally speaking, absent. But despite a relatively weak evidence base, there have been many areas of success and there is, in consequence, pressure to apply apparently successful techniques and treatments to ever younger, smaller and sicker infants [1].

Support for the Respiratory System—Mechanical Ventilation of the Lungs.

Spontaneous ventilation contains many subtleties. If one uses the frequency and tidal volumes of an infant (or adult) breathing spontaneously as the settings for mechanical ventilation, then this tends to produce a hypercarbic, hypoxic patient with atelectatic lungs. In order to replicate the gas exchange produced by spontaneous breathing, mechanical ventilation requires fewer breaths of greater tidal volume, with an overall increase in the minute volume. In mechanical ventilation, for any one breath, there is a decision as to which of two variables, the volume of the breath or the positive pressure with which it is given, is to be the controlled variable, with the other being the dependent variable.

Within paediatric practice, pressure controlled ventilation (PCV) has generally been the default mode of ventilation. Originally this was because infants and small children were always ventilated using uncuffed endotracheal tubes. With each breath, some variable volume of gas would be lost to the breathing system through the leak around the tube, and it was easier to compensate for this leak by inflating the lungs to a particular pressure rather than a particular volume. Volume controlled ventilation was reserved for circumstances in which it was important to guarantee a particular minute ventilation, such as in attempting to control intracranial pressure by controlling the arterial partial pressure of carbon dioxide.

However, variants of pressure controlled ventilation have become the predominant form of ventilation across the spectrum of intensive care medicine. This has come about because of the recognition that, at least in sick patients, all mechanical ventilation damages the lung and that it is high peak pressure, high tidal volume ventilation which does this most effectively, probably because it maximises the shearing forces involved in opening and closing lung units.

It is easy to demonstrate this lung damage in experimental animals and clinical experience confirms this notion. The past half century has seen a search for the best (more correctly, the least harmful) mode of ventilation. Outcome trials in adults [2, 3], culminating in the ARDS network study [4] have produced the present consensus on ventilation strategy, often referred to as the ‘open lung’ approach:

Mechanical ventilation should be done with a low tidal volume (6 mL/kg) between a relatively high end expiratory pressure (and volume) and a relatively low peak inspiratory pressure (and volume) that is between the two ‘inflexion points’ of the compliance loop of the lung. In theory, any group of ventilated alveoli should never contain so little gas that their walls come together so that the alveoli collapse, or so much gas that their walls are overly stretched.

In circumstances where an infant needs mechanical ventilation, the starting position is that the lungs will contain at least some groups of alveoli that have collapsed and need to be reinflated (regions of atelectasis). However, such lungs are both prone to atelectasis and are, inevitably, inhomogeneous: thus airway pressures sufficient to open up one atelectatic lung region are likely to be overdistending (and so damaging) other, more normal, lung regions, while airway pressures low enough not to overdistend any lung region will almost certainly both leave other regions of alveoli atelectatic, and allow more alveoli to collapse.

The gas used for ventilation should have the lowest concentration of oxygen as is compatible with delivery of sufficient oxygen to the tissues so as to minimise oxygen toxicity. The gas should, if at all possible, contain some nitrogen thus avoiding collapse of alveoli from diffusion atelectasis if all the oxygen within an alveolus is absorbed .

Above some threshold of respiratory acidosis, (usually taken that the arterial pH should be greater than 7.2) the ventilatory minute volume is dictated by its 'cost' in terms by the ventilatory pressures and volumes produced rather than pursuit of a particular arterial carbon dioxide reading (permissive hypercapnoea) [5].

At least some spontaneous respiratory effort should be maintained in an effort to prevent disuse atrophy of the respiratory muscles [6], but spontaneous respiration should be synchronized with the ventilator.

An absolute feature of this strategy, perhaps unspoken, is that mechanical ventilation should always be for as short a time as necessary.

This strategy has been extrapolated to the intensive care of the surgical neonate. The ventilatory mode that is used most commonly in our paediatric intensive care unit is that of biphasic positive airways pressure (BIPAP).

In BIPAP mode, the ventilator provides two levels of continuous airways pressure and cycles between the two at a chosen frequency. Thus if the upper pressure chosen was 15 cmH_2O, the lower 5 cmH_2O, the upper: lower ratio 1:3 and the frequency 30 times each minute then, if the infant made no spontaneous effort, the ventilator would effectively deliver 30 pressure controlled breaths each minute, each breath consisting of a 2 s cycle with one half second of inspiration and one and a half seconds of expiration.

If, however the infant were breathing spontaneously, say 50 times each minute, then these spontaneous breaths could occur during a lower (5 cmH_2O) or upper (15 cmH_2O) pressure phase no matter how these breaths happened to be distributed. The response times of the inspiratory and expiratory valves are very short; hence, in BIPAP mode, the valves can open and close so as to allow spontaneous breaths to occur at any time in the respiratory cycle without losing or adding significantly to the pressure in the child's airways and ventilator tubing.

In addition, an extra variation on BIPAP—additional supported breath mode (ASB)—allows a spontaneous breath occurring during the lower pressure phase of the BIPAP cycle, to trigger a supported ventilator breath (Fig. 12.1).

This mode of ventilation allows provision of a varying degree of support of breathing through the course of the infant's illness. Immediately post-operation or when the infant is most sick, it provides full pressure controlled ventilation operating between the lower and upper BIPAP pressures at the chosen frequency.(In practice, BPAP is often set up for neonates with settings that effectively provide simply pressure controlled ventilation at a rate of 35–40 breaths a minute and an inspiratory time of 0.4–0.5 s.) As the infants condition improves, it allows spontaneous breathing to occur without producing airway pressure surges (when breathing out at the upper pressure level) or losing airway pressure (when breathing in). At this stage, the infant will be receiving some combination of mandatory pressure controlled breaths, spontaneously triggered, supported, breaths and will also be able to take spontaneous breaths at any time. The infant is guaranteed a background minute volume of breaths from the machine, while additional spontaneous respiratory efforts are readily accommodated.

Other modes of ventilation, synchronised intermittent mandatory ventilation (SIMV), assisted control-mode ventilation (ACMV), may be used in intensive care for the surgical neonate. Some small premature infants appear much more comfortable if they are ventilated using synchronized intermittent positive pressure ventilation (SIPPV) mode in which any spontaneous inspiratory effort on the infant's part triggers a pressure controlled breath from the ventilator (using this mode of ventilation outwith of premature infants tends to result in gross hyperventilation) It remains the case that since no one form of conventional mechanical ventilation has been conclusively shown to be intrinsically superior to any other it is important to fit the mode of ventilation to the infant rather than the other way about.

An obvious difference between the short-term (hours) mechanical ventilation associated with surgical anaesthesia and the long-term (days) mechanical ventilation of intensive care comes at the end of the process. After an operation, the patient returns to full spontaneous ventilation within a matter of a few minutes of reversal of

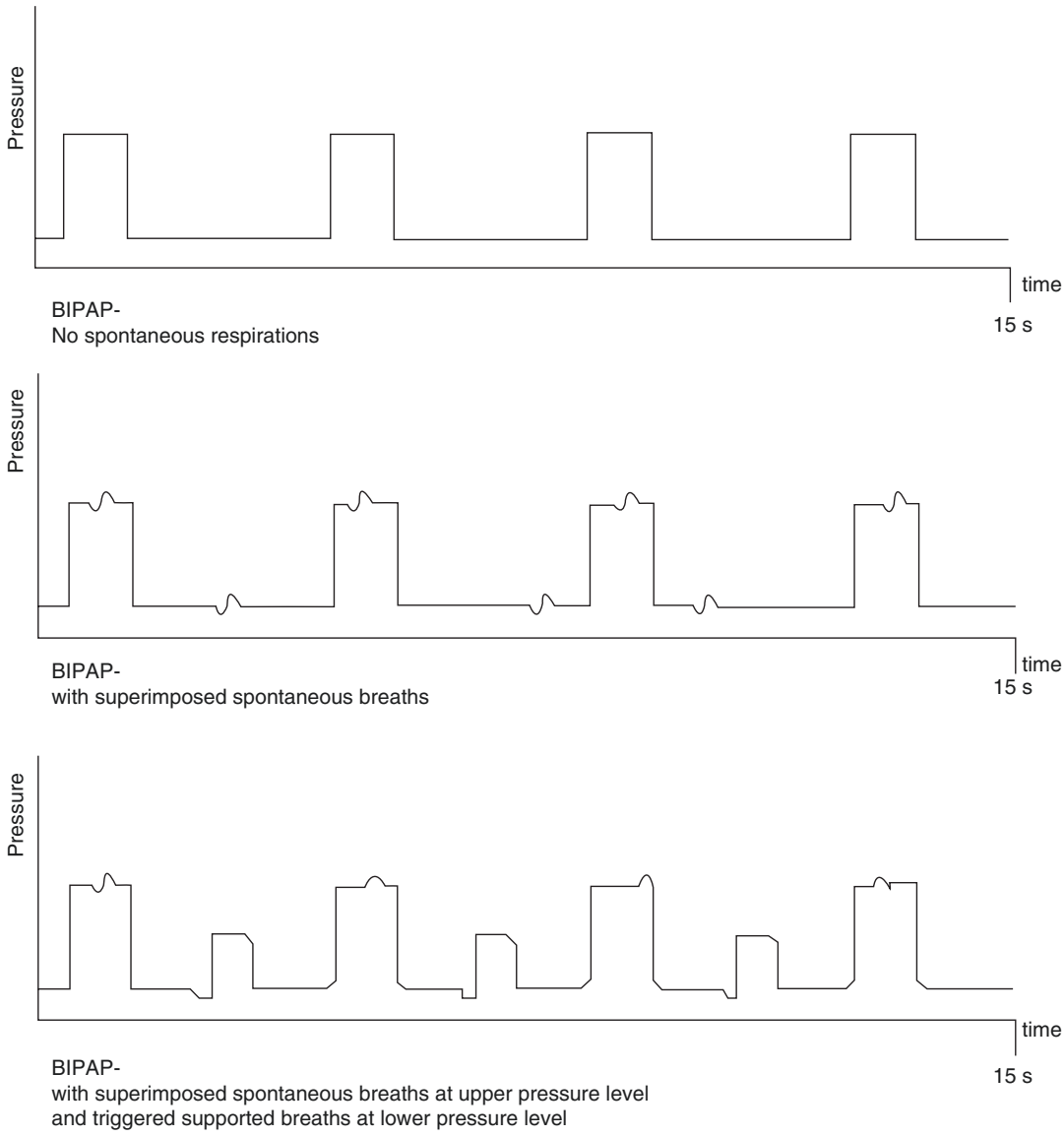

Fig. 12.1 Patterns of ventilation with BIPAP

neuromuscular blockade. After days of mechanical ventilation, a sick infant is gradually accustomed to breathing spontaneously once more in a process termed 'weaning'. Originally, the technique involved taking the infant off mechanical ventilation for a short period (5–10 min) and then returning her (doubtless tired) to mechanical ventilation for the rest of the hour, repeating the process with progressive prolongation of the period of spontaneous respiration until adequate continuous spontaneous respiration was re-established.

Today the process involves using the sophistication of a modern intensive care ventilator to achieve the same aim in a less labour intensive manner. The ventilator provides progressively less of the work of breathing while the infant takes on more of the burden. In BIPAP mode weaning is achieved by decreasing the magnitude of the upper pressure level, decreasing the proportion of time spent at the upper pressure in each minute and decreasing the amount of sup-

port pressure (ASB) given to spontaneous breaths.

Among the subtleties of spontaneous respiration that have been lost with mechanical ventilation to date are the intrinsic variability of tidal volume and respiratory frequency. There is now a body of animal work [7] and mathematical explanation [8] that might well result in the introduction of biologically variable ventilation (BVV) in the next few years. If, for example, the upper pressure that a ventilator delivers is varied breath-by-breath in a normal distribution about a mean pressure instead of invariably delivering the same mean pressure, then the mean inspiratory volume that is produced is increased (see Fig. 12.2). This concept may offer a significant further improvement of infant care.

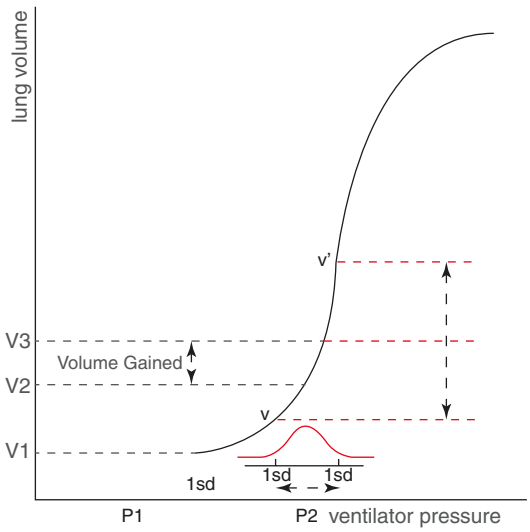

Fig. 12.2 The Effect of 'Noise' on Mechanical Ventilation. In the example of a ventilator operating constantly between pressures P1 and P2, the volume change imposed on the lung is (V2−V1). Now, if the ventilator upper pressure were to be a Gaussian distribution with the mean pressure P2, then, because of the shape of the lung compliance curve, the 'loss' of volume for a pressure of 1sd below mean P2, (v−V1) is more than compensated by the 'gain' of volume for a pressure of 1sd above mean P2, (v′−V1), so that overall, for the same mean pressure change, an additional lung volume (V3−V2) is gained. Based on a figure reprinted with permission from Macmillan Publishers Ltd.: by Suki B et al. published in Nature, 393:128, copyright 1998

12.1 High Frequency Oscillatory Ventilation (HFOV)

HFOV differs from conventional mechanical ventilation in three respects. The tidal volume of each breath is very small (usually less than the anatomical dead space), inspiration and expiration are both active, rather than expiration being passive, and the respiratory frequency is some 8–30 times greater—such that it is measured in cycles per second (Hz) rather than breaths per minute. Gas is moved in and out of the airway by movement of what is, in essence, a loudspeaker diaphragm and gas exchange occurs by facilitated diffusion rather than bulk flow. Proponents of HFOV argue that it is a logical way of achieving the aims of the present consensus for good ventilation.

First, the lung is opened to a relatively high mean volume by the distending pressure (mean airway pressure MAP). Then, the lung is oscillated about this point by the small tidal volume so that the peak lung volume is smaller and the minimum lung volume greater than would be the case with conventional mechanical ventilation- thus minimising the lung damage produced by high peak pressures and the shearing forces of opening and closing broncho-alveolar units.

To use an emotive shorthand, HFOV may be thought of as a 'gentler' means of ventilation than conventional mechanical ventilation—a lovely concept- but there is currently little first class evidence that HFOV leads to superior outcomes.

Some have argued that HFOV has seemingly fallen at the hurdle of randomised trials because, at the time that the trials were conducted, insufficient attention was given to the initial use of a high mean airway pressure to recruit collapsed alveoli- something that has been emphasised with increasing experience of the technique [9].

Alternatively, it has been suggested that, as the strategic aims ('opening' of alveoli and maintaining 'open' alveoli with minimal overdistention) of both conventional ventilation and HFOV are the same, in the majority of cases it matters little which ventilatory method is used. The superior-

ity of HFOV, say its champions, is best discerned in the very sick, but not moribund, patient [10]. There is a good deal of small-study evidence and much clinical experience that HFOV can produce marked improvement in oxygenation in certain patients, and so its present position is that it is usually used as a rescue therapy when conventional mechanical ventilation in the supine position appears to be failing.

Prone positioning [11] and inhaled nitric oxide (iNO) [12] are two other therapies that often give physiological improvement but have yet to definitively demonstrate that they improve outcome for infants. Both prone positioning and inhaled nitric oxide (iNO) are thought to improve oxygenation by improving ventilation:perfusion matching within the lungs.

With prone positioning, the alteration of chest and lung mechanics and the effect of gravity have several effects including increasing the functional residual capacity and redistributing perfusion towards better ventilated regions of the lung and redistributing ventilation towards better perfused lung regions.

In the case of inhaled nitric oxide, the gas acts as a vasodilator. Because nitric oxide is inhaled and very rapidly inactivated by the haem moiety within red blood cells, then its greatest effect is on the pulmonary vessels associated with ventilated alveoli; improving ventilation-perfusion matching without producing generalised vasodilatation and systemic hypotension [13].

12.2 Extra-Corporeal Membrane Oxygenation (ECMO)

This is the most invasive therapy yet devised in the treatment of acute respiratory failure.

The idea is to produce a state of complete lung rest during which specific therapy (e.g. antibiotics for bacterial infection, steroids for asthma) or the patient's own defences (e.g. viral infection) produce resolution of the lung problem. Meantime a sufficient part of the patient's blood is directed via the extra-corporeal circuit to a membrane oxygenator and then returned (oxygenated), to the patient's circulation. For 'Respiratory' ECMO, when the infant has good cardiac function, this is usually done by means of a double-lumen cannula inserted into the internal jugular vein (veno-venous ECMO). 'Cardiac' ECMO, when the main problem is poor cardiac function, more closely resembles prolonged cardio-pulmonary by-pass, with blood being led to the oxygenator from right atrial or bi-caval cannulation and then returned to the patient via an aortic cannula, all being achieved via a sternotomy.

There is a risk of mortality or morbidity from mechanical failure of any part of the circuit and since the extra-corporeal circuit requires that the patient's blood is fully anticoagulated there is also the risk of bleeding (particularly within the Central Nervous System). In the United Kingdom, there has been a conscious decision to offer this therapy only within a small number of specialized units, with the idea that the relatively high throughput of such cases through these units helps to maintain skills and minimises iatrogenic problems.

There is good quality data on the outcome of using ECMO in different situations. The results in the neonatal period for 'medical' respiratory failure- particularly that caused by meconium aspiration syndrome are very good [14]. The use of this treatment for neonatal surgical conditions has produced more equivocal results [15]. In particular it has been suggested that an obvious application for ECMO therapy is in the treatment of diaphragmatic hernia. In this context, ECMO has been used as a rescue therapy when infants have developed respiratory failure following their surgical correction. More radically, ECMO has been used as a primary therapy for infants with actual or incipient respiratory failure pre-operatively [16]. These infants have then undergone surgical repair while receiving ECMO. Both of these approaches have produced instances of individual success, but neither approach has been demonstrated to be unequivocally better than 'conventional' treatment of diaphragmatic hernia.

12.3 Control of the Airway

Infants requiring surgical intensive care nearly always require an endotracheal tube to facilitate mechanical ventilation of their lungs. There has always been concern over the effects of long-term endotracheal intubation. Nasal intubation (championed by its supporters as facilitating secure fixation) can produce loss of alar cartilage from pressure necrosis, oral intubation may similarly produce cosmetic damage to the tongue and lips and, more importantly, the presence of a snugly fitting or too big endotracheal tube can damage the larynx and, in particular, produce sub-glottic stenosis.

The reported incidence of subglottic stenosis has declined over the past 40 years, even in very-low birthweight infants who are intubated for substantial lengths of time [17]. The common presumption is that this decrease has come about because of more widespread awareness of the problem and a tendency to undersize tracheal tubes so as to ensure that a leak is present at all times at a low inflation pressure (often quoted in studies as being about 10 cmH_2O). The leak, it was argued, meant that radial pressure exerted on the subglottis from the tube must be small, certainly below the pressure at which subglottic mucosal perfusion would be compromised (the purported mechanism of sub-glottic injury). This approach carries its own problems- too great a leak producing inadequate ventilation, poor performance of in-line capnography, greater potential for aspiration—and so may necessitate multiple changes of endotracheal tubes to obtain a near-perfect 'cricoid fit' [18].

Over the past decade, this approach has been challenged. Within anaesthesia, there has been a move towards using cuffed tubes for all but the very smallest of infants. Better designed, high-volume, low-pressure (HVLP) cuffs may, provided due attention is paid to cuff pressures, produce as little damage as uncuffed tubes but allow better monitoring and fewer tube changes [19]. The use of cuffed tubes in small children and infants has become more widespread in anaesthetic practice and is entering the PICU–literally *in situ* in post-operative patients.

12.4 Support for the Cardiovascular System

The mainstays of support for the cardiovascular system in patients treated in intensive therapy units are sufficient fluids as to provide adequate filling of the circulation and the use of drugs to either increase cardiac contractility (positive inotropes), or alter the tone of blood vessels (vasoconstrictors or vasodilators) in an effort to optimise tissue perfusion and oxygen delivery (Table 12.1).

Here again, the emphasis is very much on clinical experience and reliance on extrapolation from knowledge gained from work on healthy volunteers, laboratory animals, and sick adults. The lack of class one evidence has not prevented an overall improvement in clinical outcome, but the paucity of randomised controlled trials does need to be borne in mind .

The main cardiovascular derangement affecting the surgical neonate is shock. Recognition is easier than definition. The adult literature continues, for the moment, to use clinical hypotension for this purpose, and in neonatal practice, even allowing for gestational age adjustment, there is no absolute agreement as to exact cut-off points. Good practice for the sick infant would have shock recognised and acted upon from clinical signs—heart rate (<90 bpm or >160 bpm), peripheral pulse palpability, skin perfusion, altered consciousness, hypo- or hyperthermia-before actual hypotension had arisen.

Shock is evaluated and treatment is directed by haemodynamic variables. In everyday clinical practice, the variables that are used and the way that they are measured often differ, in both trivial and important ways, from those used in older children and adults. Invasive arterial monitoring is often done using femoral or umbilical lines rather than using more peripheral arteries (difficulty of access and fear of vascular compromise). Cardiac output, despite usually being the variable of greatest concern, is seldom the subject of continuous invasive measurement in infants, although it is possible that this situation may change in the near future if newer methods

Table 12.1 Drugs for the cardiovascular system

Drug	Receptor	Actions	Caveats and comments
Dopamine (low dose)	DA_1	↑ blood pressure ↑ diuresis	
Dopamine	DA1, DA2, α_1	↑ blood pressure ↑ cardiac inotropy	
Dopamine (high dose)	DA1, DA2, α_1, β_1	↑ blood pressure ↑ cardiac output	↑ bp may be at expense of ↑ SVR →↔ or↓ cardiac output
Low dose adrenaline	β_2 β_1	↑ cardiac inotropy ↑ chronotropy ↑ cardiac output ↓ SVR	↓ SVR primarily because of vasodilatation in skeletal muscle- may divert blood Flow from viscera ↑ [lactate] in serum- multifactorial- makes [lactate] less useful as a marker of adequate tissue perfusion
High dose adrenaline	β_2 β_1	↑ inotropy ↑ chronotropy ↑ cardiac output ↑ SVR	Danger of arrhythmias
Noradrenaline	α_1	↑ blood pressure CO↑ or ↔ or ↓	↑ SVR may → ↓ cardiac output Cardiac output may be ↑ because ↑ aortic diastolic pressure may ↑ coronary perfusion and so ↑ cardiac contractility
Vasopressin	V_1 V_2 V_3	↑ blood pressure ?↑ cardiac output	Cardiac output may be ↑ because ↑ aortic diastolic pressure may ↑ coronary perfusion and so ↑ cardiac contractility May restore depleted blood [vasopressin]

such as pulse index contour analysis [20] or lithium dilution monitoring [21] enter everyday practice. On the other hand, it is probably technically easier to obtain intermittent echocardiographic evidence of cardiac performance in small infants than is the case for adults in intensive care.

The American College of Critical Care Medicine (ACCM) issued guidelines, based on literature and best practice review, covering the treatment of septic shock in infants and children in 2002. Application of these guidelines (which were updated in 2007) has been associated with improved outcomes in many centres [22].

In terms of which fluid to use to achieve adequate filling of the circulation, there are still many areas of reasonable doubt. Rather than being prescriptive as to particular fluids, the emphasis of the guidelines was more on early rapid infusion of isotonic fluid with the aim of restoring normal perfusion and blood pressure. Failure to achieve these end points should prompt establishment of invasive monitoring so as to allow determination of perfusion pressure—the difference between mean arterial pressure and central venous pressure (MAP-CVP)—to help guide further fluid therapy. Put simply, if a fluid bolus produces no appreciable rise in CVP the patient needs more fluid; if more fluid produces a rise in CVP and a fall in (MAP-CVP) value, then this suggests that too much fluid has been given. Present preferences as to which fluid to use include the idea of using blood to maintain haemoglobin concentration above 10 g/dL [23] and an inclination to the idea that near-isotonic crystalloids may be as good as colloid in most circumstances [24].

Several features of crystalloid fluid management need further consideration. An infant's daily water and electrolyte requirements may be met by infusing dilute saline (one-fifth 'normal' saline −0.18%NaCl) at about 4 mL/kg/h. It has long been appreciated that starved infants are at risk of hypoglycaemia which could produce dev-

astating neurological damage. Since dilute saline could be made iso-osmolar with plasma (and thus painless to infuse) by the addition of dextrose—guarding against hypoglycaemia- it came about that dextrose 4% with sodium chloride 0.18% ('four and a fifth') became the near-universal standard infant, and indeed, paediatric intravenous fluid. However, this is an inefficient and dangerous fluid to give for the purpose of volume expansion. The dextrose is metabolised, rendering once iso-osmolar fluid very hypotonic, so very large volumes of this hypotonic fluid are required to achieve any appreciable expansion of vascular volume, producing potentially catastrophic hyponatraemia [25].

The crystalloid solutions needed for adequate volume expansion are those nearer to isotonic solutions; 0.9% saline, Hartmann's solution or Polyionique solution. No solution is perfect: polyionique is not readily available outside France, Hartmann's is less than isotonic and 0.9% saline tends to produce a marked hyperchloraemic acidosis which may have important clinical consequences [26]. None of these solutions alone provides any dextrose, although this problem has been addressed by commercial manufacturers who have produced preparations such as 1% dextrose in Hartmann's solution. The lesser quantities of dextrose in modern solutions reflect both the idea that less glucose is required to maintain normoglycaemia in most circumstances and an increasing concern that hyperglycaemia may have adverse effects on outcome in critically ill children—although a multicentre randomised trial showed no overall benefit from tight glycaemic control [27].

After the question of adequate fluid loading of the circulation, the picture with inotropic and vasoactive drugs is hardly any more clear. The main group of drugs used here is the catecholamine family. These drugs act via a variety of adrenergic receptors (α,β_1,β_2) (alpha, beta one, beta two) and dopamine (DA_1, DA_2) receptors to produce degrees of alteration in vascular resistance (vasodilatation and vasoconstriction), contractility (inotropy), and heart rate (chronotropy). The specificity of action of these drugs varies with their dose and their pharmacokinetics and pharmacodynamics are often altered by the patient's illness. Add in developmental differences between neonates (premature or term), infants, children and adults and it is clear that the effect of any particular drug on an individual patient in a particular circumstance is more amenable to close observation than it is to accurate prediction.

Bearing these caveats in mind, where does one start? In the context of surgical neonates requiring cardiovascular support, this will usually be because of either hypovolaemia or 'septic' shock (whether or not an infective organism is ever isolated) The ACCM recommend dopamine (5 μg/kg/min) or adrenaline (0.05–0.3 μg/kg/min) as the first line inotropic drug as it is thought that most infants with septic shock have diminished cardiac output with normal or raised systemic vascular resistance (SVR). Both drugs have been demonstrated to counteract hypotension in the smallest of infants; adrenaline produces more of a chronotropic effect (which points to it having a greater effect on actual increase in cardiac output) [28]. The ACCM specifically recommends early intervention with inotropic drugs- giving these drugs either into a peripheral vein or intraosseous needle pending the insertion of a central line, notwithstanding the risk of tissue damage from exravasation of the inotrope.

If dopamine fails to bring about satisfactory improvement, adrenaline is started as the second inotrope. In distinction with adult practice, where noradrenaline is commonly used as a vasoconstrictor, noradrenaline is used in surgical neonates only as rescue therapy when the dopamine/adrenaline combination is manifestly failing or where there is clear clinical suspicion of low systemic vascular resistance (very low diastolic pressure).

Particular features of septic shock in neonates are that catecholamine therapy is sometimes less effective than expected and that such therapy demonstrates tachyphylaxis. Proposed reasons for these observations include the idea that the vasoconstrictive effects of the catecholamines are opposed by the vasodilatory effects of endogenous nitric oxide, production of which is increased in sepsis [29], and that there is down-

regulation of catecholamine receptors with continued exposure to catecholamines [30]. Endocrine status is thought to be important in this downregulation. Treatment of sub-clinical hypothyroidism (with tri-iodothyronine T3) has been demonstrated to restore catecholamine effectiveness in children following cardiac surgery [31, 32], while there has been much greater debate over the role of cortisol and the significance of any degree of impairment of the hypothalamic-pituitary-adrenal axis in paediatric critical illness. Low dose hydrocortisone has been demonstrated to improve refractory hypotension in low birthweight infants receiving dopamine [33] though this has yet to be demonstrated as having a proven effect of improved outcome [34].

Vasopressin (Anti-Diuretic Hormone) acts via its own receptors (V_{1a}) in vascular smooth muscle to increase blood pressure, systemic vascular resistance and urine output in catecholamine-resistant shock. Vasopressin is almost always used in combination with catecholamines as rescue therapy for refractory hypotension and while it has several theoretical advantages in this regard [35], favourable outcome trials are lacking, even in adults [36].

Another approach to the treatment of shock has been the use of phospherodiesterase inhibitors. Intracellularly, catecholamines act via 'second messenger' mechanisms to increase intracellular concentrations of cyclic adenosine monophosphate (cAMP). Phospherodiesterase type III inhibitor drugs (inamarinone, milrinone, enoximone) inhibit the breakdown of cAMP and so should act synergistically with catecholamines. This group of drugs has become widely used-particularly in the post-operative phase of infants who have undergone cardiac surgery-despite the relative paucity of outcome evidence for their use [37].

Levosimenden re-sensitises the actin-myosin-tropomyosin complex within the cardiac muscle cell to calcium ions–thereby increasing contractility. It also has vasodilating properties through its action on potassium channels in vascular smooth muscle cells. It has active metabolites and so a loading dose and 24 h infusion produce clinical effects for several days. Up to the present, its reported use in children has been pretty well confined to instances of severe heart failure [38].

12.5 Renal Support

Providing support for the neonatal surgical patient who has suffered an acute kidney injury is one of the most difficult areas of neonatal intensive care. There are three main reasons why an infant might require renal replacement therapy: fluid overload, metabolic derangement (acidosis, uraemia) and acute hyperkalaemia; severe fluid overload producing generalized systemic and pulmonary oedema is the commonest problem in the surgical infant. Commonly, options for renal replacement therapy are intermittent haemodialysis, peritoneal dialysis and continuous haemofiltration; each has particular problems associated with its use in the context of the surgical neonate.

Intermittent haemodialysis gives the best overall metabolic control of kidney failure, but generally speaking the volume of the circuitry and the potential cardiovascular disturbance of the osmotic fluid shifts caused by dialysis make the technique unsuitable for a sick surgical infant [39].

12.5.1 Peritoneal Dialysis

In this technique, dextrose-containing dialysate fluid is run into the peritoneal cavity by way of a dedicated catheter (which can be inserted either at open operation or percutaneously). The peritoneum acts as a semi-permeable membrane across which solutes move down their concentration gradients and tissue fluid moves down its osmotic gradient, expanding the volume of the peritoneal fluid during it's 'dwell time'. This fluid is then run out of the infant and the cycle is repeated. The technique is usually well tolerated, particularly in infants who are on mechanical ventilation (the increased work of breathing from limitation of movement of the diaphragm is less of a problem than when the infant is breathing spontaneously) and the technique has proved useful in infants who have undergone cardiac surgery [40].

Recent abdominal surgery is a strong relative contra-indication to peritoneal dialysis, and so the technique has a very limited applicability in surgical infants.

12.5.2 Haemofiltration

In this technique, part of the infant's cardiac output is directed through an extra-corporeal circuit where the blood undergoes ultrafiltration through a synthetic semi-permeable membrane, the ultrafiltrated plasma being partly or wholly replaced with crystalloid solution. Originally, blood was taken from the arterial side of the circulation and returned to a large vein, but nowadays blood is usually taken and returned to the circulation via a double-lumen intravenous line and is pumped around the circuit by a roller-pump. As with dialysis, the technique involves a degree of anticoagulation and the relative size of the circuitry (150–300 mL) compared to the blood volume of the patient (150–400 mL) necessitates both that the circuit is primed with autologous blood and that nursing management of the circuit is impeccable. Haemofiltration provides the best management of the fluid overloaded patient, and is usually the technique used for surgical infants, but the technical challenges of line insertion and maintenance can be very exacting in infants of less than 2 kg [41].

For smaller infants, renal support usually consists of maintaining renal perfusion as best as one can (inotropic and vasodilatory support,) avoidance of further renal insult (aminoglycosides, NSAIDs, X-ray contrast media) and managing the problems of fluid overload with a judicious combination of mechanical ventilation, limitation of input and diuretics while waiting for spontaneous recovery of kidney function.

12.6 Nutritional Support

Babies have less in the way of nutritional reserves than do older children and adults. Premature infants have even less reserve and so infants, and especially premature infants, need nutritional support early. A newborn infant has an energy requirement of 100–120 kcal/kg/day (compared to a young adult's 30–40 kcal/kg/day). Two fifths of this energy is required for maintenance metabolism and the same amount again is required for growth. One fifth of the energy intake is accounted for by the cost of enteral absorption and excreted losses. Thus a parenterally-fed, incubated infant needs only 80–100 kcal/kg/day.

Unlike adults, infants show an immediate (within hours), brief (return to baseline after 24 h) and modest (20–30%) increase in energy requirements following quite major surgery [42].

Critically ill infants suffer fewer infective and immunological problems and generally do better if they are enterally fed rather than receiving their nutrition intravenously. However, it is often difficult, or even impossible, to achieve this seemingly straightforward goal in clinical practice. Enteral nutrition may be precluded by intestinal obstruction from a congenital lesion. There is often a degree of malabsorption. This may be relatively modest—gut dysmotility commonly accompanies both surgery and critical illness—or it may be very severe as when the bowel is very slowly recovering from necrotizing enterocolitis or when extensive bowel resection has reduced the absorptive surface area to a critical minimum.

There has been an increasing appreciation of the immunological and anti-infective benefits of maintaining some enteral nutrition—such as will maintain small bowel villous integrity—in virtually all circumstances even when it is of no effective nutritional value [43]. Thus some 'trophic feeding' should be maintained, even when 'large gastric aspirates' and vomiting are real practical problems. Because infants have limited nutritional reserves, parenteral nutrition is required when enteral feeding is likely to be significantly compromised for 48 h or more, but the default position should be to have some enteral feeding whenever possible and to make the transition from parenteral to enteral nutrition as quickly as possible as gut function returns.

It is generally accepted that expressed breast milk is the best enteral feed for infants. On occasion, (e.g. disaccharide intolerance, fat malab-

sorption) then specific formula feeds are required (soy-based disaccharide free, medium chain triglyceride (MCT) formulae). Very severe malabsorption sometimes requires elemental (amino acid, glucose, MCT) or near-elemental (containing dipeptides rather than individual amino acids) feeds [44]. These solutions have a high osmolarity and frequently produce diarrhoea and a form of dumping syndrome. They usually have to be given as slow, continuous, pump feeds.

The way that feeds are given is important. Bolus feeding is more physiological and appears to maintain gut motility, the enterohepatic circulation of bile acids and gall bladder activity [45]. However continuous pump feeds guard against hypoglycaemia, and are often required because of poor absorption or gastro-oesophageal reflux.

When intravenous feeding is required, the tailored formula contains carbohydrate, fats, electrolytes, protein, micronutrients and water. Sufficient amino acids are provided to allow for protein turnover and growth but caloric requirements are met by the lipid and carbohydrate components. If more glucose is given that the infant can utilise, then this is converted to fat. Such lipogenesis has two undesirable features; it increases carbon dioxide production and so increases the work of breathing, and newly synthesized fat may be deposited in the liver.

If, however the amount of glucose given is less than the daily caloric requirement and the caloric deficit is made up with intravenous lipid, then the lipid is oxidised rather than being stored. Giving some of the caloric requirement as fat provides essential fatty acids and increases the efficiency of energy use. It also reduces protein breakdown.

Infants require about 3 g of protein per day. In parenteral nutrition solutions, this protein requirement is given as a mixture of essential amino acids. The exact composition varies; there have been vogues for increasing the content of one or other amino acids to optimise growth or to obtain other benefits. Presently, glutamine supplementation is under investigation. Glutamine is not very soluble and so was not used in many commercial parenteral nutrition solutions. There are studies in animals and adult patients which suggest that glutamine supplementation may help gastro-intestinal function, but large-scale trials are lacking [46].

12.7 Sedation

Adults and older children are able to report their distress at receiving intensive care and there is no good reason to suppose that neonates would enjoy the experience any more than their older brethren. This notion that neonates should be provided with sedation and analgesia has come to be accepted over the last 40 years or so. The primary purpose of giving sedation to neonates undergoing mechanical ventilation and other unpleasant procedures on an intensive care unit is humane consideration, though other benefits may accrue. Good sedation is not physiologically 'cost-free' either in terms of obvious depression of the cardiovascular or respiratory systems or less obvious alterations of the endocrine and immune systems. Sedation for an appreciable length of time often gives rise to a withdrawal syndrome characterised by agitation and autonomic features.

A distinction should be made between analgesia and sedation. Sedation is always given systemically–usually with intravenous drugs, but analgesia may well be best provided using regional techniques such as an epidural or paravertebral block. At other times systemic analgesia (intravenous opioids) may provide sufficient sedation as to allow good toleration of tracheal intubation and mechanical ventilation.

For most infants, induction of sedation (more accurately, induction of anaesthesia) is a prerequisite for intubation of the trachea and establishment of access and cardiovascular monitoring lines. There is a clear role for muscle relaxant (paralysing) drugs at this stage, but thereafter it usually the case that relaxants can be allowed to wear off and sedative drugs alone are given in sufficient quantity as to allow compliance with ventilation. Very occasionally, usually when faced with profound hypoxic respiratory failure, complete muscle paralysis is necessary, but it

should only be done after doing everything possible to ensure lack of awareness.

As with much else in paediatric intensive care, the adequate clinical trial base for sedation practice is small and clinical experience has to be relied on more than is readily comfortable.

'Standard sedation' for paediatric intensive care units in the UK has been a combination of an opiate (typically morphine or fentanyl) and a benzodiazepine—usually midazolam [47] and this combination is often used for surgical neonates.

Midazolam (a water-soluble, short-acting benzodiazepine) in doses of 50–100 μg/kg/h is an effective sedative and has the great advantage of having little depressant effect on the cardiovascular system when given by infusion. It is so widely used that it is disconcerting that a recent Cochrane review felt that it could not be recommended for use in premature infants, because the few small trials that have examined the use of midazolam in such infants have identified higher instances of complications in the midazolam group [48].

Clonidine (an α-adrenoceptor agonist) has come to be seen as an alternative to midazolam in paediatric intensive care practise. A recent attempt to compare midazolam and clonidine in a randomised controlled trial was unable to give a definitive answer [49].

Opiates are the most commonly used agents given to facilitate mechanical ventilation in premature infants. Morphine is the most commonly used drug. It is metabolised, in the liver and elsewhere, by two forms of glucuronidation. Morphine-6-glucuronide is active and its excretion is reduced in renal impairment, potentiating the action of the drug. Newborn infants tend to form morphine-3-glucuronide which is pharmacologically inactive. Metabolism of morphine shifts towards the adult pattern (predominantly morphine-6-glucuronide)within a few months of life [50]. Advocates of fentanyl see its lack of histamine release as an advantage in avoiding cardiovascular depression. In theory, constantly infused remifentanil, which is rapidly metabolised by non-specific esterases in blood and so does not rely on unpredictable hepatic or renal metabolism for its elimination, should be a good drug to use in neonates, as its effects dissipate quickly even after prolonged infusion. At present, routine use of remifentil would be expensive. Infants develop tolerance to opiates, and many authorities think that this happens quickly with fentanyl and remifentanil.

A variety of other enterally given sedative agents are commonly used (either alone or more usually in combination with intravenous analgesics). These enteral drugs include promethazine, trimeprazine, triclofos and chloral hydrate. As gut absorption is often poor during critical illness, the effects of these drugs may be variable.

Over the past decade there has been increasing awareness of the problem of withdrawal syndromes (agitation, seizures, sweating, vomiting) following discontinuation of opiates and other sedative drugs, particularly midazolam. Various strategies have been tried to reduce the incidence and severity of such withdrawal effects, including tapering of dosages of drugs, prospective cycling of combinations of sedatives and analgesics and substitution of sedative drugs (particularly with drugs such as clonidine which can be given both intravenously and enterally). Overall, the question of sedation continues to pose problems, and it appears to be particularly resistant to disentanglement by randomized clinical trial. The views of physicians, nurses and parents on sedation may be varied, but they seem, invariably, to be firmly held.

12.8 Some Aspects of Intensive Care for Particular Conditions in Neonatal Surgery

With virtually all lesions, the greatest challenges and ethical dilemmas are thrown up by the occurrence of the lesion in an infant who has been born very prematurely or who has other co-existing problems. There are few, if any, hard and fast rules left to guide one as to what is possible, still less as to what is right, and the importance of honest communication between all those involved in the care of a particular infant cannot be over-emphasised.

12.8.1 Necrotizing Enterocolitis (NEC)

This disease is strongly associated with prematurity, thus the main practical problems usually relate to the size of the infant. Infants with severe necrotising enterocolitis are likely to present for intensive care because of a degree of septic shock. Increased vascular permeability means that fluid therapy that is sufficient to maintain the circulation almost invariably produces a degree of pulmonary and systemic oedema which exacerbates the cardio-respiratory failure that is already present. Treatment of this fluid overload is usually at the limits of what can be achieved from mechanical ventilation, adjustment of fluid intake and diuretic therapy but haemofiltration is often fraught with concerns about lines being too large to allow adequate limb perfusion or the infant's circulation being able to cope with the whole process. Most intensivists have little doubt that the placement of percutaneous lines in such infants for monitoring, giving parenteral nutrition and intravenous drugs has been facilitated by the increasing availability and use of ultrasound control for vascular access procedures.

12.8.2 Congenital Diaphragmatic Hernia (CDH)

There has been increasing appreciation that the main problem for an infant with CDH is the degree of lung hypoplasia present. The task for the intensivist is to add as little as possible to the burden of problems for the infant's lungs. The aims are to avoid injurious effects of mechanical ventilation, attenuate the problem of pulmonary hypertension as much as possible and to minimise problems of infection.

Most infants with CDH are intubated and started on mechanical ventilation at birth. The principles of low tidal volume, high end-expiratory and low peak airway pressure ventilation with permissive hypercapnoea are followed. Common targets are to obtain a pre-ductal oxygen saturation of greater than 85% with an arterial pH of greater than 7.35, but with a peak inspiratory pressure of less than 25 cmH_2O High frequency oscillatory ventilation is often used if these targets cannot be met with conventional ventilation. Centres reporting good results with HFOV for diaphragmatic hernia stress the importance of keeping mean airway pressure as low as possible (<20 cmH_2O).

HFOV is a means of avoiding injurious ventilation in these infants rather than rescue therapy for hypoxia and hypercapnoea [51].

All infants see a decrease in their pulmonary vascular pressures over the first hours and days of their extra-uterine life, but characteristically this fall in pulmonary vascular resistance can be interrupted or reversed if the infant is subjected to a significant physiological insult. Pulmonary hypertensive crises may manifest as episodes of arterial oxygen desaturation. Other than very rare instances of direct pulmonary arterial pressure measurement, quantification of pulmonary hypertension is usually by means of signs of tricuspid regurgitation seen on Doppler echocardiography.

In infants with CDH, the fall in pulmonary vascular resistance is delayed and the infant is prone to pulmonary hypertension.. Surgery for repair of the hernia often exacerbates the respiratory failure seen in this condition. It has become accepted practice to delay surgical repair until there is evidence both of satisfactory ventilation (low inspiratory pressures and oxygen requirements) and of lowered pulmonary vascular pressures (no right-to-left shunt on echocardiographic assessment).

In the past, treatment of pulmonary hypertension in these babies was principally by manipulation of mechanical ventilation so as to try to maintain a near-normal arterial carbon dioxide to avoid respiratory acidosis. Now, with the primacy of avoiding injurious ventilation, pulmonary vasoconstriction is opposed by the use of inhaled nitric oxide as a specific pulmonary vasodilator. Prostacyclin is sometimes used as second-line therapy for this purpose. Inhaled nitric oxide therapy for CDH infants is widely practiced but the results of randomised trials of iNO in such infants show no marked effect on outcome [52]. However, the widespread adoption of the combi-

nation of 'gentler' ventilation and nitric oxide therapy as standard therapy has coincided with improved survival figures [53].

12.8.3 Oesophageal Atresia/Tracheo-Oesophageal Fistula (OA/TOF)

There have been reports of successful management of infants with OA/TOF using regional anaesthetic techniques to obviate post–operative mechanical ventilation [54], but in most cases infants are ventilated immediately following surgery when pain is likely to be at its worst and analgesic requirements greatest. A particular problem in infants with these conditions is tracheobronchomalacia.

Tracheobronchomalacia commonly presents as either difficulty in reducing the level of respiratory support as mechanical ventilation is reduced or as a 'failure of extubation'. As the index of suspicion for this condition has risen in the past decades, so its incidence has increased. It is also recognised as occurring in association with congenital cardiovascular anomalies and an acquired form of the disease may arise after severe tracheobronchial inflammation or after formation of a tracheostomy.

The diagnosis is usually made by a combination of bronchoscopy and bronchography. Flexible fibreoptic bronchoscopy via the endotracheal tube may be performed at the bedside on PICU and bronchography is best performed using a biplanar fluoroscopy unit. In both cases it is important to maintain spontaneous ventilation of the infant to demonstrate dynamic collapse of the trachea. The stenting effect of the endotracheal tube is minimised by carefully withdrawing the tube to the immediate subglottic region. The two investigations are complementary [55].

There is controversy as to how tracheobronchomalacia is best treated. The traditional view has been that tracheobronchomalacia tends to improve spontaneously over a time course of months/years and so there has been a school of thought that infants with severe tracheobronchomalacia should undergo a tracheostomy followed by whatever degree of 'pneumatic stent' is required (varying from nothing, through a continuous positive airways pressure circuit (CPAP) to actual long-term ventilation of the lungs pending resolution of the condition.) This approach involves a very protracted hospital stay, (many, many months if long-term ventilation is required) is labour intensive, and carries all the risks inherent in managing a infant with a tracheostomy.

Thus there are many advocates of taking a different course in an effort to avoid tracheostomy. This usually entails the operation of aortopexy-securing the anterior surface of the ascending aorta to the posterior surface of the sternum, with the effect of pulling the anterior wall of the trachea forwards, helping to maintain tracheal patency throughout the respiratory cycle. Various techniques of aortopexy have been described, including thoracoscopic procedures; usually in short case series, and usually with very good results. A recent single-centre retrospective study, looking at infants and children who had undergone aortopexy, suggested that the procedure was effective in over 80% of cases [56]. Nonetheless, a diagnosis of severe tracheobronchomalacia in infancy, particularly if there are significant co-morbidities, is still associated with a heavy burden of treatment and significant mortality.

12.8.4 Abdominal Wall Defects (Gastroschisis and Exomphalos)

The majority of infants undergoing primary repair of abdominal wall defects will receive a short period of post operative mechanical ventilation and cardiovascular monitoring. This may be extended as appropriate for infants undergoing staged repair with a silo. The challenge for intensive care comes with infants with giant (liver-out) defects with severe viscero-abdominal disproportion. Having the resources to be able to offer days of mechanical ventilation allows consideration of traction-compression-closure as a technique for treating such infants [57]. Infants with giant exomphalos point up many of the challenges and dilemmas of paediatric surgical intensive care:

consideration of multiple co-morbidities, each individually treatable, but possibly insurmountable in their totality, the necessity for prolonged, meticulous, system support in the face of the threat of sepsis, and the flexibility to improvise or extend techniques to the treatment of the smallest patients.

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Infections and Antibiotic Therapy in Surgical Newborn Infants

13

Hendrik K.F. van Saene, Nia Taylor, Shijie Cai, Nicola Reilly, Andy Petros, and Stephen C. Donnell

Abstract

Colonisation of the gastro-intestinal tract of newborn infants starts immediately after birth and occurs within a few days. Initially, the type of delivery (passage through the birth canal versus caesarean section) and the type of diet (breast versus formula feeding) might affect the colonisation pattern. Nearly all full-term, formula-fed, vaginally delivered infants were colonised with anaerobic bacteria within 4–6 days. 61% harboured *Bacteroides fragilis*. In contrast, anaerobes were present in 59% and *B. fragilis* in only 9% of infants delivered by caesarean section, suggesting that significant contamination occurred during passage through the birth canal. Both prematurity and breast feeding reduced the likelihood of isolating anaerobic species. Enterococci were isolated from all neonates, *Escherichia coli* from 82.6%, anaerobic cocci from 52.2% and both streptococci and staphylococci from 34.8%. Colonisation of the small bowel occurs perorally. In newborn infants with congenital small bowel obstruction, a faecal-type flora is found immediately proximal to the site of obstruction, and the distal bowel remains sterile.

Keywords

Infection • Newborns • Sepsis • Antibiotics • Selective decontamination of the digestive tract (SDD)

In memory of Shankar, his kindness, dedication and superb professionalism.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_13

13.1 Pathogenesis of Infections: Gut Overgrowth

13.1.1 Introduction: Flora Development in the Neonate

Colonisation of the gastro-intestinal tract of newborn infants starts immediately after birth and occurs within a few days. Initially, the type of delivery (passage through the birth canal versus caesarean section) and the type of diet (breast versus formula feeding) might affect the colonisation pattern. Nearly all full-term, formula-fed, vaginally delivered infants were colonised with anaerobic bacteria within 4–6 days. 61% harboured *Bacteroides fragilis*. In contrast, anaerobes were present in 59% and *B. fragilis* in only 9% of infants delivered by caesarean section, suggesting that significant contamination occurred during passage through the birth canal. Both prematurity and breast feeding reduced the likelihood of isolating anaerobic species. Enterococci were isolated from all neonates, *Escherichia coli* from 82.6%, anaerobic cocci from 52.2% and both streptococci and staphylococci from 34.8% [1]. Colonisation of the small bowel occurs perorally. In newborn infants with congenital small bowel obstruction, a faecal-type flora is found immediately proximal to the site of obstruction, and the distal bowel remains sterile [2].

Other environmental factors also have a major role since differences exist between infants from different hospital wards. Critical illness predisposes surgical neonates to acquisition and subsequent carriage of abnormal aerobic Gram-negative bacilli (AGNB) and methicillin-resistant *Staphylococcus aureus* (MRSA). These abnormal bacteria are most often transmitted amongst neonates via the hands of health care workers (HCW) [3].

13.1.2 Definition

The fundamental pathophysiological event in the surgical neonate is gut overgrowth. Gut overgrowth can be conveniently defined as abnormal bacteria in abnormal concentrations at an abnormal site. More scientifically, gut overgrowth is defined as $\geq 10^5$ AGNB and/or MRSA per ml of digestive tract (small intestine) secretion [4].

13.1.3 Four Harmful Side-Effects

Gut overgrowth harms the surgical neonate in four main ways:

1. Immunosuppression—overgrowth of abnormal AGNB (and associated endotoxin) has been shown to impair systemic immunity due to generalised inflammation following absorption of AGNB and/or endotoxin [5];
2. Inflammation—overgrowth of abnormal AGNB and/or endotoxin has been shown to lead to cytokinaemia and inflammation of major organ systems [6];
3. Infection—there is a quantitative relationship between surveillance and diagnostic samples. As soon as there is overgrowth in surveillance samples the diagnostic samples become positive which is the first stage in the development of infection [7];
4. Resistance—the abnormal carrier state in overgrowth concentrations guarantees increased spontaneous mutation leading to polyclonality and antibiotic resistance [8].

Selective decontamination of the digestive tract (SDD) is a prophylactic measure using selected antimicrobials to control gut overgrowth thereby reducing the four harmful side effects of it. Immunosuppression was reverted to normality in patients who were successfully decontaminated [9]. Patients free from AGNB overgrowth were able to control generalised inflammation [10]. SDD has been shown to control severe infections of lower airways and blood, to reduce mortality without resistance emerging [11].

13.1.4 Risk Factors

1. Critical illness related carriage in overgrowth concentrations (CIRCO) is common on admission [12]
2. CIRCO often develops during treatment on ICU [13]
   Drugs including opiate analogues [14], H_2 antagonists [15, 16] and antibiotics [17] promote gut overgrowth of potential pathogens following the impairment of gut motility, the

increase in gastric pH of ≥4, and the suppression of the indigenous anaerobic flora required for colonisation resistance, respectively.

13.1.4.1 Diagnosis

The traditional microbiological approach of obtaining and culturing diagnostic samples such as tracheal aspirate, blood and urine can never detect gut overgrowth, as these samples only confirm the clinical diagnosis of infection. Surveillance samples of throat and gut are the only samples that allow the detection of overgrowth [18].

13.2 Prevention

13.2.1 Surgical Prophylaxis

All neonates undergoing operations classified as potentially contaminated, contaminated or 'dirty' were given 48 h of antibiotic prophylaxis in the form of cefotaxime and metronidazole [19]. Infants with suspected central venous line-related blood stream infections were prescribed teicoplanin and gentamicin initially, pending blood culture results [20]. The standards of hygiene recommended by the Centres of Disease Control (CDC) were used [21].

13.2.2 Early Enteral Feeding

A period of starvation ('nil by mouth') is common practice after gastro-intestinal surgery during which an intestinal anastomosis has been formed [22]. The stomach is decompressed with a nasogastric tube and parenteral nutrition is given, with oral feeding being introduced as gastric dysmotility resolves. The rationale of 'nil by mouth' is to prevent post-operative nausea and vomiting and to protect the anastomosis, allowing it time to heal before being stressed by food. It is, however, unclear whether deferral of enteral feeding is beneficial.

Contrary to widespread opinion, evidence from clinical studies directly comparing strategies of early feeding with 'nil by mouth' after elective gastro-intestinal surgery, suggests that initiating feeding early is advantageous. Eleven studies with 837 patients who met the inclusion criteria have been meta-analysed [22]. Early feeding reduced the risk of any type of infection (relative risk 0.72, 95% confidence interval 0.54–0.98, p = 0.036) and the mean length of stay in hospital (number of days reduced by 0.84, 0.36–1.33, p = 0.001). Risk reductions were also seen for anastomotic dehiscence (0.53, 0.26–1.08, p = 0.080), wound infection, pneumonia, intra-abdominal abscess, and mortality, but these failed to reach significance. The risk of vomiting was increased among patients fed early (1.27, 1.01–1.61, p = 0.046). There seems to be no clear advantage to keeping patients nil by mouth after elective gastro-intestinal surgery. Early feeding may be of benefit. The significantly reduced risk of infection following early feeding may be due to the control of overgrowth achieved in patients who received early enteral feeding.

13.2.3 Enteral Antimicrobials: SDD

Recently, four studies with 355 children who met the inclusion criteria for randomisation have been meta-analysed [23]. Pneumonia was diagnosed in 5 of 170 children (2.9%) for SDD and 16 of 165 patients (9.7%) for controls (odds ratio, 0.31; 95% confidence interval, 0.11–0.87; p = 0.027). There was no difference in overall mortality. The significant reduction in infectious morbidity is highly likely due to overgrowth control, and the sample size was too small to impact survival for a paediatric mortality varying between 5 and 10%. A recent French Consensus Conference recommends SDD as pneumonia prophylaxis in critically ill children [24].

13.3 Treatment

Shankar was the first to classify infections in surgical new born infants, using the carrier state [25]. Out of a total of 167 infants, 21 infants (15%) had 33 episodes of infection. The predominant infecting micro-organism was *Staphylococcus aureus* (n = 11), others were enterococci, coagulase negative staphylococcus, *Candida* spp., AGNB and

anaerobes. A total of 27 out of 33 infective episodes (82%) were caused by micro-organisms carried by the infants on admission (primary endogenous). Only six (18%) infections were caused by micro-organisms acquired in the unit: three secondary endogenous infections (micro-organisms not present in the admission flora, but acquired and carried later on during treatment on the unit) and three exogenous infections (not preceded by previous carriage). The micro-organisms causing infections were mostly low level pathogens such as coagulase-negative staphylococci, enterococci and anaerobes. 'Normal' potential pathogens included *S.aureus* and *Candida* spp. Only two infections were caused by 'abnormal' flora, and the responsible micro-organisms were *Klebsiella* and MRSA causing one secondary and one exogenous infection each. Bloodstream and wound infections were the two main infection types in the surgical newborn infants. Lower airway infections were not diagnosed, highly likely because none of them were mechanically ventilated.

The pathogenesis of practically all infections is endogenous in surgical new born infants [26–29]. The same pathogenesis applies to all types of micro-organisms whether they are low level or potential pathogens both normal and abnormal. If the surgical new born infant was admitted immediately after delivery the pathogens are low level and 'normal' such as *Escherichia coli*, *S.aureus* and *Candida* species. If the patient is admitted from another hospital, or has been treated on the surgical neonatal unit, the abnormal pathogens such as AGNB and MRSA may be carried by the new born infant apart from low level and normal pathogens.

13.4 Septicaemia

Septicaemia [11] is defined as sepsis (i.e. clinical picture caused by generalised inflammation due to micro-organisms and/or their toxic products) combined with a positive blood culture. Once the diagnosis of sepsis has been made and blood cultures taken, immediate antibiotic combination therapy should be started in order to provide an adequate spectrum of antimicrobial therapy. This is a combination of an aminoglycoside with cefotaxime. If an intra-abdominal focus is suspected, metronidazole and amphotericin B are added to this treatment. Initial empirical therapy is adjusted according to diagnostic culture results. The source of sepsis should be identified and eliminated as soon as possible. SDD using enteral polymyxin/tobramycin/amphotericin B should be commenced immediately to eradicate the internal source [11].

13.5 Wound Infection

Clinical signs of wound infection [11] are purulent discharge, redness, swelling, tenderness, and local warmth. The clinical diagnosis is microbiologically confirmed by isolating $\geq$3+ or $\geq 10^5$ micro-organisms from the purulent discharge in which $\geq$2+ leukocytes can be seen. Systemic antimicrobial therapy is seldom indicated, unless symptoms of sepsis occur. Local treatment, drainage, debridement, and removal of plastic devices are essential and generally sufficient. Following treatment, the wounds are rinsed twice daily with a disinfectant, 2% taurolin, for 3 days. Aquaform gel mixed with 2% polymyxin/tobramycin/amphotericin B and/or vancomycin can be applied to colonised/infected wounds [11].

13.6 Control of Antibiotic Resistance

The two potential pathogens that display antimicrobial resistance are AGNB producing extended spectrum beta-lactamase (ESBL) and MRSA.

Available parenteral antimicrobials with good activity against many resistant potential pathogens include the carbapenems and cefepime [30]. The enteral antimicrobials polymyxin/tobramycin need to be added to the parenteral antimicrobials, to eradicate gut overgrowth that promotes polyclonality and resistance [31]. Compounds directed against resistant Gram-positive bacteria include streptogramin combinations such as quinupristin/dalfopristin and linezolid. Similarly, enteral vancomycin needs to be added to the parenteral anti-

microbials active against Gram-positive bacteria to control gut overgrowth.

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Fetal Surgery

14

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Abstract

Maternal fetal surgery for correction of an anatomic defect was first performed 30 years ago by Michael Harrison. At that time, the concept of the fetus as a patient was the subject of philosophical and ethical debate and the rationale and pre-requisites for prenatal surgical treatment were in evolution. Over the past three decades, the concept of the fetus as a patient has become commonly accepted and the ethical framework for maternal fetal intervention is now well developed. Improvements in prenatal diagnosis now provide certainty for the primary diagnosis and, in competent hands, can identify or exclude virtually all significant associated anomalies. Clinical experience with prenatally diagnosed fetuses has provided insight into the natural history of specific anomalies, improved our ability to predict the outcome for an individual fetus, and allowed more accurate selection of fetuses that will benefit from prenatal surgery. While application of open fetal surgery has remained limited to only a few anomalies, it is important to appreciate that the development of this field has accelerated

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_14

technological progress in prenatal diagnosis and intervention, led to improved understanding of the pathophysiology and natural history of candidate disorders, allowed comprehensive counseling of prospective parents in centers with focused expertise in fetal anomalies, and driven the evolution of less invasive therapeutic approaches. In this chapter we will discuss the rationale and current indications for open fetal surgery, the evidence supporting its efficacy, and basic physiologic and technical considerations common to all fetal surgical interventions.

Keywords
Fetal surgery • Birth defects • Fetus • Outcomes

Maternal fetal surgery for correction of an anatomic defect was first performed 30 years ago by Michael Harrison [1]. At that time, the concept of the fetus as a patient was the subject of philosophical and ethical debate [2] and the rationale and pre-requisites for prenatal surgical treatment were in evolution. Over the past three decades, the concept of the fetus as a patient has become commonly accepted and the ethical framework for maternal fetal intervention is now well developed [3]. Improvements in prenatal diagnosis now provide certainty for the primary diagnosis and, in competent hands, can identify or exclude virtually all significant associated anomalies. Clinical experience with prenatally diagnosed fetuses has provided insight into the natural history of specific anomalies, improved our ability to predict the outcome for an individual fetus, and allowed more accurate selection of fetuses that will benefit from prenatal surgery. While application of open fetal surgery has remained limited to only a few anomalies, it is important to appreciate that the development of this field has accelerated technological progress in prenatal diagnosis and intervention, led to improved understanding of the pathophysiology and natural history of candidate disorders, allowed comprehensive counseling of prospective parents in centers with focused expertise in fetal anomalies, and driven the evolution of less invasive therapeutic approaches. In this chapter we will discuss the rationale and current indications for open fetal surgery, the evidence supporting its efficacy, and basic physiologic and technical considerations common to all fetal surgical interventions.

14.1 Rationale and Foundation for Fetal Surgery

Observations by clinicians of neonates with specific anatomic defects born with secondary irreversible organ damage led to the conclusion that the damage occurred before birth and the compelling rationale that the only way to prevent that damage, was to correct the defect by fetal intervention. This led to experimental validation of the pathophysiology of specific fetal defects in the lamb model and to the development of techniques for their prenatal surgical correction [4–6]. Finally, pre-clinical studies in the primate model defined the anesthetic, tocolytic, and technical methods and devices [7] that proved essential for clinical translation [8–10]. Ultimately, these efforts supported the first systematic clinical application of fetal surgery in the early 1980's.

The pre-requisites for fetal surgery were developed during this formative period and, with slight modification, still apply today (Table 14.1). However, with advances in prenatal diagnosis, increased prenatal experience, and technical progress in fetal surgery, our ability to meet these

Table 14.1 Prerequisites for fetal surgery

• Accurate Prenatal Diagnosis
• No Associated Anomalies
• Defined Natural History
• Correctable Lesion Leading to Fetal Death or Organ Destruction
• Technical Feasibility

criteria for specific anomalies has improved dramatically. For instance, the requirement for an accurate prenatal diagnosis and the exclusion of associated anomalies is now practically taken for granted. The armamentarium for examining the fetus in the womb, including high resolution ultrasound (2D, 3D and 4D), haste MRI, and fetal echocardiography, when expertly applied, are capable of detecting essentially any significant fetal structural anomaly. When combined with maternal serum screening, karyotype analysis, and molecular diagnostic techniques, the likelihood of missing an associated anomaly or performing an intervention on an unrecognized syndromic fetus has been dramatically reduced. In addition, with accumulated experience and normograms for many fetal parameters, the limits of normality and abnormality have been clarified, allowing appropriate interpretation of normal variation (for instance, minimal renal pelviectasis). The presumed pathophysiology of specific anatomic defects has been confirmed either in animal models when possible, or by clinical observation, and the ability to reverse the pathophysiology by fetal surgical correction has been validated. Finally, significant progress in our ability to safely operate on the mother and her fetus has been made. Advances in the technical aspects of fetal intervention, maternal anesthesia, tocolysis and the accumulation of clinical experience have evolved to the point where open fetal surgery can be performed in experienced centers with a minimum of maternal morbidity, and to this date no maternal mortality [11]. Nevertheless, fetal surgical interventions have until recently been limited to fetal anomalies perceived to be lethal because of the potential risk of this major surgical procedure to the usually young, healthy mother. The fetal surgical treatment of myelomeningocele (MMC), a non-lethal disorder, has extended the original pre-requisites for fetal surgery to disorders causing irreversible organ damage with associated quality of life impacting morbidities prior to birth.

Despite this progress, fetal surgery remains controversial. The controversies primarily relate to our understanding of the "natural history" of specific anomalies, and whether we can accurately select fetuses that will benefit from fetal intervention. Our knowledge of the natural history of many disorders without fetal treatment has improved allowing accurate selection of fetuses that might benefit from fetal intervention. The natural history of Congenital Pulmonary Airway Malformation (CPAM), fetal Sacrococcygeal Teratoma (SCT), and Lower Urinary Tract Obstruction (LUTO) for instance, are relatively well understood. However, the natural history remains controversial for Congenital Diaphragmatic Hernia (CDH) and cardiac outflow tract anomalies making interpretation of the results of fetal therapy more difficult. The importance of randomized controlled trials (RCT) to resolve these controversies cannot be overemphasized and the design and implementation of such trials is a current focus for fetal treatment centers [12, 13]. Challenges in performing RCTs include the rarity of appropriate subjects, ethical challenges, and the resources required for organization, financing, and impartial evaluation of results obtained. The future of fetal intervention depends upon developing evidence based support for fetal interventional procedures which will be a major focus in coming years.

Currently, there is a relatively limited list of fetal anomalies for which a compelling rationale exists for fetal intervention. Anatomic anomalies that are currently treated by fetal intervention and their associated pathophysiology are shown in Table 14.2. However, there are basic considerations common to all fetal surgery that will be discussed as a basis for discussion of specific anomalies.

Table 14.2 Anatomic anomalies treated by fetal intervention

Anomaly	Pathophysiologic consequences	Fetal treatment
Cystic adenomatoid malformation	Hydrops; Lung hypoplasia	Open surgery or Thoracoamniotic shunt
Sacrococcygeal teratoma	High output cardiac failure	Open surgery; Tumor debulking
Myelomeningocele	Spinal chord damage; Brain stem compression; Hydrocephalus	Open Surgery; Defect closure

14.2 Basic Considerations that are Common to all Open Fetal Surgery

14.2.1 Ethical Considerations and Preoperative Management

Fetal surgery is unique in its involvement of a healthy patient who undertakes considerable surgical risk without expectation of direct benefit, creating a unique subset of ethical concerns. Such concerns have been explored and an ethical framework has been well established [14]. In general, the fetus achieves independent moral status as a patient once he/she reaches the point of viability. The pre-viable fetus, then, is a patient only when the pregnant woman chooses to continue her pregnancy and presents for treatment on behalf of her fetus. For the eligible fetus, the risks of such a procedure are clearly offset by the considerable benefit of salvage, but the fetus cannot be considered to be an independent or autonomous decision-maker, and the beneficence-based obligation to the fetus must be balanced with both beneficence-based and autonomy-based obligations to the mother. Thus, the fetus is not a separate patient, and maternal safety is a primary concern in considering fetal intervention.

Furthermore, the mother is under no obligation to present her fetus for treatment, and she must be provided all necessary information for truly informed consent. The treatment team has a responsibility to consider the risks to the mother in the context of the likelihood of fetal loss or severe, reversible disability. For this reason, both fetal and maternal factors can be contraindications to open fetal surgery, including chromosomal abnormalities, significant anatomic abnormalities, maternal obesity, heavy smoking history or other medical conditions. Patient selection should take place through multidisciplinary evaluation following a screening process including detailed ultrasonographic examination for characterization of the defect and any other abnormalities, ultra-fast fetal MRI for anatomic definition, fetal echocardiogram to assess heart function and detect any cardiac abnormality, and karyotyping and/or more high resolution genetic analysis. Following this evaluation, cases should be reviewed by a multidisciplinary team of fetal surgeons, obstetricians, anesthesiologists, radiologists, a nurse coordinator, geneticist, and social workers.

Eligible families must undergo extensive counseling to discuss the proposed surgical procedure, postoperative and postnatal care. A team meeting provides an appropriate forum for the family to learn about the procedure and its risks, benefits and alternatives. Depending upon gestational age, all appropriate options should be discussed in a non-directive manner, including termination, expectant management with palliative or best available postnatal treatment, and prenatal therapy. Parents must understand the likely outcomes of all possibilities, as well as the risks involved. For any fetal surgery, complications may include preterm labor, premature rupture of membranes, chorioamnionitis, uterine rupture, medication side effects, risk of fetal demise, as well as surgical complications and future reproductive issues. The mother must be counseled regarding the need for caesarean section in this and all future pregnancies, and care must be taken to “allow” families to opt for non-surgical management.

14.2.2 General Principles of Open Fetal Surgery

14.2.2.1 Personnel and Equipment

Care of the fetal surgery patient requires a multidisciplinary team with clearly defined roles, as well as highly specialized equipment. Because the mother and fetus have separate, though co-dependent anesthetic concerns, both an obstetric anesthesiologist and a pediatric anesthesiologist are necessary. A sonographer and an echocardiographer should be an integral part of the surgery team, and a high-resolution ultrasound machine with color Doppler should be used to identify fetal and placental anatomy and to assess for potential hazards such as velamentous cord insertion. Ultrasound images before and after maternal incision are used to select the optimal site for hysterotomy. During the procedure, continuous echocardiography should be used in combination with pulse oximetry, when possible, to monitor fetal heart rate, cardiac function, and volume status. An OR nursing team trained in fetal surgical procedures and familiar with the specialized instrumentation is of critical importance. The surgical team should be led by a pediatric surgeon or a perinatologist with specific training in fetal surgical techniques. In our institution, two pediatric surgeons with experience in all aspects of fetal therapy are scrubbed on all fetal surgical procedures, to assure maximal expertise with these uncommon procedures.

14.2.2.2 Anesthesia

Patients should be admitted prior to the planned procedure for monitoring and initiation of tocolysis with Indomethecin. Antibiotics should also be administered preoperatively to decrease the risk of maternal complications and chorioamnionitis. At the time of the procedure, anesthetic management should be initiated with placement of an epidural catheter to assist in both intra-operative and post-operative pain management. Typically, a Fentanyl/Bupivicaine mixture provides optimal pain control and reduces uterine irritability. General anesthesia is induced with inhalational agents, generally at a MAC of 2–2.5, sufficient to provide uterine relaxation. Maternal monitoring should include a radial arterial line, frequent cuff pressures, multiple large bore IV catheters, a foley catheter, pulse oximetry, and continuous EKG. Fluid management strategies should be aimed at euvolemia, given the predilection to postoperative non-cardiac pulmonary edema in the pregnant patient.

14.2.2.3 Positioning and Draping

Patients should be positioned supine with a left lateral tilt provided by a roll under the right side, in order to maximize venous return by preventing inferior vena caval compression by the uterus. Skin prep should include mid-abdomen to mid-thigh, and the operative field can be squared with sterile towels and covered with a fenestrated and pocketed drape.

14.2.2.4 Incision and Exposure

In general, the uterus is exposed through a low transverse abdominal incision. Placental position may guide the fascial incision. In general, subcutaneous flaps can be raised and the fascia may be divided in the midline from the umbilicus to the symphysis pubis. For posterior placentas, a ring retractor can then be positioned for retraction of the abdominal wall. A late gestational uterus with an anterior placenta may dictate that the fascia be divided transversely to allow anterior rotation of the uterus and a posterior hysterotomy.

14.2.2.5 Opening the Gravid Uterus

Prior to hysterotomy, the uterus is palpated to determine whether sufficient relaxation has been achieved. Transuterine ultrasound is used to confirm fetal and placental position prior to hysterotomy. Under ultrasound guidance, electrocautery is used to map the placental margins on the surface of the uterus and a safe site for hysterotomy (>6 cm from the placenta) is determined, avoiding uterine vasculature. Unlike a standard caesarean section, the lower segment of the uterus is avoided due to increased risk of amniotic fluid leak, chorioamnionitis and preterm labor.

Once a site is chosen, opposing 0 PDS traction sutures are placed through the uterine wall and fetal membranes under ultrasound guidance. Using electrocautery, a 2 cm incision is made in the myometrium between the sutures and the membranes are visualized and opened in a controlled fashion. A specialized uterine stapler is then placed through the fetal membranes and the stapler is fired once in either direction. It is important to use a uterine stapler intended for fetal surgery, as it compresses the myometrium and controls the membranes to minimize blood loss during hysterotomy while maintaining membrane integrity for closure. Absorbable staples are used to avoid subsequent fertility issues. Using a Level I rapid infuser, warmed Lactated Ringer's solution is infused into the amniotic space via a catheter to maintain amniotic fluid volumes and fetal temperature, while preventing cord compression. When an extremity is available (CPAM, SCT) a fetal peripheral intravenous line is then placed for infusion of fluids, blood, or medications.

14.2.2.6 Closure of the Gravid Uterus

Proper uterine closure is critically important, as the fetus must be returned to the amniotic space in such a way as to allow gestation to continue as normally as possible. The closure must have adequate strength to prevent uterine rupture, must be watertight to prevent amniotic fluid leaks, and must not contribute to preterm labor or future infertility. A two-layer closure should be performed, using double-armed full thickness 0 PDS stay sutures approximately 2 cm apart and 2 cm back from the staple line and a running 2–0 PDS suture through myometrium and membranes. Prior to completing the running layer, approximately 400 cc of warmed Lactated Ringer's solution containing 500 mg of Oxacillin should be instilled into the amniotic cavity and adequate amniotic fluid volumes should be confirmed by ultrasound. An omental flap should be used to buttress the uterine closure, and the maternal laparotomy should be closed in layers. Skin closure should be performed with an absorbable subcuticular layer, and dressings should consist only of a transparent Tegaderm, in order to allow continued fetal monitoring by ultrasound postoperatively.

14.2.2.7 Tocolysis and Postoperative Care

Preterm labor can compromise even the most carefully conducted intervention, and adequate tocolysis is of paramount importance to the success of any open fetal surgical procedure. Preoperative placement of an epidural catheter provides analgesia once the uterine relaxing effects of inhaled anesthesia have worn off, preventing a maternal stress response and uterine irritability. Placement of an Indomethacin suppository preoperatively begins the process, and a loading dose of 6 g IV magnesium sulfate is administered during hysterotomy closure. A maintenance infusion of magnesium sulfate is continued at 2–4 g/h for 18–24 h postoperatively, and Indomethacin suppositories are placed every 6 h postoperatively through 24 h. Patients must be closely monitored for signs of magnesium toxicity and serum magnesium levels should be checked frequently during this period. In addition, daily fetal echocardiography is required to detect any signs of Indomethacin toxicity, which can manifest as ductal constriction, oligohydramnios or tricuspid regurgitation. Uterine activity is monitored by tocodynamometer, and fetal heart rate is followed for any signs of distress. Daily ultrasound performed during the inpatient hospitalization assesses for fetal movement, amniotic fluid and membrane status, and serial anatomic evaluation.

During the postoperative period, fluid status must be carefully managed. Both the physiology of pregnancy and the magnesium sulfate regimen predispose the patient to noncardiogenic pulmonary edema, one of the most serious complications observed in otherwise healthy mothers. Empiric furosemide diuresis can be added if signs of pulmonary edema develop. After 48 h, patients begin a tocolytic regimen of 10–20 mg oral Nifedipine every 6 h, which is continued through delivery. Patients can usually be discharged by postoperative day 4, but should be required to remain on modified bedrest for the first 2 weeks after discharge. In the absence of uterine irritability, patients can then be allowed moderate activity, though they should remain nearby and return for twice-weekly ultrasounds

with obstetrical assessment. Once the fetus reaches 36 weeks' gestation, lung maturity is assessed by amniocentesis, and caesarean section is performed once the lungs are mature.

14.3 Anatomic Anomalies Currently Treated by Open Fetal Surgery

14.3.1 Fetal Lung Lesions

Fetal lung lesions represent a spectrum of pulmonary maldevelopment and for the purpose of discussion can be divided into four classifications: Congenital Pulmonary Airway Malformations (CPAM); Extralobar Bronchopulmonary Sequestration (BPS); Intralobar BPS; and Hybrid Lesions. It is important to realize that CPAMs may have features suggestive of BPS, such as systemic blood supply (hybrid lesions) or BPS may contain CPAM histology often suggested by a cyst within an extralobar BPS. In addition, lobar or segmental bronchial stenosis or atresia may be present suggesting an etiologic link with obstruction. CPAM is a hamartomatous tumor that is thought to arise from aberrant events during lung branching morphogenesis [15]. Grossly CPAMs appear as a discrete intraparenchymal masses that derive their blood supply from the pulmonary circulation and can contain cysts of any size ranging from the visually imperceptible (microcystic CCAM) to the predominantly cystic (macrocystic CCAM). Histologically CCAM is characterized by an overgrowth of one or several components of lung tissue with typically bronchial and epithelial elements. Bronchopulmonary Sequestration (BPS) consists of a mass of nonfunctional lung tissue that arises as an aberrant outpouching from the developing foregut. Characteristic features include the absence of a communicating bronchus and aberrant systemic blood supply. Intralobar sequestration shares a visceral pleural lining with usually a lower pulmonary lobe and may be aerated by intra-alveolar communications. The combination of systemic vascular inflow with pulmonary venous outflow in these lesions often results in a high-flow, low-resistance circuit leading to cardiac failure in childhood.

The differential diagnosis of fetal lung lesions also includes bronchogenic cysts, congenital lobar emphysema, segmental bronchial stenosis, bronchial atresia, unilateral lung agenesis, congenital diaphragmatic hernia (particularly right sided), mediastinal tumors, and congenital high airway obstruction (CHAOS). Detailed ultrasonographic features including lesion volume, consistency, location, arterial blood supply, and venous drainage will usually provide a definitive diagnosis.

14.3.1.1 Pathophysiology and Natural History

The natural history of postnatally recognized CCAM includes recurrent pulmonary infection that is resistant to antibiotic treatment, pneumothorax, and ultimately a propensity for malignant degeneration [16–18]. For these reasons we recommend resection of all CCAMs even when asymptomatic. The postnatal natural history of BPS is dependent upon whether they are intralobar or extralobar. Intralobar BPS should always be resected due to likely events of infection or high output cardiac failure. Extralobar BPS should be resected if there appears to be risk for cardiac failure, there is significant mass effect, or lymphatic congestion results in associated pleural effusion. In contrast to postnatally diagnosed lesions, the natural history of prenatal cystic lung lesions is relatively unpredictable. Approximately 15–20% of fetal CPAM lesions will decrease in size and 2/3rds of BPS lesions shrink considerably prior to birth [19, 20]. Despite a relative or absolute decrease in size and a tendency to become iso-echogenic with lung tissue by ultrasound examination in the third trimester, few if any of these lesions truly disappear and postnatal CT scan will confirm the persistence of the lesion after birth. Other CPAMs will grow dramatically during gestation with secondary compression of the surrounding lung and mediastinal structures. This may result in heart failure (hydrops) in the fetus or the presence of a large mass preventing ventilation at term. In addition, there is a low incidence of significant pulmonary hypoplasia

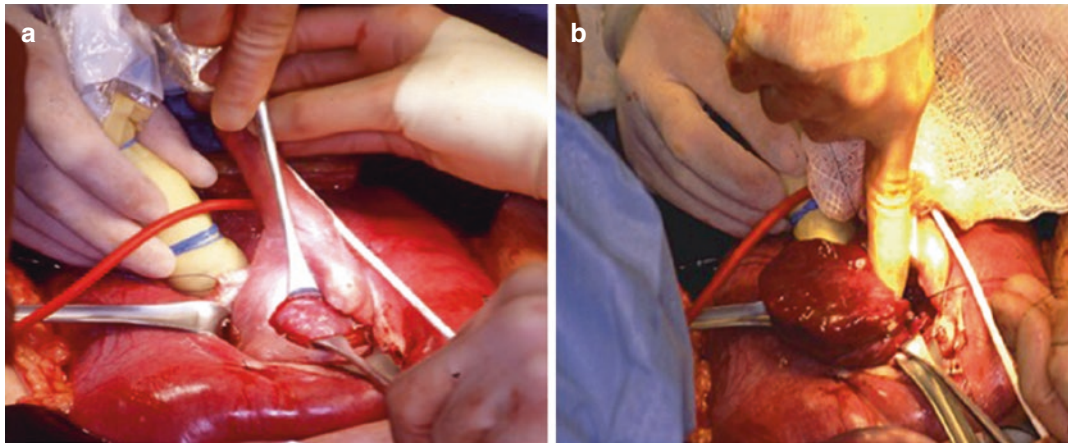

Fig. 14.1 (**a**) Resection of a fetal CPAM. The picture illustrates the fetal position with the arm and chest wall exposed and the head within the uterus. Continuous echocardiographic monitoring is performed during the procedure and an IC and pulse oximeter are placed on the exposed hand. A thoracotomy has been performed and the tumor can be seen bulging out of the incision. (**b**) A hilar dissection is performed. Here the pulmonary artery and bronchus have already been divided and the pulmonary vein is being ligated prior to removal of the tumor

that may impact survival after birth. The evolution of hydrops associated with CPAM is nearly uniformly fatal without intervention and is the sole indication for fetal surgery [19]. Given the uncertain natural history of these lesions, and the requirement for early intervention when hydrops develops, it was important to develop predictive parameters for the development of hydrops. One such parameter is the CPAM volume (using the formula for a prolate ellipse—length × height × width × 0.52) divided by the head circumference (to control for gestational age) ratio, called the CVR [21]. By serial measurement of the CVR, we have determined that most CPAMs follow a predictable growth profile, increasing in size until they plateau at around 28 weeks gestation. A CVR on presentation of ≥1.6 in a microcystic CPAM predicts an 80% likelihood of the development of hydrops, and these fetuses require very close sonographic surveillance (2–3 times per week) to monitor for signs of hydrops. A CVR of <1.6 portends a low likelihood of hydrops and we recommend initial weekly surveillance with decreasing frequency after 28 weeks. CPAMs with a predominant macrocystic component must be observed frequently throughout pregnancy as their growth is less predictable than microcystic CPAMs and we have observed rapid growth after 28 weeks in a few cases.

14.3.1.2 Fetal Intervention for Lung Lesions

Fetal intervention for CPAM is one of the unequivocal success stories of fetal surgery. The majority of lung lesions require no fetal intervention and can be managed postnatally as described above with excellent outcomes [22]. CPAMs that present with CVRs of ≥1.6 are a high risk category and require close surveillance. We [23] and others [24, 25] have observed growth arrest of microcystic CPAMs with steroid therapy reducing the need for fetal surgical resection. At the present time, we empirically treat CPAMs at risk for evolution of hydrops, or in early stages of hydrops, with steroids prior to fetal intervention. If signs of hydrops persist or progress in the fetus less than 32 weeks gestation, fetal surgery is indicated, either open resection for microcystic lesions (Fig. 14.1), or thoracoamniotic shunt placement for macrocystic lesions with a single dominant cyst or multiple communicating cysts. If hydrops develops in a fetus after 32 weeks gestation, or if there is persistence of major mediastinal shift closer to term, we recommend delivery and resection by the Ex Utero Intrapartum Treatment (EXIT) procedure [26]. The results of fetal therapy for hydrops induced by fetal lung lesions have significantly improved upon the natural history. Of 24 fetuses undergoing open fetal

surgery at the Children's Hospital of Philadelphia between 21 and 31 weeks gestation, there are 13 healthy survivors with 1–16 years of follow up. Resections involved a single lobectomy in 18 cases, right middle and lower lobectomies in 4 cases, extralobar BPS resection in 1 case, and 1 left pneumonectomy for CCAM. In survivors resection resulted in resolution of hydrops within 1–2 weeks after resection and impressive compensatory lung growth prior to delivery. Follow up developmental testing has been normal in all survivors. The results of thoracoamniotic shunt placement for hydrops due to CCAMs with a predominant cyst are even better with good quality of life survival of approximately 75% of shunted patients.

14.3.2 Sacrococcygeal Teratoma

A particularly challenging fetal anomaly requiring expertise in its pre and perinatal management is Sacrococcygeal Teratoma (SCT) [27, 28]. SCT is a teratoma arising from the presacral area that occurs in 1/30,000–1/40,000 live births. SCTs have malignant potential but are predominantly benign at birth. By definition they are comprised of elements from all three germ layers on microscopic examination and usually contain cystic and solid elements. Fetal karyotype is usually normal and there are usually no associated anomalies. SCTs have been classified (AAP Surgical Section Classification) based on the anatomic distribution of the tumor [29]. Type I SCT is predominantly external with a minimal presacral component. Type IV SCT is predominantly presacral with extension into the pelvis and abdomen and Types II and III are intermediate between these extremes. The majority of SCTs are Types I or II. Type IV is of significance because it can be missed after birth if not detected prenatally with subsequent presentation with pelvic outlet obstruction or malignancy.

14.3.2.1 Pathophysiology and Natural History

The natural history of prenatally diagnosed SCT is considerably worse than that after delivery [30]. After birth, the majority of patients with SCT do well after early surgical resection, which must include the coccyx to prevent recurrence of the tumor. In contrast, the mortality associated with prenatally diagnosed SCT ranges from 30% to 50%. The high mortality rate of fetal SCT can be attributed to a variety of mechanisms all of which relate to the size or blood flow of the tumor. Mass effect can result in preterm labor and/or dystocia and these were common mechanisms of fetal demise prior to the advent of prenatal diagnosis. SCTs can hemorrhage internally resulting in rapid enlargement of the tumor and fetal anemia, or rupture and bleed into the amniotic fluid resulting in fetal anemia or sudden death. Finally, predominantly solid SCT have high associated blood flow with arteriovenous shunting. This represents a low resistance vascular steal from the fetus and placenta and can ultimately result in high output cardiac failure [31]. Serial echocardiographic assessment can document the evolution of high output failure with increasing combined cardiac outputs and descending aortic blood flow, increasing left and right ventricular end diastolic diameters, increasing inferior vena caval diameter, and increasing placental thickness [32]. Fetal hydrops and placentomegaly may subsequently occur with the end result being fetal demise and often the maternal mirror syndrome. The evolution of hydrops secondary to high output cardiac failure in the immature fetus with SCT is associated with near 100% mortality and is the sole indication for fetal resection of these tumors.

14.3.2.2 Fetal Intervention for SCT

The fetus presenting with a large predominantly solid SCT is at high risk for progression to hydrops [33]. We recommend frequent surveillance by sonography and echocardiography with measurement of the cardiovascular parameters noted above. This may be as often as 3 times per week in the fetus verging on hydrops as they can decompensate rapidly and success of fetal treatment is dependent upon intervention before progression of hydrops. Fetal debulking of the tumor to remove the vascular steal is recommended when the evolution of high output cardiac failure

is recognized at prior to 28 weeks gestation in a fetus with Type I SCT. Timing of intervention is critical and should be recommended when the first overt evidence of hydrops occurs. The presence of advanced hydrops and/or the presence of placentomegaly are contraindications for fetal intervention. A significant number of pregnancies complicated by high-risk SCT will manifest signs of fetal or maternal decompensation, or both, between 27 and 32 weeks of gestation. In this grey zone between fetal intervention and adequate maturation for delivery, we have moved toward pre-emptive delivery by the EXIT procedure with debulking of the tumor on placental support [28]. Once the cardiac failure has resolved and the infant has been stabilized after birth, a formal resection of the residual tumor and coccyx can be performed. After fetal resection of the SCT, hydrops will generally resolve within 2–3 weeks. Since 1995, we have operated on 7 anatomically appropriate fetuses with SCT and associated high output failure with 5 survivors. One survivor has required postnatal treatment of pulmonary metastases of germ cell tumor but at 11 years of age has no evidence of disease. Another survivor had significant morbidity likely related to emboli at the time of tumor resection. The other three survivors remain healthy. These cases demonstrate that fetal resection of a large tumor can reverse the pathophysiology of high output cardiac failure in carefully selected cases and that early intervention offers the best hope of survival once high output failure is documented. However, SCT remains one of the most difficult and challenging fetal anomalies to manage and parents should be counseled appropriately. Our algorithm for pre and perinatal management of high risk fetal SCT is shown in Fig. 14.2.

14.3.3 Fetal Myelomeningocele

Myelomeningocele (MMC) or open spina bifida is a common and devastating congenital anomaly for which there is no satisfactory postnatal treatment. It is the first non-fatal anomaly considered for fetal surgical intervention necessitating a careful analysis of risks and benefit. It is

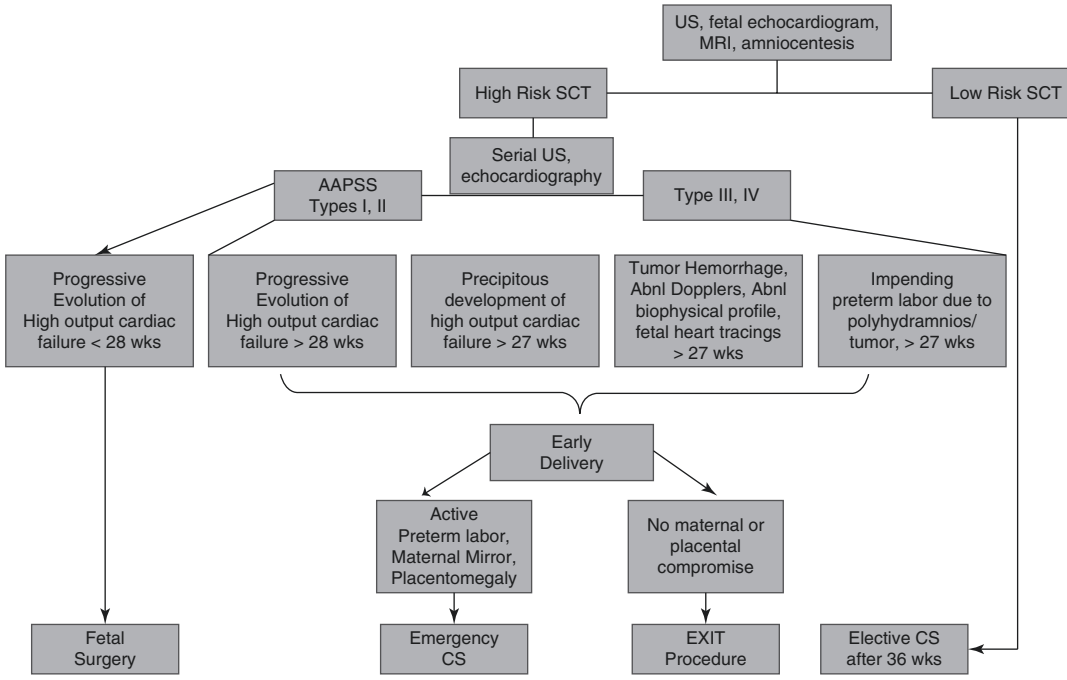

Fig. 14.2 CHOP Algorithm for pre and perinatal management of fetal SCT. (Reprinted with permission from Ref. [28])

characterized by protrusion of meninges and neural elements through a defect in the vertebral arches with secondary complications of lifelong paralysis and varying degrees of mental retardation, bowel and bladder dysfunction, and orthopedic disabilities [34]. MMC has been determined to have both genetic and micronutrient causes. While substantial progress could be made in preventing this disorder through folic acid supplementation, MMC still effects approximately 1/2000 live births and this figure does not include the 23% of MMC pregnancies in which the fetus is aborted [35–38].

14.3.3.1 Pathophysiology and Natural History

There is experimental and clinical evidence implicating the "two hit hypothesis" in the pathophysiology of MMC recently reviewed by Adzick [13]. The first "hit" is failure of neurulation resulting in an open spinal defect. Interestingly, there is minimal evidence for primary neural injury during this phase of the pathogenesis. The second "hit" results from exposure of the neural elements to the amniotic fluid and mechanical effects within the intrauterine environment. This is where evidence suggests the neural damage occurs and this evidence constitutes the rationale for fetal coverage of the MMC defect. A secondary result of the open spinal defect is the Arnold-Chiari malformation which is responsible for a significant component of the morbidity and mortality of MMC. Loss of cerebral spinal fluid through the defect results in a sump effect that causes descent of the hindbrain into the posterior fossa with secondary brainstem compression. With current postnatal treatment nearly 14% of all MMC neonates do not survive past 5 years of age, with the mortality rising to 35% of those with symptoms of brainstem compression from the Arnold-Chiari malformation. Whereas 70% of patients have an IQ >80, only half are able to live independently as adults, even with adapted accommodations [39, 40]. In addition to the motor and sensory deficits due to the spinal cord lesion, MMC patients have significant complications from hydrocephalus, the Arnold-Chiari II malformation, and tethering of the cord at the site of surgical repair. Hydrocephalus occurs in more than 85% of patients with MMC and at least 80% require placement of shunts to prevent neurologic and intellectual compromise associated with hydrocephalus. The rate of shunt related complications and morbidity is high contributing significantly to the overall morbidity of MMC. Thus it is clear that improvements in treatment are desperately needed.

14.3.3.2 Fetal Intervention for MMC

The rationale for open fetal MMC repair is based upon the prevention of neurologic deficits and associated morbidities. With evidence from animal models supporting the likelihood of improved functional outcomes, the first attempts at human MMC repair were reported in the late 1990s. The first endoscopic attempts at MMC repair were reported in 1997 with no apparent improvement in clinical outcome [41]. A subsequent report comparing outcomes between endoscopic and open repair demonstrated superior results with the open approach [42], and thus far attempts at endoscopic repair have not been proven effective in a well designed study. The first successful open fetal surgery for MMC demonstrating improved neurologic function was performed at CHOP in 1998 [43], and was followed by two studies of open MMC repairs reported in 1999 ($n = 10$) [44] and 2003 ($n = 50$) [45] at CHOP. The technique consists of excision of the MMC sac with preservation of the neural placode, closure of mobilized paravertebral myofascial flaps which are lined by Dura, and direct closure of the skin if possible with the use of an alloderm patch in larger defects. In these series overall survival was 90 and 94% respectively, with partial or complete reversal of hindbrain herniation in 100% of fetuses within 3 weeks of operation (Fig. 14.3), and VP shunt rates were significantly lower than expected based on historical controls.

Based on these promising initial results for open MMC repair, a group of three centers in the United States undertook a randomized clinical trial comparing prenatal open MMC surgery with postnatal surgery, the Management of Myelomeningocele Study (MOMS), in 2003. The study was carried out at CHOP, Vanderbilt University and UCSF, with an independent Data

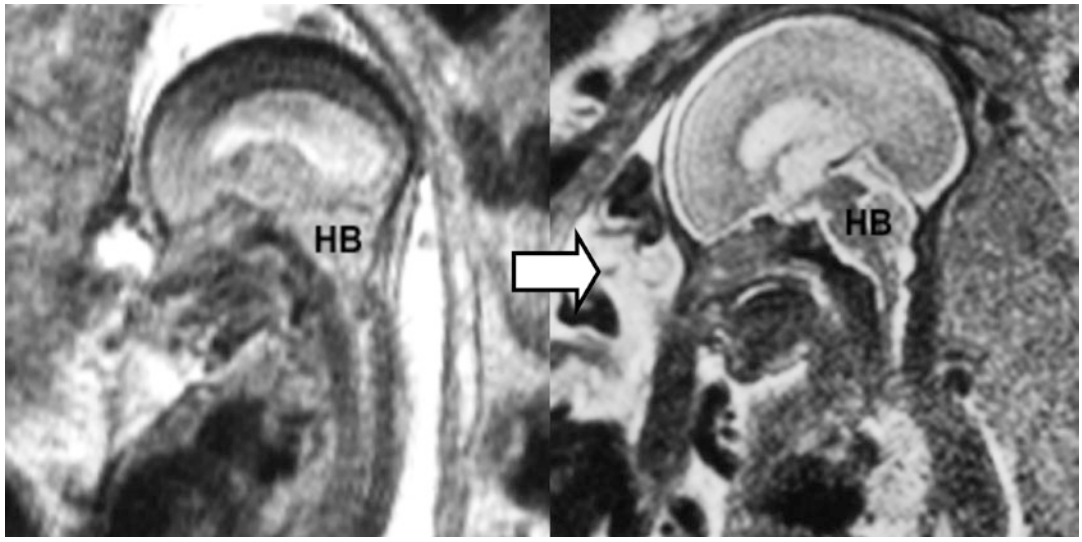

Fig. 14.3 (**a**) MRI appearance of hindbrain herniation in Arnold-Chiari II malformation. (**b**) Reversal of hindbrain herniation 3 weeks after fetal repair of MMC. Fluid spaces in the cisterna magna are uniformly restored after fetal repair. (**c**) Algorithm for management of fetal MMC

and Study Coordinating Center at George Washington University Biostatistics Center. While the trial was being conducted, a moratorium on open fetal MMC repair outside the trial was agreed upon by other fetal centers in the US. The study was powered to recruit 200 patients but was halted in December 2010 when a planned interim analysis demonstrated clear benefit for prenatal surgery after randomization of 183 patients. The results were reported in 2011 [46] and included 158 women randomized prior to July 1, 2009, with 78 in the prenatal group and 90 in the postnatal repair group. The inclusion criteria required that the fetus be 19–25.9 weeks of gestation, with MMC located between T1-S1, with evidence of hindbrain herniation, and normal karyotype without evidence of other abnormalities. The first primary endpoint of the study was a composite of fetal or neonatal death and the need for a CSF shunt at 12 months of age. Sixty-eight percent of the prenatal surgery group versus 98% of the postnatal group fulfilled the primary endpoint, with actual shunt rates of 40% versus 82% respectively. At 12 months of age, rates of moderate or severe hindbrain herniation were significantly lower in the prenatal group (25%) compared the postnatal group (67%). The secondary outcome was a score derived from the Bayley Mental Development Index and the difference between the functional and anatomic level of the lesion at 30 months of age, and was significantly better in the prenatal group versus postnatal repair. Children in the prenatal group were significantly more likely to walk without the use of orthotics or devices (42% vs. 21%), and scored significantly higher in parent-reported self-care and mobility scores. Importantly, prenatal surgery was associated with higher rates of prematurity and maternal morbidity, though infant mortality rates were equal and no maternal mortalities occurred.

Long-term follow-up on neurodevelopmental outcomes at age 5 through 9 of the MOMS cohort (MOMS II) will be a fundamental component of evaluation of the overall efficacy of prenatal therapy for MMC. Results of 5-year follow-up on the cohort of patients treated at CHOP prior to the MOMS trial were recently reported [47]. The majority of children achieved complete independence in cognitive (84%) and mobility (68%) scores, but continued to require significant assistance in self-care. Improved understanding of long-term functional limitations will allow for more effective interventions to maximize clinical outcomes following MMC repair.

14.3.4 Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) occurs in 1 in 3000 to 1 in 5000 live births and is associated with high rates of morbidity and mortality due to pulmonary underdevelopment resulting from the anatomic defect. CDH was one of the first anomalies considered for fetal intervention, however the early experiences with open fetal surgery and tracheal occlusion have produced mixed results and raised controversies regarding the natural history of the anomaly and identification of patients likely to benefit from prenatal therapy.

14.3.4.1 Pathophysiology and Natural History

CDH results from failure of closure of the foramen of Bochdalek between 8 and 10 weeks of gestation. The cause of that failure is the subject of active investigation, with strong evidence implicating genetic factors including disruption of retinoid signaling [48]. Herniation of abdominal contents into the thoracic space results in pulmonary hypoplasia (PH) due to interference with branching morphogenesis during lung development, resulting in a reduction in the number of airways, alveolar, and vascular structures, in turn leading to decreased surface area for gas exchange and fixed increased vascular resistance [49]. Pulmonary vasculature in CDH is also grossly abnormal, with hypermuscular peripheral pulmonary arteries resulting in increased pulmonary vasoreactivity and persistent pulmonary hypertension (PPH). As hypoxemia and acidosis stimulate further pulmonary vasospasm, patients may decompensate rapidly and prove refractory to ventilation by conventional modalities [50]. Improvements in neonatal management, including immediate intubation and ventilation with low peak pressures, blood pressure support, delayed surgery, and extracorporeal membrane oxygenation (ECMO), have resulted in improved outcomes [51]. However, CDH resulting in severe pulmonary insufficiency remains a clinical problem with no adequate postnatal treatment option. The frustration of physicians and surgeons observing the effects of this prenatal insult has prompted considerable exploration of fetal interventions to prevent or reverse pulmonary hypoplasia and restore sufficient lung mass for neonatal survival.

14.3.4.2 Fetal Intervention for CDH

To meet the fundamental criteria for consideration of fetal intervention, the natural history of the condition must be well-described. While advances in prenatal imaging have led to detailed analysis of the anatomic abnormalities encountered in CDH, controversy exists regarding their prognostic power. The most significant prognostic factor for poor outcome is a finding of herniation of the liver into the thorax ('liver-up'), which is associated with a 55% mortality rate compared to mortality of 26% in 'liver-down' cases [52]. Measurements of lung volume, whether by direct measurement or lung-to-head ratio (LHR), calculated using the contralateral lung at the level of the four-chamber view of the heart [53, 54], or "observed to expected" LHR or lung volume determined by US or MRI, do not provide additional independent predictive value for mortality over liver herniation, but do provide additional evidence of severity. With improving survival and no validated prenatal prognostic indicator of morbidity, selection of a group with a defined expected mortality or quality-of-life-impacting morbidity for fetal intervention poses a significant challenge to trial design and analysis.

Initial trials of prenatal treatment employed open fetal surgery and a patch repair of the diaphragmatic defect, however fetuses with liver herniation could not be salvaged by this approach due to kinking of the umbilical vein resulting in intrauterine demise [55]. While no differences in survival were found in 'liver-down' CDH repaired in utero compared to postnatal repair, these patients were later determined to have favorable outcomes with postnatal therapy, and the open approach was ultimately abandoned. More recently, tracheal occlusion (TO) has been studied as a potential treatment for CDH-induced pulmonary hypoplasia. The lungs are net producers of amniotic fluid, and lung fluid volumes are normally regulated by fetal laryngeal tone. In

animal models, pulmonary hypoplasia may be induced by shunting of fluid from the lungs to the amniotic space, while obstruction of tracheal outflow generates large fetal lungs [56]. Fetal lamb models of TO in CDH demonstrated accelerated lung growth and improved pulmonary function [57, 58], although these studies raised concerns regarding lung maturity as measured by surfactant production and type II pneumocyte levels [59]. Based on the experimental data in animals, clinical trials were initiated at UCSF in the late 1990s, with an uncontrolled case series suggesting benefit for TO by a fetoscopic approach in CDH [60]. A subsequent RCT at UCSF demonstrated no benefit in the TO group [61], and an interim prospective trial at CHOP observed that even in cases when lung growth occurred, many of the neonates had severe respiratory compromise raising doubts about the biology of TO in severe CDH [62]. These results led to diminished interest in pursuing TO in North America. However, Jan Deprest and the Eurofetus study group have developed a minimally-invasive approach to TO utilizing a deployable balloon through a single small trocar, and have reported promising initial results [63]. However, there are serious flaws in this data including a 28% rate of primary repair of the diaphragm, suggesting the patients were not as severe as the selection criteria would suggest, no concurrent controls, and a simultaneous improvement in CDH survival in Europe due to adoption of permissive hypercapnia techniques during the decade of these reports [64]. Recently a multi-center RCT, the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) Trial was initiated by Eurofetus and the results of this trial are anticipated with interest. A US consortium to investigate FETO is currently being organized to augment the European trial.

14.4 Other Invasive Maternal/ Fetal Procedures

While the most common fetal anomalies treated by open fetal surgery are emphasized above, the spectrum of fetal intervention includes not only open fetal surgery, but also minimally invasive fetal surgeries such as shunting or fetoscopic procedures, as well as the Ex Utero Intrapartum Treatment (EXIT) procedure.

Fetoscopy first became available in the 1970's, and was initially used primarily as a diagnostic tool. With the development of more sophisticated camera equipment and specialized endoscopic tools, minimally invasive interventions have become not only feasible, but widely applied. Procedures performed in this manner range from laser coagulation of placental anastomoses in TTTS to balloon tracheal occlusion for CDH. Complications of these procedures may include bleeding, separation or rupture of fetal membranes, chorioamnionitis or preterm delivery. Most fetoscopic procedures can be performed entirely percutaneously, minimizing maternal and fetal risks. Such cases usually require only local anesthesia, while procedures which could cause fetal pain generally involve intraumbilical or usually intramuscular administration of opioid and/or muscle relaxant. Similarly, the lack of a hysterotomy obviates the need for extensive tocolysis, and most procedures are performed with only a single dose of indomethacin or nifedipine, if any tocolysis is required. Randomized controlled trials have demonstrated benefit for fetoscopic laser ablation in TTTS [65] and are currently being conducted for fetoscopic tracheal occlusion for CDH.

The EXIT procedure was originally used to deal with surgically applied clips in the early experience with TO for treatment of CDH [66] and was subsequently applied to the difficult airway in cases of large anterior neck mass. The indications for the procedure have now expanded [67], and it is used in any case in which difficulty obtaining an airway after birth is expected or in some circumstances where instability immediately after seperation from the placenta is anticipated (massive SCT with hydrops). Some such indications include not only giant anterior neck masses, but congenital high airway obstruction syndrome (CHAOS), hypoplastic craniofacial syndrome, thoracic masses, mediastinal tumors, pleural effusions, large CCAM's, premature infants with large SCTs, or as a bridge to extracorporeal membrane oxygenation (ECMO) for

severe CDH with a combined cardiac defect or other cyanotic lesion, minimizing any time during which the fetus might be hypoxic or acidotic.

During an EXIT procedure, the mother is positioned supine with a left lateral tilt to maximize venous return and maximize blood supply to the uterus and placenta. A deep general anesthetic is maintained with halogenated agents to achieve uterine relaxation. Although inhaled agents cross the placenta and may provide sufficient fetal anesthesia, fetal anesthesia is supplemented by an intramuscular dose of narcotic and a paralytic agent to prevent fetal discomfort and breathing during the procedure. Careful mapping by ultrasound of the placental edges is performed and the uterus is opened with the same absorbable stapler used in open fetal surgery to control blood loss during the procedure. A peripheral intravenous line is always established for fluid resuscitation, blood transfusion, and drug administration if necessary. A pulse oximeter should be applied to the exposed fetal hand in order to monitor oxygenation during the procedure, and continuous transthoracic fetal echocardiography provides constant assessment of fetal cardiac function and volume status. Infusion of warmed Lactated Ringer's solution is used to maintain uterine volume and to prevent spasm of the cord vessels, and the fetus is maintained on placental circulation while an airway is established. In cases of giant fetal neck masses, tracheal anatomy may be significantly distorted or compressed, and the carina may be displaced superiorly, yielding a small window through which to establish an airway. Rigid bronchoscopy and/or operative tracheostomy may be sufficient, but in some cases decompression of a cystic mass or partial tumor resection may be required.

Success of this procedure rests upon adequate uterine relaxation to maintain utero-placental blood flow and prevent placental separation. This relaxation can cause bleeding complications postoperatively, and Oxytocin is routinely administered immediately following division of the fetal cord. Maternal risks inherent to this procedure include hemorrhage, scar dehiscence or uterine rupture in a subsequent pregnancy (due often to classical cesarean incision required to avoid the placenta or atraumatically deliver a large tumor), and wound infection. Generally, the fetus is felt to be able to be maintained on placental circulation for around 60 min, though procedures as long as 2.5 h have been performed successfully [68]. Fetal risks of this procedure include bradycardia, hypoxic/anoxic brain injury, hemorrhage and death. These complications may occur due to cord compression, placental abruption, or loss of myometrial relaxation all of which result in inadequate uteroplacental gas exchange. Nevertheless, in competent hands the EXIT procedure has been applied with excellent results and minimal maternal or fetal morbity and is an essential component of the Fetal Treatment Center armamentarium.

14.5 Efficacy and Future of Fetal Surgery

The anomalies discussed in this chapter represent the full spectrum of efficacy in fetal surgery. In some cases, fetal surgery has clearly altered the natural history of the disease and improved outcomes (CPAM, TTTS, MMC). For some lesions there is too limited an experience for definitive statements to be made (SCT). For CDH, fetal intervention remains controversial as interventions have not yet shown benefit and selection of a cohort appropriate for fetal therapy has become increasingly difficult as improvements in postnatal management have increased survival rates even in severely affected fetuses.

Dramatic progress has been made in imaging and diagnosis of fetal anomalies, and technical development continues to allow more minimally invasive forms of therapy. As imaging modalities become more sophisticated, our capabilities for image-guided intervention will move to ever earlier gestational time points. In doing so, preterm labor and premature delivery can likely be decreased, though improvements in tocolysis should be a priority to optimize patient outcomes. In the future, randomized controlled trials must be conducted where appropriate to establish clear benefit to patients, allowing fetal surgery to transition from experimental therapy to standard of care.

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Minimal Access Neonatal Surgery

15

Gordon Alexander MacKinlay

Abstract

Minimal access techniques—Laparoscopy, thoracoscopy and retroperitoneoscopy—have gradually been adopted in many centres undertaking paediatric surgery. In some units the approach has become commonplace but in others the skills required are developing more slowly or the necessary equipment is unavailable. Hopefully this will change as more and more paediatric surgeons learn to appreciate the benefits that endoscopic surgery provides to the young patients in their care.

Keywords

Minimally invasive surgery • Newborn surgery • Outcomes

In the twenty-first century it is unacceptable to perform any surgical procedure on a child by the open route if it can be safely and easily be carried out through minimally invasive surgery.

Minimal access techniques—laparoscopy, thoracoscopy, and retroperitoneoscopy—have gradually been adopted in many centres undertaking paediatric surgery. In some units the approach has become commonplace but in others the skills required are developing more slowly or the necessary equipment is unavailable. Hopefully this will change as more and more paediatric surgeons learn to appreciate the benefits that endoscopic surgery provides to the young patients in their care.

Endoscopic surgery involves minimal access wounds in the abdominal or thoracic wall and leads to reduced handling, drying and retraction of viscera. This results in less post-operative ileus and therefore earlier feeding is possible. There is less adhesion formation which is not only beneficial should further surgery be required but also prevents long-term complications. As the degree of the surgical insult is reduced there appears to be less immunosuppression and this may also lead to faster recovery. There are fewer respiratory complications and fewer wound infections. For the surgeon there is improved visualisation in 'difficult' areas of the abdomen such as the pelvis or the oesophageal hiatus. As far as the parents and child are concerned the minimal scarring is

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_15

the most obvious benefit. It has been said that 'each scar on a child is a scar on the soul of the parents' [1].

The application of minimal access techniques to the neonate requiring surgery is dependent on the experience of the individual surgeon and an advanced degree of expertise and confidence in minimal access techniques on older children. Many neonatal surgical conditions are amenable to minimal access techniques. These are encompassed in this chapter although individual disease entities are covered in greater detail throughout this book.

15.1 Physiological Considerations in Neonates Undergoing Minimal Access Surgery

It is important for both the surgeon and the anaesthetist to be aware of the likely physiological effects of endoscopic surgery on the neonate.

The metabolic response to surgery differs in neonates to that seen in older children and adults [2]. There is a small increase in oxygen consumption and resting energy expenditure immediately after surgery with a return to normal levels by 12–24 h. The increase in resting energy expenditure is significantly greater in infants undergoing a major operation than in those subjected to a minor procedure. The limited increase in energy expenditure may be due to diversion of energy from growth to tissue repair. There are limited data available on older children, but they appear to have a different pattern of postoperative resting energy expenditure. There is a fall in the early postoperative period, similar to data collected in adults, but no late hypermetabolism. Protein metabolism mirrors energy expenditure and contributes to the overall changes observed. Various factors affect the magnitude of the response. It seems that in children intraoperative thermoregulation and metabolism are significant drivers of many of the postoperative changes. Minimally invasive surgery may maintain preoperative metabolic processes by altering the postoperative processes on a physiological level or by maintaining thermoregulation in children.

The carbon dioxide gas used in insufflation of the body cavity, thorax or abdomen will have a more significant effect in small infants. In thoracoscopy the impaired respiratory capacity imposed by lung collapse has significant implications for oxygenation and CO_2 excretion [3]. Further, the absorption of CO_2 insufflated into the chest, coupled with the impaired ventilation, can lead to a marked increase in arterial CO_2 concentration. The ability to increase CO_2 excretion, in the face of the increased load created by its absorption, is crucial to safe thoracoscopy in children.

The CO_2 is absorbed and excreted via the lungs. There is an increase in end-tidal CO_2 as a result of absorption from the pleura or peritoneum. In thoracoscopy there is the additional factor of ipsilateral lung collapse further increasing the $EtCO_2$ [4]. Single lung ventilation has a significant effect on $EtCO_2$.

There are also haemodynamic changes due to right to left shunting, a phenomenon that is very important in the early stages of thoracoscopy for oesophageal atresia during which the anaesthetist may find it easiest to control the situation by a period of hand 'bagging' the infant.

The insufflation of cold CO_2 into the thorax does not appear to cool the infant. In our study [4] we found that thoracoscopy was associated with an increase in core temperature in the intraoperative period. This may be due to maintained thermoregulation due to the absence of an open surgical wound. This finding is in keeping with the increase in core temperature noted in children undergoing laparoscopy [5] and during thoracoscopy in another study [6]. Thoracoscopy may, therefore, alter intraoperative core-temperature regulation.

15.2 Thoracic Procedures

15.2.1 Diaphragmatic Hernia

It is recommended that thoracoscopic repair of congenital diaphragmatic hernia should only be carried out by surgeons with specific training and experience in laparoscopic and thoracoscopic surgery in neonates and children [7].

The first laparoscopic repair of a posterolateral Bochdalek diaphragmatic hernia was by van der Zee and Bax in 1995 [8]. The first reported congenital diaphragmatic hernia surgically corrected by a thoracoscopic approach was by Becmeur et al. [9] in 2001 although these were in older infants of 8 and 19 months.

The baby should be in a stable cardiovascular and respiratory condition and under general anaesthesia. Endo-tracheal intubation is sufficient without single lung intubation and the patient is placed in a lateral decubitus position on the operating table. The surgeon stands at the head of the table with the assistant to his left and the scrub nurse on the opposite side of the table.

The telescope port (usually 5 mm) is placed below the tip of the scapula and two working ports (3 mm) are placed, one in the anterior axillary line in the 4th intercostal space and the other half way between the telescope port and the spine in the 4th or 5th space.

The first port is inserted after injecting 0.25% Marcaine and adrenaline and is inserted using an open technique, gently opening the space first with an artery forceps and then the port is introduced with a blunt trocar. CO_2 is insufflated at a flow rate of 0.5 L/min at a pressure of 6 mmHg to begin with (it may be increased to 8 mmHg later if necessary and with the agreement of the anaesthetist. A 30° telescope is introduced and gradually the bowel will reduce through the defect sufficiently to allow the two working ports to be introduced under direct vision. Reduction is best achieved using blunt atraumatic instruments such as 3 mm Johan forceps that are fenestrated and handle bowel safely.

The bowel is gradually reduced through the defect. Pushing the stomach down carries the spleen safely into the abdomen without potential trauma from handling the spleen directly.

Once the abdominal contents are reduced the defect is best repaired with non-absorbable sutures. Care should especially be taken at careful repair of the lateral corner of the defect as recurrence can occur here. If necessary a suture passed from outside the chest wall at this point and tied subcutaneously will secure this area safely. It may be necessary to use a patch such as a GORE-TEX® soft tissue patch. This needs to be cut to size externally, rolled and passed through a port. It can then be sutured into position with non-absorbable sutures tied intra-corporeally.

A chest drain is not necessary allowing the hypoplastic lung to expand slowly.

15.2.2 Oesophageal Atresia

Tovar [10] observed—'Only a handful of cases of this particularly rare condition are treated every year in most large centers and it is obviously difficult to acquire the necessary skills for this particular operation in small babies with tiny thoracic spaces. How to achieve this goal when not so many consultants operate upon more than one or two cases per year?'

Thoracoscopic repair of oesophageal atresia was first successfully achieved by Lobe and Rothenberg at the International Pediatric Endosurgery Group (IPEG) meeting in Berlin in 1999 [11]. This was in a 2-month-old infant with isolated oesophageal atresia. In 2000 Rothenberg [12] reported the first thoracoscopic division of a tracheoesophageal fistula and repair of oesophageal atresia in an infant. The first in the UK was in Edinburgh in 2001 [13].

The baby is anaesthetised with endotracheal intubation and placed semi-prone on the operating table (Fig. 15.1). Some use a bronchial blocker to achieve single lung ventilation but this

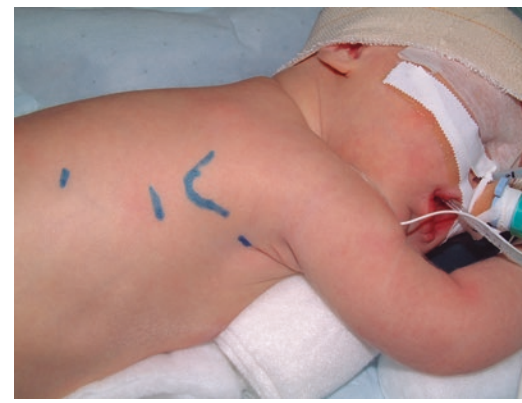

Fig. 15.1 Semi-prone position on table

adds to the anaesthetic time and has little advantage over endotracheal intubation. When the first port is inserted, CO_2 is insufflated at a flow rate of 0.5 L per minute to a pressure of 6 mmHg. Initially there is usually a period of desaturation and a rise in pCO_2, requiring ventilation to be adjusted accordingly. Within a few minutes however the baby stabilises and the other two ports can be inserted.

The first port (5 mm) is inserted below the tip of the scapula. As CO_2 is insufflated the lung gradually collapses. A short 4.5 mm 30° telescope is used. Two further ports are inserted, both 3.5 mm, one up in the axilla and the other more posteriorly in a line with the other two (Fig. 15.2). It is important that valved ports are used with good seals round the instruments to maintain the tension pneumothorax. The pressure on the insufflator may read 6 mmHg but with a leaky seal the lung will not collapse.

The assistant stands (or sits) to the right of the surgeon to hold the camera and the table height is adjusted to give a comfortable ergonomic position for the surgeon (Fig. 15.2).

With the lung collapsed a good view of the posterior mediastinum is obtained. The distal pouch is seen to distend and collapse with respiration. The azygos vein may be divided if necessary using a 3 mm monopolar hook diathermy. Lifting the vein gently with the hook, it empties, and is easily divided. Dissection commences around the distal pouch to free it circumferentially. A right-angled forceps such as a 3 mm Mixter forceps facilitates this. The fistula is then transfixed and ligated, close to its junction with the trachea, with a 5/0 non-absorbable suture such as braided polyester. The fistula is then divided.

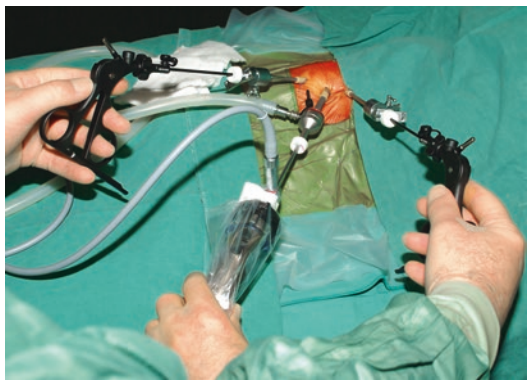

Fig. 15.2 Comfortable ergonomic position of instruments

The upper pouch is then identified; asking the anaesthetist to gently jiggle the Replogle tube will help in its location. Little dissection of the upper pouch is usually necessary unless there is a long gap. With pressure on the Replogle tube an opening in the distal end of the upper pouch is made with scissors. Cutting across three-quarters of the diameter in the first instance creates a flap (later excised) that can be used for traction to facilitate initial suture placement. Care must be taken to ensure that the mucosa is opened. The anastomosis is achieved with interrupted 5/0 braided polyglycolic acid sutures. Some prefer monofilament sutures but the braided suture ensures secure knot tying without slipping. If there is any tension, by using the tumbled square knot technique, the ends can be approximated safely. In cases of tension it is also helpful to paralyse and ventilate the infant for a few days to prevent disruption of the anastomosis [14]. Once the first few sutures are placed, a fine (5 Fr) silastic nasogastric tube is passed by the anaesthetist and advanced into the stomach with surgical guidance. This tube facilitates suture placement (ensure that sutures include the mucosa) and can be used to commence nasogastric feeds within 24 h.

Once the anastomosis is complete then a small chest drain may be passed through the lowest port site, if desired, and the lung is seen to expand as the other ports are removed. The port sites are closed with absorbable sutures to deeper layers and tissue glue to skin. An excellent cosmetic result is achieved without the potential sequelae of a thoracotomy incision. A contrast swallow at 5 days may be performed, prior to commencing oral feeds.

15.2.3 Aortopexy

If tracheomalacia is present and related to the oesophageal atresia it is usually due to an intrinsic

localized anomaly of the trachea at the site of the distal fistula. Aortopexy is appropriate in such cases and may be performed thoracoscopically [15].

The patient is placed supine on the operating table with a pad of Gamgee under the left side of the chest to elevate it 15–20°. The surgeon stands to the left of the operating table with the assistant seated to his left. The monitor is at the opposite side of the table. A 5 mm cannula is inserted in the mid axillary line by an open technique after infiltrating the skin and subcutaneous tissue with 0.25% Marcaine with adrenaline. CO_2 is insufflated at a pressure of 5 mmHg and a flow rate of 0.5 L/min. A 30° telescope is introduced and then two 3.5 mm ports are inserted above and below the first. The anterior mediastinum is visualized and the thymus swept away to the right from the aortic root, taking care of the phrenic nerve. The ascending aorta is identified and if required the pericardial reflection over the aorta can be opened. A hollow needle is passed through the sternum to check the appropriate position for the sutures and a tiny skin incision is made alongside it. A 3/0 prolene suture on a round-bodied needle is inserted through this incision and through the sternum, which is soft at this age, and then carefully a superficial bite of the aortic wall is taken with the needle ensuring that it does not enter the lumen! The suture is then cut so that the needle can be passed through the chest wall for extraction leaving sufficient length of suture intra-thoracically to be passed back out through the previously positioned hollow needle. This suture is then held externally in an artery forceps whilst two or three other sutures are positioned in a similar manner, above and below the first.

Under bronchoscopic control the 3–4 sutures are then pulled upwards and tied subcutaneously as the tracheal lumen is observed to open up. The lung is then allowed to re-expand, the port holes are closed and no drain is required.

15.2.4 Lung Resection

Thoracoscopic resection of lung lesions in the neonatal period is seldom necessary as many conditions can be left until the child is older. It requires advanced paediatric endoscopic skills, as the working space is limited. Congenital lung cysts, congenital cystic adenomatoid malformations, pulmonary sequestrations and congenital lobar emphysema can all be treated thoracoscopically. There is no difference in measurable outcomes between early and delayed resection of congenital lung lesions [16]. It is appropriate to use a management strategy of observation, with delayed resection, for asymptomatic patients [17].

Congenital lobar emphysema can often be treated conservatively [18]. Congenital cystic adenomatoid malformation (CCAM) is often diagnosed antenatally. Whilst some surgeons perform lobectomy for CCAM in the neonatal period, most will wait until the infant is older but it is wise to undertake surgery before infection arises as this can make lobectomy more difficult [19]. In my practice we choose to perform a thoracoscopic lobectomy before the infant's first winter.

Pulmonary sequestration may be intra or extra-lobar and surgery can be postponed until the infant is a few months of age.

Congenital lung cysts usually present beyond the neonatal period and elective surgery can be planned appropriately.

Thoracoscopy for all these conditions is feasible and best performed in a lateral decubitus position. Anaesthesia is best administered via a right or left mainstem intubation of the contralateral side or by introducing a bronchial blocker (a Fogarty catheter is usually used). The baby is supported on a bean bag with a cotton wool roll under the chest to allow the rib spaces to open up and taped to the table which can then be tilted toward or away from the surgeon as necessary to allow gravity to displace the collapsed lung appropriately during the procedure. The surgeon and assistant stand on the same side of the operating table with the baby facing them. The monitor is positioned on the opposite side of the table.

Each port site in turn is infiltrated with 0.25% Marcaine with adrenaline prior to incision. The first port is inserted by an open technique, a 5 mm incision is made in the mid axillary line in the 5th

or 6th space and blunt dissection is used to find a way through the intercostal muscles into the pleural cavity. A 5 mm cannula is then inserted using a blunt trocar and then a short 4.5 or 5 mm 30° telescope is introduced. If desired a smaller port and 'scope may be used but a larger telescope gives a better view. Once it is confirmed that the port is intra-pleural, CO_2 is insufflated at a pressure of 5 mmHg at a low flow rate (0.5 L/min). The port at this level should be looking directly into the oblique fissure. Appropriate positioning of two further 3 mm ports is under direct vision. These are usually in the anterior axillary line above and below the level of the optic port. For a lobectomy a pulsed bipolar sealing device is desirable for dividing the branches of the pulmonary artery to the affected lobe. This may be a 3 mm or 5 mm instrument depending on the manufacturer. If a 3 mm instrument is not available then a 5 mm port will be required, or ligation and division of the vessels may be performed but this is more time consuming. Dissection is performed from anterior to posterior [20].

For a lower lobectomy first the inferior pulmonary ligament is mobilized and the inferior pulmonary vein is identified but not mobilized at this point. In the case of a sequestration a systemic vessel (sometimes more than one) is usually identified coming directly from the aorta below the diaphragm (or sometimes above). This vessel is ligated (or clipped) and divided first in sequestration. After division of all the vessels the bronchus to the lobe is divided and oversewn with non-absorbable sutures. A stapling device is too large for neonates or small infants.

The lobe is then extracted through the lowest port site and a chest drain inserted and connected to an underwater seal.

15.2.5 Cyst Excision

Bronchogenic or other cysts are dissected out as appropriate and by keeping close to the cyst wall during mobilization most can be excised safely and relatively easily.

Foregut duplication cysts such as oesophageal duplication are best approached with the baby semi-prone as for oesophageal atresia repair. The pleura overlying the cyst is incised and the duplication is carefully mobilized from the oesophageal wall. The oesophageal mucosa is exposed but should be left intact and the defect in the oesophageal muscle is then repaired.

15.2.6 Chylothorax

Thoracoscopic ligation of the thoracic duct may be performed in cases of chylothorax. The magnification obtained in thoracoscopy can make the identification of a chyle leak easier. The approach is similar to that for oesophageal atresia repair and the port sites described for that (above) allow excellent visualization of the posterior mediastinum. The duct may either be ligated or clipped.

15.2.7 Mediastinal Masses

Mediastinal masses are uncommon in the neonate and usually arise from the sympathetic chain as a neuroblastoma, ganglioneuroblastoma or ganglioneuroma. Rarely is it necessary to undertake surgery for these in the newborn and it is important to evaluate the case in conjunction with the oncological multi-disciplinary team. Thoracoscopic excision and extraction of the tumour in a bag is required.

15.3 Abdominal Procedures

Neonatal laparoscopic surgical procedures have become widely accepted over recent years. Laparoscopy is well tolerated in the neonate and many congenital abdominal conditions can be approached in this way with the benefits of minimal access surgery.

For the majority of laparoscopic procedures the primary (optic) port is best placed at the umbilicus. This not only gives access to all quadrants of the abdomen but is also the most cosmetic. I always use the inferior umbilical fold for the umbilical

port site. The incision should, if possible, be within the fold, which can be everted to achieve optimal placement. Some surgeons choose the upper fold for example in the approach for pyloric stenosis but this is illogical as it places the optic closer to the operative field and thus achieves a more restricted view. In the neonate, in particular, the lower fold is best as often the umbilical vein is still patent and can bleed whereas the arteries in the inferior fold are rapidly occluded.

Others choose the centre of the umbilicus for their incision as the most direct approach but this distorts the appearance of the normal umbilicus. An incision within the inferior umbilical fold can be widened if necessary to allow exteriorization of bowel for extra-corporeal surgery. Simply stretching the skin incision with an artery forceps will extend the incision along Langer's lines, which are circumferential at the umbilicus. Extending it with a scalpel may cross the lines and create a cosmetically inferior scar.

15.3.1 Pyloromyotomy

Pyloromyotomy can easily be performed laparoscopically and this is the preferred approach. A double-blind multicenter randomized controlled trial of open versus laparoscopic pyloromyotomy was halted at the recommendation of the data monitoring and ethics committee because of significant treatment benefit in the laparoscopic group [21]. My own unit chose not to participate in that trial as we already considered laparoscopy was the best approach and this study proved it.

The baby is placed either at the foot of a shortened operating table or, if preferred, across the table. The surgeon stands at the baby's feet and the assistant to the left. The monitor is best placed across the table if a flat screen is available otherwise at the head of the table.

A 5 mm port is inserted in the inferior umbilical fold under direct vision having infiltrated the skin and subcutaneous tissue with 0.25% Marcaine with adrenaline. Only a very short length of port should be inside the abdomen so it is best sheathed with a short length of catheter to limit its excursion into the abdomen. The catheter may be sutured to the skin and fascia to prevent dislodgement. The instruments are introduced directly into the abdomen through 3 mm access wounds, one in the right hypochondrium, the other just to the left of the midline in the epigastrium (Fig. 15.3). A 3 mm fenestrated forceps of the Johan type is passed through the right hypochondrial site and used to grasp the duodenum gently, just beyond the pylorus. A laparoscopic retractable pyloromyotomy knife or a suitably narrow blade such as an ophthalmic 69 Beaver, on a handle, is carefully introduced through the epigastric site and an incision is made along the length of the pylorus from the pyloro-duodenal junction onto the antrum of the stomach. It is important that this incision is down into the muscle of the pylorus. The blade is removed and replaced with a 3 mm laparoscopic spreader that is introduced into the split in the pyloric tumour (Fig. 15.4). As the

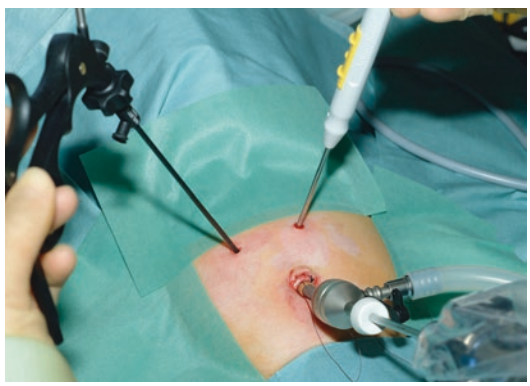

Fig. 15.3 Instrument sites in pyloromyotomy

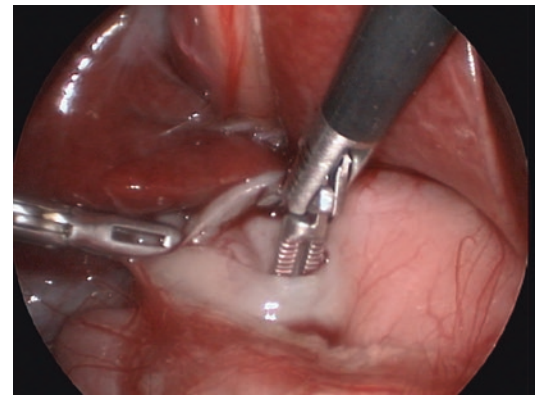

Fig. 15.4 Spreading the pyloromyotomy

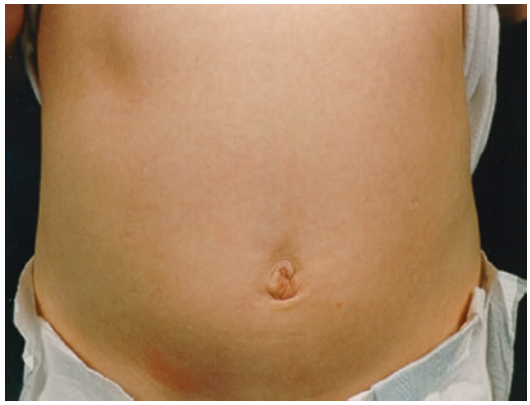

Fig. 15.5 Barely perceptible wounds post pyloromyotomy

spreader is opened to its full extent the muscle is widely separated to show the intact mucosa bulging. Changing the graspers to either side of the split allows further separation and moving the instruments in opposite directions parallel to the pylorus confirms that an adequate length pyloromyotomy has been achieved.

The instruments are carefully removed, taking care not to draw the flimsy omentum out behind them. The wounds are closed with a deep 4/0 polyglycolic acid suture and tissue glue to skin (Fig. 15.5). The operation takes only a few minutes. Feeding can commence as soon as the baby returns to the ward as the gastric paresis that occurs in some open techniques is seldom seen.

15.3.2 Fundoplication

Occasionally pre-term infants with severe gastro-oesophageal reflux may have difficulty weaning from ventilation or suffer recurrent severe respiratory symptoms due to aspiration until an anti-reflux operation is performed. Laparoscopic fundoplication is well tolerated [22] and significantly improves the outcome. The baby is placed on the operating table in a position similar to that for pyloromyotomy.

A 5 mm port is inserted by the open technique through a 5 mm incision in the inferior umbilical fold having infiltrated the skin and subcutaneous tissue with 0.25% Marcaine with adrenaline. Pneumoperitoneum is established with CO_2 at a pressure of 8–10 mmHg at a flow rate of 0.5–1 L/min depending on the size of the baby. Two further 'working' ports each 3.5 mm are inserted, one in the right, the other in the left hypochondrium. The exact position is dependent on the size of the baby. If the baby is too small for a Nathanson liver retractor an instrument is passed through a 3 mm stab wound in the right side of the abdomen just below the edge of the liver and the left lobe of the liver is elevated by this instrument which if ratcheted can be fixed to the peritoneum in the left flank. A further 3 mm stab incision in the left flank is used for an instrument to retract the gastric fundus (Fig. 15.6). The short gastric vessels rarely need to be divided in these cases. The oesophagus is gently mobilized at the hiatus with minimal dissection and a window developed behind the oesophagus where the two limbs of the right crus of the diaphragm will be visualized. Care is taken to leave the posterior vagus attached to the oesophagus. The two limbs of the right crus are approximated with one suture of braided polyester to narrow the hiatus, taking care to leave room for normal swallowing. A wide bore nasogastric tube in situ at this stage can prevent too tight a closure. It is removed at the end of the procedure or replaced with an appropriate sized tube for post-operative feeding if required. The fundus is then grasped by an instrument passed from right to left behind the oesophagus and gently drawn

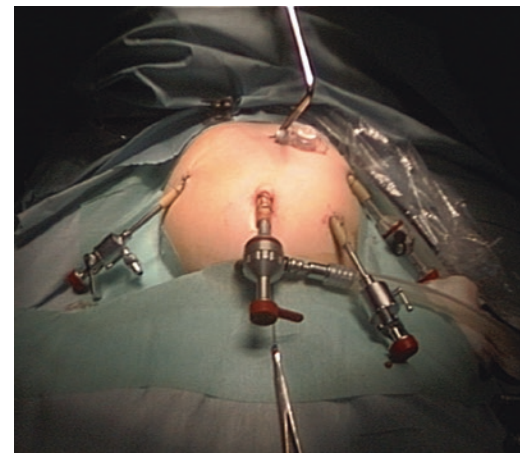

Fig. 15.6 Port sites for laparoscopic fundoplication (note gastrostomy button)

through to allow a loose wrap of fundus around the intra-abdominal portion of the oesophagus. This is approximated using three sutures of 3/0 braided polyester. The first suture brings the two parts of fundus together. The second suture, above the first, approximates the two sides and is also attached to the diaphragm at the hiatus. The third suture approximates the two sides also taking a bite of the anterior wall of the oesophagus. The latter two sutures help to prevent wrap migration into the thorax.

The ports are removed and closed with absorbable sutures to fascia and tissue glue to skin.

15.3.3 Gastrostomy

If a gastrostomy is required in the neonatal period it is safest to place it under laparoscopic guidance. In a small baby a telescope port is placed at the umbilicus and a further 3 mm 'stab' wound made in the right hypochondrium through which an atraumatic grasper is passed. The site of the proposed gastrostomy is chosen and the stomach held close to the abdominal wall as a 2/0 polyglycolic acid suture on a curved, round bodied needle is passed though the abdominal wall picking up the anterior gastric wall and back out through the abdominal wall a few mm away from the entry site. A further suture about 1 cm from the first is passed in similar fashion such that traction on the two 'U' sutures will bring the stomach up to the anterior abdominal wall. Suitable reduction in insufflation pressure facilitates this manoeuvre.

Using a Seldinger technique a cannula is passed percutaneously into the stomach between the two sutures followed by a guide wire. Graduated dilators are then passed though the abdominal wall into the stomach dilating up to 14Fr for a 12Fr button gastrostomy tube (of measured length) that is finally passed over the guide wire, into the stomach. Using one of the smaller size dilators to stiffen and guide the tube into the stomach facilitates this. The two sutures are then tied over the wings of the button device to retain it in place (Fig. 15.6). These sutures are removed in 7 days.

15.3.4 Duodenal Atresia

Laparoscopic repair of duodenal atresia has developed since 2001. The baby is placed at the end of the operating table as described for pyloric stenosis. The surgeon stands at the foot of the table with the assistant to the left. The first (5 mm) port is inserted in the inferior umbilical fold and once pneumoperitoneum is established two further 3.5 mm ports are placed, one in the right lower quadrant, the other in the left hypochondrium. An instrument for a liver retractor may be introduced through a stab wound in the epigastric region or the liver may be hitched up with a percutaneous suture through the falciform ligament. Alternatively the apical stitch in the anastomosis can be brought out through the abdominal wall to stabilize the enterostomies for the anastomosis [23, 24]. The duodenum is Kocherised, the proximal dilated and collapsed distal segments are identified and a diamond shaped anastomosis is made after incising the proximal bowel transversely and the distal bowel longitudinally. This is achieved with interrupted polyglycolic acid sutures. Others have used nitinol u-clips with good results [25].

Laparoscopic repair of duodenal atresia remains one of the most demanding paediatric laparoscopic surgical procedures [26].

15.3.5 Malrotation

Laparoscopic correction of malrotation in the neonate was first described in 1998 [27]. At first many considered it should only be considered for cases without volvulus but it is feasible even with volvulus and signs of ischaemia [28].

The baby is placed supine at the end of the table as for pyloromyotomy.

A 5 mm port is inserted in the inferior umbilical fold and the abdomen insufflated with CO_2 at a pressure of 8–10 mmHg with a flow rate of 0.5 L/min. A 5 mm 30° telescope is inserted and the bowel inspected. In the case of volvulus there may be evidence of chylous fluid in the peritoneal cavity. The bowel is collapsed and shows a dusky appearance with only the stomach and duodenum

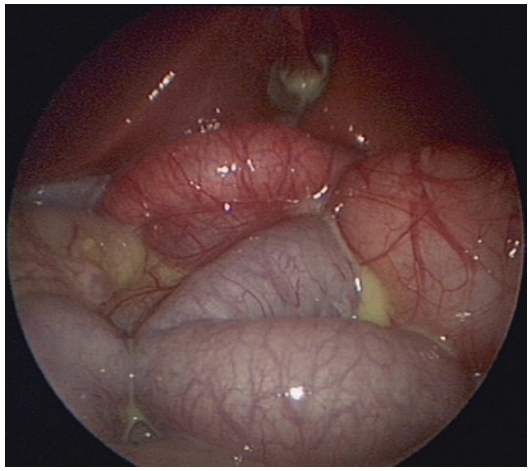

Fig. 15.7 Ischaemic bowel and chylous fluid in volvulus neonatorum

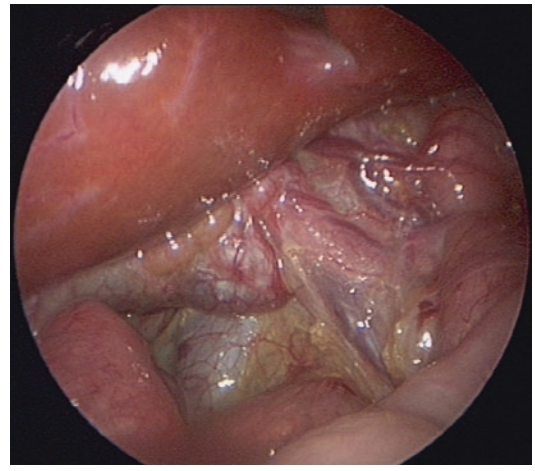

Fig. 15.8 Wide separation of root of mesentery, having corrected the volvulus

appearing pink (Fig. 15.7). Two 3.5 mm ports are placed on either side of the abdomen slightly below the level of the umbilicus and using two atraumatic bowel graspers such as fenestrated Johan forceps the bowel is gently inspected. As the bowel always rotates in a clockwise direction (north and south of the equator unlike water emptying down a plug hole) the bowel is gently rotated en masse in an anticlockwise direction. As the bowel is derotated the colour improves and returns to normal. Once this has been achieved Ladd's bands are visualised and divided with a 3 mm monopolar hook diathermy. The root of the mesentery is widely separated by carefully dividing the peritoneum with the hook diathermy. Once wide separation has been achieved the operative procedure is complete (Fig. 15.8). The ports are removed and the wounds closed (Fig. 15.9). Feeding can recommence within 24 h.

15.3.6 Small Bowel Atresias and Duplications

Small bowel atresias can be dealt with using a laparoscopically assisted approach, identifying the atresia laparoscopically and exteriorizing the loop of bowel via the umbilical port site and performing the resection, tapering (if necessary) and anastomosis externally [29, 30].

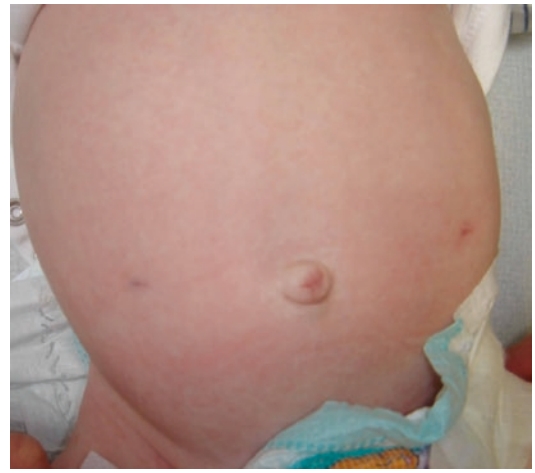

Fig. 15.9 Post operative wounds following correction of volvulus neonatorum

Duplication cysts can also be treated using this technique, aspirating the fluid from the cyst before exteriorizing the affected loop of bowel.

15.3.7 Hirschsprung Disease

In the early 1990s Georgeson [31] described the laparoscopic approach to endo-rectal pull-through for Hirschsprung disease. This can be performed in the neonatal period or delayed for a

period during which the bowel is decompressed by regular irrigations every 6–8 h.

The advantage of the laparoscopic approach is the ability to obtain biopsies to determine the exact level of the disease. Others prefer a purely transanal approach [32] but occasionally one may encounter a total colonic Hirschsprung's or a higher than expected transition zone so the laparoscopic biopsy technique is safer.

For the laparoscopic endo-rectal pull through the baby is placed in a supine position across the end of the operating table with the right side towards the foot of the table. The surgeon stands at the head of the baby and the assistant is best seated at the end of the table to hold the camera. The first port (5 mm) is inserted either in the inferior umbilical fold or as suggested by Georgeson it may be placed in the right hypochondrium to provide a wider view of the abdomen. Either way it is placed using an open technique having first infiltrated the skin and subcutaneous tissue with 0.25% Marcaine with adrenaline.

The abdomen is insufflated with CO_2 at a flow rate of 0.5 L/min to a pressure of 8 mmHg. Two further 3.5 mm ports are inserted, one to the right side of the abdomen at umbilical level and the other a little higher on the left.

The baby is placed in a Trendelenburg position and prepped front and back from the lower chest downwards including the legs that are encased in sterile stockinette or similar. The baby's bottom should be close to the edge of the table to facilitate the rectal dissection. Some padding is used to support the legs comfortably at the edge of the table.

First seromuscular biopsies are taken using a fine grasper and curved laparoscopic Metzenbaum scissors. These are sent for frozen section to confirm the level of disease prior to commencing dissection. With an atraumatic instrument lifting the colon towards the anterior abdominal wall, a window is developed in the mesocolon using a 3 mm hook diathermy. This is continued, staying close to the bowel wall, down to the peritoneal reflection and circumferential dissection at this level for a further 1–2 cm is performed. Staying close to the bowel wall prevents damage to the nervi erigentes and the vas in the male. The bowel is thus mobilized from the transition zone down to below the peritoneal reflection.

The ports are left in position and the CO_2 insufflation discontinued allowing the abdomen to deflate. The surgeon and assistant move to the opposite side of the table. The baby's feet are elevated using the stockinette, which can be fixed to the drapes over the baby's torso giving access to the anus. The rectal mucosa is accessed by placing 6–8 traction sutures through the perianal skin and the muco-cutaneous junction to radially retract the anal margin. Alternatively a retractor ring and hooks provides excellent exposure. Care must be taken not to overstretch the anal sphincters at this stage and during the dissection.

The mucosa is marked with cautery 5–10 mm above the dentate line circumferentially and then using a fine cautery needle the mucosa is incised at this level attaching multiple 5/0 silk sutures to the edge of the mucosa to provide traction. It is imperative that only the mucosa is dissected free from the underlying internal sphincter. Once a good submucosal plane is developed the dissection becomes easier and is continued until the rectal sleeve prolapses down. The advantage of the previous laparoscopic dissection is that there is little bleeding at this stage. Once the sleeve has prolapsed easily it is incised circumferentially and the mobilized bowel is pulled through it until the highest (ganglionic) biopsy site is seen. It is preferable to pull down a further 5–10 cm to ensure that the affected disease is fully resected. The muscle cuff is split posteriorly and pushed back into the pelvis. The affected bowel is sent to pathology for confirmation of the level of disease and the pulled through bowel is anastomosed carefully to the distal mucosal cuff using multiple 5/0 absorbable sutures to ensure that there is no leak.

On completion of the anastomosis the retraction sutures/ hooks are removed and the anus retracts. The surgeon, after a change of gloves, moves back to the other side of the table to check with the 'scope that there is no twist on the bowel. The ports are removed and the sites closed. Feeds can recommence the following morning.

15.3.8 High Ano-Rectal Malformations

Georgeson described a similar approach to high ano-rectal malformations [33]. In the neonatal period these cases are usually treated with a colostomy initially and the rectal pull through procedure is usually performed when the baby is a few weeks of age. It can be successfully treated with a primary single stage procedure within a day or two of birth [34].

The aim is to correct the high anorectal anomaly without the mid sagittal division of the muscles in the widely accepted approach described by Peña. The dissection is similar to the dissection for Hirshsprung's disease beginning at the peritoneal reflection continuing deeply close to the rectal wall until it tapers into the fistula distally. When the rectourinary or high rectovaginal fistula is reached the bowel is divided and the fistula usually sutured or clipped.

The legs are then elevated and the perineal dissection commenced after defining the perineal anal site using a muscle stimulator. A vertical 1 cm incision is made and the initial dissection is commenced with an artery forceps followed by a Veress needle with a radially expanding sheath, which is advanced in the midline with laparoscopic guidance from above entering the pelvis in the midline immediately posterior to the urethra in the male. The magnified view of the pelvic floor afforded by the laparoscope enables accurate placement in the 'v' of the puborectalis sling. The sheath is left in situ and the needle removed prior to gently dilating the tract in a gradual manner to 5 mm and then 10 or 12 mm. The rectum is then grasped from below and drawn down through the tract to be anastomosed to the skin at the neo-anus. A recent study has compared the anorectal angle and continence using this technique with that in the posterior sagittal approach [35]. This confirmed that a similar anorectal angle is achieved in both operations and that the laparoscopic approach has less detrimental functional impact.

15.3.9 Necrotising Enterocolitis

Laparoscopy in the initial evaluation of NEC is invaluable and can help to avoid potentially un-necessary surgery in an already extremely unwell infant [36]. In tiny preterm infants it is best to insert a 3.5 mm port at the umbilicus by the open technique and then the abdomen is insufflated with CO_2 at a flow rate of 0.2 L/min to a pressure of 5 mmHg. A 3 mm 30° telescope is used. In some cases free intestinal content may appear at the umbilicus whilst performing open access for the first port in which case there is obvious perforation and little visibility on inserting the telescope may indicate the need for laparotomy. On the other hand if there is no sign of free fluid on gentle inspection at laparoscopy then conservative management can be continued and the morbidity of a laparotomy in an extremely sick premature infant is avoided. Pneumatosis may be clearly visible (Fig. 15.10). This correlates with the preoperative radiological appearance (Fig. 15.11).

If necessary the laparoscopy can be performed in the neonatal unit. After an appropriate period of conservative management contrast studies of the bowel are advised prior to re-introducing feeds. If an isolated stricture is identified then further laparoscopy allows the area to be mobilized and exteriorized at the umbilical port site for resection and anastomosis. Even a tiny premature infant with severe necrotizing entero-

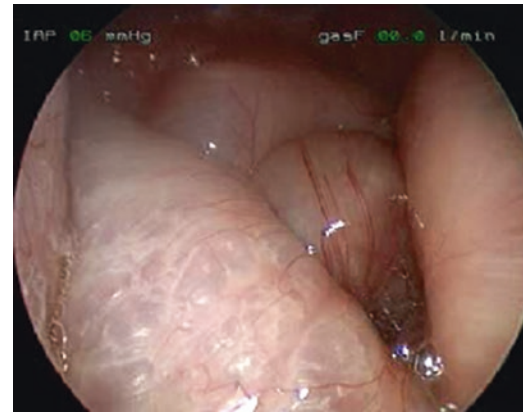

Fig. 15.10 Visualisation of pneumatosis intestinalis in NEC

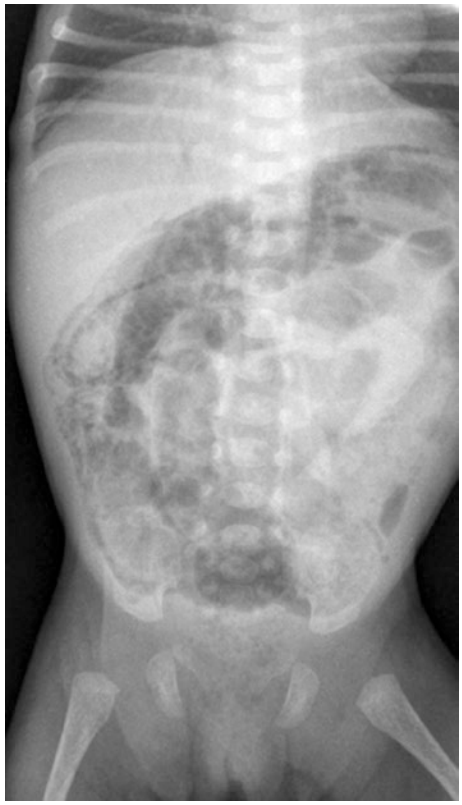

Fig. 15.11 Pre-operative x-ray showing pneumatosis

colitis can grow up with an abdomen with imperceptible scars.

15.3.10 Biliary Tract

The laparoscopic Kasai procedure was first described in 2002 [37] and subsequently a few cases were published but the results seemed not as good as the conventional open repair. At a meeting of the International Pediatric Endosurgery Group in 2007 it was concluded that the results were inferior and the procedure was not recommended [38]. A prospective study was stopped after inclusion of 12 laparoscopically operated infants due to a lower survival with the native liver after laparoscopic versus conventional Kasai operation [39].

In Japan and elsewhere in the East where the condition is more common they aim to make the laparoscopic dissection of the porta hepatis as close as possible to Kasai's original description and the longer term results are awaited [40, 41].

Certainly the laparoscopic approach for correctable biliary atresia is well suited to the laparoscopic approach as is choledochal cyst excision. Whilst I have successfully performed a number of these resections laparoscopically we cannot compete with the large numbers in the Far East [42].

For choledochal cyst excision a 5 mm port is placed in the inferior umbilical fold by an open technique. CO_2 pneumoperitoneum is established at 10 mmHg with a flow rate of 1 L/min. Two further 3.5 mm working ports are positioned in the left and right upper quadrants. A Nathanson Liver retractor is inserted in the epigastrium to give good exposure of the gallbladder, choledochal cyst and porta hepatis (Fig. 15.12). An intraoperative cholangiogram is performed via a flexible needle passed through the abdominal wall into the gallbladder.

It is sometimes helpful to mobilise the gallbladder from its bed early in the dissection and it can be used to provide traction during dissection of the cyst. Dissection is largely performed using a 3 mm monopolar diathermy hook. The cyst is dissected carefully keeping close to the

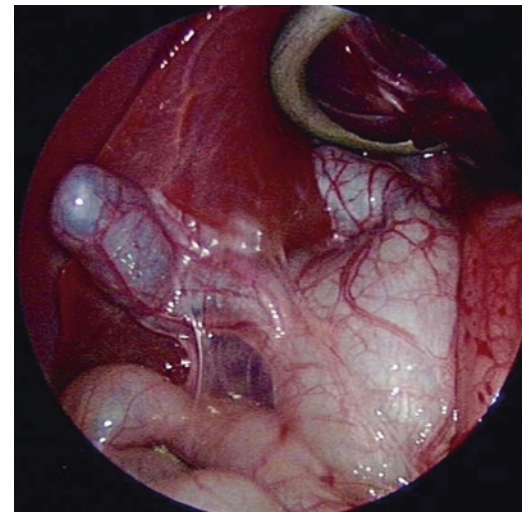

Fig. 15.12 Laparoscopic view of gall bladder and dilated cystic duct leading into choledochal cyst

cyst wall and separating it from the pancreas, duodenum, portal vein and hepatic artery. Occasionally I find that the communication with the duodenum is barely perceptible but if identified it is closed with an absorbable suture. Once the cyst is freed right up to the common hepatic duct it is left in situ whilst a Roux-en-Y jejunal loop is constructed. The jejunum is traced down from the duodeno-jejunal junction and the chosen loop exteriorized at the umbilical port site for the Roux-en Y construction prior to returning it taking it retro-colically up to the porta. The cyst content is aspirated percutaneously and the common hepatic duct transected. The cyst can be extracted via the umbilical port site (Fig. 15.13). An end to side hepato-jejunostomy is performed using interrupted 5/0 absorbable sutures. A suction drain is positioned below the anastomosis and the ports removed and the wounds closed.

If preferred it is simpler and quicker to perform a hepato-duodenostomy and Liem [42] claims that the incidence of ascending cholangitis is not significantly greater than hepato-jejunostomy. (I have used this technique in one case with an operative time of around 2 h, less than half the time taken for hepato-jejunostomy).

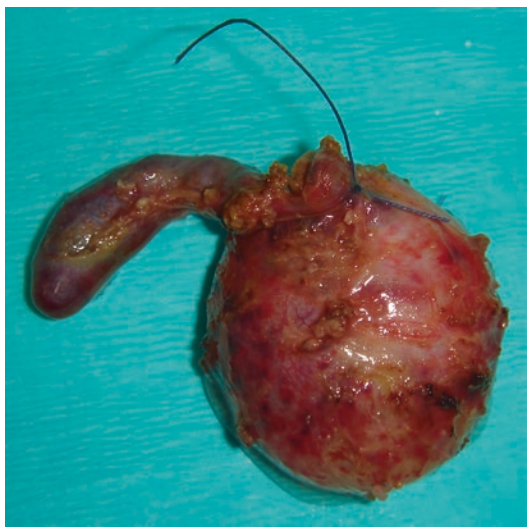

Fig. 15.13 Excised choledochal cyst with gallbladder attached

15.3.11 Pancreas

For hyperinsulinism in the neonatal period, refractory to medical management, the laparoscopic approach to the pancreas is easier than open surgery in view of the great magnification of the anatomy, which is beautifully displayed. Laparoscopic pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy was first described in 2001 [43]. The approach is with a 5 mm port at the inferior umbilical fold and two further 3.5 mm ports in the right and left upper quadrants. Exposure is facilitated with two stay sutures through the abdominal wall picking up the antrum and body of the stomach [44]. Dissection is performed using a monopolar 3 mm diathermy hook carefully dissecting the pancreas from surrounding structures. If a focal nodule is identified this can be excised otherwise, as in open surgery, dissection is continued up to the common bile duct and the pancreas transected at this level and suture ligated.

15.3.12 Ovarian Cyst

Laparoscopy is excellent in establishing the diagnosis in a neonatal intra-abdominal cyst distinguishing ovarian cysts from duplication and other intra-abdominal cysts. Percutaneous aspiration under ultrasound guidance is potentially dangerous [45].

A 5 mm port is placed in the inferior umbilical fold by open technique after infiltrating with 0.25% Marcaine with adrenaline. The abdomen is insufflated to 8 mmHg at a flow rate of 0.5 L/min. A 30° telescope is introduced and the cyst is visualized. The cyst may be punctured under direct vision inside the abdomen and then the deflated cyst can be exteriorized via the umbilical port site and treated as appropriate depending on how necrotic it is. Occasionally on inspection a cyst may be auto-amputated with no attachment and the ovary may be absent on one side confirming the diagnosis [46].

15.3.13 Intersex

Laparoscopy can be useful as part of the multidisciplinary work up of a neonate with ambiguous genitalia. Laparoscopic biopsies of gonads may be taken if required.

15.4 Tumour Surgery

15.4.1 Renal Tumours

Laparoscopic nephrectomy may be performed in the neonate for conditions such as mesoblastic nephroma in which case the tumour is mobilized laparoscopically and extracted via a Pfannenstiel incision in a bag.

15.4.2 Hepatic Tumours

As part of the diagnostic work up of a newborn with a hepatic lesion it is safe to perform trucut biopsy under laparoscopic guidance. As bleeding may be quite significant this is safer than percutaneous ultrasound guided biopsy. It is very important to position an additional 5 mm port prior to the biopsy to enable the introduction of an endopledget. This is held close to the biopsy site as the needle is withdrawn to be able to apply local pressure and control any potential haemorrhage.

15.4.3 Sacrococcygeal Teratoma

In cases of large sacrococcygeal teratoma in a haemodynamically unstable infant it is helpful to use a laparoscopic approach to interrupt the median sacral artery. It is also helpful in dissection of the intrapelvic component [47].

15.5 Inguinal Hernia

Whether or not inguinal herniae in children should be routinely performed laparoscopically is a matter for debate. The numbers of cases are large and the majority, in most centres, are performed by open surgery.

In the neonate and premature baby however the hernia sac is easily torn during open surgery and it can become a frustrating and tedious operation particularly for surgeons in training. The laparoscopic approach, providing that the surgeon has acquired the necessary skills, may be simpler and also may reduce the likelihood of injury to the vas in males, as the magnification is so great. It also enables the evaluation of the contralateral side.

The baby is placed supine on the operating table and the bladder emptied by a Credé manoeuvre a 5 mm port, or smaller, is inserted in the inferior umbilical fold. The abdomen is insufflated with CO_2 to a pressure of 8 mmHg at a flow rate of 0.5 L/min. A 30° telescope is used. Two further 3.5 mm ports are inserted at a slightly lower level in either flank. If desired the instruments can be passed through tiny stab wounds, avoiding the use of ports and affording greater cosmetic benefit. Putting the baby in a Trendelenberg position gives good exposure of the internal inguinal rings as the bowel is displaced by gravity. A 3/0 absorbable suture on a round-bodied needle is inserted through the abdominal wall and grasped with a laparoscopic needle holder. The internal inguinal ring can be closed with a purse string suture or an N or Z type closure is achieved [48]. Some prefer to incise at least part of the peritoneum at the internal ring prior to the suturing in the hope of reducing recurrence.

Others use a laparoscopic assisted extraperitoneal technique [49] in which a special 'herniotomy hook needle' (similar to an aneurysm needle) is used. The hook is prepared with a monofilament absorbable suture and passed through a 2 mm stab incision made over the internal inguinal ring and the hook is passed retroperitoneally from lateral to medial lifting the peritoneum forward from the vas and vessels and once beyond them is brought into the peritoneal cavity where a grasper holds the suture as the needle is withdrawn to a subcutaneous position prior to advancing it round the

remainder of the circumference of the internal ring back to the suture. This is threaded through the needle, which is withdrawn, thus completely encircling the hernial sac. It is then ligated externally closing the internal ring and burying the knot subcutaneously. The recurrence rate with this method is said to be minimal.

Conclusion

Many senior paediatric surgeons argue that evidence is lacking for changing from open surgery to minimal access surgery. It is true that there have been very few randomised controlled trials to support the approach. Small incisions for laparoscopic ports are just a different approach to the abdomen. I doubt that when surgeons determined that they could open the abdomen via a midline, paramedian, subcostal, Pfannenstiel incision etc. that randomised trials were demanded. The time has come to accept the laparoscopic approach that has been proving its success in paediatric surgery over more than two decades. Although we as paediatric surgeons pride ourselves in making small neat wounds which are closed with subcuticular sutures or even skin glue the scars grow with them and underlying them is a potential for adhesive problems which are not as common with endoscopic surgery. Children deserve to grow up without scar even if they require major surgery. I am sure that the next generation of surgeons will be surprised to learn that surgeons used to open up body cavities through big incisions. Our adult surgical colleagues have adopted the endoscopic approach in many areas. We are fortunate that paediatric surgery covers an age range rather than an organ system and these techniques are applicable for most of the surgery that we perform. The neonate especially can benefit with less long-term morbidity.

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The Genetics of Neonatal Surgical Conditions

16

Ian Ellis

Abstract

It is noteworthy that in 1953, the same year that Peter Paul Rickham was establishing the first neonatal surgical unit at Alder Hey Children's Hospital in Liverpool, just 200 miles away in Cambridge, Francis Crick and James Watson were unraveling the structure of DNA, the fundamental genetic material. Crick and Watson's Nobel Prize winning work describing the double helix structure of DNA also described a mechanism for its replication. The two parent DNA strands each acting as the framework for copying into the two daughter strands. The usual accuracy of the copying of billions of base-pairs into gametes at meiosis and daughter cells during mitosis is itself a marvel. Changes in the usually faithful copying of DNA strands (mutations) can be the basis of positive genetic change that encourages our evolution over generations. Or the sudden deleterious change in a DNA sequence may be the pathogenic mutation that underlies a congenital malformation that presents to a neonatal surgeon. Here lies the origin of many neonatal surgical conditions and ultimately important clues to their improved management and ultimately their reduction or even prevention.

Keywords

Human Genome Project (HGP) • Gene • Mutation • Birth defect • Malformation • Clinical genetics • Syndrome diagnosis • Dysmorphology • Mendelian • Multifactorial • Polygenic inheritance • Recurrence risk • Chromosome • Fluorescent in situ hybridisation (FISH) • Micro-array analysis • DNA transcription factor • Embryogenesis • *Hox* • SOX • PAX genes • Genotype • Phenotype • Gene expression • Incomplete penetrance • Variable expression • Heritability • Hirschprung disease (HSCR) • Genome wide association study (GWAS) • Single nucleotide polymorphism

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_16

(SNP) • Copy number variant (CNV) • Unclassified variant (UCV) • Epigenetic imprinting • Anti-sense oligonucleotide • RNA interference • Gene silencing • Next generation sequencing (NGS) • Exome sequencing • Whole genome sequencing (WGS) • DECIPHER database • Genetic counselling • Family tree • Pedigree • Prenatal diagnosis • Fetal ultrasound • Chorionic villus sampling (CVS) • Amniocentesis • Cell free fetal DNA (cffDNA) • Non-invasive prenatal diagnosis (NIPD) • Pre-implantation genetic diagnosis (PGD) • Termination of pregnancy • Non-directive • Non-judgmental counselling • Support

16.1 Introduction

It is noteworthy that in 1953, the same year that Peter Paul Rickham was establishing the first neonatal surgical unit at Alder Hey Children's Hospital in Liverpool, just 200 miles away in Cambridge, Francis Crick and James Watson were unraveling the structure of DNA, the fundamental genetic material. Crick and Watson's Nobel Prize winning work describing the double helix structure of DNA also described a mechanism for its replication [1]. The two parent DNA strands each acting as the framework for copying into the two daughter strands. The usual accuracy of the copying of billions of base-pairs into gametes at meiosis and daughter cells during mitosis is itself a marvel. Changes in the usually faithful copying of DNA strands (mutations) can be the basis of positive genetic change that encourages our evolution over generations. Or the sudden deleterious change in a DNA sequence may be the pathogenic mutation that underlies a congenital malformation that presents to a neonatal surgeon. Here lies the origin of many neonatal surgical conditions and ultimately important clues to their improved management and ultimately their reduction or even prevention.

16.2 DNA Structure and Genetic Function

The human genome contains approximately 3200×10^6 base-pairs of which approximately 2000×10^6 is non-coding, intervening DNA sequences. This has been referred to as '*junk DNA*', but it is now realized that this term undervalues its evolutionary legacy in the creation of new genes, its repository of old pseudogenes and its rich patterning with variable sequence DNA and single-nucleotide polymorphisms (SNPs) that allow the tracking of DNA within the individual genome, between family members and across population groups. Only about 48×10^6 bases of DNA is actually devoted to coding genes, about 1.5% of the entire human genome. In 1993 the first physical map of the human genome was achieved locating the major chromosome fragments and their marker probes. The Human Genome Project was completed in 2003 and is available in the public domain [2]. It has 20,000 genes of which more than 4000 are now known to be associated with genetic disorders.

DNA, (Deoxyribonucleic Acid) is the chemical chain composed of a specific sequence of four chemical bases (nucleotides); adenine (A), guanine (G), cytosine (C), and thymine (T) held together with a sugar and phosphate backbone. The two DNA strands are themselves held together by hydrogen bonds between mutual base-pairs of purine and pyrimidine bases, adenine pairing with thymine (A:T) and guanine pairing with cytosine (G:C). The linking of these nucleotide bases A to T and G with C, form the cross-bridging rungs of the DNA helix ladder, with the sugar-phosphate backbones forming the vertical sides of the ladder. The two DNA chains twist together in the double helix, one reading in the 5′–3′ direction, referred to as the sense chain. The opposite strand with its complementary nucleotide sequence running 3′–5′ is referred to as the anti-sense chain. As noted by Crick and

Watson the double stranded, double helix structure of DNA allows copying, either of itself (DNA replication) or as a template (DNA transcription) to direct gene expression via messenger RNA (mRNA) in protein synthesis. Apart from gamete egg and sperm cells all other body cells regardless of the degree of differentiation or tissue specialization of that cell carries the same DNA within the nucleus for that person. A small amount of DNA is also present in the mitochondria of the cell cytoplasm. Mitochondrial DNA is maternally transmitted via the cytoplasm of the ovum cell and is associated with disorders related to mitochondrial function and high energy ATP tissue activity; MELAS and MERFF, Leigh's syndrome, (myopathy, encephalopathy epilepsy, multiple strokes, lactic acidosis, ptosis and eye muscle disorders). When the nuclear DNA strands unwind each strand forms the template, for its replication by DNA polymerase. This is referred to as semi-conservative replication into daughter strands, in either DNA repair or when the entire DNA genome is copied prior to cell division. The process whereby specific regions of DNA are transcribed into messenger RNA is under strict control. DNA expression is regulated by sequence specific transcription factors that can open or close the reading grooves of DNA, allowing or denying access to RNA polymerase. Similarly the methylation of DNA can modify that region of the DNA preventing RNA polymerase binding and hence suppress the expression of gene sequences (see below). The process of DNA modification may occur during gametogenesis whereby paternally derived (from the sperm) DNA or maternally derived (from the ovum) gene sequence(s) can be turned on or off. This process of DNA methylation is known as imprinting and along with other changes in the DNA (for example the expansion of DNA triplet repeats in specific genes) are referred to as epigenetic effects. More detailed texts describe the molecular structure and function of the DNA and genes [3–5].

DNA is expressed by RNA polymerase copying specific gene sequence(s) into messenger RNA (mRNA). This passes out of the nuclear envelope into the cytoplasm where the mRNA is translated on the ribosome into a specified sequence of amino-acids forming the peptide chain of a synthesized protein. The sequence of mRNA bases is read in groups of three;

A-G-C- T-G-C- A-G-G- etc.,

the permutations of the four bases forming triplets in the messenger RNA (mRNA) with 4^3 ($4 \times 4 \times 4 = 64$) permutations that creates the genetic code. Each triplet in the genetic code is referred to as a codon. One codon AUG (as uracil substitutes for thymine in mRNA) is the initiation codon that begins protein synthesis (translation), whilst the codons UAA, UGA and UAG are stop codons signaling the termination of protein synthesis. With 61 remaining codons, there is overlap (referred to as degeneracy) in the ability of several codons to code for the same amino acid. In this way, some changes in the sequence of bases in the DNA may not lead to a change in the amino-acid sequence of a synthesized protein. Mutations that do not change the sequence of amino-acids are referred to as silent mutations and are part of the complex picture whereby not all DNA mutations may be pathogenic. DNA mutations that occur at key promoter binding sites where RNA polymerase binds to initiate mRNA synthesis and DNA sequence changes at intron/exon boundaries may be tolerated or they may lead to significant failure of DNA expression, gene function and hence adverse clinical consequences.

16.3 The Objectives of Clinical Genetics

It is fitting that the two specialties of neonatal surgery and clinical genetics that have made tremendous advances in the last 50 years should come together in this volume. Each now contributes significantly to the shared understanding of the cause of malformations and to offering strategies for more specific treatment and prevention of these conditions. Working co-operatively an international European network *EUROCAT*, of local and national congenital malformation registries for the epidemiologic surveillance of congenital anomalies was established in 1979 [6].

The combined registries now survey more than 1.7 million births per annum, (nearly 30% of all European births) drawn from 43 registries in 23 countries and collaborates with the World Health Organization (WHO) Collaborating Centre for the Surveillance of Congenital Anomalies [7]. A number of information toolkits related to congenital disorders and birth defects, particularly for developing countries are now available on the Internet [8].

The terms medical and clinical genetics are used interchangeably. Medical genetics is usually used as an overarching term to include the clinical and laboratory research, and resulting genetic counselling of a birth defect. Clinical genetics is a term reserved for the more direct patient and family based contact involved in this, particularly associated with the process of diagnosis and genetic counselling. Most specialist tertiary (teaching) hospital centres that perform neonatal surgery might also provide a clinical genetics service with access to medical genetics laboratories providing chromosome and molecular genetic (DNA) analysis. Human genetics is a broader term to describe the study of all human traits, those normally occurring and those that are disease (medical/clinically) associated. Medical (clinical) genetics including genetic counselling is best delivered as a co-ordinated package delivered by a multi-disciplinary team of medical geneticists, genetic counsellors, clinical psychologists and social support workers. The services offered by clinical genetics in the context of a neonatal surgical referral may include some or all of the following:

1. Examining the child, interpreting prenatal and other genetic test results. Advising on further specialised examinations and assessments for the child and relevant family members. Gathering relevant medical, pregnancy and 3-generation family history and interpreting this. Where appropriate examining parents, affected or at-risk family members.
2. Identifying the syndrome or differential genetic diagnosis. Communicating this to the family and the multi-disciplinary team caring for the neonate. Working in liaison with the neonatal surgical team to arrange referral to other clinicians for on-going care and assessment, or where the child does not survive involving agencies for bereavement counselling etc.,
3. With an appropriate diagnosis, discussing recurrence risks and who else in the family may be at risk. Offering discussion or a further genetics referral for members of the extended family, for appropriate screening, reproductive and pre-natal diagnosis options.
4. Offering support to the parents over the acute period and longer term, addressing their information and psychosocial needs. Putting families in touch with support groups and where requested and appropriate, with similarly affected families
5. Participation in data collection and malformation registers for incidence, outcome and research and teaching.

One chapter on Medical Genetics alone cannot do justice, nor can it remain up to date in such a rapidly expanding field. Rather this chapter presents an outline of approaches and describes what is the state of the science and art of medical genetics at this time (2016). The principles upon which medical genetics has been built will be described, its' approaches and what it can offer to neonatal surgery, to the child at the time of neonatal surgery, as they grow and to their parents and to the extended family.

Practice will vary between neonatal surgical units and their available medical genetic diagnostic services and access to clinical genetics expertise. Many will be placed in tertiary teaching and research hospitals where clinical and laboratory genetic services may be highly developed. It may be routine practise for all neonates with one and particularly more than one malformation, or a complex series of birth anomalies to be reviewed by a general paediatrician or a specialist clinical geneticist or dysmorphologist with an interest in birth defects. Much will depend upon the experience and expertise locally, what level of genetics service has been developed alongside the neonatal surgical unit. Standard chromosome analysis may be available to all infants or a genetics

opinion might only be sought for more highly selected cases. I have tried to indicate those 'red flag conditions' that should be recognised and those babies who would more likely benefit from seeking a clinical genetics opinion prior to expensive genetic investigation. It is for example now easy to E mail clinical photographs for a clinical genetics opinion. Even if genetic testing facilities are not available locally, samples for the newer techniques of DNA analysis are small, stable and can be sent internationally at low cost. However, the cost of laboratory analysis may be prohibitively high for some countries and their families. With prior arrangements, there may be a collaborating or research centre pleased to receive such samples from neonatal surgical centres especially in the developing, emerging world.

16.4 Syndromes, Sequences and Malformations

As genetics has dissected into the human genome and identified critical developmental genes, there has been a significant contribution to understanding the embryology and patho-physiology process of many paediatric surgical conditions. The emphasis must be on closer liaison between specialties, particularly between the paediatric surgeon and the clinical geneticist for diagnosis, management and in research. A syndrome (from the Greek, meaning *'running together'*), is a group of features that occur together without necessarily stating or knowing what that cause is. A malformation is an observed morphologic abnormality that arises from an abnormal developmental process that might be genetic (inherited or sporadic, (de novo, acquired) or may be secondary to a teratogen, vascular or disruptive event, e.g. cleft lip or neural tube defect (spina bifida) with associated anencephaly, hydrocephalus, talipes. A deformation sequence—is a pattern of (sometimes multiple) anomalies that result from physical force acting on an otherwise normal structure e.g. abnormal uterine or twin compression or the Potter sequence that follows oligohydramnios. A disruption process—is the loss of a tissue that was previously normal e.g. the effect of constricting amniotic bands. Some malformations may occur together in an associated group, for example the VACTERL Association (that includes *V* vertebral anomalies, *A* anal atresia, *C* cardiac abnormalities, *T* tracheo-oesophageal fistula, *R* renal /or radial, *L* limb abnormalities) or as the CHARGE Association, (the variable combination of congenital malformations including: *C* coloboma, *H* heart disease, *A* atresia choanae, *R* retarded growth and retarded development and/or CNS anomalies, *G* genital hypoplasia, and *E* ear anomalies and/or deafness). Dysplasia is the abnormal organisation of cells that results in a structural change of that tissue e.g. the altered cartilage and bone that occurs in skeletal dysplasia conditions.

Multifactorial / polygenic inheritance—are those common disorders with a significant genetic component and environmental influences, for example cleft lip and /or palate and congenital heart disease. Apart from genetic causes, vascular disruptions, physical deformations, amniotic bands and teratogens can affect the development of the fetus. Notable amongst teratogens are the viruses, rubella (German measles) CMV (cytomegalovirus) and perhaps the Coxsackie viruses. Prescribed drugs such as phenytoin and sodium valproate given for epilepsy, retinoids used for acne and psoriasis treatment and their effects on Vitamin A, or the fetal malformations seen with maternal exposure to warfarin, lithium therapy and thalidomide treatment. These may affect embryonic development in a recognised teratogenic syndrome, non-specifically or produce a syndrome that mimics a genetic disorder (known as a phenocopy) and may lead to the mistaken belief of a higher recurrence risk than actually applies if that drug is subsequently avoided. Other teratogenic effects may be due to cytotoxic drugs given for cancer treatment, effects upon the developing genitalia in children whose mothers' have taken sex hormones during the pregnancy, the increased risk of neural tube defects and facial clefts in children whose mothers' smoked before and during early pregnancy, the consequences of maternal alcohol ingestion, and the effects of low maternal folate levels for those women who have taken anti-folate drugs, for example methotrexate.

16.5 Developmental Genes and Malformations

Only a brief summary is presented here of the structure and function of the 22 pairs of autosomes and 2 sex chromosomes, XX in the female and XY in the male that make up the human complement in the nucleus of every diploid cell. The reader is directed to a number of general and specialist texts for more background and detailed explanation. The 23 pairs of human chromosomes consist of extremely tightly coiled DNA bearing the 20,000 genes that encode human heredity and function. Far from being merely an inert information store with genes dispersed at intervals, the human genome is highly organised and regulated. Genetic information flows in a dynamic and highly controlled process, with key genes switched on and off at critical points of embryogenesis, organ and limb formation, cell differentiation and tissue repair. Chromosomal DNA is intimately wound around histone protein clusters and regions of DNA can be methylated (imprinted) to restrict DNA copying (transcription) into active mRNA prior to translation into the amino-acid chains during ribosomal protein synthesis. Furthermore key proteins (see below) can bind DNA at specific sites to act as gene repressors controlling the switching on and off of genes in what can best be described as a carefully conducted orchestra of developmental regulation and careful control of the day to day function of a mature neonatal or adult cell [9, 10].

An increasing number of the genes associated with surgical malformations have now been identified. They are either DNA transcription factors acting directly on the regulatory genes or they code for proteins associated with them. Genes coding for DNA transcription factors produce proteins that are highly sequence specific and are therefore able to recognise and hence to regulate key segments of the genomic DNA. The ability of these proteins to bind and control DNA expression is mediated via DNA binding domains (DBD) configured as a zinc finger, basic helix-loop helix, fork-head or with a basic-leucine zipper structure. Transcription factors are gene specific proteins able to locate the enhancer or promoter region within the spiral groove of double stranded DNA and control the expression of developmental genes, promoting RNA polymerase binding or repressing gene transcription and hence expression. Together with other genes and their expressed protein products; co-activators, chromatin and histone acetylases, kinases and especially methylases they can selectively turn gene expression on and off in a usually co-ordinated orchestra of organised development. An example of such a genes is CHD7 a helicase DNA-binding protein where loss-of-function mutations cause the CHARGE syndrome [11]. Mutation analysis of CHD7 identifies a mutation in about 60% of cases with CHARGE syndrome. Information on the effects of CHD7 mutations is available from a dedicated website [12], that is updated with genotype and phenotype information [13, 14].

16.6 *Hox* Homeobox Genes

Hox (Homeobox) genes are involved in body pattern formation and orientation, acting as regulators of embryonic development. They were first identified as the genes controlling segmentation, antenna, leg and wing formation in the fruit fly, *Drosophila melangomaster* and have been found in plants, fungi and unicellular organisms and to be very highly conserved across species over 700 million years of evolution. The 39 human *Hox* genes are located in four clusters (A–D), (see Table 16.1). They are believed to have developed from the duplication and divergence from a primordial homeobox gene.

Each *Hox* gene is small composed of two coding exons with an intervening intron. The DNA sequence (180 base-pairs long homeobox) contains a highly conserved region that codes for a protein of 60 amino-acids creating three helical regions. These helical regions (helix-turn-helix) are able to bind to the DNA structure; helix 3 lying within the major grove and helices 1 and 2 lie above the DNA. The ordering A–D of these transcription factor genes in their chromosome clusters is important as it controls rostral (head) to caudal (tail) development in the human

Table 16.1 The chromosome location of the four human *Hox* gene clusters

Cluster	Chromosome	*Hox* Genes
HOXA	Chrom. 7p14–15	HOXD1, HOXD3, HOXD4, HOXD8, HOXD9, HOXD10, HOXD11, HOXD12, HOXD13
HOXB	Chrom. 17q21–22	HOXB1, HOXB2, HOXB3, HOXB4, HOXB5, HOXB6, HOXB7, HOXB8, HOXB9, HOXB13
HOXC	Chrom. 12q12–13	HOXC4, HOXC5, HOXC6, HOXC8, HOXC9, HOXC10, HOXC11, HOXC12, HOXC13
HOXD	Chrom. 2q31-q37	HOXD1, HOXD3, HOXD4, HOXD8, HOXD9, HOXD10, HOXD11, HOXD12, HOXD13

embryo. The 3′ genes in the clusters are expressed earlier and more anteriorly than the 5′ genes. The *Hox* genes control the differentiation of uncommitted cells in the embryo as they form limbs and organs in the segmentation process. The *Hox* genes relate positional information along the AP axis of the developing embryo creating functional domains for groups of cells. *Hox* gene expression occurs during early gastrulation when the embryo is generating its body axis. Segmentation involves processes of programmed cell death and the migration of cells, with the target genes of *Hox* genes acting to promote cell division, cell adhesion, apoptosis, and cell migration. In the fruit fly, mutations in the Antennapedia gene cause legs instead of the antenna to develop on the head of a fly.

Human *Hox* gene mutations are particularly associated with limb and digit abnormalities, including polydactyly, hypodactyly and syndactyly and genital anomalies. HOXB5 expression affects lung development and mutations are associated with congenital cystic adenomatoid malformation. HOXA5, HOXB4 and HOXB6 are also associated with pulmonary development [15–19]. HOXA10 and HAOXA11 mutations are found in congenital malformations of the female genital tract, especially with uterine malformations. HOXA11 and HOXA13 and HOXD10 and HOXD13 are active in the developing limb, and mutations in HOXA13 lead to hand-foot-genital syndrome, whilst HOXD13 mutations are associated with synpolydactyly and the HOXD13 allele, 180A > G (A60A) has been identified as a risk factor for cryptorchidism [20–24].

16.7 SOX Genes

A super-family series of 20 SOX genes play a critical role during embryonic development and in the differentiation of precursor multi-potential stem cells. The SOX genes are highly conserved across eukaryotic cells and mammalian development. These genes produce proteins that are transcription factors, able to recognise and bind to specific sequences of DNA. By binding to the minor groove of DNA their carefully formed protein shapes can enable or prevent RNA polymerase access and hence regulate transcription of specific target genes. Mutations in these genes lead to disorders that involve the abnormal development of tissues in which a particular SOX gene is active (expressed). As a result, the genetic disorders caused by SOX mutations typically have a wide variety of signs and symptoms. The 20 human SOX genes mostly share >50% amino acid homology with each other and with the HMG (high mobility group) in the Sry gene on the Y chromosome that plays a major signalling role in determining testis differentiation and hence male development. Mutations in SOX2 (chrom. 3q276.3-q27) are associated with microphthalmia and its pathway interacts with PAX6. The SOX9 (chrom. 17q23) gene product regulates chondrocyte differentiation and also acts to regulate transcription of the anti-Müllerian hormone, AMH. Mutations in SOX9 are associated with campomelic dysplasia, a skeletal malformation syndrome with bowed tibiae and often sex-reversal. The SOX-10 protein is important for the development of the neural crest and the peripheral nervous system development. SOX10 (chrom. 22q13.1) is active in the development of the neural crest. It interacts with PAX3

and may be regulated by another transcription factor, MIcrophthalmia-associated Transcription Factor (MITF). SOX10 mutations are seen in Waardenburg-Hirschprung disease. Mutations in SOX14 (chrom3q22–23) are associated with limb defects seen in the blepharophimosis, ptosis, epicanthus inversus syndrome (BPES) and in the Mobius syndrome. The SOX17 gene and particularly the c.775 T > A (p.Y259N) mutation has been found to be a recurrent mutation in human kidney and urinary tract malformations including vesicoureteric reflux [25].

16.8 PAX Genes

The PAX family of 9 genes (PAired Box) are transcription factors that contain a paired domain and a partial or complete homeodomain. They are active in the early embryonic development of specific tissues, and are organised into four groups, (see Table 16.2).

PAX gene activity tends to be inactivated after birth, except in tissues that can regrow for healing or regeneration. The following tissue activities for PAX genes have been proposed or confirmed. PAX1 is involved in vertebral development and segmentation of the embryo. PAX2 is active in the kidney and optic nerve development and PAX2 mutations cause renal-coloboma syndrome. PAX3 is involved in ear, eye and facial development and mutations occur in Waardenburg syndrome, PAX4 with pancreatic islet beta cells and PAX5 are involved with neural and spermatogenesis development and b-cell differentiation, PAX6 appears as a master controller gene for the development of the eyes and sensory organs, neural and epidermal tissues as well as other ectodermal derived structures. PAX6 is the gene associated with aniridia. PAX7 associated with myogenesis, PAX8 with thyroid development and PAX9 has wide expression in organ, skeletal and teeth development. There are nine genes in the PAX gene family. These genes are divided into subgroups based on various aspects of similarity. Subgroup I includes PAX1 and PAX9; subgroup II includes PAX2, PAX5, and PAX8; subgroup III includes PAX3 and PAX7; and subgroup IV includes PAX4 and PAX6. Mutations in PAX genes lead to disorders that involve the incomplete development of tissues in which a particular PAX gene is expressed. Additionally, the over-expression of PAX genes has been noted in a variety of cancers. It is thought that the cell protection function of PAX genes prevents cell death and permits tumour growth (proliferation).

Table 16.2 Pax group organisation

Pax group	Pax genes
1	Pax 1 and Pax 9
2	Pax 2, Pax 5 and Pax 8
3	Pax 3 and Pax 7
4	Pax 4 and Pax 6

The gene TBX5 from the family of T-box transcription factors [26], encodes a protein transcription factor, T-box 5 that controls DNA expression. It is related to the T-box 3 gene implicated in ulnar mammary syndrome. TBX5 mutations are associated with pre-axial radial ray abnormalities of the upper limb and cardiac development abnormalities of Holt-Oram syndrome. Mutations in TBX5 are found in more than 70% of Holt-Oram patients [27–29].

16.9 Multi-factorial Conditions and Polygenic Inheritance

These are a wide group of conditions and malformations in which inheritance and environment contribute. Literally *'nature and nurture'*, it is the contribution of variable numbers of genes, (polygenic inheritance) together with an environmental influences that can include diet, drug and teratogen effects bacterial or virus infection, occupation and lifestyle including smoking and alcohol exposure that determines whether a condition will or will not develop. This is the accepted background for continuous traits such as height, blood pressure, intelligence. The heritability of any trait or condition is the degree to which its occurrence is due to inherited genetic factors. It is recognised that some common malformations, for example cleft

lip and/or palate, congenital heart disease and neural tube defects (spina bifida) cluster in some families and that after the first or second case has occurred in one family, the recurrence risk for close family members is increased over the population (prior) risk. This was studied by the statistician Fisher [30] who suggested the additive effects of multiple pairs of genes each contributing to (or diminishing) the relative risk of that condition occurring. Falconer [31] developed a model that a threshold exists, beyond which the condition or malformation would be expressed. Families who had already experienced that malformation are in a higher risk group shifted further towards the threshold than the general population who are at lower risk. It is suggested that affected families carry a higher genetic predisposition and/or indeed share an adverse environment accounting for their higher risk of recurrence. Where the genetics are complex and still poorly understood, empiric recurrence risks are quoted. For example the risk of cleft palate in the general population is about 1%. If parents have had a child with an otherwise isolated cleft, their empiric risk of recurrence is increased to around a 2–3% risk. After their second affected child, their risk increases to around a 10% risk with adjusted risks for relatives of the parents and for the affected child and their sibs when they in turn seek genetic advice. Heritability is the degree to which inherited / genetics factors as opposed to other factors (diet, lifestyle, environment) contribute to the aetiology for any condition. This may be based upon observation that all gene carriers manifest (for example all children who have the FGFR3 achondroplasia gene mutation show disproportionate short limb short stature). In this condition the gene penetrance is said to be complete as all gene carriers manifest the condition. In contrast many other dominant genes characteristically show very variable expression ranging from complete expression of that gene's full spectrum of effects in some family members, through to mildly relatives. There may also be carriers of that gene mutation who show no clinical signs, but can yet pass the gene mutation on and have a fully affected child. The later is referred to as non-penetrance.

The heritability of congenital malformation can vary for congenital heart disease or cleft lip and palate. There may be a sex difference for congenital pyloric stenosis or congenital dislocation of the hip. Careful assessment is needed not to miss a syndrome that might have a chromosomal or single gene cause. Twin and adoption studies may be needed to demonstrate the variable inheritance of complex multi-factorial, polygenic traits. Surveys of congenital malformations and the introduction of more formal systematic Malformation Registers indicate that 2–3% of children are born with some congenital anomaly of varying severity. Depending on definitions and how the data is acquired, these malformations may range from those lethal conditions that may be detected antenatally through to those conditions referred to the neonatal surgeon. Observation, delayed or staged treatment may be suggested and clinical genetics may be involved in parallel to this.

16.10 The Genetics of Hirschprung Disease

Hirschprung disease (HSCR) causes intestinal immotility in 1 in 5000 live births. It is an example of a congenital disorder with a complex polygenic aetiology. HSCR results from the congenital absence of intestinal ganglions. In 80% of children with HSCR this may affect the rectosigmoid junction (short segment), but in 15–20% the aganglionosis may extend proximal to the sigmoid colon (long segment). In about 5% there may be total colonic aganglionosis or rarely the entire bowel may be involved in total intestinal aganglionosis. Hirschprung disease may be an isolated condition in a child or occur as part of a complex syndrome [32] or it may be an isolated finding [33]. HSCR and its associated multisystem disorders are referred to as the neurocristopathies.

First analysed by Cedric Carter [34], the recurrence risk and severity of HSCR depends on the family history, the proximity of affected relative(s) to the person seeking advice, the severity (higher recurrence risk for long and especially

total colonic aganglionosis versus short segment diseases) and a higher recurrence risk when the affected member(s) have been in the less frequently affected sex. An empiric recurrence risk of about 4% is quoted in short segment HSCR where there is no other family history and no other syndromic features are present. The receptor tyrosine kinase (RET) gene has been identified as the major gene, with RET mutations accounting for than 80% of cases where a gene mutation has been found [35]. The research technique of genome-wide association studies (GWAS) has been used to find multiple regions of the genome that predispose individuals to a disease using commonly occurring markers known as single-nucleotide polymorphisms (SNPs). GWAS studies collect hundreds of DNA samples from subjects with the condition (cases) and from people from the same population who do not show the conditions (controls). The DNA samples are then tested against the millions of SNP variants that are widely distributed across the genome as random genetic markers using SNP arrays. If there is a SNP pattern (one allele) that is more frequent amongst the cases than the controls, then the map location of that SNP suggests that there may be a closely linked region of the DNA or indeed a gene that is *'associated'* with that disease or trait. The power of GWAS is that no candidate region or gene needs to be suggested in advance of the study, single cases of the disease can be used and samples can be pooled across multiple study groups and populations, provided that the diagnostic criteria for the disease are robust and reliable and that adequate controls can be found from amongst the multiple study populations [36].

So far another ten genes (GDNF, NRTN, SOX10, EDNRB, EDN3, ECE1, ZFHX1B, PHOX2B, TCF4, and KIAA1279) [37] have also been identified in the aetiology of HSCR. Other genes acting as modifiers and enhancers (SOX10) affecting the expression of Hirschprung disease have been found, making this a truly complex disorder. A gene mutation is found in about 50% of familial cases of Hirschsprung's and in up to 20% of isolated cases. Despite these advances the ability of genetic testing to reliably predict an affected pregnancy, estimate the likely severity and explain the heritability versus non-genetic factors in the aetiology of HSCR remains limited to about 2% of cases.

16.11 Investigation of Malformations and Syndrome Recognition

Syndrome diagnosis is arguably one of the greatest clinical arts practised. It requires consummate knowledge of the growing list of genetic and malformation syndromes, and their variable presentation. There may be age specific facial features that are present for perhaps only the first months or year of life and then fade into a general coarsening or non-specific facial dysmorphism. Conversely the facial appearance may not appear until older or the diagnosis may remain elusive until other physical or behavioural features appear. Observation and return visits over a number of years may be needed before the careful eye of the dysmorphologist can make a diagnosis. Syndrome diagnosis may be an 'all or none effect'. Recognising a facial appearance, (the gestält, *"I have seen this before—I know what this is"*), or it can be a long process of watching and re-evaluating [38]. One needs to allow for the often variable expression of syndromes or malformation sequences, or it may be a painstaking process of identifying facial and malformation features, known as '*handles*' that occur sufficiently often with that syndrome / condition to be diagnostically useful. These diagnostic '*handles*' need to be clues that are specific enough to be useful without generating too wide a diagnostic differential. For example agenesis of the corpus callosum is more diagnostically useful and a better handle for syndrome diagnosis than the non-specific mild ventricular dilatation. Similarly pre-axial polydactyly, (duplication of the thumb) is more closely associated with specific syndromes than post-axial polydactyly (duplication of the little finger or ulnar placed finger digit(s)). Post-axial duplication occurs in the general population, and it may be coincidental and not an associated feature of the child's syndrome.

Referral to a paediatrician with an interest in neonatal malformations, dysmorphologist or clinical geneticist is suggested, if any of the following are present:

- more than one malformation present
- more severe or a more symmetric pattern than might usually be expected
- microcephaly or growth retardation (less than the third centile)
- a family history of this, or other congenital abnormalities
- 3 or more parental miscarriages
- parental consanguinity (cousin) partnership

Depending on local practice, complete assessment may be undertaken by a geneticist/dysmorphologist or they may provide initial telephone advice. The following information, gathered for the discussion is most helpful:

- a complete description of the neonate
- facial appearance and relevant photographs
- birth weight and head circumference
- pregnancy history including growth charts, ante-natal scans and any pre-natal tests, particularly chromosome analysis
- record of maternal drugs (both prescribed and non-prescribed), smoking and detailed alcohol history
- parental medical history and exposure to potential teratogens
- a three generation family history, including the child and any siblings (brothers and sisters) from either parent, the child's aunts and uncles through both parents and details of their children, the child's four-grandparents and their siblings
- specific questioning of the parents for any other children in the family who have had a similar condition, a malformation, surgical problem, learning difficulty or who have died young
- any family history of consanguinity or of parents being related or distant cousins

Depending on circumstances the geneticist may request any of the following:

- further clinical photographs
- specific X-rays or a skeletal survey
- chromosome analysis
- DNA for storage
- specific samples for metabolite or enzyme studies
- a skin biopsy to establish a fibroblast cell line, liver or muscle biopsy (these may be post-mortem)
- a cardiac echo, a renal ultrasound and either a brain ultrasound or a brain MRI scan due to the increased risk of finding an associated malformation

Syndrome diagnosis can be certainly aided, but not itself made by using dysmorphology databases and their associated searching tools. They require the clinical assessment of the child with a malformation or series/sequence of congenital anomalies. Carefully selected features (*handles*) can then be entered into such search databases to generate a syndrome diagnosis differential to aid further investigation and hopefully diagnosis. Widely used and easy to navigate databases include the series of London Dysmorphology Databases; 1990, (Baraitser and Winter), http://www.lmdatabases.com/about_lmd.html#lddb that include specific dysmorphology, neurogenetics and eye malformation databases. The dysmorphology database contains information on nearly 5000 dysmorphic and multiple congenital anomaly syndromes with over 20,000 images of facial and malformation features and relevant radiographs. The dysmorphology database currently (2012) costs UK £600 and a subscription for three updates currently cost UK £200. A similar internet based subscription limited access application developed in Australia is POSSUM, http://www.possum.net.au/index.html. Online Mendelian Inheritance in Man [39] is an open access internet based resource catalogue that is continuously updated with comprehensive clinical, research and genetic testing information on over 12,000 single gene (Mendelian) conditions. It is a rich source of diagnostic information and its multiple links allow clinicians ready access to management and support group information [40], published literature and where applicable genetic

testing resources [41]. A number of dedicated textbooks for dysmorphology can also be used [42–45].

Making a diagnosis allows the geneticist to explain to the parents' what has happened and if known why this has occurred. Information can be shared with the child's surgical team and with the often multiple members of the multidisciplinary team caring for the child with congenital anomalies. For the parents' a specific diagnosis allows access to genetic counselling with a more accurate recurrence risk and discussion of the options available for pre-natal diagnosis. A diagnosis may only be a label for a very rare combination of malformations, but it allows forms and statements to be completed, and thereby facilitates access to special educational needs, financial welfare and social care benefits. Parents can achieve a degree of closure in their search for a cause, sometimes their need for something or someone to blame and to begin the process of coming to terms with what has happened and begin to deal with the understandable, but incorrect feelings of guilt over what has happened to their child. Support for families is available from support groups that are specific for that condition/malformation or from these umbrella organisations:

- http://www.rarediseases.org/
- http://www.orpha.net/consor/cgi-bin/Disease_Search_List.php?lng=EN
- http://www.geneticalliance.org/about
- http://www.geneticalliance.org.uk/
- http://www.cafamily.org.uk/
- http://www.raredisease.org.uk/
- http://www.rarechromo.org/html/home.asp

Without a syndrome diagnosis, follow-up visits to the genetics clinic for careful review, access to syndrome diagnosis databases, relevant books and publications with targeted investigation and referral for other opinion(s) may occur over several years. In challenging cases the clinical history and photographs will be shared with dysmorphology colleagues at national or international meetings and may result in publication. Families may spend years searching for a more specific diagnosis with their clinicians. If a confident diagnosis cannot be made, that child's condition may be regarded as a SWAN (Syndrome Without A Name) for which more general support groups exist, http://www.undiagnosed-usa.org/ in the United States and http://www.undiagnosed.org.uk/ in the United Kingdom.

16.12 Methods of Genetic Investigation

In 1956, Tijo and Levan correctly identified the number of human chromosomes in the cell as 46 and in 1959 Lejeune identified the first human chromosome karyotype abnormality in Down syndrome. Non-disjunction is the failure of chromosomes to separate in cell division into daughter cells and is the commonest cause of trisomy, for example age related trisomy 21, Down syndrome. A chromosome might be lost, resulting in monosomy which apart from those affecting the sex chromosomes (45,X—Turner's syndrome) are rare. They can occur in mosaic form where there is a mixed population of body cells with the normal complement 46 chromosomes and abnormal cells with 45 chromosomes. Careful karyotype analysis of 100 blood cells or examination of another tissue; buccal scrape or a cultured skin biopsy might be required to reveal mosaicism especially if it is only present at a low level or confined to one tissue or body region. Deletions, duplications, and more complex re-arrangements including translocations that can be 2-way or even 3-way, inversions can all affect a child's chromosome pattern and produce varying congenital malformation depending on the increase or decrease of chromosome material that results [46].

For many years, light microscopy analysis of banded (chemically stained), cultured cell metaphase chromosomes had to suffice. This can be enhanced by the development of techniques for the preparation of longer chromosomes for higher resolution chromosome analysis. Chromosomes have a shorter (p for petit) and a longer (q) arm separated by the centromere. Chromosomes with a centrally placed centromere are known as meta-

centric chromosomes, the centromere displaced from the centre produces a sub-metacentric chromosome and the acrocentric chromosomes has their centromere at one end, with a very small p arm composed of DNA coding for rRNA. The human centromeric chromosomes 13, 14, 15, 21 and 22 are prone to form translocations with another acrocentric chromosome. These fusion products are known as Robertsonian translocations and when unbalanced can lead to trisomy 13 (Patau's syndrome) and trisomy 21 (Down's syndrome). Chromosome analysis should be offered to the parents of these children as one might be the unknowing carrier of a balanced (45 chromosome karyotype) and at high risk of having further affected children [47].

The resolution of light microscopy is approximately 4 Mb (4 million base-pairs of DNA), but a chromosome loss smaller than this cannot be seen even by high resolution chromosome banding without more specific identification techniques. The early 1990s saw the introduction of an increasing range of specific chromosome analysis probes. The technique of Fluorescent In Situ Hybridisation (FISH), exploits the property of single stranded DNA to bind to its specific complementary sequence. By making fluorescently labelled unique sequence probes, specific DNA regions (for the common chromosome trisomies 13, 18 and 21 and now all of the human chromosomes) can be identified. This technique allows the identification of a chromosome microdeletion (for example the chromosome 22q11 region that is deleted in the contiguous gene of the Di George / Velo-Cardio-Facial/ CATCH-22 syndrome associated with cleft palate, hypocalcaemia and congenital heart disease) or submicroscopic duplications. With an increasing range of chromosome probes, complex translocation re-arrangements and inversions, and the formation of derived chromosome rings can be identified as well as the tips (telomeres) of chromosomes screened for deletions where 2–3% of children with multiple congenital anomalies may be found to have a telomeric chromosome abnormality. A checklist has been developed for identifying patients with suspected sub-microscopic sub-telomeric rearrangements [48–50]. Criteria for genetic investigation / referral are: multiple congenital anomalies (two or more major anomalies) or a single major anomaly together with abnormal neurology, dysmorphic features or an abnormal growth (length, weight, OFC) pattern with 2 or more growth parameters +/− >3SD or a single growth parameter +/− >4SD.

In the technique known as 'chromosome painting' the origin and possible functional significance of unknown chromosome fragments, sometimes appearing as small chromosome rings can be discerned using a range of chromosome specific FISH probes ('*paints*'). The limitation of FISH analysis has been that it only answers a specific question, what is this chromosome fragment?—is it for example derived from chromosome 21 and therefore does this child have a form of Down's syndrome? Or FISH testing can be used to address the clinical enquiry does this fetus / child with congenital heart disease or a cleft palate have Down syndrome or Di George syndrome?, In each case only a limited number of questions can be asked and answered by using a selected number of available chromosome FISH probes.

16.13 Microarray Analysis

It is in the molecular investigation (molecular cytogenetics) of genetic syndromes and malformations that the most rapid progress is occurring. The limited resolution of chromosome studies by light microscopy analysis, even when supplemented by the increased diagnostic yield of telomere analysis and targeted FISH probe analysis has led to the development of the technique of genomic micro-array chromosome analysis. This semi-automated technique introduced in the year 2000, allows for the more sensitive analysis of the whole genome than previous chromosome analysis. The diagnostic yield, finding genomic imbalances (duplications, trisomy or deletions, monosomy) for children with previously undiagnosed congenital anomalies, facial dysmorphism, developmental delay or growth retardation has been highly significant. The wider availability and falling cost (current cost per case analysed

around US$ 1200) of micro-array analysis has led to this becoming increasingly adopted as the first line investigation, in preference to the conventional analysis of stained and banded chromosome metaphase preparations. The cost is likely to fall quickly, as the technique becomes more widely available and DNA chips become commercially mass produced [51, 52].

Microarray analysis depends upon using many thousands of DNA probes already immobilised on a chip to interrogate the patient's DNA by a process of comparative genomic hybridisation (CGH). Also known as array CGH, the technique depends on immobilizing fluorescently labelled probe DNA to the solid surface of the chip surface. Affymetrix uses a glass or silicon chip surface whereas the Illumina chip uses microscopic beads. The target (patient sample) DNA for investigation is rendered single stranded and fluorescently labelled prior to being applied to the chip that might have anything from 2000 to 30,000 or even up to 300,000 oligonucleotide probes from which the non-hybridised patient DNA is washed off. Where the patient DNA (for example fluorescently labelled red) has covalently bonded (bases G to C; bases A to T) to the immobilised probe DNA of the chip, (for example fluorescently labelled green, there will be a 1:1 ratio of the complementary fluorescent signals, and in this example, the red to green ratio will thus be 1. But where a region of the patient's DNA is deleted there will be an excess of unhybridized green target probe and the red to green ratio will be less than 1. If the patient's DNA has a region of duplication, there will be relatively more red signal (patient DNA) retained at that point (spot) on the array and the red to green ratio will be greater than 1. This technique can identify deletions or duplications down to a resolution that varies with the size (60-mer probes produced by Agilent or shorter 25-mer probes produced by Affymetrix) and the genome density of the probes and their cost. Microarray analysis will identify an abnormality in between 3% and 5% and in more carefully selected series up to 10% of previously undiagnosed children. Array CGH will not identify balanced (reciprocal translocations) chromosomal rearrangements in which no genetic material is gained or lost. It will not identify sequence changes at the base-pair or rearrangements at the gene level below the resolution of the probe set used. The limitation of microarray testing (sensitivity) is down to a resolution of 5–10 Mb or using the more expensive high-density arrays, deletions and duplications as small as $\approx$ 1–3 Mb changes can be identified. Microarray chip designs vary between manufacturers and should be chosen for their intended use, as much as for cost. One chip design may for example have a 180 kB backbone spanning the human genome, but have enhancement of 15 kB in approximately 1500 regions that are particularly associated with major diseases.

A current, but significant drawback of CGH micro-array is the frequent identification of variants in the genome of tested patients that are of no clinical significance. It is increasingly recognised that about 0.5% of human genomic DNA has regional variation with regions of DNA varying in length from 1 kb (1000 base-pairs) up to several megabases in length that are repeated / duplicated or deleted. These regions of variation are known as copy number variants (CNVs) and vary across different chromosomal regions. They are part of the normal variation in the structure of genomic DNA that are usually stably inherited from parent to child and are not believed to be associated with any disease phenotype. These variants in segments of the DNA are in addition to the variation in single base-pairs (nucleotide) polymorphisms (SNPs) that are widely scattered through the human genome and that act as prolific markers to track variation and inheritance. Current research studies such as the Deciphering Developmental Disorders (DDD) study [53], is gathering information on their frequency and if there is any malformation/disease association. The finding of an apparent micro-array variant in a child needs careful interpretation, asking the following questions:

1. Is this a region of the genome known to be associated with copy number variants (CNV)?
2. Requesting parental samples for testing. If the micro-array finding is de novo then it is circumstantially, but not definitely proven to be

causal for the child's condition. It remains possible that the apparent stable inheritance of a chromosomal region anomaly does cause a malformation/disease by an epigenetic imprinting effect.
3. Have other people been reported with this micro-array abnormality and do they have a similar malformation/disease phenotype?

Despite these cautions, the introduction of microarray analysis and their falling costs has opened an exciting window for the investigation of children with malformations. Specific treatment my still elude us, but for the clinicians involved and particularly parents, there is at last some explanation for what has happened [54, 55]. Stem cell research and forms of gene therapy using anti-sense oligonucleotides (ASOs) and RNA interference (RNAi) sequences to target the suppression of mutant genes are under development.

16.14 Molecular Genetic (DNA) Testing

Nowhere has growth been more explosive than in the range of DNA analysis techniques and the exponential expansion in the number of genes that can now be screened. The current and still moving horizon of DNA sequencing has moved from slow and laborious chemical and pyrosequencing methods introduced in 1977 by Maxam and Gilbert and refined by Fred Sanger as Sanger sequencing, sharing the 1980 Nobel Prize for chemistry [56]. The technique of MLPA (multiplex ligation-dependent probe amplification) developed from multiplex polymerase chain reaction (PCR) allows multiple DNA targets to be amplified and analysed. Provided the gene sequence of the wild-type DNA sequence is known, designed oligonucleotide primers can be used to amplify specific DNA regions (referred to as amplicons) for capillary sequencing or further analysis [57]. In the 1980s Applied Biosystems developed the first automated sequencing machine the ABI 370, and in the 1990s came high-throughput sequencing in what is now termed, Next Generation Sequencing (NGS) or massively parallel sequencing using robotics [58]. It is now possible to sequence a person's exome (the approximately 180,000 expressed exons, about 30 megabases of DNA that constitutes about 1% of the total genome), in a few days at a cost rapidly approaching USD $1000. Perhaps the only limitation of microarray analysis and of sequencing the genome—is the vast amount of data generated. Deciding whether a sequence change or a small deletion/duplication is clinically significant in a neonate with an undiagnosed multiple malformation condition is complex. If the sequence change or microarray finding has been reported before, it may be possible to say that it is causally or even functionally associated with that pattern of malformation(s). Changes in the DNA sequence may not be disease causing if the alteration occurs in a non-coding or non-regulatory of the genome; if the change of a single nucleotide does not lead to an amino acid change, known as a silent mutation because the genetic code is degenerate with multiple combinations of the 3 base codons accounting for any of the 20 amino acids. DNA sequence changes may affect RNA splicing if the recognition sequence of an intron-exon boundary is disrupted. The DNA mutation may be a missense mutation that changes the amino acid sequence, but the consequence of this will depend on the amino acids substituted. If an amino acid is changed for one of similar size, acidity/base, hydrophilic/hydrophobic character or this occurs in a non-critical region of the protein the change may be neutral and not clinically evident. However, the amino acid change may for example, involve cysteine that can form disulphide bridges and significantly change the 3D conformation of protein folding and hence its function.

Mutations may create a stop codon (nonsense mutation) that leads to premature termination of mRNA translation. Protein synthesis will stop at that point and the closer this is to the start of polypeptide synthesis at the 5′ end, the greater will be the functional loss of the intended protein. Likewise mutations at promoter end of genes will led to the failure of gene transcription and function. The deletion of 1 or 2 nucleotides in the

DNA will lead to frame-shift mutation disrupting the ordered reading of triplet codons and produce a complete change of the consequent protein sequence and the likely downstream appearance of a stop codon. It is now realised that genes are far more dynamic than its mere nucleotide sequence would suggest. Epigenetic effects occur where key areas of the genome can be methylated that leads to the non-expression of that gene (gene silencing) in future cell divisions. The imprint occurs in meiosis and differentially affects the expression of maternally and paternally inherited copies of the same gene in all subsequent somatic cell divisions. It is thus important not only what DNA sequence you inherit, but also whether this was inherited from the mother or the father. Imprinting particularly affects the Prader-Wiili and Angelman syndrome region (15q11–13) of the human genome and the Beckwith-Wiedemann syndrome region (11p15).

DNA changes are referred to as a mutation if they are believed to be causally related to the disease/ condition. A sequence change that is not believed to be pathogenic, but occurs in more than 1% of the population is termed a polymorphism. A private polymorphism is a neutral change that is rarer than this, (less than 1% of the population). If a DNA sequence change has not been previously reported, its presence may be coincidental. If the variant is found in an unaffected parent, it is probably a polymorphic variant that is unlikely to contribute to the malformation seen in the affected child. If the DNA sequence change is not present in either parent (therefore occurring de novo) then it is likely to be associated with the aetiology of the malformation(s) in that child. Internet based databases such as the DECIPHER database at the Sanger Centre [59] have been established to collect information on these new findings and to collate updates on their functional and clinical significance. The new science of bioinformatics has been born out of the need to collect, collate and ultimately interpret the literally billions of nucleotide sequence changes that have been generated from sequencing individual genomes. With the increasing availability and decreasing cost of next generation / whole genome sequencing the challenge is the interpretation of so much sequence data and the likely finding of numerous sequence variants of unknown clinical significance. Known as unclassified variants (UCVs), or copy number variants (CNVs) or single nucleotide variants (SNVs) they be disregarded if they are known to occur in regions of known DNA variation. If present in a parent they may be innocent polymorphisms; but it is possible that they contribute to the pathogenesis of a multifactorial or polygenic condition as genetic modifiers or that sequence change itself is susceptible to imprinting by methylation and hence variation in expression. If a sequence change has been found to be de novo, (not present in the parents and non-paternity can be excluded), then that apparent DNA mutation can be circumstantially associated with the aetiology of a malformation or syndrome. Further evidence of causation would come from its finding this mutation in multiple other cases and being able to implicate its role in the embryology and pathogenesis of that condition. Microarray reports and extensive sequencing data must therefore be interpreted with caution. The reporting laboratory and reference to the literature may help to classify whether this mutation has clinical validity and ranges from Class 5: definitely pathogenic (>99% probability) and can be used for prenatal testing, Class 4b: probably pathogenic (95–99% probability) that requires additional confirmatory evidence, Class 4a: possibly pathogenic (80–95% probability) that may help with clinical diagnosis, but cannot be reliably used for prenatal testing; Class 3: uncertain where there is no clear evidence of whether the finding is causal or benign through to Class 2 and Class 1: likely benign (1–5% probability) or benign (<1% probability) respectively that the variant found is pathogenic. This requires careful explanation of this to the clinical team and counselling of the family to avoid a genetic change being over interpreted and wrongly accepted as the genetic cause of a child's condition. The consequences may be failure to pursue other investigations, the risk of giving incorrect information to the parents and hence inaccurate recurrence risks to them and

close family members. Ultimately this can lead to false reassurance in a future pregnancy or a missed recurrence. Non-specialists are cautioned to seek advice and to tread carefully.

16.15 Non-genetic Investigation of Malformations

Emphasising that not all malformations are genetic, let alone inherited, other causes may need to be sought. These may include teratogens either ingested as prescribed or non-prescribed or abused drugs, exposure to environmental toxins and chemicals and maternal alcohol ingestion and smoking during the pregnancy. The effect of teratogenic infections such as rubella virus for which careful examination of the neonate, taking a maternal and pregnancy history and confirmatory viral antibody titres may be diagnostic. Clinical photographs are an essential record of the child, their malformation(s) and to include views of their face (full face, with frontal and lateral views, full body standing to show proportions and any distinguishing features) that may be shown to dysmorphologists to allow them to search amongst hundreds of possible syndromes for specific malformation(s) and distinguishing features. Building up a picture of the key malformations and those supporting features whilst ignoring common or co-incidental features, a likelihood of perhaps 4–6 syndromes in the differential diagnosis can be derived for further exploration.

The investigation of other malformation conditions may require a skeletal survey, targeted biochemical analysis, enzyme assays or the screening for either excessive or insufficient levels of key metabolites. For example measurement of the 17-OH steroid profile in congenital adrenal hyperplasia (CAH) or of the 7-dehydrocholesterol level to diagnose Smith-Lemli-Opitz (SLO) syndrome. Both of these conditions are associated with ambiguous genitalia and need to be considered amongst the many other chromosomal, single gene and mosaic genetic causes of disorders of sexual development (DSD) [60, 61]. If a metabolic syndrome is suspected, it may be prudent to ask the parents, particularly when a child is moribund or has died for consent to store plasma, urine, CSF, liver and often to take a skin biopsy sample to establish a skin fibroblast cell line. If an EDTA blood sample has not already been taken, spleen or liver tissue even many hours post-mortem provides a highly cellular sample for DNA extraction.

16.16 Approaches to Genetic Counselling

The process of genetic counselling is intended to inform and support patients and their families about their condition and help them make informed decisions. The American National Society of Genetic Counselors' (NSGC) developed a revised definition of genetic counseling: 'Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- interpretation of family and medical histories to assess the chance of disease occurrence or recurrence
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.' [62]

Some genetic counselling sessions may be straight-forward, informing the family of the diagnosis, sources of information, perhaps just a low recurrence risk and will require only one visit. Other referrals might require several sessions to collect additional information, to update the family or to deal with ongoing medical and/or psychosocial problems.

A detailed history (pedigree) should be taken to at least three generations to include the patient's brothers and sisters and any children they have, the grandparents and their siblings and

families. A shorthand notation for drawing the family tree uses square symbols for male family members, circles for females and a diamond symbol where the sex is unknown, those of the same genetic generation are kept on the same line, their children drawn below and so on [63].

The parents should be asked about their other children, any miscarriages, stillbirths or neonatal deaths. Questions should include the parents' medical history, history of the pregnancy and asking about all drugs and potential teratogen exposure information is important. It may be necessary to seek old medical records if something relevant is mentioned by the family. It is important to particularly ask whether the parents' or their families are related as consanguinity (inbreeding) makes autosomal recessive conditions with a high, (25% or 1 in 4) recurrence risk to further children likely, but not necessarily the cause. Autosomal recessive conditions may be the underlying cause even if no previous family history is yet known. With autosomal recessive conditions, parents are healthy, and more often unknowing carriers of one copy of the mutant gene. Consanguinity is a particularly common practice in some Middle Eastern, south Asian and Muslim ethnic communities and also with within geographically and socially isolated communities. A pedigree is useful in the assessment and diagnosis of a genetic disease and to determine a person's risk of developing a genetic disease or to determine the risk of having a child with a genetic disease. The family tree may help particularly if there have been other affected family members that helps to identify the pattern of inheritance. Typically autosomal dominant inheritance shows transmission from an affected parent to half the children (50% risk, a 1 in 2 chance) independent of their sex. There is often very variable expression (varying from mild to severely affected). With small families the dominant pattern may not be obvious and incomplete penetrance of a malformation gene, may lead to the apparent 'skipping of generations', only for the condition to re-appear in a grandchild or niece/nephew. It may sometimes be difficult to determine if a condition represents a new dominant gene mutation, a multi-factorial condition or result from the transmission of a non-penetrant gene from one parent, or be the result of a '*rogue gene*' appearing from non-paternity! Sex-linked recessive (X-chromosome) conditions are carried by women, who are usually healthy, and may be the unknowing carriers of a mutated gene that will be passed onto affect half their boys. Sometimes a woman carrying an X-linked trait may be a manifesting carrier, expressing mild features of the condition. This may be due to unequal X-inactivation (Lyonisation) between the two X-chromosomes with preferential expression of the mutant X over the normal (wild-type) X chromosome. Further information on genetics and inheritance patterns is available from a selection of books and internet sources [64–66].

More complex family trees may underlie a chromosome re-arrangement that is balanced (no chromosome material gained or lost) in the unaffected family members, but leads to unbalanced chromosomal rearrangements in the affected children where there is a duplication (trisomy) or loss (deletion) of some chromosome segment(s). Malformation may be due to the teratogenic effects of prescribed, non-prescribed or illicit drug exposure or alcohol that may be undeclared and /or taken without clear knowledge of the pregnant mother. Viral teratogens should also be borne in mind. Besides depicting familial relationships, a pedigree should also contain medical information with birth date, age of death, cause of death, health problems, and results of genetic tests. Obtaining medical records on affected relatives with their consent will ensure the medical information is as complete and accurate as possible. Increasingly the collection of family tree information and genetic counselling for malformations with an established syndrome / genetic diagnosis is undertaken by genetic counsellors / genetic nurse specialists working alongside medical geneticists. They would have an appropriate professional background and have attained a Masters degree in Medical Genetics / Genetic Counselling. With the rapid expansion of genetic testing and the increasing finding of positive results from detailed chromosome (micro-array)

and high-throughput DNA sequencing and that soon expected form whole genome sequencing (WGS), there has been a rapidly rising demand for the delivery of genetic information by non-specialists. In the UK this has led to the listing of genetic competencies by nurses and health visitors [67]. These include:

1. identifying those who might benefit from genetic information & services
2. providing genetic information appropriate to family's culture, knowledge & language
3. ensure clients have informed decision making and voluntary action
4. knowledge of genetic & other factors in the manifestation of the condition
5. understanding of the utility & limitations of genetic testing
6. recognize limitation of one's own genetic expertise
7. communicate this information effectively to family and other clinicians

During a clinical genetics / genetic counseling visit which may be held jointly with the neonatal surgical team, the parents may ask questions, depending on many factors—the type of malformation(s) the child has and its surgical prognosis. The family will also often ask about the following:

The Condition

1. what is this condition, what happened?, why?, what caused it?, what else might affect the child, what will happen now?

The Prognosis

2. is it treatable / fully correctable?, will it get better, is there a treatment?, can their child lead a normal, pain free life?, is it life threatening, could more problems appear?, could there be learning difficulties?, what about mobility, limb function?

The Cause

3. whose fault was it?, what can I / we do?, what are the chances of this condition occurring again?

Recurrence Risk and Options

4. if this condition does recur, could it be milder or more severe? what are our options, are there any tests?, who else is at risk? can they be tested?, what can I do?, who can help us?

16.17 Methods of Ante-natal Diagnosis

Antenatal ultrasound was first used in 1964 and 2 years later the first prenatal chromosome analysis by amniocentesis was performed. Chorionic villus sampling (CVS) performed around 11 weeks gestation followed and DNA from the sample was first used for the prenatal diagnosis of sickle cell disease by Kan and Dozy [68] in the 1970s, and subsequently for an increasing range of single gene disorders. After the success of 'in vitro' fertilisation (IVF) by Edwards and Steptoe, the technique has been used alongside molecular genetic testing of single cells to achieve pre-implantation genetic diagnosis (PGD) by Handyside and Winston in 1990. In this way families at risk of already identified single gene disorders, or known chromosome rearrangements can have fertilised embryos screened. Molecular analysis of single cells using modified techniques of the polymerase chain reaction (PCR) allows the amplification of targeted genomic regions and only those unaffected conceptions implanted into the mother's uterus. Couples at high risk are thus able to continue with a pregnancy from an early stage reassured that they have escaped the *'genetic lottery'* and should be able to have unaffected children without needing to resort to selective termination of pregnancy. At present techniques of early and non-invasive prenatal diagnosis (NIPD) and even population screening are being developed based on the identification of cell-free fetal DNA (cffDNA) in the maternal blood. This is DNA derived from the pregnancy that can be found from as early as 4 to 6 weeks gestation in the maternal circulation, but is completely cleared within a few hours of birth or the end of the pregnancy. Initially used to determine the Rhesus status and then for fetal sexing in sex-linked conditions, the

use of cffDNA is currently being explored for a range of single-gene and chromosomal conditions. The advantages of requiring only a maternal blood sample is easier, less skilled and less costly sampling than current CVS under ultrasound guidance, it can be offered to many more women or indeed become population based with no risk of unintended pregnancy loss. With appropriate laboratory testing facilities, cffDNA testing can provide results well before a CVS or an amniocentesis could be performed. The sensitivity and specificity of cffDNA analysis remains to be determined for an increasing range of conditions, but when coupled with the increasing speed and falling cost of high-throughput DNA analysis will provide an important option to be developed [69]. The challenge will be its acceptability and the potential use / abuse in, for example Internet based requests for pre-natal sex selection for family / social planning outside of the context of serious genetic disorders [70, 71].

16.18 Approaches to and the Ethics of Pre-natal Diagnosis

Faced with the finding of anomalies in their child from ante-natal testing or more often and unexpectedly from an ultrasound scan; parents will want to ask many of the questions listed above. The recurrence risk may range from a low risk for a sporadic condition (<1%), through the empiric recurrence risk after the first occurrence of a multi-factorial condition (say 2–3% risk) through to the 25% recurrence of an autosomal or X (sex)-linked condition and up to 50% risk with variable expression (severity) of a dominant disorder. The surgical options and outcomes will vary depending on the condition, from a single and fully corrective procedure with no expected adverse sequelae; through the multi-stage repair of a complex bilateral cleft lip and palate to the uncertain outcome for a child with a complex ano-rectal or urogenital malformation in terms of control over continence, sexual function and the psycho-social and sexual consequences for the child and their family. Discussing the neonatal surgical option(s) and likely outcomes will often be led by the neonatal surgical team, but in depth discussion will require a multi-disciplinary approach from the many specialties and therapists (speech, educational, dietetic, psychologist etc.,) that may be involved in the repair, recovery and adjustment of the growing child. Parents will vary in their response to this information; what may be seen as a minor anomaly, easily repaired by the surgical team with an apparently good cosmetic appearance, may because of the shock of its initial diagnosis, uncertainly over its long-term outcome and the perceived social stigmatisation of the condition lead to requests for pre-natal testing in a subsequent pregnancy and even consideration of termination for a similarly affected pregnancy. Advances in surgical techniques for that condition, the family's access to that surgical expertise (its cost, geographical access, other children) will all influence the parents' decision making.

Parents may decline the offer of pre-natal testing if they have had a very positive experience of their child's condition, if they have strong personal religious views, "*that it is God's will*", or a moral view that they would not intervene to terminate an affected pregnancy. There are many factors in an intensely personal discussion that cannot be predicted and should not be predicated. Parents will weigh up the severity of the condition, their experience of the condition, if they feel they can cope with that condition or a second affected child, the gestation at which the diagnosis can be made and if a termination can be performed in the first or second trimester. Attitudes and the legal position on therapeutic termination of pregnancy will vary from country to country and from culture to culture. What is legal, what is acceptable and what defines disability and handicap as well as the availability of surgical excellence and its support teams as well as the cost to the family or if state funded care is available, all contribute to the complexity of decision making. Denial of the diagnosis or of a progressive or lethal outcome is most difficult in the context of a newborn child, and when many health professionals are involved in giving information

about the prognosis. The challenge is to identify the needs of the family and to carefully share the information at the rate and in the depth that the family needs. The role of genetic counselling in a European / North American setting, based on Judaeo-Christian ethics is to equip the parents to make these incredibly emotive and long lasting decisions themselves. These discussions are often in very difficult and time-pressured circumstances giving the family as much unbiased information as they need and can understand. Parents should be supported, perhaps guided, but never led [72, 73]. The most difficult questions to respond to are, "What should I do, or what would you do if this was your child or pregnancy?" The response should be to sensitively explain that this is not our child, the long term care will not fall to us, the consequences of the parents' decision will be theirs and they will have to live with this. They should have our support, whatever decision they make, whether to continue an affected pregnancy and seek pre-natal or post natal treatment or to terminate the pregnancy. We have to be non-directive and non-judgemental in our approach and support whatever the parents' decide, even if we might have made a different decision ourselves [74–76]. A consequence of the greatly improved survival rates for children operated on for neonatal surgical conditions, is discussing with them now as young adults, their attitude to their own condition, the risks of recurrence and what their feelings might be of having an affected child themselves. Sources of information and support for families are available from multiple sources included with this chapter [77].

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Part II

Trauma, Pierre Robin Sequence, and Twins

Birth Trauma

17

Mark Tattersall, Devender Roberts,
and Leanne Bricker

Abstract

Birth trauma refers to the variety of injuries that can be sustained by the infant during the process of labour and delivery. It is a significant cause of neonatal morbidity and mortality. The process of birth involves a combination of mechanical forces acting upon the fetus that can produce tissue haemorrhage and disruption of physiological integrity. These factors may result from the method of delivery, route of delivery or fetal position and size. In addition, obstetric intervention may amplify the effects of these forces and cause or exacerbate birth trauma. Whilst one aim of the obstetrician is to prevent birth trauma by identifying fetuses at risk and making appropriate plans for delivery, most birth injuries are unavoidable and occur despite skilled obstetric and neonatal care. In any discussion of birth trauma it is important to realise that whilst caesarean delivery may be protective of some types of birth trauma, fetal injuries can be seen with caesarean section, even when this is performed as an elective procedure.

Keywords

Fetus • Birth injuries • Newborn • Newborn surgery

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_17

Birth trauma refers to the variety of injuries that can be sustained by the infant during the process of labour and delivery. It is a significant cause of neonatal morbidity and mortality. The process of birth involves a combination of mechanical forces acting upon the fetus that can produce tissue haemorrhage and disruption of physiological integrity. These factors may result from the method of delivery, route of delivery or fetal position and size [1]. In addition, obstetric intervention may amplify the effects of these forces and cause or exacerbate birth trauma. Whilst one aim of the obstetrician is to prevent birth trauma by identifying fetuses at risk and making appropriate plans for delivery, most birth injuries are unavoidable and occur despite skilled obstetric and neonatal care. In any discussion of birth trauma it is important to realise that whilst caesarean delivery may be protective of some types of birth trauma, fetal injuries can be seen with caesarean section, even when this is performed as an elective procedure [2].

Birth trauma has been estimated to occur in 3% of all live births and accounts for 2% of all neonatal mortality and 10% of all neonatal deaths in infants delivered at term [3]. Whilst the cause of much birth trauma is difficult to define and it can sometimes prove impossible to explain, a large number of risk factors have been identified for birth trauma and these can be divided into those pertaining to the mother and those relevant to the fetus, as shown in Table 17.1.

There are a wide variety of types of injury that can occur during the process of labour and birth and which will be discussed in this chapter. For ease, injuries have been broken down into the following types:

- Injuries to the Head
- Fractures
- Nerve injuries
- Anoxic injuries

Table 17.1 Risk factors for birth trauma [72]

Maternal	Fetal
Diabetes	Macrosomia
Obesity	Pregnancy prolonged beyond Term +18 days
Small pelvis	Abnormal presentation
Large pregnancy weight gain	Instrumental delivery
Short maternal stature	Perinatal depression
Induction of labour	Shoulder dystocia
Epidural usage	
History of macrosomic infant	

17.1 Head Injuries

The head is the most common part of the body injured during labour and delivery, which is due to the fact that this is usually the presenting part.

17.1.1 Superficial Injuries

Superficial head injuries can occur at all types of delivery and are relatively common. Bruising, abrasions and lacerations can occur at the time of spontaneous vaginal and instrumental deliveries. Rates of 0.1% of all deliveries [4], around 10% with ventouse deliveries and approximately 35% with forceps deliveries [5] have been quoted. Lacerations to the scalp, face, cheek or ear can occur at Caesarean section and it is good practice to specifically counsel mothers regarding this risk. It is estimated that the risk of such lacerations is approximately 1%, with the risk not necessarily being associated with any particular type of Caesarean section, the presentation, dilatation, presence of intact membranes or the experience of the surgeon [6–8]. If a full-thickness laceration is present, suturing is often required and consultation with a plastic surgeon is recommended to achieve a cosmetically satisfactory result, particularly for injuries to the face. The two most common types of injuries to the head are caput succedaneum and cephalohaematoma. Other head injuries include subgaleal haemorrhages, intracranial haemorrhages, nasal injuries and eye injuries. Figure 17.1 illustrates the location of the fluid collections in the major types of scalp injuries.

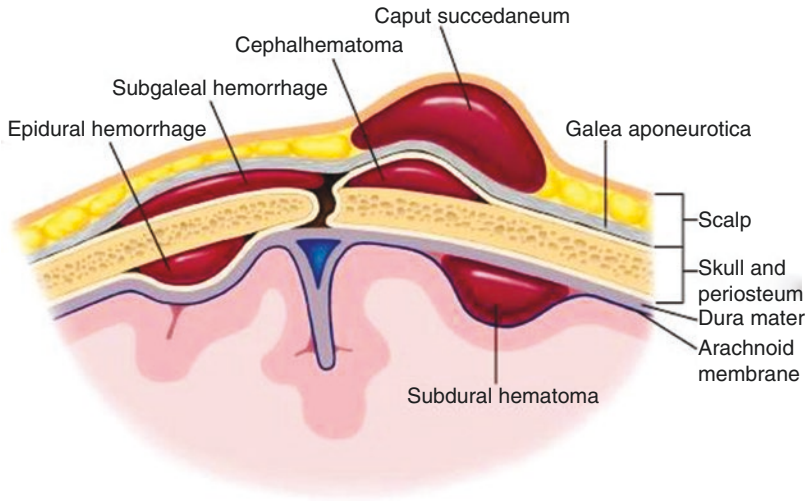

Fig. 17.1 Schematic diagram illustrating anatomical regions of the newborn skull and site(s) for potential birth injury(s)

17.1.2 Caput Succedaneum

A caput succedaneum is a subcutaneous, extra-periosteal collection of serosanguinous fluid which is associated with head moulding. This common lesion at birth is usually seen on the presenting portion of an infant's skull during vaginal birth and is often accompanied by bruising and petechiae. It is caused by the high pressure exerted on the fetal head during labour by the uterus and vaginal walls as the head passes through the birth canal. This prolonged pressure causes leakage of serosanguinous fluid from the subcutaneous tissues into the area between the scalp and the lining of the periosteum, causing oedema and bruising. Caput succedaneum is easily differentiated from a cephalohaematoma by the fact that the fluid accumulation crosses over the cranial sutures due to the collection being above the periosteum. Again in contrast to cephalohaematoma, a caput succedaneum is evident immediately after delivery and will subsequently decrease in size over time. A caput succedaneum has a soft, boggy feel and may display petechiae, purpura or ecchymosis. The swelling is generally 1–2 cm in depth and is most commonly seen in the midline with the circumference being highly variable in size and the margins usually being irregular in shape. In caput succedaneum, the collection of serous fluid characteristically shifts from side to side as the infant's head position is changed.

Risk factors for caput succedaneum include nulliparity, a prolonged second stage of labour, premature rupture of membranes and ventouse delivery, with the latter being a particular risk where the vacuum is applied for over 10 min, there is inappropriate cup placement or repetitive cup detachments. In the case of ventouse delivery, the 'artificial' caput succedaneum (commonly known as a 'chignon') is caused by a collection of interstitial fluid and microhaemorrhages occurring under the cup site and is helpful in keeping the vacuum cup more attached to the fetal scalp [9]. In rare cases of ventouse delivery, caput succedaneum can be associated with breakage of the skin of the scalp if the cup "pops off" the head and abrades the underlying skin. Although it is thought that pressure exerted on the fetal head during labour and delivery is the causative factor in the development of caput succedaneum, it is important to note that there are several cases reported in the literature where this injury has been described as being identified by ultrasound in the third trimester, suggesting that this injury does not always occur during labour and delivery. Caput succedaneum does not usually require any treatment, resolving spontaneously within the first few days after birth [10, 11].

Alopecia can occur in conjunction with caput succedaneum. This is usually in the form of a halo scalp ring, where hair loss develops as a result of tissue necrosis from prolonged pressure of the

scalp against the ring of the cervical os during the birth process. In most cases, the hair grows back over time, but scarring and permanent hair loss have been reported in association with caput succedaneum [12]. An important final point to note is that caput succedaneum can be confused with a subgaleal haemorrhage (discussed below), as this also crosses the suture lines. It is important that such a misdiagnosis is not made as this can have potentially catastrophic results due to the more serious nature of the latter diagnosis.

17.1.3 Cephalohaematoma

A cephalohaematoma is a collection of blood below the periosteum of the skull. This extracranial haemorrhage occurs when friction during the birth process causes the emissary and diploic veins between the periosteum and the skull to rupture. As the haematoma is subperiosteal, it does not extend across suture lines as the ligaments which attach the periosteum to the skull at the cranial suture lines contain the blood. A cephalohaematoma can thus usually be easily distinguished from a caput succedaneum or a subgaleeal haemorrhage, although where there is a caput succedaneum or scalp swelling overlying a cephalohaematoma, this can obscure its boundaries and make diagnosis more difficult. Figure 17.2 shows a MRI where the differences between a caput succedaneum and a cephalohaematoma can be clearly seen. A cephalohaematoma is not usually present at birth unless there is a history of prolonged head engagement and usually develops during the first 24 h of life due to the slow nature of subperiosteal bleeding. In contrast to caput succedaneum, there is not usually any discolouration of the overlying skin due to the accumulation being in a deeper, more vascular tissue plane. This also accounts for the increased blood content of cephalohaematomas, which continue to increase in size until pressure in the space builds and acts as a tamponade to stop further bleeding. Cephalohaematomas present as firm masses that may be either unilateral or bilateral covering one or more bones of the scalp. The lesion cannot usually be transillumi-

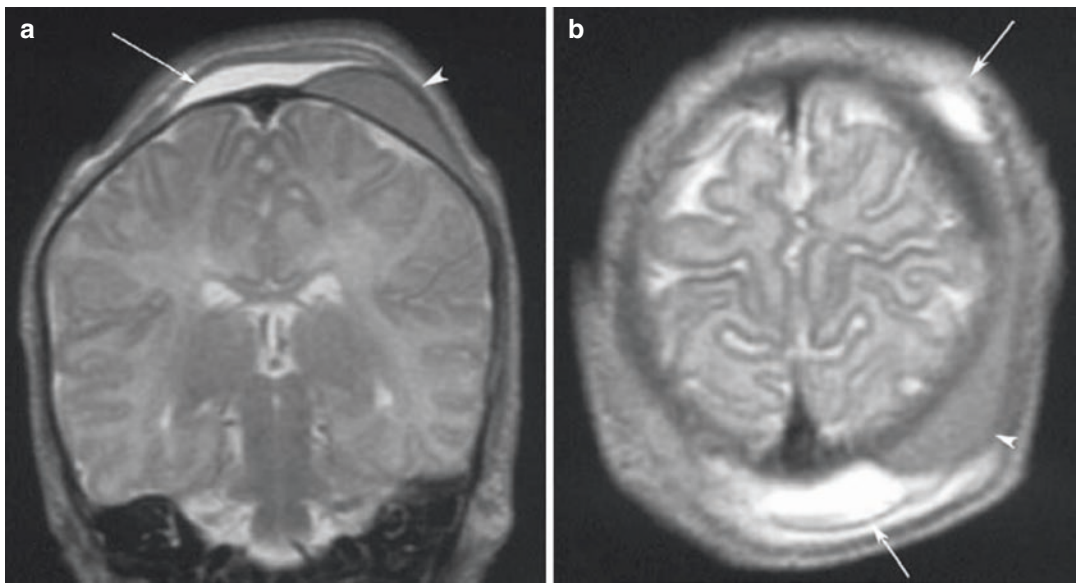

Fig. 17.2 Brain MRI. Coronal (**a**) and axial (**b**) images reveal the caput succedaneum (*arrow*) with crossing the suture line and the cephalhaematoma (*arrowhead*) without crossing the suture line. The low signal intensity of the cephalhaematoma suggests the subacute haematoma. From: Choi JW, Lee CH, Suh SI. Scalp swelling crossing the suture line on skull radiograph: is it always a sign of caput succedaneum? Pediatr Radiol (2006) 36: 364. doi:10.1007/s00247-006-0113-6

nated and are most commonly found in the parietal region, although it may occur over any of the bones of the skull. The right parietal bone is involved twice as commonly as the left and unilateral lesions are five-times more common than bilateral ones.

The incidence of cephalohaematomas has been estimated to be up to 2.5% of all live births [13–15]. The rate of cephalohaematoma is significantly increased with ventouse delivery (compared with normal vaginal delivery) [16, 17] and is also increased to a smaller extent by forceps delivery [18]. Other risk factors for cephalohaematomas include primiparity, macrosomic infants, prolonged labours and abnormal fetal positions such as occipito-transverse or occipito-posterior. Cephalohaematoma is twice as common in males than in females for reasons that are unknown. Although cephalohaematomas may be potentially more serious than caput succedaneum, they are usually benign if there is no underlying coagulation disorder and treatment is rarely indicated. The haematoma generally resolves spontaneously and completely by 3 months of age.

There are a number of important complications which may be associated with a cephalohaematoma. Linear skull fractures occur in approximately 5% of unilateral and 18% of bilateral cephalohaematomas. Routine radiography is not recommended, but should be undertaken if the cephalohaematoma is excessively large, there are neurological signs present or when a particularly difficult delivery has taken place. Such linear skull fractures rarely require treatment. Cephalohaematomas can become infected and when signs of sepsis are present and the focus of the infection cannot otherwise be explained, the cephalohaematoma should be suspected as the site of infection. There is an increased risk of infection if a scalp electrode has been used during labour, if a needle aspiration of the cephalohaematoma has previously been attempted or if there is already systemic infection existing in the infant. The most common organisms include E. coli and S. aureus. Needle aspiration is used to diagnose infection of a cephalohaematoma, but is only performed when other possible sources of infection have been excluded, as it may introduce organisms into a previously sterile area. Treatment of infected cephalohaematoma is usually with intravenous antibiotics for up to 2 weeks, with initial antibiotic selection made to cover both E. coli and S. aureus. When infection has been diagnosed following needle aspiration, antibiotics are usually adjusted according to sensitivity results and CT can be used to reveal any evidence of osteomyelitis, epidural abscess or subdural empyema, which may necessitate a longer course of intravenous antibiotics. In cases where there is no clinical improvement despite antibiotic treatment, surgical incision, drainage and evacuation may also be considered.

Anaemia may be a complication associated with larger cephalohaematomas and can occasionally require transfusion. Hyperbilirubinaemia is a common side effect of cephalohaematoma, which occurs when the red blood cells in a cephalohaematoma are destroyed, with an end metabolic product being bilirubin. Bilirubin levels should therefore be monitored whilst a significant cephalohaematoma resolves and phototherapy is effective is returning unconjugated bilirubin levels to normal.

Calcification can rarely be a complication of cephalohaematoma, which usually occurs when the lesion persists beyond 4 weeks of age. It can cause a misshapen head and such skull deformities can require treatment. Figure 17.3 shows a CT scan of a calcified haematoma. A persistent

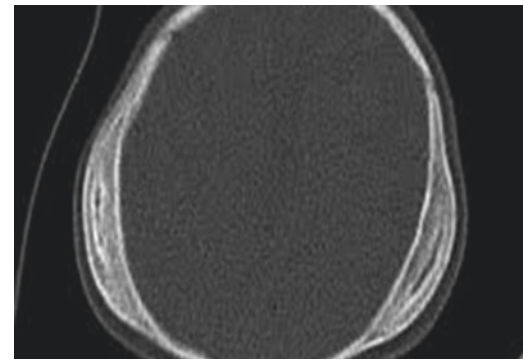

Fig. 17.3 Computed tomography scan showing calcified cephalohematoma. From: Kestle JRW. Tumors of the cranial vault in children. In Tonn J-C, Westphal M, Rutka, JT, eds. Oncology of CNS Tumors. Springer-Verlag: Berlin Heidelberg; 2010: 629–635

disfiguring calcified cephalohaematoma can require surgical treatment. The bony cap of a calcified cephalohaematoma is removed and the underlying material is debrided. A contouring surgical burr is used to reshape the skull and reform the correct anatomical form, with bony shavings used to fill in any depression left. Passive cranial moulding helmet therapy has also been used as an effective non-surgical treatment for calcified cephalohaematomas. It relies upon the malleability of the infant's head prior to 12 months of age and involves placing a moulded helmet on the infant's head for 18–20 h per day until the desired cranial shape is achieved. This non-surgical treatment is usually only successful in the case of partially calcified cephalohaematomas, as fully calcified cephalohaematomas do not usually respond as well.

17.1.4 Subgaleal Haemorrhage

Subgaleal haemorrhage is a potentially fatal lesion, which results from bleeding into the subaponeurotic space, a potential space between the epicranial aponeurosis of the scalp and the periosteum of bone. The epicranial aponeurosis is a sheet of fibrous tissue which covers the entire cranial vault from the orbital ridges anteriorly to the nuchal ridge posteriorly. Its lateral margins blend with the temporal fascia. The space formed is potentially a large one, estimated to be able to accommodate up to 360 ml of blood. The fact that such extensive blood loss is possible means that mortality rates from subgaleal haemorrhage have been estimated to be up to 22%. Diagnosis of subgaleal haemorrhage is generally made clinically, with a boggy swelling over the scalp generally being noted between 12 and 72 h after delivery, although in severe cases signs may be present at delivery. The swelling may be associated with bruising and periorbital or periauricular oedema. The infant usually has an irritable cry and signs of pain, especially when the head or scalp is manipulated. Severe cases are associated with cardiovascular collapse. Subgaleal haemaorrhage can be distinguished from cephalohaematoma in that the swelling crosses the suture lines. The presentation can often be insidious, which can cause delay in diagnosis and treatment, which contributes significantly to the high mortality. Subgaleal haemarrhage is most common after ventouse delivery [19, 20]. It is thought that use of a ventouse produces a shearing force to the scalp that tears the emissary veins and produces the haemorrhage, but it is important to note that subgaleal haemorrhage has also been observed in association with Caesarean section delivery. Subgaleal haemorrhage has been estimated to occur in less than 0.1% of all deliveries, but in up to 1% of ventouse deliveries [21].

The diagnosis of subgaleal haemorrhage is usually made by careful physical examination demonstrating a ballotable lesion which crosses the suture lines. It is important that treatment is not delayed whilst waiting for CT or MRI confirmation of the diagnosis. The priority is to stabilise the infant and radiologic examination can be safely deferred useless there are focal neurological signs indicating the potential for a subdural lesion. Serial head measurements can be used to monitor the evolution of a subgaleal haemorrhage, with it having been estimated that approximately 38 ml of blood have accumulated for each centimetre increase in head circumference. Signs that indicate increasing severity include severe anaemia, hypotension, weak pulses and tachycardia and once hypovolaemic shock has developed the infant's chances of survival are poor, due to decreased organ perfusion, myocardial damage and widespread cellular death. It is thus critical that a subgaleal haemorrhage is recognised early and treated with aggressive volume resuscitation in order to provide the best chances of full recovery. Treatment also requires careful monitoring of the infant's condition, regularly assessing vital signs, neurological status and clotting variables. If blood products are transfused, it is essential to monitor the haematocrit, coagulation studies and the platelet count until haemostasis is achieved.

17.1.5 Intracranial Haemorrhage

Intracranial haemorrhage, including subarachnoid haemorrhage and subdural haemorrhage should be considered after any difficult delivery

to prevent life-threatening complications. However, it is important to realise that the presence of such lesions in newborns is not always subsequent to birth trauma. For example, a series of six cases have been reported where intracranial haemorrhage occurred in the absence of birth trauma [22]. In three of these cases, there was a clotting factor deficiency, highlighting the role that such abnormalities play in intracranial haemorrhage. Intracranial haemorrhage is regarded as the most serious complication of neonatal alloimmune thrombocytopenia, a condition estimated to occur in 1 in 2000–5000 neonates [23].

Subarachnoid haemorrhage is the most common intracranial lesion detected after birth. Where it is secondary to birth trauma, it commonly occurs in conjunction with another cranial lesion, such as caput succedaneum, cephalohaematoma or a skull fracture. A subarachnoid haemorrhage occurs when bridging veins tear or vessels rupture and bleed into the subarchnoid space. It is a relatively benign lesion and rarely has complications, being often discovered as an incidental finding on CT scan. When symptomatic, the most common presentation is with transient seizure activity on day 2 or 3 of life in an otherwise healthy infant. If signs of apnoea, lethargy or abnormal neurology are present, imaging should be undertaken to confirm the diagnosis and exclude other pathology. In rare cases, massive haemorrhage can develop leading to progressive hypovolaemic shock and death. Severe cases can require craniotomy and haematoma evacuation and aggressive management of coagulopathies. Hydrocephalus is a rare complication, which develops due to adhesions or meningeal inflammation blocking the flow of cerebrospinal fluid.

A subdural haemorrhage occurs when tears in the falx, tentorium or bridging cortical veins bleed between the dura and arachnoid. It is thought that excessive vertical moulding of the cranium in a difficult delivery provides excessive stretch on these vessels. Subdural haemorrhages can vary in severity from small asymptomatic lesions which may present as an incidental finding on imaging to a massive haemorrhage associated with deteriorating neurological function and signs of brain stem compression. Severe haemorrhages tend to present between 12 and 72 h after birth with abnormal neurological signs that may include seizures, apnoea, hypotonia, cyanotic episodes, hemiparesis, decreased movements and unequal or sluggish pupils. A full fontanelle or a rapidly increasing head circumference can be indicative of raised intracranial pressure and should therefore prompt urgent review of management. The majority of subdural haemorrhages occur over the cerebral hemispheres or within the posterior fossa. Haemorrhages in the posterior fossa are clinically important as they can cause brainstem compression, which may present with symptoms of abnormal pupil reactivity, changes in vital signs, severe, progressive neurological deterioration or even coma. Subdural haemorrhage associated with tentorial tears can cause particularly severe haemorrhage and are generally seen in situations where there is rapid forcing of the head through the birth canal, for example in precipitate labour or vaginal breech delivery.

Subdural haemorrhages are best diagnosed by the use of CT or MRI, although cranial ultrasound may detect a very large bleed. The treatment of subdural haemorrhages depends upon the location and extent of the haemorrhage, as well as its progression. Small haemorrhages may be successfully managed conservatively with careful continuing assessment of vital signs, haematocrit, platelet count and perfusion status [24]. Transfusion of packed red cells, platelets and clotting factors should take place as indicated. Anticonvulsant treatment should be added if seizure activity is present. If there is seizure activity of abnormal or focal neurological findings, consultation should taken place with a neurologist and neurosurgeon. Surgery is needed the minority of cases [24–26] and is considered if there are signs of brainstem compression or deterioration in neurological status. Smaller lesions may be treated using Burr holes or subdural drains in order to decrease brain compression from accumulated blood, but severe lesions may require craniotomy and haematoma removal. The prognosis for subdural haemorrhage depends upon the extent and severity of the bleeding. The prognosis is generally good if only a small haemorrhage is present and the infant experiences only transient seizure activity. However, developmental delay

or cerebral palsy have been described in severe cases. Although short-term outcome appears favourable in the majority of cases, long-term outcome remains unclear and careful follow-up is required [26].

17.1.6 Nasal Injuries

Nasal injuries of some form are estimated to occur in between 0.5% and 1% of live births [4]. The injury usually involves dislocation of the cartilaginous portion of the septum from the vomerine groove and columella and present with deviation of the tip of the nose to one side with leaning of the columella and flattening of the nasal aperture and frequently bruising. These injuries are usually benign and rarely result in long-term complications, but as newborn infants are obligate nose breathers, severe septal deviation can compromise breathing. Ideally, nasal injuries should be detected and treated early, ideally within the first 3 days of life. Manual manipulation of the nose into proper alignment is usually performed by an Ear Nose and Throat specialist and involves, steadying the head, grasping the dorsum of the nose and lifting a nasal elevator to push the anterior end of the septum into the septal groove and columella.

17.1.7 Eye Injuries

Birth trauma to the eye is relatively common. The commonest type of injury are benign conjunctival haemorrhages, which are frequently observed after normal vaginal delivery [10]. These appear as a bright red patch or crescentic band located on one side of the iris or completely surrounding it and are due to the rupture of small capillaries in the conjunctivae. These dilated blood vessels are thought to be damaged due to increased venous pressure in the head and neck produced by compression of the fetal thorax and/or abdomen by uterine contractions during labour and delivery. The presence of a nuchal cord may also contribute [27]. These conjunctival haemorrhages require no treatment and resolve within 7–10 days with no risk of permanent damage [28].

More serious eye damage is rare, but damage to the cornea and haemorrhage into the orbit of the eye have been described [29]. Corneal damage can occur due to an inappropriately placed forceps blade slipping over the orbital wall and exerting pressure on the cornea. Such an injury may permanently impair vision. Orbital haemorrhage can occur during difficult delivery and presents as either unilateral or bilateral proptosis. Treatment with antibiotic ointment is essential to prevent infection and patching usually results in complete recovery.

17.2 Fractures

17.2.1 Skull Fractures

Skull fracture should be suspected in any case of cephalohaematoma or subarachnoid haemorrhage. Between 10 and 25% of cephalohaematomas are associated with a skull fracture. Skull X-ray is indicated when physical assessment suggests a fracture or there are abnormal neurological signs [11]. Skull fractures can occur with any type of delivery, including Caesarean section, but are most commonly associated with instrumental delivery [30]. Neurosurgical consultation is highly recommended in the case of any fracture. Skull fractures can be linear or depressed. Linear skull fractures are usually asymptomatic and heal without intervention, although a repeat X-ray should be performed at 6 weeks of age to exclude a leptomeningeal cyst, an uncommon complication that results from extrusion of the leptomeninges into the fracture site and can interfere with the normal healing process. A depressed skull fracture is seen as either an indentation of the skull or a “ping-pong” type defect. Surgical intervention is usually needed to elevate the skull and prevent brain compression, as when such fractures are treated early they have an excellent prognosis in the absence of underlying brain injury.

17.2.2 Clavicular Fracture

Clavicular fractures are the most common type of fracture that may occur as a result of birth trauma.

In some studies, they have been reported to be the most common type of birth trauma. Rates of between 0.2% and 5% have been reported [3, 31–37]. This large variability in observed incidence probably results from differences in the way in which infants were screened for clavicular fracture as many fractures are asymptomatic or present late and also whether the study was prospective or retrospective. Although a displaced fractured clavicle may be easy to diagnose clinically, a non-displaced fracture may often only be apparent if the neonate is subjected to X-rays or multiple physical examinations as some fractures may not be apparent until 1 week after birth.

Although some clavicular fractures may occur either intentionally or non-intentionally during attempts to relieve shoulder dystocia, the majority occur following vaginal deliveries not reported as being complicated by difficulty delivering the shoulders [33, 35]. Although clavicular fractures are also associated with higher birth weights [3, 33], nearly 80% of newborns with clavicular fractures weigh less than 4000 grams [36]. This means that in the majority of cases, the risk of clavicular fracture cannot be appreciated prior to delivery. Isolated clavicular fractures usually heal without sequelae, although they can be associated with brachial plexus, phrenic and right recurrent laryngeal nerve injuries and so these must be excluded if a clavicular fracture is diagnosed in a newborn.

17.2.3 Long Bone Fractures

Fractures of the long bones due to birth trauma are uncommon, since the force required to break such bones is much higher [38]. For example, femoral fractures have been estimated to occur once in every 10,000 deliveries [38, 39].

17.3 Nerve Injuries

17.3.1 Brachial Plexus Injury

Brachial plexus injuries at birth are frequently attributed to the use of excessive lateral traction on the neck during a difficult delivery of the shoulders in a vertex presentation or the delivery of the aftercoming head in a vaginal breech delivery and it is also thought that direct compression of the plexus may occur with the use of forceps. Early studies implicated vaginal breech deliveries as the cause of the majority of brachial plexus injuries. For example, in 1973, 72% of neonates with this type of injury were estimated to have been delivered in this way [40] and the risk of brachial plexus injury in vaginal breech delivery has been estimated to be 17 times that of a vertex presentation [32]. However, with changes in the management of breech presentation the association of brachial plexus injury with shoulder dystocia has become more important. Other risk factors for brachial plexus injury include primiparity, prolonged labour, heavier birth weight and forceps delivery [3, 16, 41, 42]. The incidence of brachial plexus injury has been estimated by a variety of studies to be between 0.4 and 0.9 per 1000 live births [40, 41, 43–47], although a single study suggested a rate as high as 2.6 per 1000 live births [3].

Upper brachial plexus injuries are the most common type seen following delivery. These palsies were first described clinically by Smellie in 1764 in his midwifery text and in 1874 Erb localised the lesion to the junction of 5th and 6th cervical roots (now known as Erb's point) and also credited Duchenne with the original clinical dissection 2 years previously. It is noteworthy that Erb recognised that the cause of the palsy was excessive lateral traction of the neck during delivery and condemned the use of the 'Prague manoeuvre' common at the time, in which strong traction was placed on the shoulder to deliver the aftercoming head in breech presentations. Erb-Duchenne palsies comprise 90% of all brachial plexus injuries and cause paralysis of the deltoid, infrascapular and flexor muscles of the forearm. The presentation is thus with a flaccid upper arm, internal shoulder rotation, elbow extension, forearm pronation, wrist and finger flexion (the "waiter's tip" deformity) and an asymetric Moro reflex. The arm falls limply to the side, but the grasp remains intact. Figure 17.4 shows the characteristic appearance of a child with an Erb-Duchenne palsy. The Moro reflex is present in cases of shoulder girdle fracture and so can differentiate such pseudopalsies from brachial

Fig. 17.4 An 8-month-old boy with Erb's palsy at birth had no shoulder abduction or elbow flexion against gravity. From: Shigematsu K, Yajima H, Kobata Y, Kawamura K, Maegawa N, Takakura Y. Oberlin partial ulnar nerve transfer for restoration in obstetric brachial plexus palsy of a newborn: case report. J Brachial Plex Peripher Nerve Inj. 2006 Sep 29;1:3

plexus palsy. The Klumpke paralysis, described in 1885, involves the 5th, 6th and 7th cervical roots. Clincially, this differs from the Erb-Duchenne paralysis in that the grasp reflex is also absent. Horner's syndrome (ptosis, miosis and anhidrosis) can also be present if sympathetic fibres from the 1st thoracic root are also involved.

Before 1970, the literature suggested a poor prognosis for brachial plexus injuries with full recovery only occurring in the minority of patients [43, 48]. However, more recent reports have suggested full recovery occurs spontaneously in 80–95% of cases [40, 45, 46, 49]. It is now generally accepted that initial management of brachial plexus injuries should be with physiotherapy and dynamic splints and surgery should be delayed for at least 3 months and reserved to cases resistant to conservative measures [50].

It has been proposed that performing elective Caesarean section for fetuses estimated to be relatively macrosomic might be effective in reducing the incidence of shoulder dystocia and hence brachial plexus injuries. However such an approach is limited by the fact that ultrasound estimation of fetal weight is relatively inaccurate and that about half of brachial plexus injuries occur in the absence of shoulder dystocia [51–53] and calculations have suggested that more than 1000 Caesarean sections and their associated expense and morbidity would be required to prevent a single permanent brachial plexus injury, using any possible threshold to perform Caesarean section [54, 55].

17.3.2 Phrenic Nerve Injury

When a phrenic nerve injury occurs as a result of birth trauma, the majority occur in conjunction with a brachial plexus injury [4]. Given that the phrenic nerve innervates the diaphragm and this is the major effector of spontaneous respiration in the newborn, the injury should be suspected when there is evidence of respiratory distress following a difficult labour or delivery, particularly if there is evidence of a brachial plexus injury. Although respiratory distress usually presents on the first day of life, this may be delayed until up to 1 month of age [4]. The infant's breathing is usually laboured and thoracic, and auscultation reveals decreased breath sounds on the affected side. The diagnosis is confirmed by chest X-ray, which will show elevation of the affected hemidiaphragm, and fluoroscopy which reveals paradoxical "see-saw" movement of the affected side. It is important to realise that radiography can sometimes provide a false negative result, particularly if the patient is receiving ventilatory support. Recovery is usually spontaneous, but pulmonary infection can be a serious complication and so prophylactic antibiotics may be helpful. An affected infant should be placed on the affected side and respiratory support provided as necessary. Feeding by nasogastric tube may be utilised to save the infant energy to utilise for breathing. Diaphragmatic pacing can be used and surgical plication of the diaphragm is occasionally necessary.

17.3.3 Facial Nerve Injury

Facial nerve palsy acquired due to birth trauma needs to be distinguished from developmental facial paralysis and is estimated to occur in less than 1% of live births [4, 56]. Factors predictive of the injury include forceps delivery, a prolonged second stage of labour, increased birth weight and primiparity [3], although over 90% of facial nerve palsies due to birth trauma occur in infants delivered with the use of forceps [32, 56]. In a forceps

delivery, the injury is thought to be caused by pressure from the forceps blade on the stylomastoid foramen or compression of the bone overlying the vertical segment of the facial canal. When an injury occurs following normal delivery, it is believed that the pressure is caused by the sacral promontory. The prognosis for these injuries is good, with spontaneous recovery usual in a timeframe ranging from hours to weeks. Electromyography (EMG) is recommended, together with recording of the auditory brainstem response to exclude auditory nerve involvement. Although some experts recommend surgical intervention as early as 1–3 months of age, most reports favour observation for up to 1 year or up to 2 years if there have been improved EMG findings.

17.3.4 Laryngeal Nerve Injury

The major problem caused by injury to the laryngeal nerve is vocal cord paralysis, due to dysfunction of the motor supply to the larynx. However, it has been estimated that only 19% of vocal cord paralysis in newborns is attributable to birth trauma [4]. The injury occurs when the laryngeal nerves are overstretched during delivery and presentation is usually immediately after delivery. The presenting signs depend upon whether the vocal cord paralysis is unilateral or bilateral. 60% of cases involve bilateral paralysis and these cases tend to present with a high-pitched cry, inspiratory stridor and potentially a compromised airway. The remaining cases involve unilateral paralysis and tend to have more mild stridor and a hoarse or breathy cry. In either group, there may also be dysphonia, dysphagia or aspiration. Laryngeal nerve injury has been reported in all types of delivery.

Direct laryngoscopy allows the otolaryngologist to directly observe paralysis of the vocal cords. Investigation usually also involves a modified barium swallow and the early involvement of a speech therapist may help optimise feeding [4]. Management of unilateral vocal cord paralysis is usually conservative with monitoring for any possible aspiration and treatment of any gastro-esophageal reflux. Bilateral vocal cord paralysis more commonly requires treatment with tracheostomy, with the mean time before decannulation being over 4 years. Further surgical management is usually reserved for cases where permanent paralysis seems likely. Arytenopexy has been used to lateralise the laryngeal structures and increase the tracheal opening, with the aim of allowing for decannulation. Alternatively, a muscle-pedicle reinnervation procedure has been described with 50% of patients successfully decannulated with no further loss of voice. Unfortunately, it has been reported that this procedure can result in a further loss of voice and so it has been suggested that procedures such as this should be delayed until the child is old enough to take part in the decision process [4].

17.4 Anoxic Injuries

Cerebral palsy is a term used to describe a group of motor impairment syndromes through to occur secondary to disorders of early brain development. Encephalopathy is the precursor of cerebral palsy and has clinical signs which include altered states of arousal (i.e. hyperalterness with or without seizures or unresponsiveness), abnormalities of muscle tone and strength, focal neurological deficits or delayed developmental milestones). Although encephalophathy is often described as ‘hypoxic-ischaemic encephalopathy (HIE)’, such clinical signs can reflect multiple mechanisms of brain injury over any time course with the underlying pathological processes including genetic, developmental, metabolic-toxic, infectious, traumatic and neoplastic-infiltrative processes [57]. Maternal infection and chorioamnionitis are associated with an increased risk of subsequent cerebral palsy [58, 59], which together with the findings of raised inflammatory cytokines in infants with HIE [60] and in those who subsequently develop cerebral palsy [61], provides evidence that inflammation also plays a significant role in the development of these brain injuries. There are a number of different mechanisms by which hypoxia and subsequent ischaemia can lead to neuronal or glial cell loss and brain damage. Brain ischaemia is associated with a fall in both extracellular and intracellular pH. Whilst mild acidosis is protective, severe aci-

dosis promotes free radical production and cytotoxic oedema. The brain is particularly vulnerable to oxidative stress injury due to its high metabolic rate and the fact that it has minimal antioxidant activity. In addition changes in pH and ionic flux induced by hypoxia lead to depolarisation of the cellular membrane and increased intracellular calcium levels, which activate multiple enyzymatic pathways that release further oxygen free radicals [57].

Despite obstetric and neonatal interventions in developed countries being successful in detecting and reducing intrapartum morbidity, particularly from intrapartum hypoxia, a number of longitudinal studies have shown that despite a decrease in perinatal mortality, the incidence of cerebral palsy has remained relatively unchanged [62, 63]. Such data suggested that the proportion of cases of cerebral palsy which are due to birth asphyxia, and which therefore could potentially be prevented due to improved intrapartum care, is much less than previously thought. Such a view has been confirmed by studies which have examined cases of cerebral palsy and come to the conclusion than intrapartum asphyxia is unlikely to be a cause in any more than 10% of all cases of cerebral palsy [64, 65]. All of this evidence points to events in the antepartum period as be causative of the majority of cases of cerebral palsy, a finding which is most important not only in relation to litigation, but also with respect to the possible causes and prevention of cerebral palsy.

Neuroimaging can be helpful to assess both severity and the timing of causation in encephalopathic infants. Cranial ultrasound can be used to detect abnormalities within the thalami and basal ganglia, as well as in the periventricular parenchymal or intraventricular regions. Cystic lesions have been shown to develop over 14 days [66] and so their detection within days after birth suggests an antenatal timing of causation. However, magnetic resonance imaging (MRI) is the most sensitive technique for imaging the neonatal brain. The gestational age at birth is predictive of the pattern of hypoxic-ischaemic injury with hypoperfusion resulting in a periventricular border zone of white matter injury in the premature, but injury to the subcortical white matter and parasagittal cortex in term neonates [67]. It has been determined that diffusion based-MRI values are usually normal on the first day after injury, decrease between 2 and 4-days after injury and return to normal after approximately 7 days [66]. Such knowledge can be useful in timing the causation of an encephalopathy. Together with electroencephalography, MRI can also be useful to predict prognosis in neonatal encephalopathy, with the presence of cortical and basal ganglia abnormalities being predictive of a poor outcome [68, 69]. Traditional care for neonatal encephalopathy has been supportive, but recent trials have shown benefits from the use of selective brain cooling to improve outcomes and it is likely that there is a short therapeutic window of up to 6 h during which interventions such as this may be effective, so early identification of the neonate with such brain injuries may become increasingly important in the future [70, 71].

Conclusion

It is clear that there are a wide variety of different injuries that can be sustained during the birth process. The majority of these will be minor and of no long-term consequence to the infant or their family, but there some of these injuries will result in long-term impairment or disability. Although some infants can be highlighted to be at increased risk of specific injuries due to factors relating to the mother, the fetus or the mechanism of delivery, it is clear that the majority of birth trauma is difficult to predict and thus avoid, despite skilled obstetric and neonatal care. Although caesarean delivery is often portrayed as the means by which all birth trauma could be avoided, it is important that medical staff remind patients that such a means of delivery is not free from risk and indeed can be associated with significant fetal trauma, as well as maternal morbidity.

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Pierre Robin Sequence

18

Rona Slator

Abstract

Pierre Robin Sequence (PRS) is a rare condition described in the early twentieth century as the triad of micrognathia, glossoptosis and upper airway obstruction occurring in infants. Up to 90% of infants affected will have a cleft palate. The severity of the condition varies widely. The airway obstruction may be immediately life threatening, or associated with difficulties with feeding and faltering growth which can also be severe. More commonly the airway obstruction is more mild, and can often be managed by conservative intervention such as positioning of the child.

Investigation and management regimes vary widely, but the specific definitions of PRS used in published literature are numerous making comparison between treatments difficult. Recently a consensus document has been published, the aim of which is to improve consistency in definition of PRS and thus improve the evidence base for intervention. This chapter describes the condition, and outlines management options and outcomes.

Keywords

Pierre Robin Sequence • Orofacial clefts • Airway • Glossoptosis

18.1 What is Pierre Robin Sequence?

Pierre Robin Sequence (PRS) is a well recognised entity made up of the triad of micrognathia (small mandible), glossoptosis (tongue falling back) and airway obstruction. In addition, up to 90% of neonates with these features will also have a cleft palate [1, 2]. This group of problems was initially recognised and described by a number of authors in the nineteenth and twentieth centuries. Subsequently Dr Pierre Robin, a French stomatologist, wrote extensively on the severity of the difficulties these infants had in maintaining their airway and feeding [3–5], and as a result the condition bears his name.

The triad of features has previously been known as Pierre Robin Syndrome and the Robin anomalad. It is now largely known as Pierre

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_18

Robin Sequence or Robin Sequence. It is described this way as it is currently generally believed that a small mandible is the starting point of a sequence of events that give rise to the clinical problems recognised as this condition, namely breathing and feeding difficulties. The clinical manifestations of PRS are very variable, however, and there has been no consensus as to the specific inclusion criteria that should be used to diagnose the condition [6, 7]. A survey published in 2010 found 14 different definitions of PRS [8]. PRS is also relatively rare [9, 10]. There has been a lack of systematic evaluation of treatment protocols and outcomes, and management of the condition remains variable and controversial. As a result and following a 2 day meeting in 2014, an international multidisciplinary consensus group came together recently to try to overcome these problems. A consensus report has been generated which provides agreed recommendations for the initial evaluation and clinical descriptors [11]. Ideally researchers and clinicians will increasingly use uniform definitions and comparable assessments so that an evidence base can be built to guide standards of care for infants and children with this condition.

18.2 Aetiology

The cause or causes of PRS are not known. It is hypothesised that mandibular hypoplasia leads to the PRS phenotype. The cause of mandibular hypoplasia may be intrinsic or extrinsic but hypoplasia starts during embryonic development and is thought to result in the tongue being displaced upwards and backwards preventing closure of the palatine shelves [6]. A classic cleft palate in PRS is described as being U shaped (see Fig. 18.1), the suggestion being that this reflects the separation of the palatine shelves by the tongue during development. Data from the West Midlands Cleft Centre, UK, suggest that the extent of the cleft palate is not directly related to the degree of airway obstruction (see Fig. 18.2) but most infants with PRS have extensive clefts of the palate [9, 12, 13].

It has been hypothesised that extrinsic events such as oligohydramnios or multiple births may induce growth restriction of the mandible. Other congenital anomalies such as cervical hemivertebrae may also result in mandibular growth restriction by preventing the extension of the neck during embryonic growth. Intrinsic causes may be part of a wider craniofacial syndrome or isolated to the mandible. These are likely to be due to genetic causes.

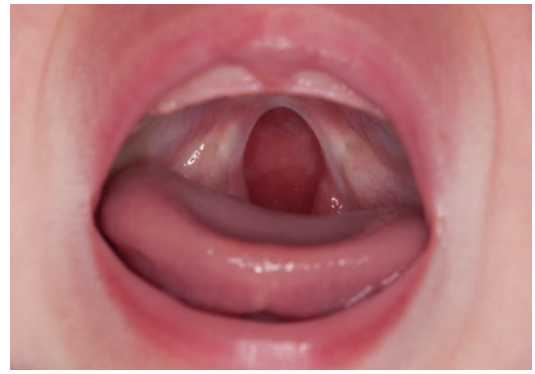

Fig. 18.1 Intra oral photograph showing the typical U shaped cleft palate of an infant with PRS

It has also been suggested that the anomalies of breathing and feeding may not be entirely due to anatomical features, but may also be related to brainstem dysfunction. Abadie and colleagues have described anomalies in oesophageal motility and pharyngolaryngeal tone which occurred more frequently in infants diagnosed with PRS who had more severe feeding and breathing problems [14].

18.3 Genetics

Retrospective studies of large series of children with PRS suggest that approximately half of the children affected will have other anomalies and/or a recognised syndrome [15–17]. The most commonly diagnosed syndromes in children with PRS are Stickler's syndrome and 22q11 deletion syndrome, but >100 syndromes include micrognathia as part of the condition and >40 syndromes have been identified in children with PRS [18]. 14–18% children with PRS will have Stickler's syndrome [16, 19, 20]. Infants with Stickler's syndrome may have severe short sight and this can in turn lead to retinal detachment. Early symptoms of retinal detachment in small children may be missed by family members as the children may not understand or be able to

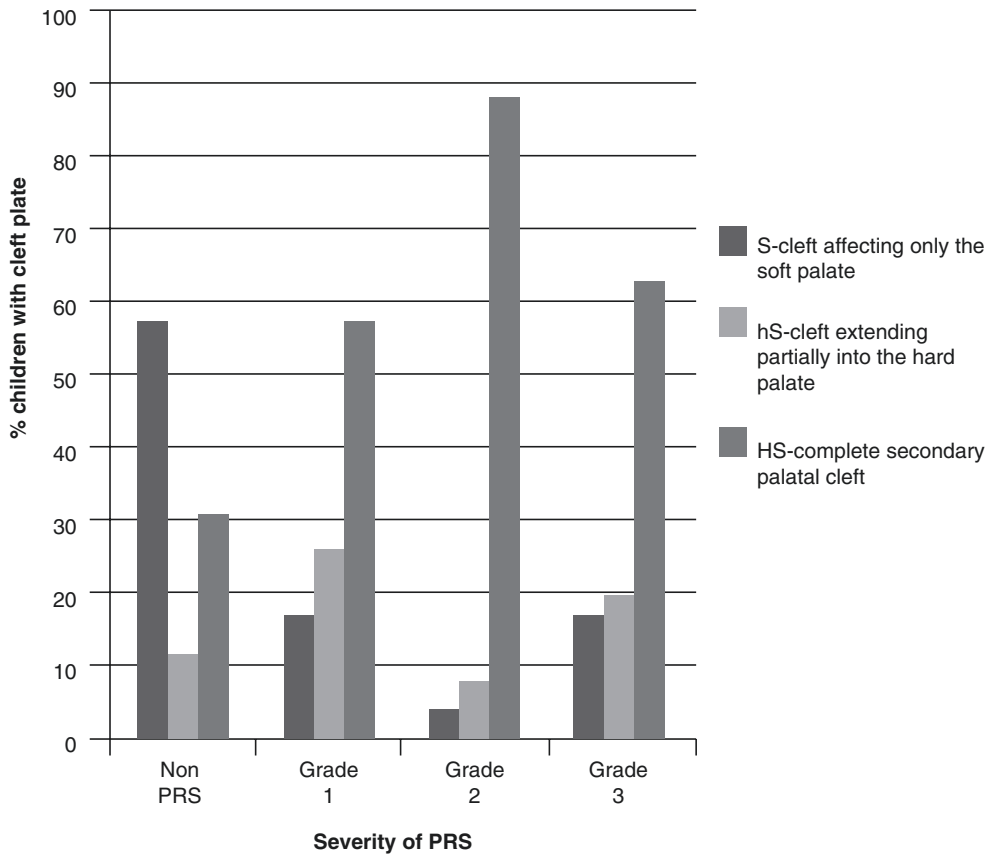

Fig. 18.2 Data from the West Midlands Cleft Centre, UK, showing the severity of PRS related to the extent of the cleft palate in all children with isolated cleft palate over a period of 5 years. Grade 1 PRS—managed by positioning alone. Grade 2 PRS—managed with positioning and nasogastric tube feeding. Grade 3 PRS—managed with NPA and nasogastric tube feeding

describe what is happening to them. Treatment to reduce the risk of retinal detachment can however be carried out if the diagnosis of Stickler's is known. A genetics review and ophthalmology opinion are important parts of the clinical management of these children.

In so called 'isolated PRS' where there is no other anomaly found a proportion of children will have a family history of PRS [15, 19, 21, 22] suggesting an hereditary cause. A number of studies have looked for chromosomal anomalies in 'isolated PRS' [23, 24] and comparison of these studies shows that no particular candidate gene has been identified for certain. However, some consistencies have been found and GAD67 on 2q31, PVRL1 on 11q23-q24 and SOX9 on 17q24.3-q25.1 are suggested to be important [25].

18.4 Incidence

The incidence of PRS in published studies varies from 1 in 5,600 [13] to 1 in 14,000 [9] births, and PRS is stated to affect from 6% to up to a third of the cleft palate population [9, 12, 13]. The variable results published probably reflect the variability in diagnostic inclusion criteria used. Personal experience indicates that the higher frequency is likely to be the more accurate one if all severities of airway obstruction are included.

18.5 Antenatal Diagnosis

Antenatal diagnosis of PRS is currently rare. It relies on the identification of a small mandible on

the profile view of the face on ultrasound scan. This is difficult to do before the 3rd trimester as the mandible is small in the early trimesters. Later scans may not be routinely carried out and this feature is not regularly looked for, making it unlikely to be diagnosed. Although oligohydramnios has been suggested as a cause for a small mandible, polyhydramnios has also been identified as being associated with PRS in several studies [26–28]. It is thought that this is the result of poor swallowing by the infant. It is recommended that examination of the facial profile is undertaken where there is a finding of polyhydramnios. Measurement of the fronto-naso-mental angle may provide an objective way to diagnose retrognathia antenatally [29].

18.6 Clinical Presentation

The Clinical Consensus Report agrees that micrognathia, glossoptosis and upper airway obstruction are required to make a diagnosis of PRS [11]. The airway obstruction is typically a high oro-pharyngeal obstruction due to the tongue falling against the pharynx and causes an inspiratory stertor sound rather than the lower stridor type sound typical of a glottic obstruction. Very many infants with PRS will also have a problem with feeding. The severity of both these problems is very variable. Some infants will have rapidly life threatening airway obstruction at or shortly after birth requiring immediate airway intervention. Others will have clearly increased respiratory effort, episodes of cyanosis and reduced oxygen saturation which can be easily identified. In these cases oral feeding is unlikely to be successful. More commonly however, the airway obstruction is quite mild initially and may only be noticeable when the baby is asleep or feeding. A mild tracheal tug and/or slightly noisy breathing when sleeping supine may be the only indicators of a problem.

It is therefore mandatory that all babies with an isolated cleft palate are assessed for the possibility of PRS. Assessment should include examination of the size of the mandible (Fig. 18.3) and of the intraoral position of the tongue as well as looking for signs of airway obstruction. It should also include a feeding assessment. In some infants with PRS the airway problem will initially only be manifest when the baby is trying to feed. It is also important to establish whether or not the infant has additional feeding problems, such as an unsafe swallow, that are independent of the cleft palate and airway obstruction. Cole and colleagues describe a protocol for such an assessment to identify neonates at risk and to classify them according to severity of symptoms and signs [30]. Infants with mild symptoms and signs are classified as Grade 1 and are managed with side to side lying. Infants in Grade 2 have slightly greater symptoms and are nursed on their side and are initially fed by nasogastric tube. Grade 3 infants are monitored in a specialist centre and have 24 h oxygen saturation assessment. These infants need more active airway intervention and are usually managed with a nasopharyngeal airway. This protocol facilitates the early identification of infants at risk, management plans, and communication with other members of the cleft/craniofacial team.

18.7 Investigations

Some centres recommend thorough investigation of all infants identified as being at risk of PRS [31]. In other centres the nature and extent of investigation will depend on the severity of the obstruction and response to treatment. Infants who have clinical signs of upper airway obstruction should have as a minimum continuous pulse oximetry to monitor whether or not oxygen desaturations occur. This is especially important at night and during deep REM sleep when the child's voluntary neck muscles are relaxed and airway obstruction may be exacerbated. Many clinicians recommend further investigation of the airway obstruction which may include CO_2 monitoring and polysomnography.

Determining the site or sites of the airway obstruction may be crucial to planning effective management [32] and some centres recommend this before any airway intervention. Endoscopic examination such as bedside laryngoscopy can be carried out to visualise the upper airway and

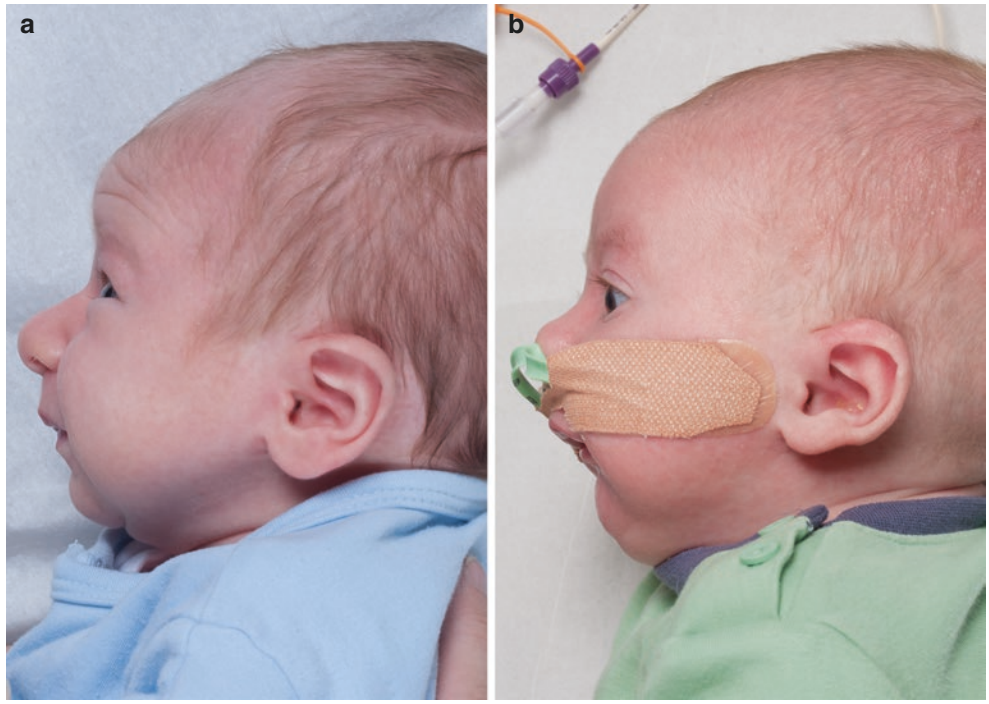

Fig. 18.3 Two infants with PRS showing differing degrees of micrognathia

vocal cord mobility. Direct laryngoscopy and bronchoscopy are required to visualise the subglottic structures including the trachea and bronchi. Severe micrognathia may make this extremely difficult however.

18.8 Management

Infants who have PRS need to have both their airway secured and feeding established so that weight gain occurs satisfactorily. Those identified with a mild degree of PRS may only require a change in position for their airway to be controlled and for them to be able to adequately feed orally and gain weight. The infants may be positioned prone or on their side to relieve the obstruction. In the UK it is not advised for babies to be nursed prone [33] and side to side lying is therefore encouraged. If this is not sufficient, further measures are introduced. It is estimated that positioning alone and positioning with feeding management is successful for about half or more of all children identified with PRS [34–36] (see Fig. 18.4).

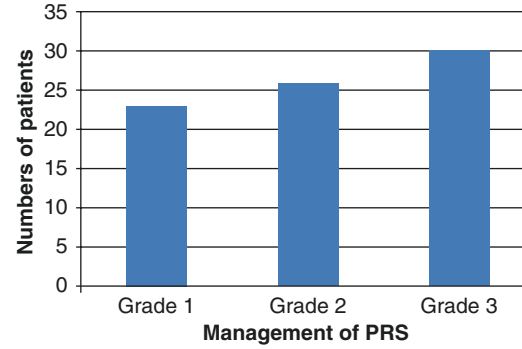

Fig. 18.4 Numbers of patients with PRS referred to the West Midlands Cleft Centre, UK, over a period of 5 years and their management regimes. Grade 1—managed by positioning alone. Grade 2—managed with positioning and nasogastric tube feeding. Grade 3—managed with NPA and nasogastric tube feeding

Babies managed by positioning alone need to be monitored carefully particularly with regard to their weight gain. If respiratory effort is not adequately relieved weight gain will falter as the

child grows. This may be due to requiring additional calories to counter the increased respiratory effort and an increased effort during feeding. If feeding is not efficient enough, calorific intake may not be sufficient and the baby may then become tired making maintenance of the airway and feeding more difficult. A downward spiral may then be encountered and weight gain falls off. Similarly, if the child develops an upper respiratory infection airway obstruction and effort may increase sufficiently for the child to not manage their airway and/or adequate feeding.

If positioning alone is not sufficient to relieve the airway and allow adequate oral feeding, nasogastric feeding may provide a solution [1, 30]. Nasogastric feeding provides the infant with nutrition and reduces/eliminates the effort of coordinating breathing and swallowing. Where the infant is stable with side lying but develops airway problems during feeding or has poor weight gain, nasogastric feeding may prevent the need for more invasive intervention while the infant grows. Weight gain must be carefully monitored in this situation, and if not sufficient further investigation of the upper airway obstruction is required.

If nasogastric feeding and side lying do not relieve the airway obstruction more invasive intervention will be needed. A nasopharyngeal airway (NPA) can be placed intranasally extending into the pharynx far enough to bypass the obstruction caused by the base of the tongue. The baby then breathes through the NPA (see Fig. 18.5). Successful use of this technique has been described in several publications [31, 37, 38]. Placement of the NPA allows the baby to be nursed supine and to be fed orally. It is extremely important to introduce oral feeding to the neonate as early as possible, and use of the NPA allows the introduction of early oral feeding. This is usually only for short periods of time and once or twice a day initially. However, as the baby grows oral feeding can be increased as tolerated by the infant.

With appropriate training and support for parents, infants can also be discharged home with the NPA in place [38–40]. As the infant grows s/he can be weaned from the NPA during the day, and the NPA removed completely

Fig. 18.5 Infant with nasopharyngeal airway and nasogastric tube

usually at the age of about 4 months [39]. Centres vary in how long they leave the NPA in place [40]. Removal of the NPA through the night is only carried out following sleep studies in hospital to demonstrate that there are no continuing airway problems.

In circumstances where it is felt that home management of a NPA is unsafe and a prolonged hospital stay is to be avoided alternative surgical options may be considered.

Other methods of conservative treatment have also been described but have not been adopted by the majority of centres regularly treating infants with PRS. A palatal plate with an extension posteriorly to push the tongue forward [12, 41] to relieve airway obstruction has been described. In a small study of 7 patients another centre has described successful use of continuous positive airway pressure as a method of overcoming the airway obstruction while the infants grow and their airway problems resolve [42]. The role for such therapies is as yet unclear.

18.9 Surgical Therapies

Surgical intervention may be required if positioning, nasogastric feeding and a NPA do not relieve the airway obstruction. In these circumstances further evaluation of the airway and consideration of a central respiratory problem is necessary. Central apnoea, hypotonia, laryngomalacia, tracheomalacia and bronchial stenosis have all been described in PRS and need to be excluded. Multiple levels of airway obstruction may also be present. Surgical treatment described for PRS is aimed at relieving the upper airway obstruction caused by the base of the tongue falling against the posterior pharyngeal wall. If other levels or causes of airway obstruction are present these need to be identified and addressed or treatment will not be successful.

Surgical treatments used regularly for PRS include tongue-lip adhesion (TLA), subperiosteal release of the floor of the mouth (SRFM), mandibular distraction osteogenesis (MDO) and tracheostomy. Different institutions have differing levels of experience with and indications for each of these interventions.

18.9.1 Tongue Lip Adhesion

Tongue lip adhesion was first descibed by Douglas in 1946 [43] and has been modified by a number of authors since [44, 45]. The ventral surface of the tongue is sutured to the inner aspect of the lower lip pulling the tongue forward and preventing it falling back into the pharynx. To prevent dehiscence suturing of tongue muscle to lip muscle is advised. The posterior tongue can also be anchored to the mandible. In some institutions where NPA placement is not used regularly TLA is the first line of intervention if positioning alone fails.

Complications described for this procedure include scarring, the need for a second procedure, and the possibility of the procedure interfering with oral feeding. It is also not always successful in relieving airway obstruction [46, 47]. Efforts are now being made to describe more accurately which patients will benefit from this procedure [48].

18.9.2 Subperiosteal Release of the Floor of the Mouth

Subperiosteal release of the floor of the mouth was first described by Delorme in 1989 [49]. This technique is predicated on the theory that the tongue is rotated backwards by an anterior insertion into the small mandible. An incision is made under the chin to the inner aspect of the mandible. Dissection proceeds subperiosteally releasing the attachments to the mandible from angle to angle of the mandible. The base of the tongue can then move posteriorly allowing the tip of the tongue to rotate into the mouth and out of the pharynx [2, 50, 51]. Patients have to remain intubated for several days until swelling has settled and the tongue has settled into its new position. This procedure is not always successful in relieving the airway problems [51].

18.9.3 Mandibular Distraction Osteogenesis

Distraction osteogenesis is a well known technique for moving and lengthening bone. Mandibular distraction has been described for the treatment of PRS [52, 53] where the level of airway obstruction is at the base of the tongue and where other treatment modalities have failed. The aim is to distract the mandible forward with its attachments to the floor of the mouth thus moving the tongue forward and increasing the size of the airway. The technique involves an osteotomy through each side of the mandible and insertion of either internal or external distractors. External devices are easier to use, adjust and remove but can also be knocked, and they result in external scars. Internal devices require further surgery to remove. Recently absorbable distractors have been used successfully [54, 55].

MDO occurs in 4 stages: osteotomies and application of distractors, a latent phase, and then a period of distraction followed by a period of consolidation. Patients remain intubated until the advancement has occurred. It is not always successful in relieving the airway obstruction and algorithms are being developed to improve patient selection [56, 57].

Authors advocating this treatment acknowledge that such treatment will not remove the possible need for further orthognathic surgery and the long term effects of distraction are not well established. Complications include loss of teeth, scarring, and marginal mandibular branch nerve palsy [53]. A recent study of longer term follow up of infants treated with mandibular distraction showed increased dental anomalies and a shorter mandible than a comparison group of children with PRS as an infant who had not been treated with mandibular distraction [55]. One child in this study required repeat distraction at the age of 5 years. MDO is reported in some studies as having a high rate of success in avoiding tracheostomy in the series published [53, 58]. Where it is successful advocates describe the rapid resolution of both airway and feeding problems in infants with PRS with reduced need for prolonged hospital stay, nasogastric tube feeding or nasopharyngeal airway. Mandibular distraction osteogenesis for PRS is only indicated for a small number of patients where other interventions have failed. Further information is required to fully evaluate the short and long term effects of this treatment as compared to other management regimes for PRS.

18.9.4 Tracheostomy

In some infants with PRS, the cause or causes of the infant's problems are not clear even after extensive investigation. In these cases management can be extremely difficult. These infants nearly always have multiple problems—'syndromic PRS'. A multidisciplinary approach to the problem is required for these complex patients. This should include input from respiratory paediatricians, ENT surgeons, dieticians, specialists in dysphagia, and gastroenterologists, as well as the cleft/craniofacial team. Where all other treatment options fail and if there is subglottic airway obstruction, tracheostomy is the only remaining option. Tracheostomy at such a young age is associated with complications and even death.

18.10 Feeding and Growth

Upper airway obstruction makes coordinating feeding and breathing difficult. Respiratory rate may be raised and the extra effort of respiration results in the infants becoming tired and using more calories for breathing than usual. Feeding and weight gain need to be carefully monitored and managed [59]. Infants who fail to gain weight may need increased calories in their feed and particularly those treated with positioning only may need to have their airway assessed further. Many infants with PRS need nasogastric feeding in the early months [1, 30]. Most infants can be weaned from nasogastric feeding by the age of one and often before palate repair surgery [37].

Upper airway obstruction results in increased negative pressure in the thorax and abdomen produced by the extra effort of respiration against the obstruction. This seems to exacerbate gastro oesophageal reflux (GOR) which is extremely common in these infants and can be very severe [60]. GOR may also exacerbate the airway obstruction if oedema is caused by the refluxing acidic stomach contents into the airway. Thickening of feeds and medical treatment of GOR are regularly needed in these infants. Some will need further investigation and may require fundoplication.

18.11 Natural History of PRS

Most infants with PRS and obstruction at the tongue base level will grow out of the problem within a few months of birth. As the infants grow the airway obstruction improves and intervention to maintain the airway can be withdrawn. It is not clear if the clinical improvement is due to an increase in airway size alone, or due to increased muscular control of the tongue and pharynx, or both. However, it does occur for most children with PRS, particularly those with no other problems. Where children have multiple problems, so called 'syndromic PRS', problems with airway and/or oral feeding may persist.

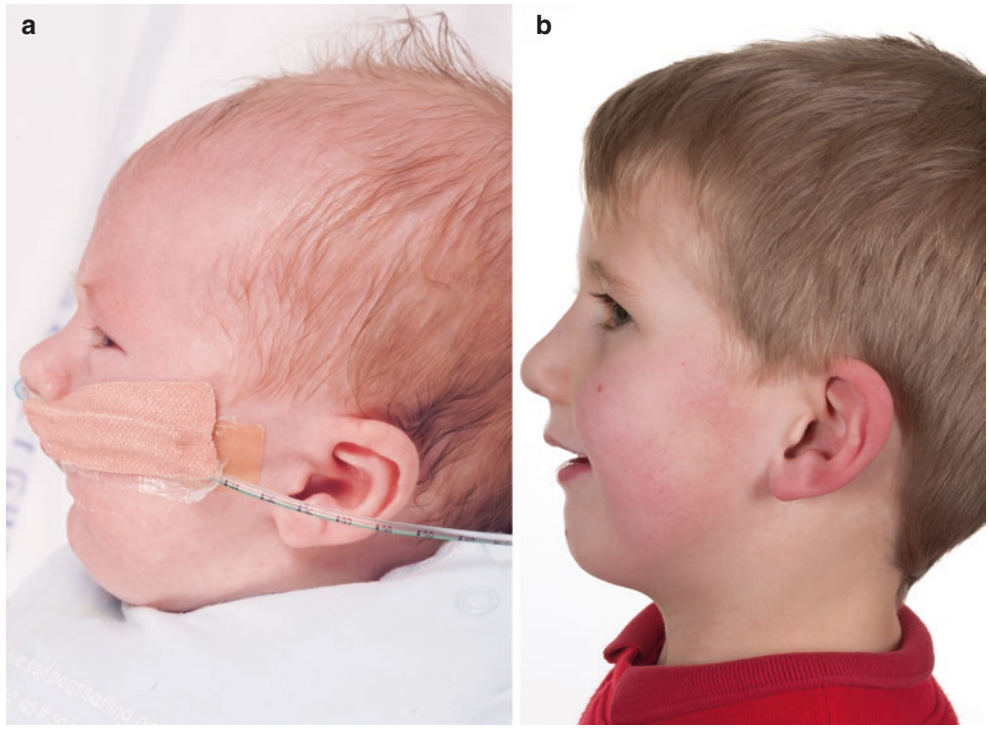

Fig. 18.6 Mandibular growth (**a**) Infant with PRS (**b**) Same child aged 5 years

Most infants will have mandibular growth that appears to catch up with the rest of the face (see Fig. 18.6). It is thought that this occurs in children where mandibular hypoplasia has been due to extrinsic factors. In other children, even though the mandible grows and the clinical problems resolve, the mandible continues to appear small in proportion to the maxilla. It is assumed that these children have an intrinsic problem with mandibular growth. There is little longitudinal data on mandibular growth in this condition [61] and at present there is no way to predict which children will have 'catch up' growth and which will not. There is indeed controversy as to whether catch up growth occurs at all.

Children who have had PRS appear to be at risk of a recurrence of upper airway obstruction during their early years. At the time of palate repair recurrence of upper airway obstruction may complicate the immediate post operative period. This can be relieved with a NPA usually placed at the end of the surgical procedure. Removal of the NPA 24–48 h after surgery is usually then uneventful. Some surgeons who undertake early palate repair (for example, at age 6 months) will plan to repair the palate a little later than their usual protocol (for example, at age 9–12 months) to avoid such complications. This also seems to be effective.

Similarly, upper respiratory tract infections may precipitate a short period of upper airway obstruction usually only manifest when the child is sleeping deeply. The episodes can often be managed by conservative supportive methods until the infective episode settles. In the longer term these children seem to grow out of these obstructive problems.

Knowledge of the long term effects of PRS is scanty. A population based study of Swedish students suggested that individuals with PRS had less favourable educational outcomes than their peers without PRS [62]. A study in Holland suggested that intellectual disability was not

present in isolated PRS but was found in approximately 40% of children with PRS and other anomalies or syndromes [20]. A recent study from the West Midlands Cleft Centre suggests that the speech outcomes of children with PRS Grade 3 are worse than those of children with similar sized clefts but without PRS or other syndrome [63]. This difference was particularly marked with articulation problems but also occurred to a lesser extent with structural speech difficulties.

Conclusions

PRS is a well recognised triad consisting of small mandible, glossptosis and airway obstruction. Most infants with this triad will also have a cleft palate and all babies with isolated cleft palate should be examined with this condition in mind in order to identify and address problems early. Up to a third of infants with cleft palate only may have a degree of upper airway obstruction. Where not identified and treated infants will fail to thrive and their airway obstruction can rapidly deteriorate.

It is imperative that infants identified as having PRS are managed by a specialist team with experience of the condition. With appropriate assessment and monitoring, many infants with this condition can be managed relatively easily and successfully, often in the home environment. These infants usually have no other problems. However, infants with 'syndromic PRS' who have anomalies in addition to the PRS triad often have extremely complex medical problems and can be extremely difficult to manage. These infants require careful and full multidisciplinary care in a unit that has regular experience of managing such problems.

Despite the fact that specific inclusion criteria for this condition vary, knowledge is increasing. Treatment protocols vary [31, 52, 53] but the aim must be in all cases to use the least invasive method of intervention that allows the infant to breathe normally and to feed and grow. Most infants will grow out of the immediate problems of airway obstruction and feeding within the first year of life, and many within the first 6 months. Further information about the long term outcomes for this condition following different treatment regimes is needed before there will be enough evidence for consistency of treatment methods. It is hoped that the Clinical Consensus Report [11] will help clinicians move in this direction. This is an exciting area of increasing knowledge.

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Conjoined Twins

19

Lewis Spitz, Edward Kiely, and Agostino Pierro

Abstract

Conjoined twins can be subdivided into (a) symmetrical conjoined twins, and (b) heteropagus or parasitic twins. This chapter presents a brief summary of the history of conjoined twins followed by a classification of the various types according to the site of attachment, the investigations required, and the operative procedure. The experience of the team at Great Ormond Street Hospital is presented.

Keywords

Siamese twins • Conjoined twins • Conjoined twin classification • Separation techniques

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_19

Conjoined twins can be subdivided into (a) symmetrical conjoined twins, and (b) heteropagus or parasitic twins.

19.1 Symmetrical Conjoined Twins

19.1.1 History

One of the earliest depictions of conjoined twins is a stone carving of pygopagus twins dating back to 80 BC, discovered in Fiesole and kept in the San Marco Museum in Florence, Italy (Fig. 19.1).

An attempt at separation of conjoined twins took place in Kappadokia, Armenia, in around AD 945. When one of the male ischiopagus twins died at the age of 30 years, the surviving twin was separated from his dead brother, but he died 3 days later [1].

The first well-documented case is that of the Biddenden maids born in Kent in AD 1100 and "joined at the hips and the shoulders" (Fig. 19.2). They lived together for 34 years. When Mary fell ill and died, Eliza was advised to be separated from her deceased twin but absolutely refused saying, "as we came together we will also go together". She died 6 hours later. It is unlikely that they were joined at the hips and shoulders as depicted in numerous illustrations. A more plausible explanation was that they were ischiopagus twins [2].

Fig. 19.1 Stone carving of pygopagus conjoined twins dating back to 80 BC

Fig. 19.2 Monument to the Biddenden maids born in Kent in AD 1100

The Scottish Brothers were born near Glasgow in 1490. They were "two complete individuals above the waist but the lower half of their bodies was fused—one set of genitalia and two legs". They were taken to the court of King James IV who ordered that they be carefully brought up and educated at court. They learned to sing, played various musical instruments and became fluent in several languages. They had different personalities, often differing in opinions and sometimes quarrelling. They died in 1518, aged 28 years [3].

In the Sixteenth Century, Ambroise Paré collected examples of six sets of conjoined twins and was one of the first to classify the different varieties of conjoined twins [4].

The Isle-Brewer xiphopagus twins, Priscilla and Aquila, were born in 1680 joined "from the navel up to a point just below the nipples". The vicar at their christening believed that the monstrous birth was a sign of impending evil. They were abducted and displayed but died in 1683 [5].

The first successful separation of conjoined twins took place in 1689. The surgeon, Johannes Fatio, separated omphalopagus twins in Basel, Switzerland, by "tracing the umbilical vessels to the navel where he tied them separately. He then transfixed and tied the bridge between the two infants with a silken cord and cut the isthmus". The ligature fell off on the ninth postoperative day and both children survived. Koenig, an observer at the procedure, published the case as his own and to him is credited the first successful separation [6, 7].

The most celebrated pair of conjoined twins was Chang and Eng Bunker, born on a river boat in Siam (Thailand) in 1811. They were joined at the xiphisternum by a short band that stretched so that they were eventually able to stand side-by-side (Fig. 19.3). They became proficient swimmers and their peculiar movement attracted the attention of Robert Hunter, a travelling Scottish merchant, who eventually persuaded their mother to permit him to take them to the United States where they were exhibited by the showman, Phineas Barnum. They married sisters, lived in separate houses in North Carolina spending 3 days in each house alternately, and had 21 children between them. Physiologically and psychologically they were different—Chang was smaller and more feeble; Eng was good-natured, Chang cross and irritable; Chang drank heavily, but Eng appeared unaffected by the alcohol. They wished to be separated but could not persuade surgeons to carry out the operation which was considered to be too hazardous at the time. They lived together for 63 years and died in 1874 [8, 9].

Fig. 19.3 Portrait of Chang and Eng from Royal College of Surgeons of England, London, UK

The Tocci Brothers, born in 1877, were extensively united parapagus conjoined twins. They also wished to be separated but the extent of their union dictated that surgery at the time was clearly not feasible. They lived together for 63 years and died in 1940 [10]. Other conjoined twins have declined any suggestion of separation. Lori and Reba Schappell, craniopagus twins, born in 1961, never wanted to be separated stating "God made us this way and He had a purpose for us and you do not ruin what God has made".

Hoyle in 1990 [11] reviewed all attempts at surgical separation of conjoined twins, performed successfully and unsuccessfully, through to 1987. Of a total of over 600 publications, separation was attempted in 167 cases. The survival rate increased dramatically in the most recent decade prior to 1987. He concluded that "the current excellent outcomes (for separation) suggest that separation should always be considered with rare exceptions". Since 1990, there have been an increasing number of publications reporting successful separation.

19.1.2 Etiology and Embryology

In the absence of an experimental model, the exact etiology of conjoined twins is unknown. The uncertainty between fission and fusion theories remains. As it seems likely that fission of a single fertilised ovum occurs in the same manner each time, the wide variety of types of conjoined twinning make fusion the more likely mechanism.

Conjoined twins often have remarkably different personalities. This difference in personality is clear from the early months of life and remains unexplained. Regardless of the mechanism, twins are always joined homologously—chest to chest, pelvis to pelvis etc.—and are always the same sex. Spencer [12, 13] has proposed that union occurs at sites where ectoderm is absent or programmed to disrupt or fuse.

The fusion theory suggests that two separate embryonic discs from a monovular pregnancy, lie on the surface of a single yolk sac. At around the third week of pregnancy, fusion occurs at sites where the ectoderm is not present or where it is disrupted. Ectoderm is absent over the precursors of the septum transversum and heart. Fusion at this level results in thoracopagus and omphalopagus twins. Ectoderm disrupts at the sites of the oro-pharyngeal and cloacal membranes and fuses at the edge of the embryonic disc. Union at these sites results in cephalopagus, ischiopagus and parapagus twins. Dorsal union—craniopagus, rachipagus, pygopagus—results in each twin having its own umbilicus and separate abdomen.

The other types of union are considered ventral and usually share a single cord and peritoneal cavity. These cords will frequently have more than three vessels. Associated anomalies are common and predominantly affect the structures which are joined. The patterns of abnormality encountered depend on the type of union and each of the eight types of twinning has a range of associated anatomical defects [14].

These abnormalities may preclude extrauterine survival and may render separation impossible. According to Spencer, thoracopagus twins always have a single heart with multiple chambers and separation is rarely an option. Others have been less rigid in their definition of thoracopagus and there have been well documented cases where separation of thoracopagus with separate hearts has been successful.

19.1.3 Incidence

The frequency of conjoined twins has been estimated at 1:50,000 pregnancies but as up to 60% of these twins succumb in utero the true incidence is 1:250,000 live births. With the advent of routine prenatal ultrasound, the anatomy is seen early in gestation and elective termination will be an option.

Female twins predominate in the ratio of 3:1.

19.1.4 Classification

Conjoined twins are classified on the basis of the site of union, with the suffix -pagus meaning fixed or fastened. The twins can have four (tetrapus), three (tripus), or two (bipus) legs. The classification of conjoined twins, limited to eight types with approximate percentages of frequency, is summarized in Table 19.1

1. Thoracopagus: (Fig. 19.4) The twins lie face to face and are joined at the sternum, diaphragm, upper abdomen wall and liver and have an exomphalos. In the majority of the cases they share the pericardium (90%) and heart (85%). They may have a common small intestine (50%) which joins at the duodenum and separates at ileum; the biliary tree can be joined in 25% of patients. There may be associated cardiac anomalies such as ventricular septal defect, atrial septal defect, tetralogy of Fallot.
2. Omphalopagus: The heart is never fused; the liver is joined in 80% of cases and there is an exomphalos. The stomach and proximal small bowel are usually separate, and each twin has a rectum. In up to one-third of omphalopagus twins, the intestines usually join at Meckel's diverticulum, the terminal ileum and colon are shared, and may also have a dual blood supply. There is usually no union of the genitourinary tract.
3. Pygopagus: (Fig. 19.5) The twins are joined dorsally, sharing the sacrococcygeal and perineal regions. They face away from each other—share the sacrum, coccyx and part of the pelvic bones. The spinal cords are usually separate [15]. Twenty-five percent share the lower GI tract and have a single anus and one or two rectums. In 15% of cases there is a single bladder. There is an increased incidence of vertebral anomalies, including hemivertebrae, hemisacral

Table 19.1 Characteristic features of different conjoined twins

Type of fusion	Incidence	Extent of union	Shared structures
Ventral (87%)			
Cephalopagus	11%	Top of head to umbilicus	
Thoracopagus	19%	Thorax, upper abdomen, conjoined hearts 85%	Liver 100% Pericardium 90% Cardiac defects 75% Upper intestine 60% Biliary tree 17%
Omphalopagus	18%	Upper abdomen; Separate hearts	Liver 90% Upper foregut 16% Cardiac 25%
Ischiopagus	11%	Cloacal membrane	Pelvis bone 100% Lower GI tract 70% Genitourinary 50%
Parapagus	28%	Cloacal membrane	Cardiac 75% Intestine 100% Liver 100% Genitourinary 100%
Dorsal (13%)			
Craniopagus	5%	Cranial neuropore	Skull, venous sinus, and meninges 100% Cerebral cortex 37%
Rachipagus	2%	Neural tube	Vertebral column
Pygopagus	6%	Caudal neuropore	Sacrum and coccyx 100% Lower GI tract 25% Genitourinary tract 15%

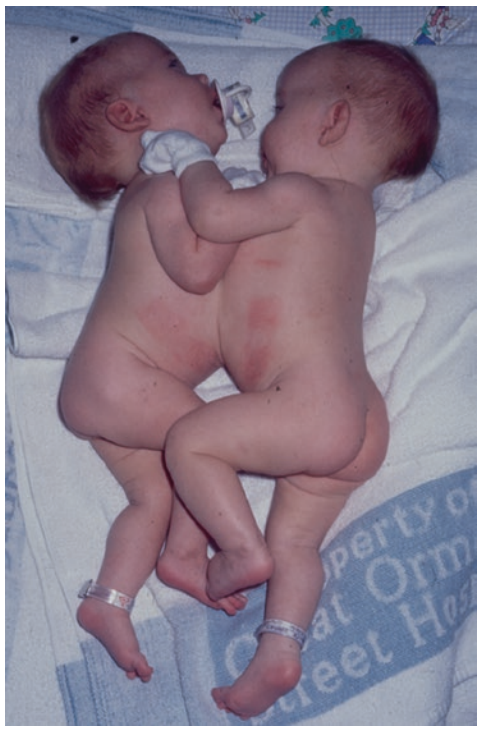

Fig. 19.4 Thoracopagus conjoined twins sharing a heart

Fig. 19.5 Pygopagus

agenesis and thoracic anomalies [16]. Although the pelvic conjunction is fundamentally different than in ischiopagus twinning, the types are similar insofar as numerous other associated orthopaedic anomalies have been reported in association with pelvic conjunction, such as hip subluxation or dislocation, congenital vertical talus, talipes equinovarus, Sprengel shoulder and scoliosis. There can also be a variable degree of spinal and cord fusion. Although there may be only one anus and rectum, the remainder of the intestines are usually separate. The upper bodies are not fused and there are four arms and four legs.

4. Ischiopagus: (Fig. 19.6) The twins may lie face to face or end to end. They have two sacra or two symphysis pubis. They may share the lower gastrointestinal tract (70%) and/or the genitourinary tract (50%) and may have crossing ureters. The twins can be tetrapus, tripus, or bipus although the most common arrangement is the presence of four legs. Pelvic conjunction leads to complex urogenital and orthopaedic anatomy. The kidneys usually function normally, but are often malrotated or ectopic in location. When two bladders are present they lie side by side in a collateral position or they may lie in a sagittal midline location with one bladder draining into the other. The ureters frequently cross over and insert into a contralateral bladder such that they will need to be re-routed during separation. Partial urethral duplication is possible but a single urethral orifice is typical. The distal gastrointestinal tract is often shared, with anorectal agenesis and rectovesical fistula. Contrast studies are necessary to delineate distal bowel anatomy. Urogenital sinus or cloaca may be present. In boys there is an increased incidence of undescended testes.
5. Craniopagus: The conjoined twins share the skull, meninges and the venous sinuses. The brains are usually separate although some cortical fusion can occur in 33% of cases.
6. Cephalopagus: The twins often have a fused thorax in addition to a fused head. The single fused head may have two faces (janiceps) facing away from each other; one face may be rudimentary. These twins are terminated or die in utero. They are nonviable.
7. Rachipagus: The twins have generally vertebral anomalies and neural tube defects.
8. Parapagus: (Fig. 19.7) This is a relatively new term denoting extensive side-to-side fusion. The twins share the umbilicus, lower abdomen, pelvis (single symphysis pubis) and the GU tract. They can have anorectal anomaly and colovesical fistula and may be at risk of anencephaly.

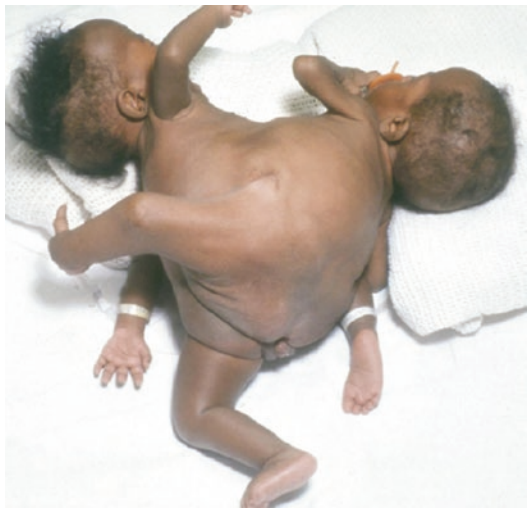

Fig. 19.6 Ischiopagus

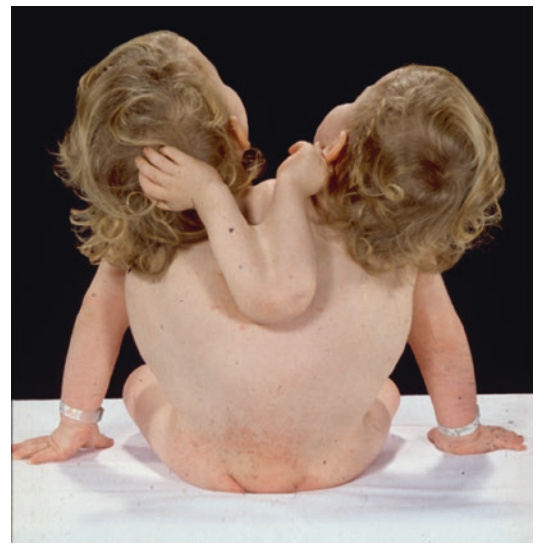

Fig. 19.7 Parapagus

19.1.5 Diagnosis

19.1.5.1 Antenatal Diagnosis and Imaging

Fetal ultrasound can detect the presence of conjoined twins in almost all cases. Accurate antenatal assessment allows the parents to be counselled as to the probable outcome of the pregnancy and the likelihood of successful postnatal separation. Prenatal diagnosis of conjoined twins is important for optimum obstetric management, including decisions regarding termination of pregnancy, timing and method of delivery to minimize maternal and fetal mortality.

19.1.5.2 Fetal Ultrasound

Prenatal ultrasonography (US) is capable of diagnosing conjoined twin pregnancies as early as 12 weeks' gestation [17–19]. Transvaginal US may also aid early diagnosis [20]. Diagnosis of conjoined twins may be straightforward when fusion of fetal parts is obvious. The possibility of conjoined twins should be suspected in a twin pregnancy with a single placenta and no visible separating amniotic membrane. The sonographic findings in conjoined twins include inseparable fetal bodies and skin contours, an unchanged relative position of the fetuses, both fetal heads persistently at the same level, bibreech or bicephalic presentations, fewer limbs than expected, and a single umbilical cord with more than three vessels [21]. Polyhydramnios occurs in as many as 50% of conjoined twin pregnancies compared with 10% of normal twins and 2% of singleton pregnancies. Detailed US assessment at around 20 weeks gestation should be able to define the site and extent of the conjoined area and provide a reasonable evaluation of which viscera are shared.

Fetal echocardiographic (ECHO) assessment of the heart needs to be detailed and accurate. A shared heart is incompatible with postnatal survival and is usually an indication for termination of the pregnancy. Hearts can be confirmed as separate when they are seen to be anatomically separate or when the heart rates are different. It has been the experience of many authors that fetal ECHO underestimates the severity of cardiac anomalies [22].

Prenatal ECHO is facilitated by amniotic fluid, particularly polyhydramnios in later pregnancy, acting as an acoustic window. Recently 3D US imaging has been advocated as a new tool to demonstrate the extent of fusion in conjoined twins.

19.1.5.3 Magnetic Resonance Imaging (MRI)

MRI, with its ability to differentiate soft tissues, provides an excellent alternative technique [23] for overall fetal assessment. Ultrafast T2-weighted (T2-W) sequences of short duration, such as the single-shot fast spin-echo sequence, allow minimal image degradation by fetal motion and high-quality images of fetal organs without the need for fetal or maternal sedation.

19.1.6 Postnatal Imaging

The choice of imaging study will depend to some degree on the site of fusion. All conjoined twins should have chest and abdominal radiography for an overall general assessment, and partly to help health professionals understand the extent of the conjoined area. Unexpected diaphragmatic hernia or vertebral anomalies can thus be detected early.

19.1.6.1 Ultrasound

All neonates should have routine cerebral US, and when indicated a spinal US, as baseline investigations. In addition, abdominal US to assess the liver, to document the presence of two spleens, gallbladders, biliary systems, and kidneys bladders, is necessary. Detailed Doppler studies to evaluate the great vessels in the abdomen and hepatic venous drainage should also be performed, but midline abdominal conjunction may make accurate Doppler assessment unreliable. Meticulous labelling of the images, ensuring the correct twin is consistently noted to be on the same side.

19.1.6.2 Echocardiography (ECHO)

ECHO is mandatory for every twin due to the high frequency of congenital heart disease. 3D ECHO has been advocated postnatally as it may

facilitate understanding of the cardiac connections, and can be helpful to plan treatment [24]. Andrews et al analysed 23 sets of conjoined twins and classified twins according to the degree of cardiac fusion as follows: separate hearts and pericardium (group A, $n = 5$), separate hearts and common pericardium (group B, $n = 7$), fused atria and separate ventricles (group C, $n = 2$), and fused atria and ventricles (group D, $n = 9$)35. None of the twins from groups C or D survived demonstrating that the outcome in twins with fused hearts remains dismal.

19.1.6.3 Computed Tomography (CT)

Due to its high spatial resolution and speed multidetector CT (MDCT), ~~is~~ the best overall modality for evaluating conjoined twins in the postnatal setting (Fig. 19.8).

Contrast enhancement is mandatory to assess the vascular anatomy. It can demonstrate the shared liver and vascular connections. Delayed images give very useful information on excretion by both twins' kidneys, the ureteric anatomy, and the location and number of bladders. Separate studies examining each twin's vascular anatomy on different days are recommended.

19.1.6.4 MRI

MRI has an increasing role in the postnatal evaluation of conjoined twins, particularly those joined at the head or thorax. MR has the capability of producing 3D reconstructed images in any direction with much improved resolution and tissue characterization and is of value in preoperative planning e.g. pygopagus (Fig 19.9). MR is the optimum examination to assess for any cortical fusion in craniopagus twins. Intracardiac and great vessel anatomy and blood flow, and ventricular wall motion can all be accurately assessed in thoracopagus cases. MR cholangiopancreatography (MRCP) is likely to offer the best hope of assessing the biliary anatomy. Liver anatomy can be best appreciated after intravenous contrast enhancement, either at CT or MRI. Demonstration of separate hepatic venous drainage into the inferior vena cava and right atrium of each twin is essential to plan separation as absent or severely anomalous hepatic venous drainage in one twin is incompatible with survival after surgery.

It is not unusual to find large calibre vessels crossing the area of fusion. It is important to visualise these vessels by CT or MRI before separation to minimise blood loss and mortality during separation.

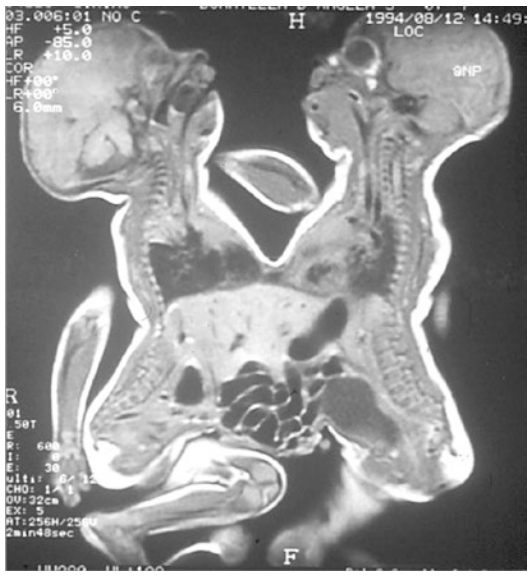

Fig. 19.8 CT scan of omphalopagus conjoined twins showing shared liver

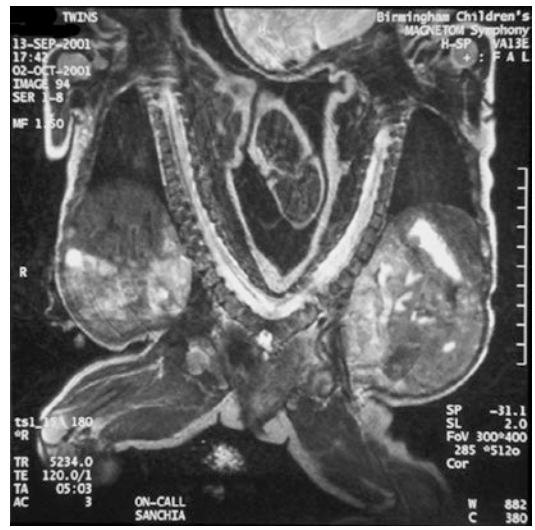

Fig. 19.9 MRI scan of pygopagus twins showing spinal cord and vertebral anatomy

19.1.6.5 Contrast Studies of the Gastrointestinal and Genitourinary Tracts

Abdominal conjunction often involves fusion of parts of the intestine. Even in the absence of fused bowel, when contrast medium is given to one twin the bowel loops may be freely mobile across the 'midline' and be seen to project into the peritoneal cavity of the other twin during fluoroscopy [25]. Pelvic conjunction leads to complex fusion and anomalies in the anorectal region. These require an individual approach with contrast studies (enemas, loopograms and cystograms) of the distal bowel and bladder. Contrast studies provide limited information and often, particularly due to overlapping bowel loops, the anatomy can only be revealed at the time of separation.

Urological abnormalities are confined to those in whom the pelvis is joined: ischiopagus, parapagus or pygopagus twins. Most twins share four kidneys and two bladders, occasionally with one ureter crossing from the contralateral twin to the other. The bladders are usually side by side but they may be sagittally placed [26]. CT scanning usually provides sufficient information regarding the upper renal tracts and bladders. Detailed urethral anatomy and possible fistulas require retrograde contrast medium examinations.

19.1.6.6 Nuclear Medicine

The kidneys, albeit ectopic or too few in number, usually function normally in conjoined twins [25]. Cross-sectional imaging can usually clarify the genitourinary anatomy without the need for isotope renography studies. There is an increased frequency of pelviureteric or ureterovesical obstruction in these twins, but this is seldom of major importance prior to separation.

19.1.7 Obstetric Management

Delivery should take place at, or close to, the surgical unit where separation will be performed. Delivery must always be by classical Caesarian section at 36–38 weeks' gestation.

19.1.8 Anaesthetic Management

Anaesthesia involves two separate anaesthetic teams with all members being clearly aware for which child is their responsibility [27]. Endotracheal intubation should be via the nose for added security. Because of repositioning and movement once separation has been performed there is a risk of accidental extubation and the nasal route is more secure.

Full arterial and central venous pressure monitoring is essential, together with ECG, pulse oximetry and capnography. Adequate wide bore venous access is essential as brisk haemorrhage may be encountered necessitating rapid large volume transfusion. All drugs and intravenous fluids administered are calculated on a total weight basis with half being delivered to each twin. Because of the cross-circulation, drugs given intravenously may have an unpredictable effect and particular care must be taken to administer such drugs incrementally. Urine output is carefully monitored.

All lines and monitoring cables are best colour coded for each twin to avoid confusion during repositioning.

19.1.9 Separation Procedure

The key to a successful outcome is thorough preoperative planning.

From the imaging, the extent of major organ union will be apparent and the details of each major system separation is planned in advance. The order in which these phases of separation will be performed is best decided during the operation itself. Many anatomical variants exist for each of the different types of union. For instance, although the liver is joined in 100% of thoracopagus twins, in 50% there is intestinal union in addition. The surgeon will need to have planned for each possibility—such as what to do if there is a single duodenum, or a single common bile duct.

In the more extensive forms of ischiopagus or parapagus union, the terminal ileum and the large bowel are single. Allocation of these structures

cannot be planned in detail as the mesenteric blood supply is abnormal and unpredictable. As a general rule, these children have two bladders which may lie side by side or may lie anteriorly and posteriorly. Plans must be in place to deal with either eventuality, together with plans for dealing with crossed or uncrossed ureters.

Most importantly, with extensive union, there will be a substantial body wall defect after separation. This is invariably more extensive than anticipated. The management of this problem also needs to be planned in advance. We have used tissue expanders in the past and found them to be troublesome and unhelpful in providing substantial extra tissue. With the sole exception of craniopagus union, where the expanders sit on bone, we would not recommend their use. We use polypropylene mesh over a plastic liner to close the defect and plicate this as tolerated. Even with the largest of defects, the body wall can be closed within 2 weeks.

Initially, one surgical team comprising both lead surgeons is sufficient to commence the procedure. Our preference is to start the operation from posteriorly. The skin and soft tissue are divided down to muscle and fascia. The wound is then sutured closed and the babies turned around. We have done this with the more extensive unions, as otherwise, it is difficult to allocate body wall equally and one may easily leave one with significantly less. Once this incision has been made, it is easy to complete the separation at the final stage of the operation.

If a vestigial limb is present posteriorly, it may be bivalved and divided and the bones filleted out. This provides vascularlised healthy tissue to assist in closure. Allocation of this extra tissue is decided at the time of surgery.

On opening the chest and abdomen anteriorly, it is usually best to divide the conjoined sternum to improve access. The lobar anatomy of conjoined livers is not readily discerned and in any case precision is unnecessary in this regard. A point is chosen, midway between the gall bladders and the porta hepatis on either side and the liver is divided in the usual manner. The use of an ultrasound dissector combined with one of the high energy sealing devices results in virtually bloodless conditions.

Once the liver is divided, the remainder of the gastrointestinal anatomy is easier to manage.

The urological aspects are dealt with before the decision about allocating the rectum [26]. Usually each twin has a bladder and at least a posterior urethra. Occasionally, two bladders lying fore and after are divided and the two halves united on either side. If the bladders are side by side, then the division takes place between them. In ischiopagus and parapagus twins the ureters may cross into the opposite twin's bladder.

Our experience suggests that in almost all cases, it is possible to preserve at least one corpus of the penis for each twin. Occasionally, there are three or more corpora cavernosa in which case a more normal penis will result.

Once the urological procedure has been completed, a decision is made on allocation of the rectum and anus. This will depend on the blood supply which is available. It has been our practice to leave the terminal ileum and colon with one twin whilst leaving the rectum with the other when conditions permit.

Once the pelvic viscera have been allocated, the posterior part of the pelvic ring is divided. Preoperative imaging will have revealed if there are substantial vessels crossing at this level. Finally, the previously sutured skin wound is opened and separation is complete.

Closure of a large body wall defect is straightforward. If the sternum is short and the heart or pericardium are exposed, a polypropylene patch is sutured to the chest wall skeleton laterally and superiorly and to the diaphragm inferiorly. This patch is left permanently in situ. The abdomen is closed by suturing two flaps of polypropylene mesh to the muscle on either side and covering the viscera with a plastic liner, such as an intestinal bag.

With wide undermining, there is usually sufficient skin to cover the chest wall defect. The skin over the abdomen is tacked to the mesh to cover the area where the mesh is sutured to muscle. This allows tissue to grow from the fascia through the mesh to the overlying subcutaneous fat and ensures a strong attachment of mesh to muscle [28–32].

19.1.10 Postoperative Management

Almost all these patients are electively ventilated after surgery with the usual monitoring which is employed after major surgery. There are, however, two problems which are not common in other children—fluid loss and cardiac performance.

If the abdomen has been closed with a mesh, there will be substantial fluid losses through the mesh for the first few days.

We estimate the losses by use of absorbent gauze dressings, weighed on an hourly basis. The fluid is then replaced ml for ml with human albumin solution. The mesh is tightened, commencing on the day after operation. Limited tension is applied for the first few days. However, after the first 4 days, increasing tension can be applied to the mesh. The abdominal wall stretches and grows rapidly, especially in young infants. It is usual to achieve abdominal wall closure within 2 weeks.

The other aspect in which conjoined twins differ is in cardiac performance. It is a feature of those who have extensive union, that one circulation supports the other. In general, the thinner and more active twin has a heart which is more robust and which supports the other twin's circulation. This difference in cardiac performance is not evident on pre-operative testing.

Once the circulations are separated, the more dependent twin may be significantly compromised. It is of critical importance that the lowest filling pressure possible is used and that the after load is also reduced. We try to maintain as low a central venous pressure as possible, together with as low a blood pressure as possible, commensurate with an adequate urine output. This phase of compromised cardiac performance lasts a number of days but is usually resolved by 7 days after operation.

The timing of enteral feeding is variable but does not await body wall closure.

In the majority, complete removal of the mesh is achieved when the abdomen is closed. On occasion, it is necessary to leave some mesh and this has not been a particular problem over the following years.

The *outcome* in our series [33] could be divided into one of three courses.

1. *Non-operative management*: Table 19.2 is indicated when there is complex cardiac union without the possibility of reconstructing even a single functioning heart or where there is extensive cerebral fusion. Parents faced with the prospect of a surviving twin having severe deformities may refuse consent for separation. In eight of nine cases in our series there was cardiac fusion while in one with extensive parapagus fusion (a normal triplet survived) parents refused surgery. All nine sets died within a short period.

2. *Emergency separation*: Table 19.3 is required when one twin is dead or dying and threatening the survival of its sibling, where there is a correctable congenital anomaly incompatible with survival if left untreated such as

Table 19.2 Separation not attempted outcomes

Classification	Sex	Shared organ(s)	Associated anomalies	Outcome
Thoracopagus	F	Cardiac fusion	Pulmonary atresia, esophageal atresia, omphalocele	Died
Thoracopagus	F	Cardiac fusion	Omphalocele	Died
Thoracopagus	F	Cardiac fusion	?	Died
Parapagus	F	Extensive union	Surviving triplet	Died
Thoracopagus	F	Cardiac fusion	?	Died
Thoracopagus	F	Cardiac fusion	?	Died
Thoracopagus	F	Cardiac fusion	?	Died
Thoracopagus	F	Cardiac fusion	?	Died
Thoracopagus	F	Cardiac fusion	?	Died

Table 19.3 Emergency separation outcomes

Classification	Sex	Shared organ(s)	Associated Anomalies	Age at operation	Outcome
Thoracopagus	F	Pericardium, diaphragm, Liver, CBD, small bowel	Pulmonary atresia	3 days	1 A&W, 1 died cardiac failure
Omphalopagus	F	Liver, small bowel	Omphalocele and liver ruptured at birth; Cloacal exstrophy	1 day	1 died before arrival, 1 dies intraop
Thoracopagus	M	Cardiac-atrial communication, liver	Unilocular heart Absent hepatic veins	8 days	1 died intraop; 1 died at 6 weeks/ SIDS
Thoracopagus	F	Liver	Unilocular heart, CDH	1 day	both died
Omphalopagus	F	Liver, jejunal atresia	Omphalocele, volvulus	2 days	Both A&W
Omphalopagus	M	Distal colon, bladder	Hypoplastic lung, Anorectal anomaly	1 day	1 died in transit, 1 A&W
Omphalopagus	F	Liver	Cardiac (DORV)	1 week	1 A&W, 1 died 3rd day
Parapagus	F	Lungs, diaphragm, aorta, liver, intestine	AV canal, PPH	1 day	Both died
Thoracopagus	F	Pericardium, cardiac defect, liver	Porencephalic cyst	5 days	1 died postop-PPH; 1 died at 2 weeks
Omphalopagus	F	Liver, small bowel	Intestinal obstruction	1 week	Both A&W
Omphalopagus	F	Ileum, 1 colon, bladders	Both ARAs	2 days	Both A&W

oesophageal or intestinal atresia, or where serious damage has occurred during birth to the connecting bridge or area of fusion (ruptured omphalocele).

Emergency separation was necessary in 11 of our cases. One had a rupture of the shared omphalocele resulting in tearing of the united liver with exsanguinating haemorrhage resulting in the death of one twin. Emergency separation was undertaken in an attempt to salvage the surviving twin who died at the end of the procedure.

In three sets of thoracopagus twins, cardiac instability prompted emergency separation. Only one of these infants survived. Prenatal volvulus with necrosis and perforation occurred in a set of omphalopagus twins necessitating emergency separation. Both twins had intestinal atresia which was repaired but developed short bowel syndrome which required many months for adaptation to occur. Both survived and eventually thrived.

Another set of omphalopagus twins were transferred soon after birth as one had severe pulmonary hypoplasia requiring mechanical ventilation. This twin died during transfer. The transport team were was instructed to digitally compress the area of union to prevent exsanguination into the surviving twin while avoiding applying a clamp as prior experience showed that much of the surviving twin's intestine may reside in the peritoneal cavity of its sibling. This twin did survive.

The survival rate for emergency separation was nine out of a possible 22 infants—40%. In retrospect survival was not possible in six of these cases.

Table 19.4 Planned separation outcomes

Classification	Sex	Shared organ(s)	Associated anomalies	Age at operation	Closure	Outcome (to discharge from hospital)
Craniopagus	F	Sagittal sinus	Nil	2 months	Skin grafts	Both A&W[a]
Ischiopagus	M	Liver, ileocolon, rectourethral fistula, penis	ARA, Crossed ureters, TRIPUS	8 months	Primary	Both A&W
Parapagus	F	Pericardiu, diaphragm, liver, ileocolon, ARA, genito-urinary	Renal agenesis	3 years	Prolene mesh	1 A&W, 1 died at 3 days
Parapagus	M	Pericardium, liver, ileocolon, genito-urinary	ARA	10 months	Prolene mesh	1 A&W[b]
Thoracopagus	F	Pericardium, liver, CBD, jejunum	Omphalocele	3 months	Prolene mesh	Both A&W
Omphalopagus	F	Liver, CBD	Nil	3 months	Prolene mesh	Both A&W
Omphalopagus	F	Liver	Nil	6 weeks	Prolene mesh	Both A&W
Pygopagus	F	Sacrum, spinal cord, vagina, ARA	Nil	3 months	Primary closure	Both A&W
Omphalopagus	M	Liver	HIV	8 months	Prolene Permacol	Both A&W[c]
Pygopagus	M	Sacrum, spinal cord, urethra, penis, anus		19 months	Primary	Both A&W
Ischiopagus	M	Urethra, penis	TRIPUS, ARA	4 months	Mesh	Both A&W (scoliosis)
Pygopagus	F	Sacrum, spinal cord		4 months	Primary	Both A&W
Ischiopagus	M	Anus, bladder extrophy, ileo-colon, Bipus		7 months	Primary	Both A&W
Ischiopagus	M	Liver, colon	TRIPUS	2 years	Primary	Both A&W
Pygopagus	M	Sacrum, spinal cord, anus, urethra, penis		8 months	Primary	Both A&W
Craniopagus		Sagittal sinus		12 months	Staged	Both A&W
Craniopagus		Sagittal sinus		6 months	Staged	Both A&W
Ischiopagus	F	Tripus, liver, ileum, large bowel, bladder		4 months	Mesh	Both A&W

[a]One died at 6 months S.I.D.S
[b]One vomited, aspirated and died at 6 months
[c]? One died after return to Nigeria? D&V

3. *Planned separation*: Table 19.4 if the twins are stable and healthy at birth, they should be allowed to feed normally and thrive with the intention to separate at around 2–3 months. This allows time to carry out investigations to define as accurately as possible the nature and extent of shared organs. The operative procedure can then be planned with involvement of all the relevant staff.

Eighteen sets underwent planned separation, of whom three died, (two at home 6 months after successful separation), and 33 survived (91%).

Table 19.5 Outcome of management of conjoined twins in the major series

Authors	Year	Number	No operation	Emergency separation Survivors (%)	Planned separation Survived (%)
O'Neill (USA) [20]	1988	18	5	5 sets 1 (10%)	8 sets 13 (81%)
Cywes/Rode (S. Africa) [25, 34]	2006	33	16	None	17 sets 22 (65%)
Al Rabeeah (Saudi Arabia) [35]	2006	29	19 (1 abandoned operation)	None	10 sets 19 (95%)
Saguil (Philippines) [36]	2009	22	6	6 sets 1 (8%)	9 sets 15 (83%)
Spitz/Kiely/Pierro (UK)	2010	40	9	11 sets 9 (40%)	18 sets 33 (91%)

The outcome for the management of conjoined twins in the literature is given in Table 19.5.

19.1.11 Follow-Up

The extent of the union will determine whether the infant/s will have minor or major residual problems. One or both twins may have congenital cardiac abnormalities which may require surgical correction. Residual scars or contractures may require plastic surgical correction. Short bowel syndrome occurs when each twin is allocated 50% of the shared intestine. There will be a need for parenteral nutrition and meticulous dietary support for a period of time pending intestinal adaptation. Intestinal stomas may be temporary or permanent and will require the input of a stoma therapist. Imperforate anus when present will need reconstruction.

Prolonged urological follow- up is essential, particularly in the cases of ischio- and pygopagus twins. Shared bladder, cross ureters, vesicoureteric reflux and renal abnormalities will require regular monitoring to prevent further damage and to diagnose early and treat urinary calculi. Lifelong orthopaedic follow- up will be needed for limb deformities, deletion of lower limb/s and for scoliosis and chest wall deformities.

Psychological support should commence preoperatively when separation is undertaken at a later age and is essential following separation especially were there is the loss of one of the twins. Where the separation has involved prolonged periods of hospitalisation (some of our twins have been discharged within 2 weeks of separation) there may been developmental and behavioural problems which will require attention.

19.2 Ethics

If separation is possible with the expected survival of both twins, we would strongly recommend that the surgical procedure should be performed. If there is complex cardiac fusion, the chances of survival of one or both twins is so remote that surgery should be declined and nature allowed to take its course.

If one twin has a lethal abnormality and cannot survive independently from its "normal" twin and if separation does not take place both twins would die, then separation should proceed even though at the expense of the abnormal twin who has survived only by being supported by its sibling.

Yet, twins can survive joined together for many years. Alice D. Dreger [37] contends that "when it comes to cases in which one twin must be 'sacrificed', it is ethically wrong to take one life so another may live". She further states that "not in a single case has the twin chosen to survive ever actually survived to go home". This is clearly incorrect as borne out in our and other series.

19.3 Heteropagus (Parasitic) Twins

19.3.1 Definition

Heteropagus or parasitic twin is a grossly defective fetus, or fetal parts, attached externally, with or without internal connections, to a relatively normal twin (the autosite) in one of the same eight areas in which symmetrical twins are united. They are usually comprised of externally attached supernumerary limbs but may also contain viscera or visceral parts but only rarely a beating heart or intact brain.

Fetus in Fetu is a fetiform mass enclosed within the body of the autosite, usually the abdominal cavity, rarely within the brain, with grossly recognisable fetal parts including an axial skeleton, attached to the autosite by a pedicle containing a few large blood vessels. Its growth rate is similar to the host within which it is discovered.

19.3.2 Incidence

The estimated incidence of heteropagus twins less than for symmetrical twins, < 1 per million births. The female preponderance seen in symmetrical twins is not evident in heteropagus twins where there is an equal distribution of the sexes.

19.3.3 Embryological Considerations

The most plausible theory for the occurrence of heteropagus twins was proposed by Dönitz in 1866 [38]. He postulated that heteropagus twins originated from symmetrical twins one of which suffered secondary damage as a consequence of vascular compromise. The affected "twin" would then have to rely on collateral blood supply from the autosite while ischemic damage occurred in various parts of the affected "twin". In support of this theory, hypoplastic umbilical vessels have been found in the heteropagus twin and vascular connections from the autosite to the heteropagus twin may be found during surgical separation. Others have disputed this theory as it cannot account for all the abnormalities found in these twins and particularly cannot explain the acephalic occurrence. It is generally accepted that the heteropagus twin is genetically identical to the autosite and this has been substantiated by DNA analyses.

19.3.4 Anatomical Types

196 reports of heteropagus twins have appeared in the literature up to 2010 [39].

The breakdown of these cases are as follows:

Thoracopagus	1
Cephalopagus	6
Parapagus	3
Omphalopagus	71
Ischiopagus	32
Pygopagus	46
Craniopagus	11
Rachipagus	28

Dipygus or caudal duplication (Fig. 19.10) is a rare abnormality comprising two sets of accessory lower limbs sited between the autosite's limbs and including accessory external genitalia.

Omphalopagus (Fig. 19.11) or epigastric heteropagus accounts for the majority of cases—more prevalent in recent series where almost 60% of cases were in this region.

Fetus in fetu [40, 41] occurs most commonly within the abdominal cavity with 57 reported cases with only 9 having a brain and 6 a heart, both always small and rudimentary. In most cases a pedicle of vessels arise from the retroperitoneal region and attaches to the umbilical area of the parasite. In the cranial region the majority of fetus in feto are epignathi attaching to the posterior pharynx near the location of Rathke's pouch. Only 7 cases of intracranial fetuses in fetu have been reported.

Sacral parasite is a rare variety of heteropagus twin and needs to be differentiated from sacrococcygeal teratoma. Some authors consider fetus in fetu and fetiform teratomas within the spectrum of teratomas, but this remains controversial.

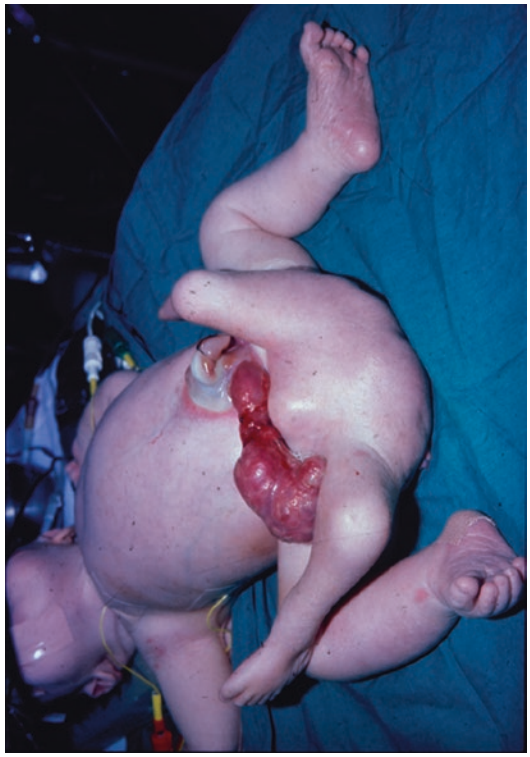

Fig. 19.10 Dipygus with prolapsed intestine

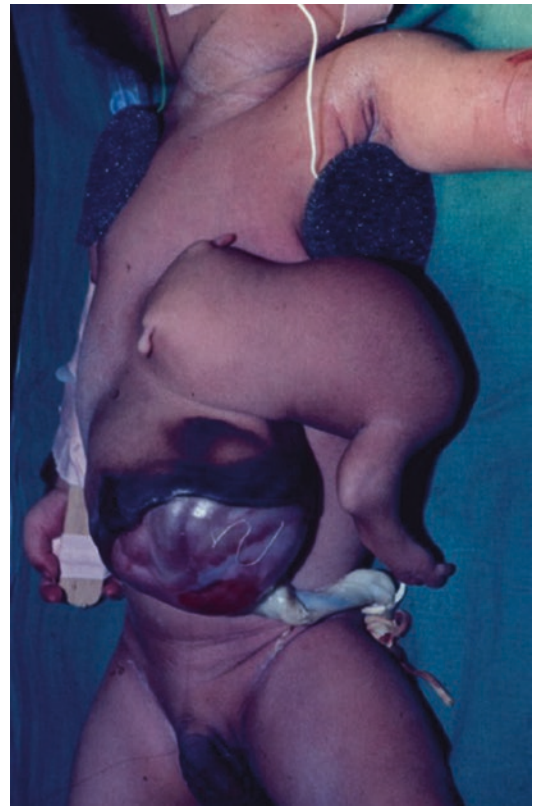

Fig. 19.11 Parasitic omphalopagus twins

19.3.5 Diagnosis

Prenatal identification of heteropagus twins has been documented on at least 7 occasions at gestational ages ranging from 9 to 28 weeks [42]. The importance of recognition of the nature of the abnormality is evident in that the condition is entirely benign and compatible with normal development. The diagnosis in utero should not be considered an indication for termination of the pregnancy provided that it is not causing gross deformity of adjacent structures.

19.3.6 Obstetric Care

Depending on the size and extent of the parasitic twin, delivery can be by normal vaginal route. If an obstructive delivery is anticipated, Caesarian section at around 38 weeks of gestation would be indicated.

19.3.7 Investigation

Sharing of organs and vascular connections are infrequent in heteropagus twins. As a result, preoperative imaging has usually been restricted to C.T., ultrasound and MRI scans which will reveal bony and soft tissue structures. Occasionally angiography has been undertaken to show vascular communications. More recently MRA (magnetic resonance angiography), has replaced invasive conventional angiography. Echocardiography of the autosite is mandatory in thoracopagus parasitic twins as over 25% have congenital cardiac defects.

19.3.8 Surgery

Separation of the parasite from the autosite is generally undertaken in early infancy. As sharing of organs and major vascular connections is

unusual, the surgical procedure is generally straightforward and uncomplicated. The initial skin incision should be carefully planned to take sufficient skin and subcutaneous tissue from the parasite to ensure tension free closure of the wound following separation. This will avoid wound breakdown or infection, the most commonly encountered complications. A thorough search of the autosite at the site of attachment must be carried out to exclude any retained abnormal or extraneous tissue and to correct possible anomalies in the autosite such as associated congenital intestinal abnormalities.

19.3.9 Outcome

The prognosis for the autosite is generally excellent with little or no consequences for the host.

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Part III

Thorax and Cardiac Surgery

Congenital Malformations of the Airway and Chest Wall

20

Emma L. Sidebotham and David C.G. Crabbe

Abstract

Malformations of the neonatal airway and chest wall are uncommon but invariably serious. As a generalisation, the earlier a congenital anomaly of the airway presents the more ominous it is likely to be. Many infants will have other major congenital malformations. Management is complex and successful treatment requires careful consideration by a multidisciplinary team that must include a sympathetic paediatric intensive care unit. The first part of this chapter deals with these conditions.

The majority of chest wall deformities in children are acquired rather than congenital. The second part of the chapter deals with true congenital deformities, many of which are due to skeletal dysplasias.

Keywords

Chest wall deformities • Pectus • Airway lesions • Airway malformations

20.1 Introduction

Malformations of the neonatal airway and chest wall are uncommon but invariably serious. As a generalisation, the earlier a congenital anomaly of the airway presents the more ominous it is likely to be. Many infants will have other major congenital malformations. Management is complex and successful treatment requires careful consideration by a multidisciplinary team that must include a sympathetic paediatric intensive care unit. The first part of this chapter deals with these conditions.

The majority of chest wall deformities in children are acquired rather than congenital. The second part of the chapter deals with true congenital deformities, many of which are due to skeletal dysplasias. Severe deformities in the neonatal period carry a poor prognosis with respiratory failure in infancy. Although not strictly congenital, chest wall deformity arising from thoracotomy in the neonatal period is discussed because of the importance of surgical technique to avoid late morbidity.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_20

20.2 Congenital Malformations of the Airway

20.2.1 History

Anatomical descriptions of congenital airway malformations appear in the literature from the eighteenth and nineteenth centuries. Sporadic reports of infants with tracheal stenosis appeared during the early twentieth century but these remained of academic importance until 1958 when Cantrell and Guild successfully resected a segmental stenosis in a 7 year old girl [1]. The subsequent history of paediatric tracheal surgery has been recorded in detail by Backer and Holinger [2]. The first reports of tracheomalacia date from North America in the late 1930s when the condition was recognised in association with vascular rings. In 1948 Gross and Neuhauser reported correction of tracheal compression by pexing an aberrant innominate artery to the sternum [3].

20.2.2 Airway Embryology

Development of the airway begins on day 22 of embryogenesis when the respiratory diverticulum forms as a bud from the ventral aspect of the pharynx at the laryngotracheal groove. As this endodermal bud grows in a caudal direction the mesoderm of the primitive mesentery, destined to become the mediastinum, proliferates and invests the bud. The endoderm gives rise to the epithelium of the trachea, bronchi and alveoli, whilst the mesoderm forms the cartilage, muscle and connective tissue of the respiratory tract. As the respiratory diverticulum elongates from day 28, lateral invaginations of mesoderm form the tracheo-oesophageal septum which separates the future airway from the foregut. This process of separation is complete by day 35.

Between day 26 and 28 the tip of the respiratory diverticulum bifurcates to form the left and right primary bronchial buds. These buds are the rudiments of the left and right main bronchi and the lungs. Around this time the blood supply switches from the splenic plexus to the definitive pulmonary vasculature. From weeks 5 to 28 of development the bronchial buds will undergo a further 16 rounds of bifurcation, together with the investing layer of mesoderm, to form the respiratory tree.

20.2.3 Nomenclature

There is no universally accepted classification of congenital malformations of the airway. Atresia refers to an orifice or passage that is absent or abnormally closed. Agenesis refers to the failure of an organ to develop during embryonic life. In the context of airway malformations these terms have entered common usage with a certain amount of interchangability—for example, tracheal atresia is commonly, but incorrectly, referred to as tracheal agenesis.

20.2.4 Congenital High Airway Obstruction Syndrome

Congenital high airway obstruction syndrome (CHAOS) is associated with intrinsic or extrinsic obstruction to the fetal airway [4]. Obstruction of the trachea or larynx results in distension of the large airways which is readily visible on fetal ultrasound (Fig. 20.1). The lungs hyperexpand and invert the diaphragms [5]. The fetus becomes hydropic. Causes include laryngeal atresia and

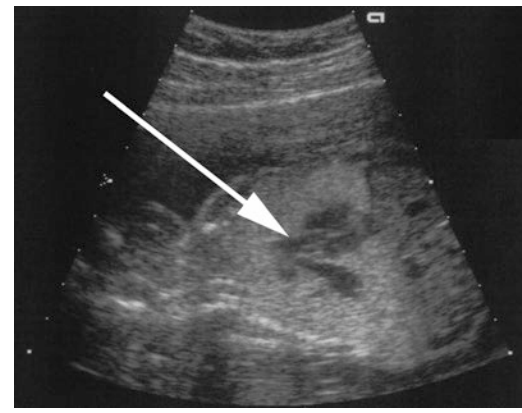

Fig. 20.1 CHAOS. The dilated trachea and main bronchi can be seen on this fetal ultrasound image

extrinsic compression of the upper airway from cervical tumours, including teratomas and lymphangiomas.

20.2.5 Laryngeal Clefts

Laryngeal clefts result from failure of caudal progression of the tracheo-oesophageal septum. They affect around 1 in 2000 births. The male to female ratio is approximately 2:1. Laryngeal clefts typically present with a combination of stridor, choking on feeds and recurrent aspiration pneumonia [6]. Stridor and a hoarse cry should alert the surgeon to the diagnosis as these symptoms are distinctly unusual in an infant with an H-type tracheo-oesophageal fistula. Stridor occurs because the posterior wall of the larynx is abnormally mobile and the redundant mucosa prolapses into the airway causing intermittent airway obstruction. Early severe symptoms are associated with extensive clefts. Minor clefts may escape detection.

20.2.5.1 Associated Malformations

Laryngeal clefts are seen in association with the Opitz–Frias and Pallister–Hall syndromes. The Opitz-Frias (G/BBB) syndrome affects midline structures [7]. The most common features of this condition are hypertelorism, defects of the larynx, trachea, and oesophagus and hypospadias. Cleft lip with or without a cleft palate, cardiac defects, anorectal malformations and agenesis of the corpus callosum affect approximately 50% cases. Opitz G/BBB syndrome may be X-linked or inherited in an autosomal dominant manner. The X-linked form is associated with a mutation in the MID1 gene on chromosome X. The autosomal dominant form is associated with a chromosome 22 mutation.

The Pallister-Hall syndrome is characterized by a spectrum of anomalies including central or postaxial polydactyly, hypothalamic hamartomata, which may be associated with pituitary insufficiency, a bifid epiglottis and a laryngotracheal cleft [8]. The condition is associated with mutations of the GLI3 gene on chromosome 7p13 and is inherited in an autosomal dominant manner.

20.2.5.2 Classification

In 1989 Benjamin and Inglis proposed a classification system for laryngeal clefts based on the extent of the cleft [9] (Table 20.1). Diagnosis of a laryngeal cleft requires careful endoscopic examination of the airway under general anaesthesia. The cleft may be obscured by redundant laryngeal or oesophageal mucosa and the only way to confirm or exclude the diagnosis with certainty is to attempt to part the inter-arytenoid notch with a right-angled probe (Fig. 20.2).

20.2.5.3 Management

Type 1 clefts can be managed conservatively in most cases [10]. If the infant remains unable to feed without aspiration endoscopic suture repair of the cleft may be necessary. Optimum management of type 2 and 3 clefts is less clear cut. The conventional approach involves open repair through an anterior laryngofissure with a covering tracheostomy. However, there is an increasing trend towards endoscopic repair without

Table 20.1 Benjamin and Inglis classification of laryngeal clefts

I above the true cords, limited to the interarytenoid region
II extension below true cords, partial involvement of the cricoid lamina
III total cricoid cleft ± extension into the cervical trachea
IV cleft involves the thoracic trachea and may extend to the carina

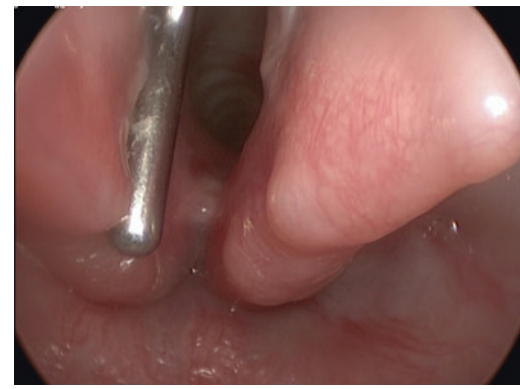

Fig. 20.2 The inter-arytenoid fissure is probed to look for a laryngeal cleft

tracheostomy. Complete larnygotracheal clefts are exceedingly difficult to repair and the complication rate is high [11]. Repair of the upper part of the cleft is performed using the anterior approach or via a lateral pharyngotomy. Repair of the lower part of the cleft is usually performed via a right thoracotomy. Tracheostomy is best avoided because of the risk of erosion and dehiscence of the repair. Careful consideration should be given to palliative care for infants with extensive clefts because associated malformations are common and the prognosis is poor.

20.2.6 Laryngeal Atresia

Laryngeal atresia is a rare, complex anomaly. In 1954 Holinger classified the condition into membranous and cartilaginous types [12]. In 1965 Smith and Bain proposed a more complex classification based on the site of the obstruction [13]. The diagnosis may be suspected antenatally if ultrasonographic features of the CHAOS are present. After birth the affected infant will make respiratory effort to no avail and expire quickly. Laryngeal atresia is frequently associated with tracheal agenesis and a tracheo-esophageal fistula. Endotracheal intubation is impossible but the lungs may be inflated with bag and mask ventilation or by esophageal intubation.

20.2.7 Tracheal Agenesis

Congenital absence of the trachea is a rare cause of severe neonatal respiratory distress. Less than 100 cases have been reported following the first description by Payne in 1900. Floyd et al. classified tracheal agenesis into three variants [14] (Table 20.2). In 90% of cases other congenital malformations are present, most frequently involving cardiovascular, gastro-intestinal and genito-urinary systems [15]. Tracheal atresia may be suspected antenatally if the CHAOS develops.

Tracheal agenesis presents at birth with severe respiratory obstruction in a baby who is unable to cry. Oxygenation can usually be improved temporarily by bag and mask ventilation by retrograde insufflation of the lungs through the tracheo-oesophageal fistula. Although the glottis can be visualised with a laryngoscope endotracheal intubation is impossible because the trachea is atretic [16].

Heroic attempts have been made to treat affected children with minimal success and considerable morbidity. Fuchimoto et al. recently reported the oldest survivor who has reached the age of five with a tracheostomy and overnight mechanical ventilation [17].

20.2.8 Pulmonary Agenesis

By longstanding convention anomalies of lung development are considered in three categories [18] (Table 20.3). The aetiology of these conditions is unknown. They are all associated with an increased incidence of cardiac, spinal and limb anomalies [19]. Pulmonary agenesis and aplasia are commonly associated with tracheal stenosis.

All three conditions may be asymptomatic. Pulmonary agenesis is well reported as an incidental finding at autopsy in the elderly [20]. More often these conditions are associated with

Table 20.2 Floyd's classification of tracheal agenesis [6]

• Type I—a short segment of trachea connects to the anterior esophagus (13%)
• Type II—the airway and esophagus are fused at the level of the carina, with no tracheal remnant (65%)
• Type III—right and left mainstem bronchi join the esophagus directly (22%)

Table 20.3 Anomalies of lung development

• Pulmonary agenesis: unilateral absence of bronchus, pulmonary vessels and lung parenchyma beyond the tracheal bifurcation
• Pulmonary aplasia: a rudimentary bronchus is present which forms a blind-end pouch without lung tissue
• Pulmonary hypoplasia: a variable reduction of lung parenchyma that may or may not be associated with a smaller than normal bronchus and pulmonary vessels

tachypnoea and frequent lower respiratory tract infection in infancy because of the reduced respiratory reserve [21]. Early presentation may signal the presence of tracheal stenosis. During childhood, particularly adolescence, asymmetrical growth of the rib cage may become obvious but scoliosis is uncommon in the absence of vertebral anomalies.

Pulmonary agenesis may be detected on prenatal ultrasound [22]. In postnatal life the diagnosis is usually made on a chest X-ray which shows displacement of the mediastinum (Fig. 20.3). The solitary lung herniates across the midline. Bronchoscopy is wise to exclude tracheal stenosis and a bronchial obstruction. Contrast enhanced CT may be necessary to excluded a vascular ring.

The prognosis depends on the presence of other anomalies [23, 24]. Tracheal stenosis associated with a solitary lung carries a poor prognosis. In the absence of other congenital anomalies symptoms improve with age although some infants succumb to recurrent infection. Pulmonary hypertension is uncommon providing the heart is structurally normal.

20.2.9 Abnormalities of Bronchial Branching

Variations of lobar or segmental bronchial anatomy are rare [25]. Major bronchial abnormalities include tracheal bronchus and accessory cardiac bronchus (ACB) (Fig. 20.4). The term *tracheal*

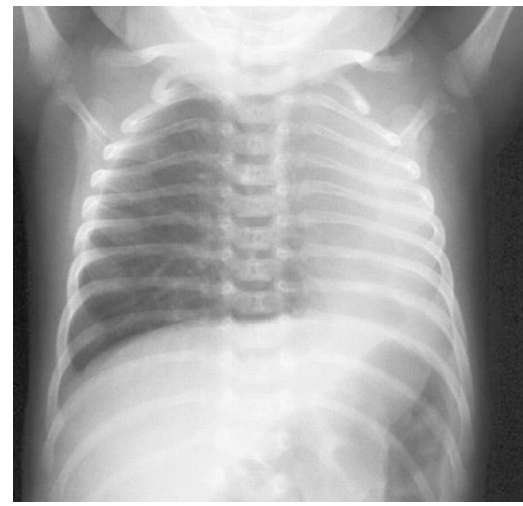

Fig. 20.3 Chest X-ray showing pulmonary agenesis

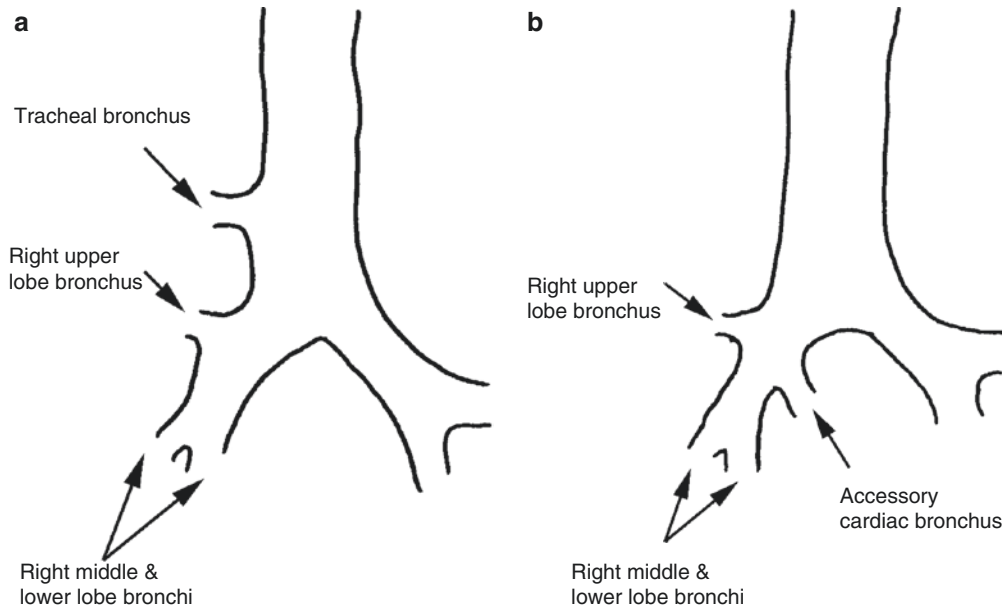

Fig. 20.4 (**a**) Tracheal bronchus (**b**) accessory cardiac bronchus

bronchus includes a variety of bronchial anomalies supplying the upper lobes (usually the right) originating from the trachea. A tracheal bronchus to the right upper lobe is seen in 0.1–2% population and a tracheal bronchus to the left upper lobe in 0.3–1% population, based on bronchographic and bronchoscopic studies. An ACB is a supernumerary bronchus arising from the inner wall of the right main bronchus or intermediate bronchus opposite to the origin of the right upper lobe bronchus.

20.2.10 Bronchial Atresia

Bronchial atresia is an uncommon congenital anomaly usually associated with atresia of a segmental bronchus [26]. The apicoposterior segment of the left upper lobe is most commonly affected [27] although a recent large series from Japan reported a predilection for the right lower lobe [28]. This study also included two children with lesions involving two lobes. Occasionally the atresia involves a lobar bronchus. The blind ending atretic bronchus fills with mucous resulting in a bronchocele. The lung parenchyma distal to the atresia is aerated via interbronchiolar channels and the pores of Kohn. This is commonly associated with air trapping.

The classical findings on chest x-ray are a mass (the bronchocele) surrounded by hyperinflated lung with decreased vascular markings. Computed tomography will confirm the diagnosis: the obstructed atretic bronchus typically points toward the hilum and the segmental nature of the emphysematous lung parenchyma distal to the obstruction is evident [29] (Fig. 20.5).

The majority of patients with bronchial atresia are asymptomatic. Symptomatic patients usually present with recurrent chest infections, dyspnoea, wheezing, or chronic cough. Secondary spontaneous pneumothorax has been reported [30]. No treatment is necessary for asymptomatic patients. Surgical excision is reserved for patients with complications. Segmental or lobar resection may be necessary with the aim to preserve normal lung parenchyma [28].

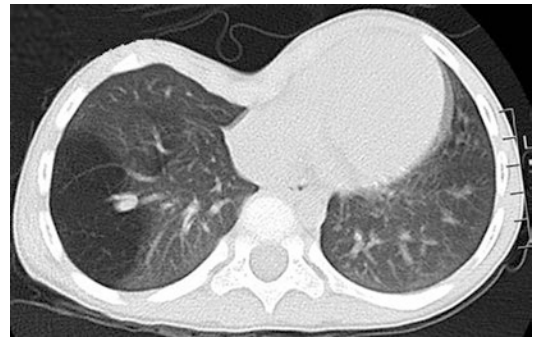

Fig. 20.5 CT scan showing bronchial atresia

20.2.11 Congenital Tracheal Stenosis

The normal trachea is supported by 16–20 horseshoe shaped cartilages and a membranous posterior wall. Congenital tracheal stenosis is associated with compete rings of cartilage which replace all or part of the normal tracheal cartilages [31]. The incidence of congenital tracheal stenosis is unknown but the condition is almost certainly underdiagnosed.

Tracheal stenosis typically presents in infancy with progressive dyspnoea and biphasic stridor. Symptoms worsen during the first few months of life as the infant grows [32, 33]. The stridor will increase substantially during feeding and at times of agitation. Infants with severe stenoses present earlier because the resistance to airflow is inversely proportional to the fourth power of the radius of the airway. Occasionally complete tracheal rings are found coincidentally at endoscopy, usually following endotracheal intubation for an unrelated procedure when the airway is found to be unexpectedly small.

20.2.11.1 Classification

The classification of congenital tracheal stenosis has been refined over the years. In 1941 Wolman described two variants—segmental stenosis and funnel stenosis [34]. In 1964 Cantrell and Guild added a third variant—diffuse hypoplasia [1]. Grillo described four variants with in a classification which is useful in clinical practice [33] (Fig. 20.6). Recently a further variant, described as a cork-screw stenosis, has been reported [35].

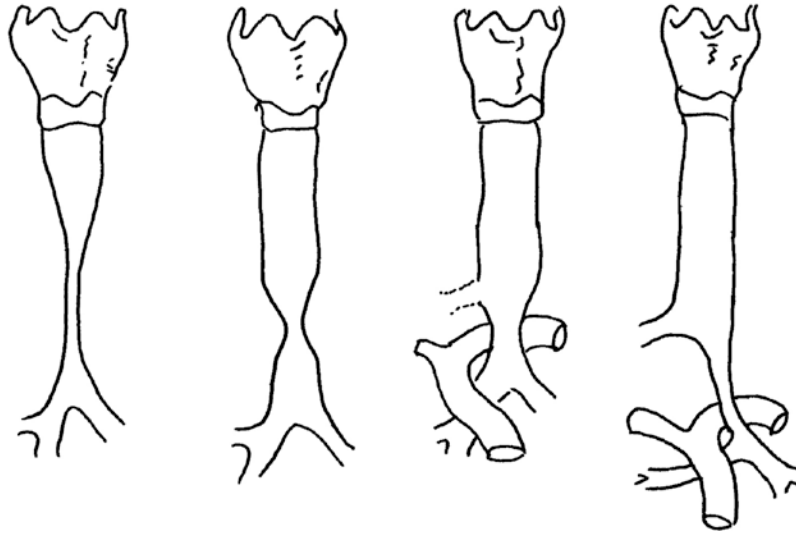

Fig. 20.6 Grillo classification of tracheal stenosis. Type I: Generalised hypoplasia. With the exception of the first 1–3 tracheal cartilages the trachea is diffusely narrow. Type II: Funnel stenosis. There is a progressive narrowing of the lower trachea. Type III: Segmental tracheal stenosis. The stenotic segment is frequently located below an anomalous tracheal bronchus supplying all or part of the right upper lobe. Type IV: Segmental tracheal stenosis associated with a bridging bronchus. A tracheal bronchus at the level of a normal carina supplies all or part of the right upper lobe. The airway continues as a stenotic bridging bronchus which supplies the remaining lobes of both lungs

Table 20.4 Anomalies associated with congenital tracheal stenosis

Congenital cardiac disease (particularly septal defects)
Pulmonary artery sling
Oesophageal atresia/tracheo-oesophageal fistula
Anorectal malformations
Renal anomalies
Radial aplasia
Downs syndrome
Crouzon syndrome
Pfeiffer syndrome

20.2.11.2 Associated Malformations

Over 50% children with congenital tracheal stenosis will have other malformations, most commonly cardiovascular [33] (Table 20.4). The association with an anomalous left pulmonary artery (pulmonary artery sling) is particularly important because successful management requires simultaneous correction of both the vascular and tracheal anomalies [36, 37]. The discovery of one necessitates a search for the other [38]. The anatomical relations between PA sling and tracheal stenosis are shown in Fig. 20.7.

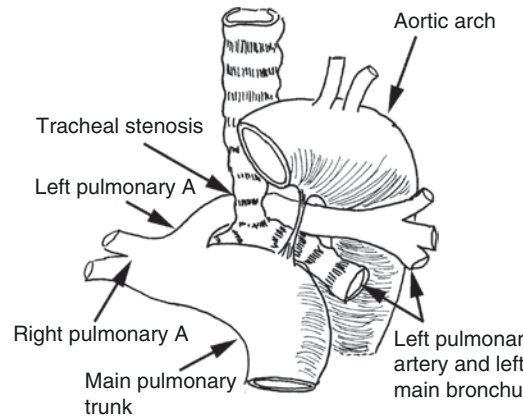

Fig. 20.7 Pulmonary artery sling diagram

The left pulmonary artery (LPA) arises from the posterior aspect of the right pulmonary artery. The LPA passes around the right bronchus and between the lower trachea and oesophagus en route to the hilum of the left lung [39]. Stenosis of the distal trachea and/or right main bronchus associated with complete tracheal rings is present in at least 50% of patients with pulmonary artery sling.

20.2.11.3 Assessment

Investigation and assessment of a child with congenital tracheal stenosis requires radiology and endoscopy. The tracheal air shadow may be abnormal on a plain chest X-ray but cross sectional imaging with contrast-enhanced CT or MR imaging is necessary to confirm the abnormality and determine the relationship of the airway to the major vessels (Fig. 20.8). Echocardiography should be performed to document intracardiac anomalies.

Bronchoscopy is an essential but potentially risky procedure in an infant with tracheal stenosis. Unintentional mucosal trauma may convert a stenotic airway into a critical airway and ideally this investigation should be postponed until radiological studies are complete. The aim of bronchoscopy is to confirm the extent and severity of the tracheal stenosis. Complete tracheal rings are relatively easy to identify (Fig. 20.9) provided the airway is not inflamed or oedematous.

20.2.11.4 Management

The management of congenital tracheal stenosis is complex and must be tailored to the patient [32, 33]. Successful results require a team familiar with the complexities of difficult airway management in young children. The outcome is invariably better if the stenosis is corrected before the airway becomes critical and the child is ventilator dependent. Medical treatment is futile, as is forcible dilatation. Tracheostomy has no role in the initial management of a child with tracheal stenosis.

Various surgical techniques have been used to correct congenital tracheal stenosis [40] (Table 20.5). Short segmental stenoses are potentially suitable for resection and direct anastomosis. In practice short segment tracheal stenosis is rare and there are better options for long segment stenoses. Approximately 25–30% of a child's trachea can be resected (roughly six rings) and followed by end-to-end anastomosis before excessive tension is likely to result in separation [41].

Pericardial patch tracheoplasty is relatively straightforward but the results are disappointing because of granulation tissue, malacia and recurrent stenosis. Cartilage graft tracheoplasty is technically difficult because of the inherent inflexibility of costal cartilage. Currently the technique used most widely to repair congenital tracheal stenosis is the slide

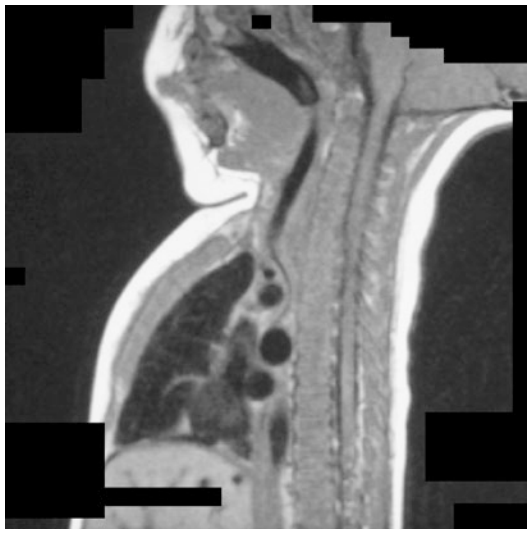

Fig. 20.8 MR scan showing long segment tracheal stenosis

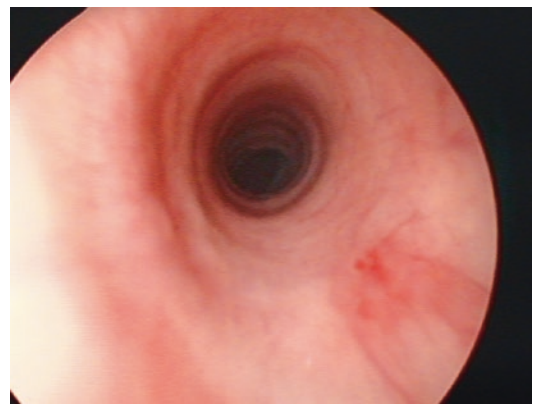

Fig. 20.9 Complete tracheal rings at bronchoscopy

Table 20.5 Surgical management of tracheal stenosis

Tracheal resection with end-to-end anastomosis
Patch tracheoplasty—cartilage, pericardium
Slide tracheoplasty
Tracheal transplantation procedures

tracheoplasty, first described by Goldstraw and colleagues in 1999 [42].

The stenotic segment of trachea is divided at the midpoint. The proximal and distal segments are incised vertically on opposite surfaces and then overlapped. Tracheal continuity is restored with a long oblique anastomosis (Fig. 20.10). The circumference of the trachea is effectively doubled and the stenotic segment shortened by half. Oxygenation is maintained during the procedure by either intubation of the distal airway through the operative field or by normothermic cardiopulmonary bypass. Follow up studies confirm good long term outcomes as the reconstructed airway grows with the child [43, 44].

The tracheal slide procedure can be adapted to treat complex variations in airway anatomy [45]. Tracheal stenosis associated with a pulmonary artery sling requires concomitant repair of both components [39]. The LPA is disconnected from

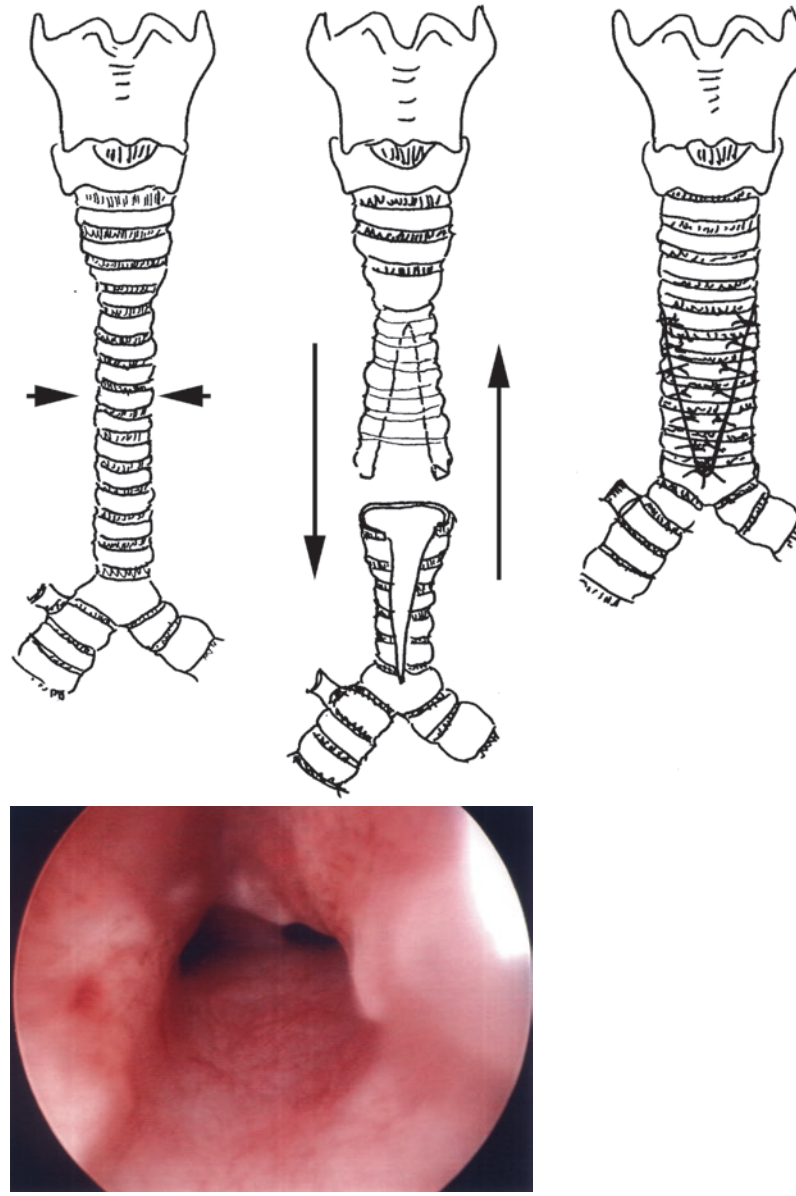

Fig. 20.10 Slide tracheoplasty including bronchoscopy photograph

the RPA and reimplanted into the main pulmonary artery at a site approximating the normal takeoff of the LPA. The associated tracheal stenosis is treated by a slide tracheoplasty (Fig. 20.11).

In recent years interest has focused on methods of tracheal replacement as a salvage procedure for children with inoperable recurrent stenoses. Attempts to reconstruct the trachea with prosthetic materials are doomed to failure [46]. Allogeneic transplantation of the trachea is not possible in the conventional sense because the trachea lacks the vascular pedicle necessary to permit reliable direct anastomosis to the recipient. Indirect revascularisation has been described by implantation of the allograft into the forearm of the recipient where it acquires a blood supply [47]. The graft is subsequently transplanted into the trachea as a free flap based on the forearm radial vessels. It seems doubtful that this procedure will ever be suitable for infants.

All or part of the trachea can be replaced with an acellular cadaveric homograft which then serves as a scaffold for host tissue ingrowth. Complication rates are high although a survival rate of 90% was reported recently [48]. It is possible to populate a cadaveric tracheal scaffold or a synthetic scaffolds with epithelial cells and chondrocytes in vitro derived from recipient stem cells and early clinical trials are underway in children [49, 50].

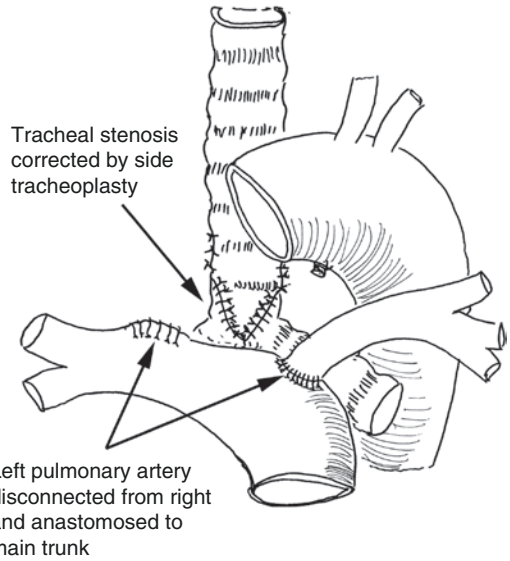

Fig. 20.11 Repair of a PA sling and associated tracheal stenosis

20.2.12 Tracheomalacia

The intrathoracic trachea dilates slightly during inspiration and narrows in expiration as a result of differences between intrathoracic and airway pressures during normal respiration. Tracheomalacia is characterised by a deficiency of the supporting cartilages which renders the airway susceptible to collapse [51, 52]. As a consequence changes in tracheal diameter during respiration increase substantially and the malacic segment collapses during expiration. This is most pronounced during forced expiration which occurs with crying or coughing.

20.2.12.1 Classification and Aetiology

Tracheomalacia most commonly affects the lower third of the trachea. Tracheomalacia can extend into the main bronchi (tracheobronchomalacia). Rarely the malacia is confined to the bronchi (bronchomalacia). Bronchomalacia is almost always associated with major cardiac anomalies [53, 54].

Tracheomalacia can be classified according to aetiology (Table 20.6). Primary tracheomalacia is caused by intrinsic abnormalities in the cartilage of the airway. Secondary tracheomalacia is the result of extrinsic compression of the airway,

Table 20.6 Classification of tracheomalacia

(A) Primary
1. In otherwise normal infants
2. In premature infants
3. Esophageal atresia and tracheo-esophageal fistula
4. Dyschonroplasias
(B) Secondary
1. Extrinsic compression
(a) Vascular rings
(b) Cardiac—enlargement of the pulmonary arteries
(c) Mediastinal masses (cysts, neoplasm, mediastinitis)
2. Prolonged mechanical ventilation

most commonly from vascular rings [55]. This distinction is convenient but simplistic. Cartilage first appears in the fetal trachea at about the seventh week of gestation. Differentiation of the paired aortic arches occurs at the same time and it seems reasonable to assume that malformations that result in vascular rings will also cause deformation of the developing tracheal cartilages during subsequent fetal development.

When tracheomalacia is seen in association with oesophageal atresia the tracheal cartilages are abnormal. Wailoo and Emery performed a detailed post-mortem study of the tracheas of 40 children born with oesophageal atresia [56]. The authors found abnormally short tracheal cartilages in 75% cases, resulting in poor support for the airway. More recent experimental work using the rat-adriamycin model has revealed a range of structural abnormalities in the tracheal cartilages, including bifid and fragmented cartilages [57].

Prolonged endotracheal intubation and tracheostomy predispose to tracheomalacia [58]. The mechanism is probably a combination of direct trauma from the tube and chronic airway inflammation. The tracheomalacia can be sufficiently severe in infancy to prevent decannulation of a tracheostomy.

20.2.12.2 Associated Conditions

Congenital cardiac abnormalities are found in up to 50% children with tracheomalacia [53]. Severe tracheomalacia is invariably associated with chronic lung disease and gastro-oesophageal reflux [59]. The latter is usually severe and many infants will require anti-reflux surgery.

20.2.12.3 Clinical Features

The symptoms and signs of tracheomalacia typically appear during the early months of life although they may be obvious from birth. Children with mild tracheomalacia may have no symptoms apart from a characteristic barking cough ('TOF cough'). Infants with more severe tracheomalacia will have intermittent stridor. Initially this is expiratory but as the tracheomalacia worsens this will become biphasic and signs of respiratory distress will appear. All the signs of tracheomalacia become more pronounced when the child is upset or suffering from a lower respiratory tract infection.

Severe episodes of airway obstruction may occur during feeding, especially with solids. This is most often seen in infants after oesophageal atresia repair although it also occurs in infants with a vascular ring. Passage of a food bolus down the oesophagus probably compresses the adjacent posterior wall of the trachea. The problem is exacerbated by an anastomotic stricture, oesophageal dysmotility and gastro-oesophageal reflux.

Hypoxia and cyanosis are characteristic of the "dying spells" seen in children with severe tracheomalacia. Usually these episodes are precipitated a bout of coughing or choking with a feed. Collapse of the trachea causes complete airway obstruction. The apnoeic child loses consciousness, collapses and becomes cyanosed and bradycardic. Once respiratory effort ceases the airway will reopen but serious hypoxia and cardiac arrest may occur if resuscitation is delayed.

20.2.12.4 Diagnosis and Assessment

The initial assessment of a child with suspected tracheomalacia is based on confirmation of the diagnosis and assessing the extent and severity of the disease (Table 20.7). The cause of the tracheomalacia may be obvious (e.g. oesophageal atresia) but if a child being investigated for stridor is found to have tracheomalacia then the underlying cause needs to be established (e.g. vascular ring).

Plain radiographs are of limited value. A barium swallow can be useful, particularly for the assessment of OA-related tracheomalacia. Changes in tracheal calibre during swallowing

Table 20.7 Investigation and assessment of tracheomalacia

Chest X-ray
Barium swallow with fluoroscopy
Airway endoscopy
CT/MR
24-h pH study
Pulmonary function testing with flow-volume loops
Bronchography
Angiography

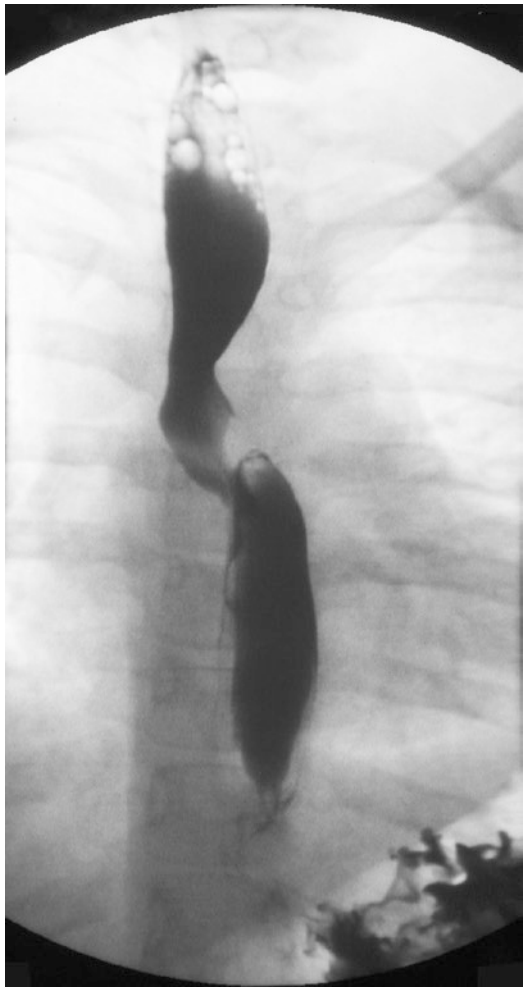

Fig. 20.12 Barium swallow showing the classical appearance of a double aortic arch with impressions on both sides of the oesophagus

can be marked and this is best seen on lateral screening. Gastro-oesophageal reflux, anastomotic stricture and oesophageal dysmotility, which all exaggerate tracheomalacia, may be identified.

An upper GI contrast study will often be the first clue to a vascular ring. The commonest vascular ring is a double aortic arch. This can produce characteristic indentations on a column of contrast in the oesophagus in the AP and lateral projections (Fig. 20.12).

Endoscopic examination of the airway is necessary to confirm the diagnosis of tracheomalacia and assess the extent and severity of the airway

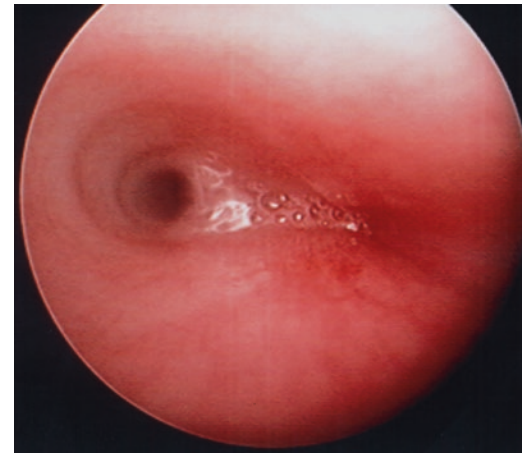

Fig. 20.13 Appearances of tracheomalacia at bronchoscopy

collapse [60] (Fig. 20.13). The examination should be performed under general anaesthesia with spontaneous respiration using a technique that minimises airway obstruction. The best methods are either fibreoptic bronchoscopy through a laryngeal mask or tracheoscopy using a Hopkins rod telescope and an operating laryngoscope.

In the 1960s Wittenborg et al. used fluoroscopy to study changes in tracheal diameter in healthy children [61]. During quiet breathing the airway calibre remained constant but crying or struggling reduced the diameter of the trachea by 50–80% in normal children. Collapse involving >50% of the diameter of the trachea during quiet breathing is abnormal. The majority of infants with symptomatic tracheomalacia will have 75–100% collapse.

Dynamic CT and MR are useful imaging techniques for suspected tracheomalacia [62, 63]. In cooperative children images can be acquired with breath-holding at full inspiration and end expiration to demonstrate changes in airway calibre and cine CT can be used to acquire images during phasic respiration. Virtual bronchoscopy is a novel CT-based imaging technique that allows three-dimensional evaluation of the airway although the quality of the images obtained in children currently lack sufficient resolution to replace conventional bronchoscopy [64]. At present none of these techniques is able to distinguish between dynamic

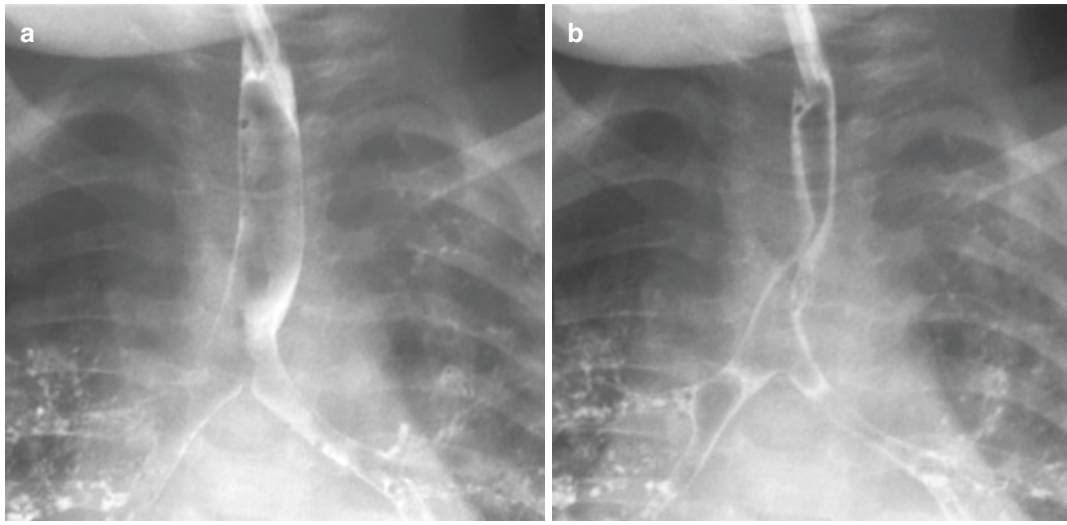

Fig. 20.14 Appearances of tracheomalacia during bronchography (**a**) inspiration (**b**) expiration

or static narrowing reliably and consequently bronchoscopy and/or bronchography remain essential investigations.

Bronchography involves injection of small volumes of water-soluble contrast into the trachea under fluoroscopic guidance [65]. The technique is capable of showing both structural abnormalities and segmental airway malacia. Images can be obtained with spontaneously respiration under anaesthesia with different levels of continuous positive airway pressure (CPAP) to determine the minimum pressure required to maintain airway patency (Fig. 20.14).

20.2.12.5 Treatment

When tracheomalacia is secondary to mediastinal pathology this should be treated. Mild to moderate tracheomalacia per se may not require any specific treatment although respiratory infections should be treated promptly. The trachea becomes more stable as the child grows and symptoms will usually abate during the first 2 years of life.

Untreated severe tracheomalacia in infancy is life threatening. In the past the mainstay of treatment was tracheostomy. Extended tracheostomy tubes were necessary to stent the distal trachea. Surgical options for tracheomalacia include aortopexy, segmental tracheal resection and stenting.

Aortopexy involves partial excision of the thymus to create a space anterior to the aortic arch. The aorta is then pexed to the back of the sternum without disturbing the tissue plane between the vessel and the trachea [66]. Intraoperative bronchoscopy is useful to ensure sutures are placed in the correct region of the aortic root and arch to provide optimum elevation of the malacic segment of trachea [67]. The procedure can be performed through a left anterior thoracotomy but safe exposure is more easily obtained through a partial upper sternotomy [68]. Apposition of the aorta and the under surface of the sternum lifts the anterior wall of the trachea forward widening the antero-posterior dimension of the airway and reducing the tendency to collapse (Fig. 20.15).

Aortopexy is not always successful and around 10% of infants will require further treatment [69]. Resection of the malacic segment is occasionally curative if satisfactory improvement in the lumen cannot be achieved by aortopexy but tracheostomy and long-term ventilation may be necessary. Procedures to increase the intrinsic rigidity of the tracheal wall by fashioning rings out of costal cartilage or wrapping the malacic segment in synthetic mesh to provide external splintage have been tried but the results are generally unsatisfactory.

Endoluminal metallic stents have been used to palliate malignant airway obstruction in adults

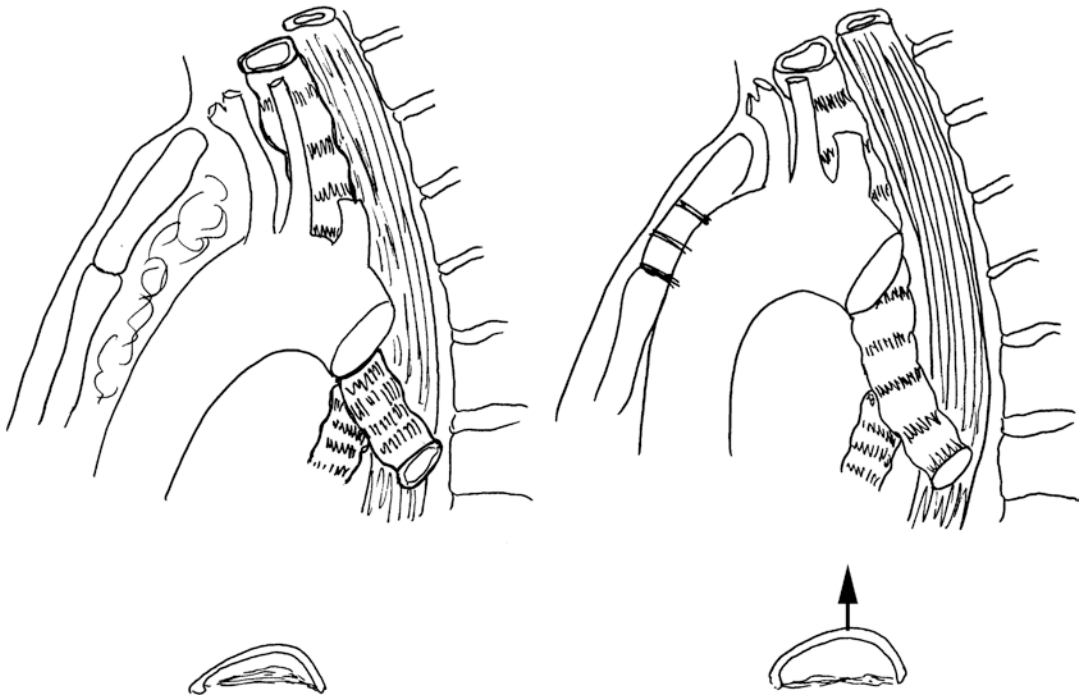

Fig. 20.15 Principles of aortopexy

since the 1980s. Bugmann et al. stented a malacic airway in an infant after cardiac surgery in 1994 [70]. Expandable metallic stents are relatively straightforward to insert using a combination of bronchoscopy and fluoroscopy. The stent is deployed over a balloon catheter which is inflated in the airway. The expanded stent is thus lodged inside the airway (Fig. 20.16). Stents can be deployed in the trachea and main bronchi. The lattice of the stent can be placed over a lobar bronchial orifice without compromising ventilation of the lung.

From a purely mechanical perspective stents are undoubtedly effective at supporting the malacic airway. However, complications from airway stenting in children are relatively common. Unless the stent is firmly impacted in the wall of the airway it is liable to migrate with loss of airway support. Airway stents do not become epithelialised in the way endovascular stents do and, as a consequence, excite the formation of granulation tissue [71]. Granulation tissue in the airway is liable to cause obstruction and bleeding. Stents can, and do, erode through the wall of the airway into adjacent large blood vessels [72]. These complications are important in the context of tracheomalacia because it is likely that the stent will become redundant as the child grows. Removal involves grasping the stent and twisting to

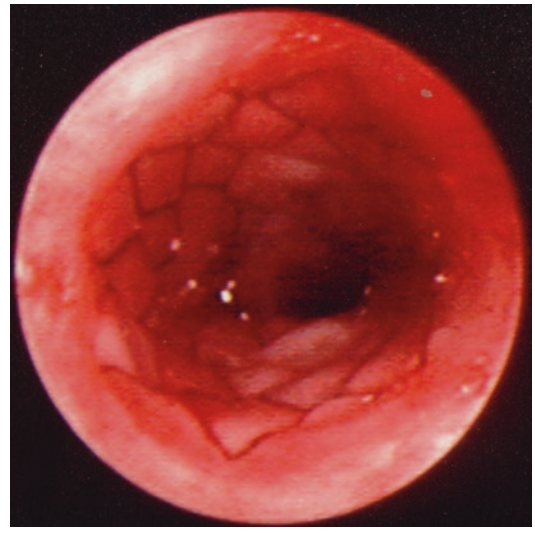

Fig. 20.16 Palmaz stent deployed in the trachea

disimpact the lattice from the wall of the airway and then retrieving the crumpled stent through a rigid bronchoscope. This manoeuvre is invariably associated with brisk bleeding from the trachea and risks loss of control of the airway. Fatalities have been recorded [73]. There is no data on the long-term consequences of stenting of the paediatric airway. Biodegradable stents have been developed for endoluminal use in the airway but these remain at an experimental stage [74].

The relationship between gastro-oesophageal reflux (GOR) and tracheomalacia is incompletely understood. Chronic respiratory disease in infancy is invariably associated with GOR as a result of increased work of breathing. Gastro-oesophageal reflux frequently exacerbates chronic respiratory disease. The mechanism is less clear but probably includes repeated microaspiration and vagal-mediated responses to acid secretions in the pharynx and oesophagus causing reflex alterations in bronchial tone. Aortopexy and fundoplication are frequently necessary to control symptoms in infants with oesophageal atresia and severe tracheomalacia and the main difficulty is deciding which operation to perform first [75].

20.3 Congenital Malformations of the Chest Wall

20.3.1 Embryology

In the future trunk region the paraxial mesoderm forms a series of block-like condensations, the somites, in a cranio-caudal progression of 3–4 somites per day from day 20 to day 30 of embryogenesis. These somites are the progenitors of the axial skeleton, trunk musculature, trunk dermis, endothelial cells and meninges of the spinal cord. The ventromedial somite undergoes an epithelial to mesenchymal transition into the sclerotome which develops into the vertebrae and ribs. The lateral portion of the sclerotome forms the vertebral transverse process and ribs, whilst the medial portion forms the vertebral body, arch and spine [76].

Small lateral mesenchymal condensations form the costal processes. Concomitantly, transverse processes grow laterally along the dorsal side of each costal process. In the thoracic region the distal tip of the costal processes lengthen to form the ribs. This process of lengthening of the thoracic costal processes begins on day 35 with the first seven ribs connecting anterior medially via the costal cartilages to the sternum by day 45. The cartilaginous precursors subsequently undergo endochondral ossification. Primary ossification centres arise in the region of the rib angle around the sixth week and progress distally along the ribs. Secondary ossification centres arise in the head and tubercles of the ribs but not until puberty [76].

The sternum develops from the lateral mesodermal plate. In the sixth week of development cells begin to migrate from parallel bars of condensed mesoderm in the lateral ventral chest. These sternal bands join first at the cephalic end at around the seventh week, progressing caudally to fuse along their length by the tenth week. The rate of fusion slows caudally. At around the same time the manubrium sternum arises separately from a cranial condensation of mesoderm, the presternum, which is associated with the developing shoulder girdle. The fused sternal bars join with the presternum cranially and the rib ends laterally. The mesoderm of the sternum chondrifies soon after migration is complete. Chondrification occurs as a continuous process whereas ossification arises from a series of ossification centres, with ossification in the manubrium and upper sternum in the 6 month of fetal life, the mid sternum in the seventh month and the lower sternum at around 1 year of post natal age. The xiphoid process at the lower pole of the sternum ossifies much later, between 5 and 18 years of age. Frequently the xiphisternum remains bifid. Complete fusion of the sternal ossification centres is not complete till after puberty [77–79].

20.3.2 Sternal Cleft

Sternal clefts are rare congenital anomalies. Early in gestation the lateral sternal primordia fail to fuse [80, 81]. The incidence is uncertain but sternal clefts are sufficiently rare to be reported in the literature as solitary or small

series case reports. Sternal clefts accounted for 0.15% of all thoracic wall anomalies seen over a 25 year period in one large paediatric thoracic practice [82]. Sternal clefts are reported to have a higher incidence in females, frequently quoted as a 2:1 female to male ratio [83].

The classical sternal cleft is a U or V shaped separation of the sternal bars to the level of the third or fourth costal cartilage. However, sternal clefts may be partial or complete and partial clefts may affect the cranial or the caudal sternum. Upper sternal clefts are typically isolated anomalies whereas lower sternal clefts are frequently associated with other anomalies, as classically seen in the Pentalogy of Cantrell [84]. Ectopia cordis is the protrusion of the heart out of the thoracic cavity in association with a sternal defect. In simple sternal clefts the heart remains in its normal position despite the overlying sternal defect. This displacement of the heart is very difficult to correct as attempts to reduce the heart result in kinking of the great vessels and disruption of blood flow. Shamberger and Welsh proposed a classification for clefts depending on the presence or absence of ectopia cordis [78, 85, 86] (Table 20.8).

The aetiology of sternal cleft deformity is unknown. A familial predisposition has not been described. Excessive alcohol ingestion during pregnancy and vitamin B_{12} deficiency have been proposed but there is no clear evidence to support this association [78]. A gene mapped to Xq25–26 has been implicated in the process of midline ventral fusion, being associated with the combination of sternal fusion, diaphragmatic, cardiac and ventral abdominal wall defects. Variable penetration giving rise to a lethal phenotype in males could explain the female predominance [87–89]. Embryological studies in mice have suggested a role for Hox genes, specifically HoxB4, in ventral fusion of this region of the thorax [90].

Table 20.8 Classification of sternal defects

Thoracic ectopia cordis
Thoracoabdominal ectopia cordis
Cleft sternum

Sternal clefts can be associated with craniofacial haemangiomas. The PHACE syndrome comprises **P**osterior fossa brain malformations, capillary **H**aemangiomas, **A**rterial malformations (especially on the carotid and vertebral arteries), Cardiac malformations (including the aorta and vena cava) and **E**ye abnormalities [91]. Sternal clefts and other midline raphe anomalies are seen in some of these patients and the acronym has been extended to PHACES syndrome. This has been reported to have an 8:1 female preponderance [92, 93].

Isolated sternal cIefts usually present at birth as a soft bulging mass in the midline with paradoxical movement on respiration and/or obvious cardiac pulsation. They are typically asymptomatic. Isolated sternal clefts can be identified on antenatal screening ultrasound [93]. Clefts associated with other midline anomalies as in Pentalogy of Cantrell have been detected in the first trimester of pregnancy by ultrasound [94, 95].

The indications for repair of a sternal cleft are shown in Table 20.9. Repair is best achieved in the neonatal period when the chest wall is most compliant because compression of the heart and lungs following closure is minimal [82, 96–98]. Correction of the sternal cleft may be deferred to allow concurrent repair of cardiac anomalies. However after about 3 months of age the chest wall becomes more rigid and this complicates repair [82, 96].

Preoperative assessment should include an echocardiogram and chest X-ray. A contrast enhanced CT scan of the thorax will demonstrate the extent of the bony lesion and may be useful to exclude vascular anomalies. If the child shows features of PHACES syndrome MRI of the head is necessary to exclude intracranial anomalies [91, 92].

Sternal clefts are best approached through a midline incision over the defect. The pectoralis

Table 20.9 Indications for repair of sternal clefts

Bony protection of the mediastinal structures
Improve respiratory dynamics by preventing paradoxical movement of the mediastinum with respiration
Cosmesis

muscles are reflected off the sternum. The edges of the defects are freed from the underlying pleura and pericardium. The edges of the sternal bars may be freshened by sharp dissection with a scalpel. Approximation of the sternum in an incomplete cleft is facilitated by excision of a wedge from the intact part of the sternum, particularly in U-shaped defects. The sternal bars are progressively apposed with a series of non-absorbable sutures around the sternum, through the medial intercostal spaces. This should be performed gradually allowing time to verify that cardiac and respiratory function is not being compromised [82, 96–99]. The presence of a distal sternal bridge of cartilage or bone makes primary repair more difficult [99].

In older children and adolescents surgical repair requires additional measures as the thoracic cavity is less compliant and the likelihood of cardiac and pulmonary compression is greater. A variety of approaches have been described. Sabiston proposed performing sliding chondrotomies, with bilateral oblique incisions through the costal cartilages to allow midline approximation of the sternal halves [100]. Alternatively, the sternal cartilages may be divided in half in the anterior posterior plane along their lateral border and the anterior portions then rotated medially and sutured together to cover the defect (*the door wing plasty*) [101–103]. Acastello et al. described closure of the defect with partial resection of the first three costal cartilages and disruption of the sternoclavicular junction to permit mobilization of the sternal bars for approximation [82]. However, disarticulation of the sternoclavicular joints gives a poor cosmetic result and risks chronic shoulder instability. Division of the medial third of the clavicles is a better alternative [103]. Various prosthetic grafts such as Teflon, polypropylene, silicone, and titanium have been used to cover sternal defects in adults. These materials have been used to cover sternal clefts in childhood with varying results [104]. In general the outcome of a sternal cleft is determined by the presence of other associated anomalies. Excellent long-term functional and cosmetic results are reported following repair of isolated sternal clefts [82, 102].

20.3.3 Pentalogy of Cantrell

Cantrell first described a syndrome of congenital defects involving the abdominal wall, sternum, diaphragm, pericardium, and heart in 1958 [84] (Table 20.10). Cantrell's pentalogy is a rare with an estimated incidence of 5.5 per million live births [87]. Not all patients are born with the full pentalogy and a revised classification was suggested by Toyama depending on the severity of the deformities [105]. A variety of other anomalies have been reported in association with Cantrell's pentalogy including cleft lip and/or palate, encephalocele, hydrocephalus, limb defects and abdominal organ defects such as agenesis of the gallbladder and polysplenia [106].

Cantrell proposed that failure of growth of the lateral plate mesoderm resulted in non-fusion of structures of the abdominal wall and ectopia cordis [84]. Other authors have suggested that amniotic bands prevent normal descent of the heart into the thorax which consequently prevents closure of the thoracoabdominal wall [107].

Van Hoorn et al. reviewed the literature in 2008 and found 37 of 58 patients with Cantrell's pentalogy had been terminated or died within days of birth. This 36% survival rate is likely to be an overestimate and the long term outcome of these patients is unclear [106].

Pentalogy of Cantrell can be detected as early as 12 weeks on antenatal scan [94, 95]. Zidere and Allan reported evolution of three cases during the course of fetal development with reduction of the heart into the chest after

Table 20.10 Cantrell's pentalogy

Exomphalos (midline supraumbilical abdominal wall defect)
Lower sternal defect
Anterior diaphragmatic defect
Pericardial defects (including ectopia cordis)
Congenital cardiac anomalies
VSD (100%)
ASD (53%)
Tetralogy of Fallot (20%)
Ventricular diverticulum (20%)

20 weeks and resolution of a pericardial effusion. This highlights the difficulty of antenatal counselling for the parents [95].

Following delivery and stabilisation an echocardiogram should be performed to look for cardiac malformations as this is the main determinant of outcome. Once the decision is made to proceed with treatment, the ventral abdominal wall, sternal, pericardial and diaphragmatic defects should be closed in the early neonatal period. Corrective or palliative surgery for the cardiac malformations can be performed subsequently when appropriate clinically.

Cervical ectopia cordis is universally fatal. There are occasional reports of survivors of thoracic ectopia cordis but in the majority of cases attempts to reduce the heart into the thoracic cavity kinks the great vessels and causes cardiac failure. The heart is covered by the exomphalos membrane in thoracoabdominal ectopia cordis and can generally be reduced into the mediastinum.

Correction is attempted by first achieving skin cover, then reducing the heart in a staged procedure, and finally repairing the sternal defect [108].

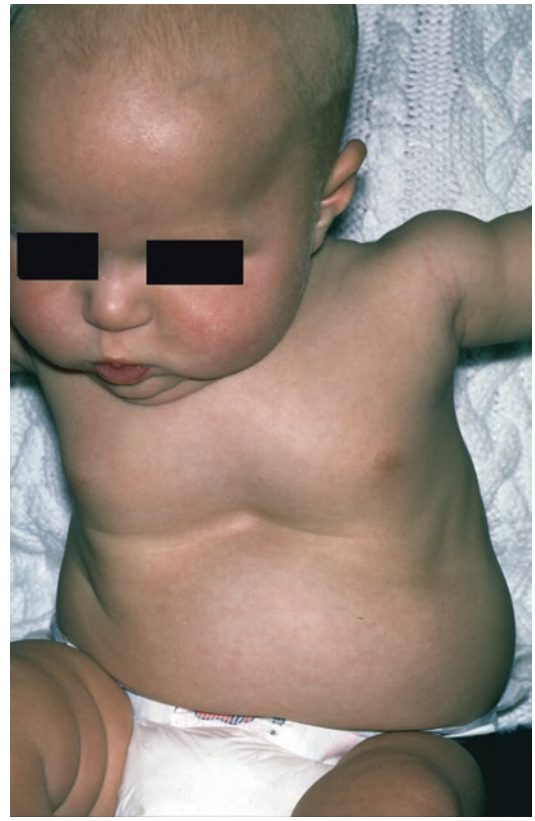

Fig. 20.17 Neonatal pectus excavatum

20.3.4 Pectus Excavatum

Pectus excavatum is a depression of the anterior chest wall, most pronounced in the region of the lower sternum. Pectus excavatum is typically symmetrical although asymmetric deformities are seen. Excavatum deformities affect approximately 1% of the population and are four times commoner in boys than girls. A family history of chest wall deformity can be elicited in up to 45% cases [109]. Racial variation is documented, pectus excavatum being much commoner in white Caucasians (38 per 10,000 live births) than those of Afro-Caribbean descent (7 per 10,000). A study of 34 families showed pedigrees suggestive of a wide variety of inheritance patterns [110].

Pectus excavatum is rarely present at birth and most commonly develops during childhood with the deformity progressing, often markedly, during puberty. Where pectus excavatum is noticed in infancy this is usually secondary to either airway obstruction (e.g. laryngomalacia) (Fig. 20.17) or connective tissue disorders (e.g. Ehlers Danlos syndrome) [109]. If the deformity is secondary to airway obstruction it will often resolve as the airway disease improves.

Childhood interstitial lung diseases such as the surfactant deficiencies result in pectus excavatum in all patients surviving beyond infancy [111]. The EPICure study following survivors of extreme prematurity (26 weeks gestation at birth) found a statistically significant increase in the incidence of pectus excavatum at age 11 years compared to a control population (17% versus 2%) [112].

Pectus excavatum in early childhood is an asymptomatic deformity. The deformity causes significant anxiety to parents and children and can markedly affect self confidence as children grow older. The traditional approach to correction of pectus excavatum was described by Ravitch. The

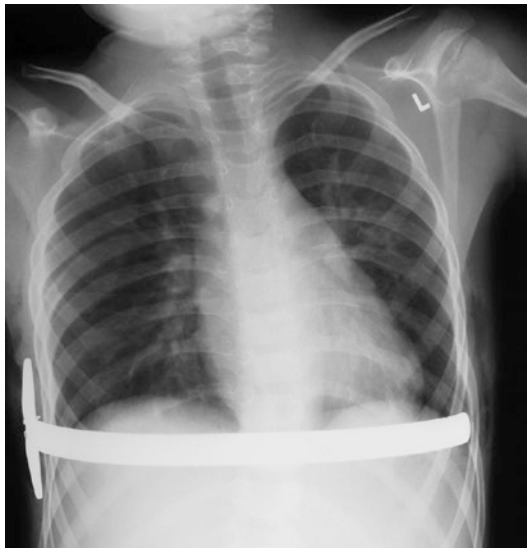

Fig. 20.18 Nuss repair pectus excavatum

anterior chest wall is exposed via a midline or transverse sub-mammary incision. The pectoral muscles are reflected. The deformed costal cartilages are removed by sub-perichondral resection followed by a sternal osteotomy to correct the sternal depression [113–115]. More recently Nuss described an alternative approach to the correction of pectus excavatum which has been widely adopted, the minimally invasive repair of pectus excavatum (MIRPE) [116]. This minimally invasive technique involves the placement of a curved metal bar, appropriately sized and shaped for the patient, through the chest, deep to the sternum in the region of the maximal depression exerting a continuous pressure, the sternum gradually becoming fixed in this new position (Fig. 20.18). The bar is removed after approximately 2 years [117, 118].

The ideal age for correction is 7–12 years whilst the chest remains malleable. Many patients present in later puberty after progression of the deformity and when they become more self-aware. There is no indication for correction of pectus excavatum in the neonate and indeed an acquired asphyxiating thoracic dystrophy has been described following correction in very young children using the Ravitch technique, ascribed to overzealous cartilage resection disrupting subsequent thoracic growth [119, 120].

20.3.5 Pectus Carinatum

Pectus carinatum is an anterior protuberance of the anterior chest wall. Pectus carinatum is not seen in infancy but tends to occur in older childhood and progress during the pubertal growth spurt. There is a four to one predominance in males and a family history of deformity can be elicited in 6.7% of cases [110]. No clear aetiological factors have been identified.

The deformity of pectus carinatum is quite variable. The protuberance of the sternum may be symmetrical or there may be torsion of the sternum resulting in an asymmetric protuberance with relative depression of the costal cartilages on one side and prominence on the other. Pectus carinatum is corrected using the Ravitch procedure with subperichondral resection of the involved costal cartilages and sternal osteotomy, in this case wedged open to create depression of the distal sternum [121]. Correction of torsion of the sternum can be challenging. Pectus carinatum is frequently associated with depressions in the lateral lower chest that persist after correction of the central deformity.

20.3.6 Jeune's Syndrome (Asphyxiating Thoracic Dystrophy)

In 1955 Jeune's described a familial asphyxiating thoracic dystrophy characterised by a small thorax and short limb dwarfism [122–124]. Jeune's syndrome affects 1 in 100,000 to 300,000 live births, with a similar incidence in males and females [125]. The cause is uncertain but familial studies have suggested an autosomal recessive inheritance pattern. A link with a locus at chromosome 15q13 has been described in some cases [126]. More recent reports suggest an association with the IFT80 gene on chromosome 3q24 which encodes an intraflagellar transport protein which is essential for the development of motile and sensory cilia [127].

The phenotype of Jeune's syndrome is variable but the chest is always involved with short horizontal ribs. Respiratory involvement is universal

but of severity from a rapidly fatal respiratory distress to minimal respiratory impairment. Restricted chest expansion causes alveolar hypoventilation. It is unclear whether there is also lung hypoplasia. Other skeletal features include dwarfism and short phalanges (thoracic-pelvic-phalangeal dystrophy). The retina, pancreas, liver and kidneys may also be involved [128]. Mild forms of Jeune's syndrome are associated with progressive renal failure. The diagnosis of Jeune's syndrome is confirmed by the classical X-ray appearances of short horizontal ribs, square iliac wings and a horizontal acetabular roof with a medial spur. Jeune's syndrome may be detected antenatally by the dimension and shape of the fetal chest [129].

A variety of surgical approaches have been tried to relieve the chest wall restriction and improve respiratory function. Median sternotomy with graft interposition has been performed to enlarge the thoracic cavity [130]. Lateral thoracic expansion has also been tried [131, 132] and, more recently, the vertical expandable prosthetic titanium rib procedure (VEPTR) [133, 134].

The vertical expandable prosthetic titanium rib (VEPTR) was developed by Dr. Robert Campbell in 1989 (Synthes Spine, USA) to treat patients with hypoplastic chest walls causing respiratory compromise. The use of this technique to treat Jeune's syndrome involves bilateral insertion of high radius curvature titanium prosthetic devices, as a staged procedure, the contralateral side being operated on approximately 2 months after the first thoracotomy. A customised device is made for each patient based on the cross-sectional imaging and planned surgery. A thoracotomy incision is made extending anteriorly to the region of the seventh/eighth intercostal space and myocutaneous flaps raised. The chest wall is mobilised by dividing the ribs anteriorly at the costo-chondral junction and posteriorly in the region of the transverse process. Usually the third to ninth ribs are divided. The vertical expandable prosthesis is attached to the 2nd and 10th to 12th ribs which have not been divided and then the free lateral rib segments are fixed to the prosthesis by K-wires, distracting the mobilised segment of chest wall laterally. The VEPTR device is then lengthened approximately every 6 months depending on the growth and well being of the child. The central segment of the prosthesis requires replacement approximately every 3 years depending on the lengthening achieved [133–137].

A review of 19 patients who had undergone VEPTR thoracic expansion for Jeune's syndrome found that four patients had died in the first year after surgery, all related to disease severity rather than surgery. Due to the rarity of the condition it is impossible to perform a randomised controlled trial of treatment. There is some suggestion of improved survival following surgery but this may reflect improvements in the general care of patients with Jeune's syndrome rather than to the effects of surgery [133].

There is anecdotal evidence that the respiratory restriction improves with age. Frequent respiratory tract infections in infancy become less problematic as the child grows. However, there is little documented evidence to support improvement in pulmonary function tests [125, 138] and indeed other authors dispute that any improvement occurs [139]. The classic form of Jeune's syndrome with severe respiratory involvement is almost universally fatal within the first year of life [133]. The long-term results of newer surgical techniques are awaited. Outcomes reported in recent series have been better than previously, with or without surgery [138].

20.3.7 Ellis-van Creveld Syndrome

Ellis-van Creveld syndrome (chondroectodermal dysplasia) is a further subtype of the short rib dysplasia syndromes. The cardinal features are short stature, short ribs, polydactyly, and dysplastic fingernails and teeth. Heart defects, especially abnormalities of atrial septation, occur in about 60% of cases [140–142]. The diagnosis is confirmed by the characteristic radiographic appearances of the slanting proximal tibial plateau and the carpus with abnormal size and shape of the carpal bones. The diagnosis may be suspected antenatally by the presence of short ribs, polydactyly and cardiac malformations [140].

Approximately 150 cases have been reported world-wide. The condition is inherited as an autosomal recessive trait with variable expression. Mutations of the EVC1 and EVC2 genes, located on chromosome 4p16, have been identified [140, 143].

The prognosis depends on respiratory function in infancy which relate both to the narrow thorax and cardiac malformations. The respiratory symptoms are often mild compared to Jeune's syndrome with most reported cases surviving to adulthood. Congenital cardiac malformations are the major determinant of survival [140].

20.3.8 Jarcho-Levin Syndrome

Jarcho-Levin syndrome is a rare genetic disorder characterised by multiple vertebral segmentation and formation defects affecting the majority of the thoracic and lumbar vertebrae. Two subtypes are recognised, spondylothoracic dysplasia and spondylocostal dysostosis.

Spondylothoracic dysplasia has an autosomal recessive inheritance pattern. The ribs are all fused posteriorly at the costovertebral junctions producing a small thorax with a typical "crab like" appearance on radiograph. Mortality from respiratory failure is high with 44% of cases dying in the first year in one recent series [144].

Rib involvement in spondylocostal dysostosis is asymmetrical and less severe. Multiple vertebral segmentation anomalies with unilateral rib malformations lead to a progressive thoracic scoliosis. Inheritance can be autosomal dominant or recessive [144]. Respiratory involvement is less severe and the long term prognosis are correspondingly better than spondylothoracic dysplasia [133, 144].

20.3.9 Poland's Syndrome

In 1841, Poland described a "deficiency of the pectoral muscles" in the cadaver of a convict who had reputedly been unable to draw his arm across his body. Poland's syndrome is a constellation of congenital defects comprising a unilateral deficiency of the pectoral and chest wall muscles associated with ipsilateral syndactyly [145]. The right side of the body is involved in 60–75% of patients [146].

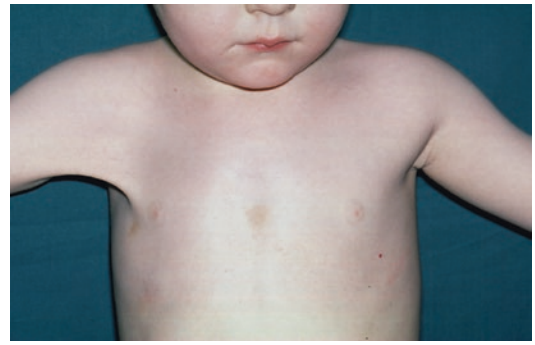

Fig. 20.19 Poland's syndrome

The clinical manifestations are variable but absence of the sternal head of pectoralis major muscle is a constant feature (Fig. 20.19). The serratus anterior and latissimus dorsi muscles may be absent or under-developed. Abnormal breast development is seen in about one third of girls, ranging from mild hypoplasia to complete absence of the breast and nipple. In most patients the chest is sunken anteriorly due to hypoplasia of the third to fifth or more rarely second to fourth costal cartilages and anterior ribs. This may lead to an asymmetrical pectus carinatum deformity in later childhood [147]. In approximately 15% of patients there is aplasia of the upper costal cartilages causing a more severe chest deformity with lung herniation [147]. Significant reduction in pulmonary function has been documented in association with lung herniation [148]. Dextroposition of the heart is reported in association with left-sided involvement.

The incidence of Poland's syndrome varies from 1 in 7000 to 1 in 100,000 and the condition is 2–3 times more common in males than females [149]. The phenotype is variable and it is extremely rare for all features to be present in one patient. Isolated breast hypoplasia and absence of the pectoralis major muscle is relatively common in patients presenting for breast augmentation. The aetiology is believed to be due interruption of the embryonic blood supply in the subclavian

artery around the sixth week of development as the upper limb bud is forming [150–152].

Surgery for the thoracic components of Poland syndrome varies from cosmetic procedures for breast hypoplasia or chest wall deformity to chest wall reconstruction to improve lung function and protect the heart and lung [146, 149]. The shoulder girdle muscle deficiency is generally well compensated for. Chest wall defects due to rib aplasia may be corrected using split subperiosteal rib grafts or prosthetic mesh. Myocutaneous latissimus dorsi flaps are the most widely used method for reconstructing the soft tissue contours of the chest wall, combined with breast implants in female patients. If chest wall reconstruction is indicated in childhood, soft tissue reconstruction should be deferred until after puberty. In adults these procedures may be combined as a single stage procedure [146, 148, 149, 153]. Preoperative assessment with CT or MRI is important as the degree of soft tissue involvement particularly, can be underestimated by simple clinical examination [154].

Small children with severe deformity may require early surgery to improve respiratory function or manage rare associated anomalies such as ectopic liver tissue [148, 153]. Gore-Tex™, Prolene™ mesh and titanium mesh have all been used and must be sutured taut to the margins of the defect in order to correct the flail segment effect of the deficient ribs. Such repairs carry the dual problems of potential prosthetic infection and the need for revision as the child grows. There is little published data on the long-term outcome of patients requiring early surgery.

In the majority of patients the problem is cosmetic and repair can wait until after puberty when a combined operation to correct the bony and soft tissue deficiencies is possible. Depending on the size of the defect and development of the ribs adjacent to the defect, the anterior portion of adjacent ribs can be split along their length leaving the deep part in situ and the superficial segments moved as split rib grafts to fill the deficient rib spaces. Where there is an associated pectus carinatum deformity requiring resection of the anterior portions of the contralateral ribs, the resected fragments can be used to bridge the defect. In the absence of suitable ribs for grafting a prosthetic mesh repair is required. Contralateral rib grafts can be harvested but this is rarely done unless there is a specific indication for surgery to the contralateral chest wall. Grafts must be securely attached to the rib end laterally and sternum medially to prevent displacement. Mesh may be used to stabilise the repair in which case the rib grafts should be sutured to the mesh in addition to the margins of the sternum and defective ribs [146, 149].

Myocutaneous latissimus dorsi flaps can be used to provide both skin and soft tissue to reconstruct the anterior chest wall and create the anterior axillary fold. A prosthetic breast implant is often necessary in girls. Not infrequently the ipsilateral latissimus dorsi muscle is also deficient in which case free flaps from the contralateral latissimus dorsi or gluteal muscles have been used [146, 147, 149].

20.4 Acquired Chest Wall Deformity Secondary to Neonatal Thoracic Surgery

Long term follow up studies of patients undergoing neonatal thoracic surgery for conditions such as oesophageal atresia or congenital diaphragmatic hernia frequently fail to comment on chest wall morbidity resulting from these procedures. In the 1960s Freeman and Walkden noted two children with marked shoulder elevation attending for follow up following thoracotomy for repair of oesophageal atresia [155]. They traced 24 other patients, 19 of whom also reported shoulder deformities. The authors reviewed the variations in surgical approach and stressed the importance of preserving the function of the serratus anterior and lastissimus dorsi muscles to minimise complications. In 1985 Jaureguizar published a long term follow up study of 89 patients who had undergone a right thoracotomy for repair of oesophageal atresia. Twenty-nine of the patients (33%) had significant musculoskeletal deformities [156] (Table 20.11).

Table 20.11 Late complications of thoracotomy in the neonatal period

Elevation of the shoulder/winged scapula
Chest wall asymmetry
Rib fusion
Scoliosis
Tethered scars limiting shoulder mobility
Breast disfigurement

Table 20.12 Factors contributing to post thoractomy deformity

Congenital vertebral anomalies
Nature of incision
– Site
– Muscle cutting/splitting
– Rib resection
– Nerve injury—denervation of serratus anterior
– Tethering of scar
Multiple thoracotomies
Anastomotic leak causing pleural/mediastinal sepsis

Reviewing the experience of treating oesophageal atresia at Melbourne Children's Hospital, Chetcuti et al. identified a variety of risk factors that contributed to a 35% incidence of chest wall deformities in 285 patients [157, 158] (Table 20.12). Deformities identified included scoliosis, anterior chest wall asymmetry and breast deformities. Congenital vertebral anomalies were present in 19% of the patients (Fig. 20.20) and in this group the incidence of chest deformity increased to 42%. Denervation of the serratus anterior muscle with consequent muscle atrophy was identified as the major cause of anterior chest wall asymmetry, this was slightly commoner in males than females, potentially being masked by breast developed in the post-pubertal females. Poorly sited incisions are the main cause of breast deformity. Multiple thoracotomies significantly increased the risk of scoliosis. Other postulated risk factors for development of scolosis were rib resection thoracotomy and scarring of chest wall musculature resulting in vertebral malalignment. Other studies have found a strong link between anastomotic leak with resultant empyema and mediastinitis and subsequent development of

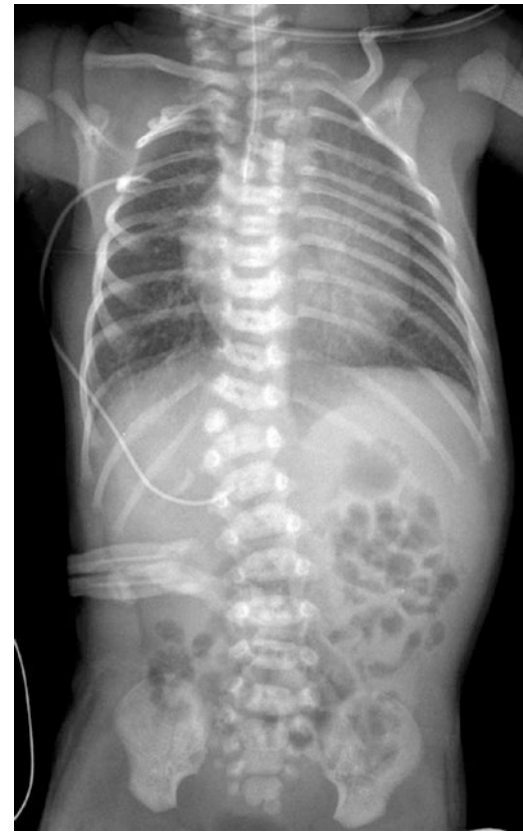

Fig. 20.20 Scoliosis associated with thoracic vertebral anomalies

scoliosis [159]. Interestingly in the Melbourne study, in the group with no underlying vertebral anomalies, two thirds of the scoliosis was convex away from the side of thoracotomy, other studies have had similar findings. Only two patients with a contralateral scoliosis had had an empyema. In a cohort study of 100 adults who had undergone surgery for oesophageal atresia, Sistonen et al. found 56% patients had a scoliosis >10° and 11% >20° Cobb angle. Risk factors included vertebral anomalies and rib fusion. The presence of associated anomalies e.g. VACTERL was also significantly associated with scoliosis. Many of the vertebral anomalies seen at adult follow up in the study were not apparent on the neonatal imaging [160].

A study of adult survivors or congenital diaphragmatic hernia (CDH) also identified a high incidence of chest wall deformity, being present

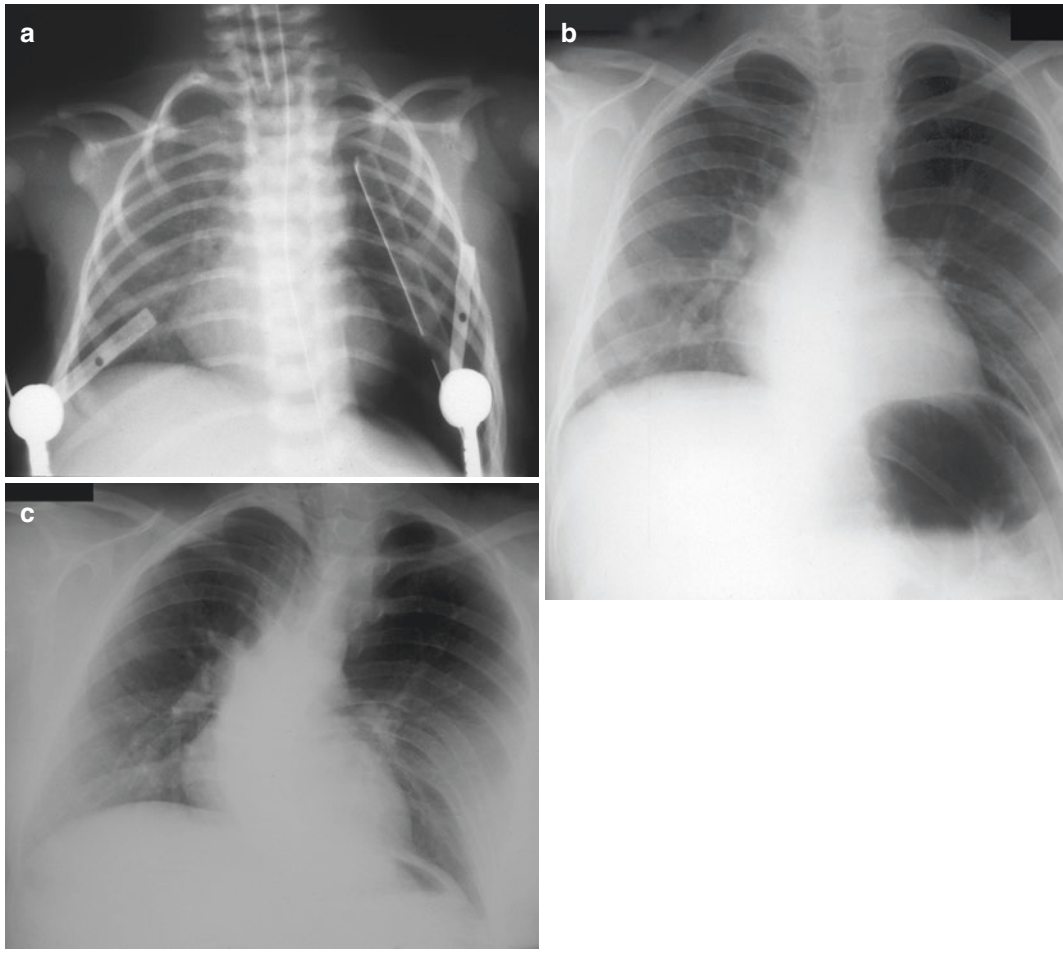

Fig. 20.21 (**a**–**c**) Progression of scoliosis following neonatal CDH repair

in 29 of 60 patients (48%). Deformities were felt to be commoner in patients who had had large defects. Eleven patients (18%) had pectus excavatum and one pectus carinatum, whilst 16 patients (27%) had significant scoliosis with a Cobb angle greater than 10%. Scoliosis was commoner in patients with documented impaired pulmonary function [161] (Fig. 20.21). The surgical approach used in these patients was not clear. Reviewing the published literature, Peetsold et al. estimated that 16–48% of CDH survivors have chest wall deformities, most commonly pectus excavatum and 5–10% have mild to moderate thoracic scoliosis [162]. It is difficult to differentiate the effects of the surgical approach from the underlying pulmonary and potential thoracic hypoplasia as the cause of these deformities though closing a large defect under tension appears to increase the incidence of long chest wall deformity [162].

Careful positioning of patients at the beginning of lengthy operative procedures is important to minimise traction on nerves and muscles which may have long term sequelae. A lateral muscle splitting thoracotomy taking care to preserve the nerve supply to the serratus anterior and latissimus dorsi muscles is crucial to normal long term function [163]. Care should be taken that the incision does not extend near the breast bud.

Assessment for chest wall deformity or scoliosis is an important part of the long term follow up of neonates who have undergone thoracotomy or repair of congenital diaphragmatic hernia.

Referral of patients with significant vertebral anomalies for assessment by a spinal surgeon should be considered.

Thoracotomy carries several risk factors for the subsequent development of thoracic deformity. Refinements in surgical technique over the decades have dramatically reduced the incidence of thoracic deformity but there remain significant potential long-term sequelae of thoracotomy. Advances in thoracoscopic surgical techniques and instrumentation over the last 20 years have permitted thoracoscopic techniques to be applied to a variety of neonatal thoracic problems including lung resections for the management of conditions such as congenital cystic adenomatoid malformations (CCAM), repair of oesophageal atresia and congenital diaphragmatic hernia [164, 165]. In theory there are advantages to this approach to reduce the long-term sequelae of chest deformity but long term follow up data is limited at present. None the less, these techniques are not without problems. The congenital diaphragmatic hernia study group found a significantly higher incidence of recurrent diaphragmatic hernia in patients whose repair had been performed using minimally invasive techniques, particularly by a thoracoscopic approach with a 7.9% versus 2.7% ($p < 0.05$) incidence of recurrence identified [166]. A multi-institutional study of thoracoscopic repair of oesophageal atresia concluded that this was a safe approach with equivalent outcomes to historical controls performed using an open approach [167]. The authors drew attention to the potential advantages of reducing musculoskeletal sequelae. Thoracoscopic repair of oesophageal atresia is performed by a transpleural approach. A recent follow up study of the open approach to oesophageal atresia repair specifically drew comparison of the thoracoscopic approach with a more contemporary open surgical approach. This study identified a 3% incidence of scoliosis, attributed to pre-existing vertebral anomalies and no other thoracic deformities [168]. More importantly the authors showed a higher incidence of anastomotic leak using the thoracoscopic approach (2.7% versus 7.6%), although this did not achieve statistical significance. This is a potentially important finding not just in terms of oesophageal function. Pleural and mediastinal infection has been identified as a significant factor in development of post-thoracotomy scoliosis [157, 159].

The importance of long-term follow up of children after neonatal thoracotomy cannot be overstated.

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Extracorporeal Membrane Oxygenation

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Abstract

Extracorporeal Membrane Oxygenation (ECMO) is a life-saving intensive care technology that uses partial heart and lung bypass for extended periods. Also known as extracorporeal life support (ECLS), it is not a therapeutic modality, but rather a supportive tool that provides sufficient gas exchange and perfusion for patients with acute, reversible cardiac or respiratory failure. This affords the patient's cardiopulmonary system time to rest, sparing them from the deleterious effects of traumatic mechanical ventilation and perfusion impairment.

Keywords

Extracorporeal Membrane Oxygenation (ECMO) • Cardio-respiratory care • Newborn • Outcomes

21.1 Introduction

Extracorporeal Membrane Oxygenation (ECMO) is a life-saving intensive care technology that uses partial heart and lung bypass for extended periods. Also known as extracorporeal life support (ECLS), it is not a therapeutic modality, but rather a supportive tool that provides sufficient gas exchange and perfusion for patients with acute, reversible cardiac or respiratory failure. This affords the patient's cardiopulmonary system time to rest, sparing them from the deleterious effects of traumatic mechanical ventilation and perfusion impairment.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_21

Table 21.1 Total international neonatal outcomes through July 2011

	Total patients	Survived ECLS		Survived to discharge or transfer	
Respiratory	24,770	20,951	85%	18,558	75%
Cardiac	4375	2649	61%	1723	39%
ECPR	694	438	63%	270	39%

Table 21.2 Total neonatal respiratory runs by diagnosis through July 2011

	Total runs	Avg run time	Longest run time	Survived	% Survived
CDH	6280	250	2549	3198	51%
MAS	7814	131	1327	7322	94%
PPHN/PFC	4129	151	1176	3200	78%
RDS	1508	135	1093	1269	84%
Sepsis	2646	140	1200	1974	75%
Pneumonia	345	237	1002	197	57%
Air leak syndrome	117	167	656	87	74%
Other	2261	176	1227	1433	63%

Run time in hours. Survived = survival to discharge or transfer based on number of runs

Table 21.3 Total neonatal cardiac runs by diagnosis through July 2011

	Total runs	Avg run time	Longest run time	Survived	% Survived
Congenital defect	3978	144	1524	1501	38%
Cardiac arrest	67	124	517	15	22%
Cardiogenic shock	67	156	621	26	39%
Cardiomyopathy	109	214	867	69	63%
Myocarditis	55	259	868	27	49%
Other	382	183	1871	163	43%

Run time in hours. Survived = survival to discharge or transfer based on number of runs

21.1.1 History of ECMO

The Extracorporeal Life Support Organization (ELSO) was formed as a study group in 1989 by a collaboration of physicians, nurses, perfusionists, and scientists with an interest in ECMO. The group provides an international registry that collects data from almost all ECMO centers in the United States and throughout the world. Since the first successful use of ECMO in neonates in 1974 through July 2011, ELSO has registered 29,839 neonates treated with ECMO for a variety of cardiopulmonary disorders (see Tables 21.1, 21.2 and 21.3) [1].

21.1.2 ECMO Outcomes

The most common indications for ECMO in newborns are meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), sepsis, persistent pulmonary hypertension of the neonate (PPHN), and cardiac support. Outcomes vary by disorder, but the overall neonatal ECLS survival for respiratory indications is 85% and for cardiac 61%. The mortality rate for these disorders without ECMO exceeds 80%.

21.2 Neonatal Patient Selection Criteria

Selecting potential ECMO candidates remains controversial. The selection criteria are based on data from multiple institutions, patient safety, risk of complications and mechanical limitations of equipment. All ECMO centers develop and maintain their own specific criteria based on their outcomes data.

21.2.1 Reversible Disease Process

ECMO is a supportive modality, not therapeutic therapy; therefore the baby should have a reversible disease process. Prior to ECMO, patients should be supported by mechanical ventilation for no longer than 10–14 days. Prolonged exposure to high concentration oxygen and positive pressure ventilation leads to the development of bronchopulmonary dysplasia (BPD) [2]. As few as 4 days of aggressive ventilation can lead to the development of BPD and prolonged ECMO runs (203 versus 122 h) [3]. Recovery from this type of irreversible lung injury may take from weeks to months to occur, if at all. Support with ECMO can be beneficial for reversible lung disease over a relatively short period of time (2–3 weeks). However, even a lengthy ECMO course is unlikely to be sufficient to permit recovery of the irreversible fibrotic changes that occur to the lung following sustained barotrauma and/or oxygen toxicity. In addition, with a longer ECMO run, the chance of infection, bleeding complications, thromboembolic events, and mechanical failure increase.

21.2.2 Gestational Age

The gestational age should be at least 34 weeks. Premature infants (<34 weeks' gestation) who were offered ECMO developed significant morbidity and mortality related to intracranial hemorrhage (ICH) [4]. The incidence of ICH appears to be directly related to gestational age, a 22% incidence of ICH at 32 weeks versus 12% at 36 weeks has been reported [5]. Ependymal cells within the brain may not be fully developed in preterm infants, thus making them susceptible to intracranial bleeding. Additionally the systemic heparinization necessary to maintain a thrombus-free ECMO circuit increases the risk of hemorrhagic complications.

21.2.3 Birth Weight

The birth weight should be 2000 g or greater due to technical consideration and limitation of cannula size. The smallest single lumen ECMO cannula is 6 French (Fr). Flow through the tube is inversely related to length of the tube as well as directly related to the radius of the tube by a power of 4. If the vein is small, then the cannula will be small, resulting in flow that will be reduced by a fourth power. If the baby weighs less than 2 kg, then the anatomical challenge of cannula placement in conjunction with the inadequate flow from small catheters make ECMO in these small babies challenging.

21.2.4 Hemorrhage and Coagulopathy Complications

There should be no active hemorrhage or major coagulopathy as these are relative contraindications to ECMO. Uncorrectable coagulopathy and uncontrollable bleeding have a high risk of bleeding complications while on ECMO. The need for continuous systemic heparin therapy while on ECMO adds to this risk of bleeding [6]. Hemorrhage should controlled and bleeding diathesis corrected prior to ECMO initiation.

21.2.5 Intracranial Hemorrhage

The infant should not have an intracranial hemorrhage (ICH). Patients with history of previous intracranial bleeds, cerebral infarcts, prematurity, coagulopathy, ischemic central nervous system injury, seizure or sepsis are particularly at high risk for ICH and severe neurologic consequences [4, 7]. Pre-existing ICH may be exacerbated secondary to the use of systemic heparin and altered cerebral blood flow while on ECMO. Infants with small intraventricular hemorrhages (grade I—restricted to germinal matrix and grade II—also inside ventricles) may be considered for ECMO on an individual case basis, but these cases should be closely monitored for worsening bleeding with frequent neurologic exam and daily head ultrasound. Pre-ECMO discussion with parents of these risks is especially critical.

21.2.6 Coexisting Anomalies

The infant should have no congenital or chromosomal anomalies incompatible with life,

i.e. trisomy 13 or 18. Many fatal congenital anomalies may initially present as reversible diseases including congenital alveolar proteinosis, alveolar capillary dysplasia and overwhelming pulmonary hypoplasia. A clear diagnosis prior to initiation of ECMO should be established as best as possible, as it is not intended to delay an inevitable death. Other treatable conditions, such as total anomalous pulmonary venous return (TAPVR), transposition of the great vessels (TOGV) and intact septum may initially manifest with respiratory failure. An echocardiogram should be rapidly obtained to determine the need for ECMO or cardiac surgery.

21.2.7 Bridge to Diagnosis

Despite best efforts, it is not always possible to establish a clear diagnosis prior to the initiation of ECMO and must be determined during its course. For example, pulmonary vein misalignment, a uniformly fatal anomaly of deficient alveolar capillaries and anomalous veins within the bronchoarterial bundles, presents with symptoms of persistent pulmonary hypertension unresponsive to treatment [8]. These children are often placed on ECMO. If the pulmonary hypertension is intractable despite support by ECMO, then the diagnosis of alveolar capillary dysplasia should be entertained [9]. The diagnosis is made via an open lung biopsy while on ECMO. If alveolar capillary dysplasia is confirmed, then withdrawal of ECMO support should occur. As mentioned in Coexisting Anomalies, some correctable cardiac conditions may present as respiratory failure and patients occasionally placed on ECMO before accurate diagnosis is made. Once established, appropriate therapy should be instituted.

21.2.8 Failure of Medical Management and Cardiopulmonary Criteria

Candidates for ECMO must have a reversible pathophysiologic process with a predicted mortality exceeding 80% and have exhausted maximum medical management. This is an admittedly subjective criterion, as conventional therapies will have great institutional variation. The term medical management encompasses ventilator and pharmaceutical modalities. Conventional medical therapy begins with positive pressure ventilation, vaso-dilatory or–constrictive agents and inotropes. These therapies may extend to administration of surfactant and alternative respiratory strategies including high-frequency ventilation, hyperventilation, hypoxia and induced respiratory or metabolic alkalosis [10]. Advanced medical strategies have been successfully employed for patients who otherwise met ECMO criteria. These strategies include high-frequency oscillation, permissive hypercapnea with spontaneous ventilation and nitric oxide. In 1985, Wung et al. used permissive hypercapnea in conjunction with spontaneous ventilation. This was employed in a series of 15 patients with persistent pulmonary hypertension [11]. A $PaCO_2$ of 50–80 mmHg and a PaO_2 of 40 mmHg were tolerated. Paralytics were not used and low-pressure ventilator settings were employed to provide adequate chest wall excursion. These patients survived with medical management alone. While some infants with reversible respiratory failure have been spared ECMO, many benefit and should be considered for ECMO if they meet criteria.

Objective criteria for assessing mortality risk in neonatal respiratory failure have been suggested [12–15]. The most commonly used measurements predictive of mortality are high-pressure ventilator settings, Alveolar-arterial oxygen gradient ($AaDO_2$) and the Oxygenation Index (OI) (see Table 21.4)

Alveolar-Arterial Oxygen Gradient:

$$AaDO_2 = (P_{ATM} - 47)(FiO_2) - [(PaCO_2)/0.8] - PaO_2$$

Oxygenation Index: $OI = MAP \times FiO_2 \times 100 / PaO_2$

where P_{ATM} is atmospheric pressure, FiO_2 is inspired oxygen fraction and MAP is mean airway pressure.

Criteria for cardiac failure include hypotension refractory to inotropes or volume resuscita-

Table 21.4 Predictive mortality alveolar-arterial oxygen gradient and Oxygenation Index

Measurement	Predictors of 80% mortality
$AaDO_2$	>625 mmHg for more than 4 h >600 mmHg for more than 12 h
OI	>40
High-pressure ventilator settings	Peak inspiratory pressure > 40 cmH_2O Positive end expiratory pressure > 7 cmH_2O Intermittent mandatory pressure > 100 FiO_2 of 1.0

tion, oliguria (urine output <0.5 ml/kg/h), decreased SvO_2 and decreased peripheral perfusion. It should be noted that survival benefit of ECMO during CPR (ECPR) and emergency cardiopulmonary bypass have not been clinically established.

21.2.9 Congenital Diaphragmatic Hernia

Patients with congenital diaphragmatic hernia who develop respiratory failure must meet unique criteria to be candidates for ECMO. The newborn must demonstrate adequate lung tissue to be able to sustain life. This includes a sustained preductal oxygen saturation ≥ 90% for at least 1 h (commonly referred to as the honeymoon period) and at least one recorded $PaCO_2$ < 50 mmHg before developing 80% mortality likelihood.

21.3 Methods of Extracorporeal Support

21.3.1 Veno-Venous ECMO

Veno-Venous (VV) support delivers oxygen for respiratory indications. In VV ECMO venous drainage is accomplished by cannulating the right internal jugular vein (RIJ) with the tip in the right atrium (RA) and reinfusion via a femoral vein. A variation is single cannula double-lumen veno-venous ECMO (DLVV) inserted via the RIJ with the tip in the RA. The double-lumen catheter both drains deoxygenated blood and returns oxygenated blood to the right atrium. Double-lumen catheters of 12–15 Fr gauge are available for use in neonates. Use of VV ECMO when indicated avoids arterial cannulation and carotid ligation while maintaining pulsatile flow. In DLVV there is mixing of oxygenated and deoxygenated blood in the RA. Oxygenated blood recirculates in the pump, artificially raising SvO_2 measurement and may limit oxygen delivery at higher flow rates.

21.3.2 Veno-Arterial ECMO

Veno-Arterial (VA) support not only delivers oxygen for respiratory failure but also provides circulatory support in the event of cardiac failure, difficulty weaning from cardiopulmonary bypass, or occasionally CDH anatomy. In these cases, VA support is provided by venous drainage of the right atrium through a cannula inserted in the RIJ (see Fig. 21.1). Oxygenated blood is returned through a cannula in the right common carotid artery (RCCA). Patients who present with profound lactic acidosis, hypoxic ischemia, and end organ failure often have a component of cardiovascular collapse and may also require the circulatory support of VA as opposed to VV ECMO. Patients with left ventricular (LV) failure are at risk of LV distension on ECMO and decompression via atrial septostomy is necessary. Preexisting atrial or ventricular septal defect may obviate need for mechanical septostomy and should be determined by echocardiogram prior to initiation of ECMO.

Transthoracic or open chest VA ECMO is common variation in patients unable to wean off intraoperative bypass or in the postoperative period. The venous cannula is in the right atrial appendage and arterial cannula in the ascending aorta. While large diameter catheters may be utilized, there is significant risk of hemorrhage and infection.

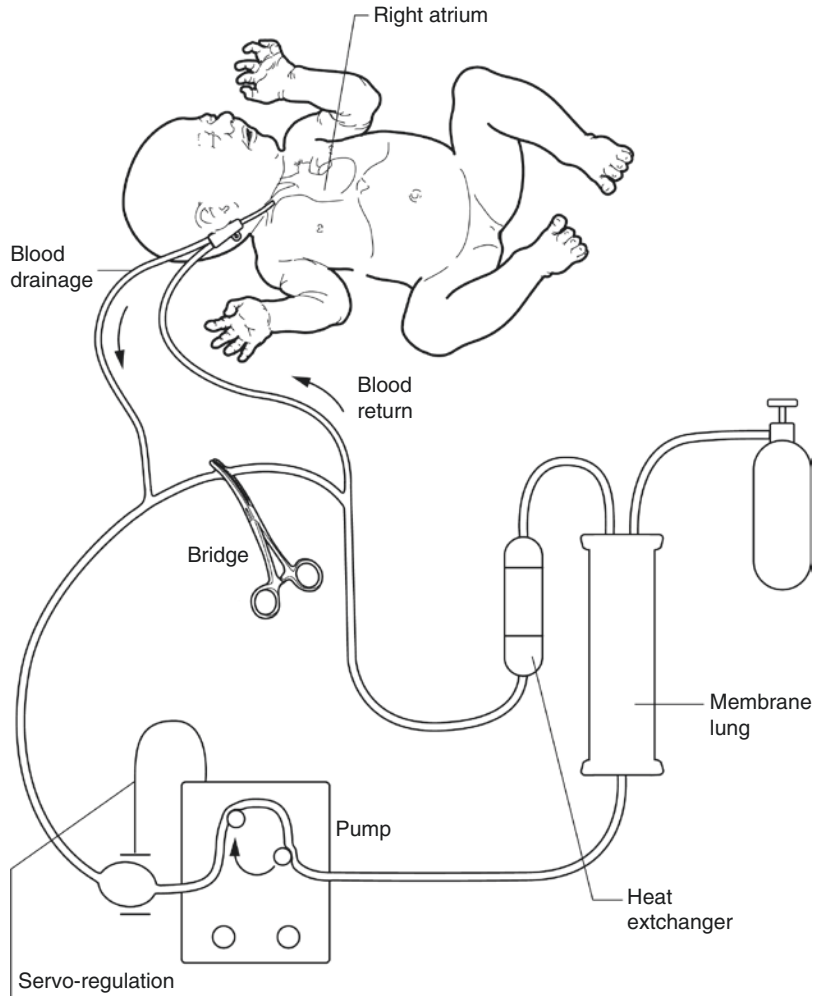

Fig. 21.1 ECMO circuit diagram. From Taylor & Francis UK. Published in Operative Pediatric Surgery 7th edition, Lewis Spitz and Arnold Coran, CRC Press, 2014 pages 196–198; used with permission

21.4 ECMO Circuit and Cannulation

21.4.1 ECMO Circuit

Venous blood is drained from the right atrium of the infant by gravity or negative pressure into a bladder reservoir. An inline oxymetric probe before the bladder accomplishes continuous monitoring of SvO_2. If venous drainage does not meet pump outflow the servo-regulator will shut off the pump. This limits risk of high negative pressures and possible damage to RA and air cavitation (entry of air into pump). Although hypovolemia is the most common cause of decreased venous inflow, occlusion of the venous line secondary to kinking or thrombus should be ruled out. A roller or centrifugal pump pushes blood through the membrane oxygenator. Continuous pressure monitoring pre- and post-oxygenator ensures that pressure in the circuit (negative and positive) does not exceed pre-set parameters. A bubble detector halts flow if air is detected in the circuit. The membrane oxygenator is either a silicone or hollow fiber with counter current flow of blood and gas providing a large surface area for gas and water vapor exchange. Post-oxygenator the blood is warmed

to physiologic temperature. Oxygenated blood returns to the baby via the RA (DDLV), Femoral Vein (VV) or aortic arch (VA) (Fig. 21.1).

21.4.2 Cannulation and Anesthesia

Cannulation can be performed in the neonatal intensive care unit with adequate sedation and analgesia. Neuromuscular blockade is critical at venous cannulation and decannulation to prevent ingress of air emboli due to spontaneous respiration, though it is not recommended during ECMO support. As with OR procedures, sterile technique is used. The cannulas are filled with heparinized saline, usually 8 Fr arterial and 10 Fr venous for neonates.

21.4.3 Patient Position and Incision

The infant is placed in the supine position with the head at the foot of the bed and turned to the left. The neck is hyperextended with use of a transverse shoulder roil. The chest, and right neck are prepped and draped. Local anesthesia is infiltrated over the right cervical neck incision site. A transverse incision is made one fingerbreadth superior to clavicle, 3 cm in length anteromedial to the right sternocleidomastoid muscle (Fig. 21.2).

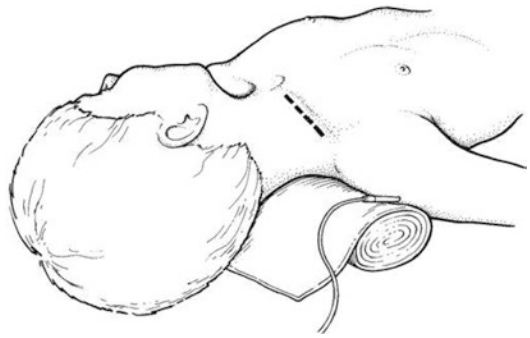

Fig. 21.2 Patient position and incision. From Taylor & Francis UK. Published in Operative Pediatric Surgery 7th edition, Lewis Spitz and Arnold Coran, CRC Press, 2014 pages 196–198; used with permission

21.4.4 Dissection and Vessel Exposure

The platysma muscle is divided, sternocleidomastoid retracted laterally and dissection carried down to the carotid sheet with electrocautery. The carotid sheath is opened and the right internal jugular, right common carotid and vagus nerve are identified. The vein is dissected first and isolated with vessel loops. Frequently the facial vein is present and must be ligated. The common carotid artery without any branches, lies medial and posterior, and is dissected and isolated with vessel loops. Once vessels are isolated, a heparin bolus of 100 units/kg is administered and allowed to circulate for 3 min. ACT level should be drawn prior to cannulation and be >300 s (Fig. 21.3).

21.4.5 Cannulation

Ligatures of 2-0 silk are passed proximally and distally on the artery and vein. For VA ECMO, the arterial cannula occurs first. The carotid artery is ligated distally and proximal control

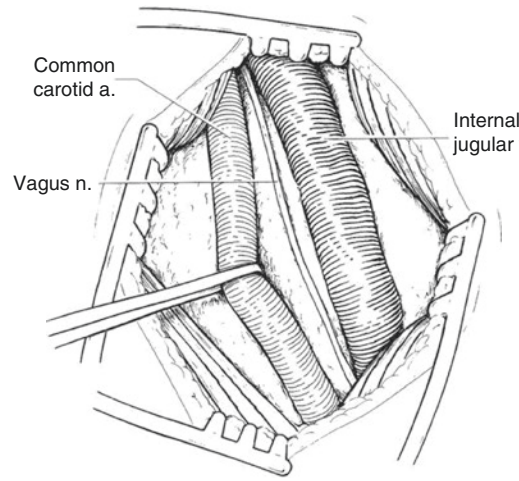

Fig. 21.3 Dissection and vessel exposure. From Taylor & Francis UK. Published in Operative Pediatric Surgery 7th edition, Lewis Spitz and Arnold Coran, CRC Press, 2014 pages 196–198; used with permission

obtained with a vessel clamp. A transverse arteriotomy is made near the distal ligature. Prolene stay sutures can be used to assist with retraction and prevent intimal dissection. The heparinize-saline filled cannula is inserted to its premeasured position, usually about 3 cm to the junction of the brachiocephalic artery and aorta. It is secured with the previously placed 2-0 silk ligatures and a small piece of vessel loop placed inside the ligatures anteriorly. These bumpers serve to protect the vessel from injury during sharp division during decannulation. Prior to venotomy, the patient must be paralyzed to prevent air embolus secondary to spontaneous respiration. Venous cannulation follows a similar pattern to arterial. The jugular vein is ligated proximally and a transverse incision made close to the ligature. The catheter is passed to the level of the right atrium, usually 5–6 cm, and secured as the arterial cannula. For VV and DLVV bypass, the RCCA is dissected and isolated with vessel loop in case conversion to VA ECMO is necessary. If using a double lumen cannula, the reinfusion port must be oriented anteriorly to ensure the oxygenated blood is directed across the tricuspid valve, minimizing recirculation. Bubbles are aspirated and the cannula(s) connected to the prep rimed ECMO circuit. Bypass is initiated. After achieving hemostasis, the wound is irrigated and closed in layers. The cannulae are secured to the skin, below the ear ensuring they remain unkinked. Cannulae positions are confirmed with chest radiograph and transthoracic echocardiogram (Fig. 21.4).

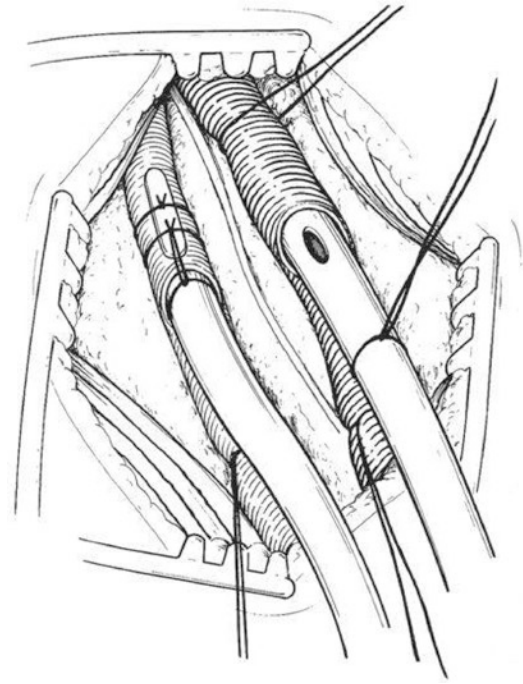

Fig. 21.4 Cannulation. From Taylor & Francis UK. Published in Operative Pediatric Surgery 7th edition, Lewis Spitz and Arnold Coran, CRC Press, 2014 pages 196–198; used with permission

21.5 Clinical Management of Extracorporeal Support

21.5.1 Cannula Management

The preferred site for cannula placement is in the vessels of the right neck. The reason for this is that the femoral vessels are too diminutive for cannulation in a neonate. The internal jugular vein is accessed via an open procedure. During the open procedure, muscle relaxants are given to prevent the inadvertent aspiration of air into the vein. In the event of VA ECMO, the carotid artery is dissected and identified for catheter placement. After placement of the catheters and initiation of ECMO flow, the catheters are carefully secured with sutures to the blood vessel and skin (see Fig. 21.2).

The position of the catheter is confirmed in two ways. First, a chest radiograph is performed, which can grossly demonstrate catheter position. The tip of the venous cannula should be located within the right atrium, while the tip of the arterial cannula should be located in the ascending aorta. The second mode of confirming cannula placement is cardiac echocardiography. The double-lumen catheter should be visualized within the right atrium, venting the return oxygenated blood through the tricuspid valve to minimize recirculation. If there is persistent difficulty maintaining flow due to poor venous withdrawal, the possibility of a catheter problem must be entertained and further imaging should be performed to confirm the proper position.

21.5.2 Prime Management

The tubing of the ECMO circuit is initially circulated with carbon dioxide gas followed by the addition of crystalloid and 25% albumin solution when using silicon sheet oxygenators. The albumin coats the tubing to decrease its reactivity to circulating blood. The carbon dioxide gas dissolves into the fluid. Packed red blood cells are required for initial priming of the pump, which displaces the crystalloid and colloid in the circuit. Blood is washed before priming the circuit as preserved blood contains non-physiologic levels of electrolytes. Otherwise, upon initiation of ECMO, a massive transfusion of unwashed blood can significantly alter infant electrolyte concentrations and induce cardiac arrest. Calcium gluconate is added to minimize arrhythmias when going onto ECMO. Sodium bicarbonate and heparin are added to the circuit as well.

The initial pH, oxygen content and carbon dioxide content of the circuit are then measured and adjusted to physiologic parameters. If the prime blood is acidotic, this may exacerbate the infant's condition; or, if the primed circuit has a low carbon dioxide content, this may cause metabolic problems for the neonate. Additionally, a heat exchanger warms the prime to normal body temperature. The primed circuit must be physiologically compatible with life prior to initiating ECMO to maximize support and prevent exacerbation of the child's condition.

21.5.3 Pump Management

The goal of ECMO is to maintain adequate pump flow providing good oxygen delivery to the tissues and organs. Oxygen delivery is dependent on the speed or rotations per minute (RPM) of the pump. Full support on VA ECMO is considered a flow rate of 120–130 cc/kg/min corresponding to a cardiac index of 2.4. Adequate perfusion and oxygen delivery can be monitored by the pH and PO_2 of a 'mixed venous' blood sample (preoxygenator blood sample). The flow of the pump should be adjusted to maintain a mixed venous PO_2 of 37–40 mmHg and saturation of 65–70%. With VV ECMO, full support is 120–150 cc/kg/h. The 'mixed venous' sample may not be a reliable indicator of perfusion as recirculation may produce a falsely elevated PO_2. Therefore, other indicators of poor perfusion should be followed: persistent metabolic acidosis, oliguria, seizures, elevated liver function tests, and hypotension. If oxygen delivery is found to be inadequate, then the RPM of the pump may need to be increased to improve perfusion.

Roller pumps use a rotary vane to trap fluid in the tubing against the pump housing to propel the blood towards the oxygenator. They propel a fixed volume (length of tubing) at constant flow rate regardless of discharge pressure dependent on RPM. This area of contact is at risk for tubing rupture over time. To reduce the risk of rupture, the 'raceway' (tubing within roller pump housing) is advanced regularly after temporarily stopping the pump flow. Tubing rupture is a rare event, less than 1% of ECMO runs per year, due to modern materials such as Supertygon† (Norton Performance Plastics Corporation, Akron, OH, USA), a chemically altered polyvinyl chloride (PVC).1.

Another type of pump, centrifugal, is also commonly used for ECMO. Centrifugal pumps work by using a rotating impeller to create flow by adding energy to a fluid. Fluid enters the housing at the rotating axis, is accelerated by the impeller and discharged at the outer casing. They do not have a mechanical degradation of tubing integrity and are not susceptible to raceway rupture. Unlike rotary pumps, centrifugal pump flow rate is dependent on inlet and outlet pressure. Though flow rate is primarily dependent on RPM, there will be some variation in flow rate due to pressure.

21.5.4 Oxygenator Management

The silicone membrane (envelope) oxygenator has been critical to the success of ECMO and long-term bypass. The mechanism of gas exchange occurs when blood in the tubing enters a manifold region and is distributed around the envelope of a silicone membrane lung. Oxygen flows through

the inside of the membrane envelope in a countercurrent direction to the flow of blood. Oxygen diffuses across the silicone membrane into the blood as carbon dioxide is eliminated. The oxygenated blood drains into a manifold and is returned to the infant via a heat exchanger.

A thrombus may form in the oxygenator over time. As a thrombus extends, the membrane surface area is decreased, resulting in decreased oxygen and carbon dioxide transfer. This can lead to increased resistance to blood flow. The gaseous portion of the oxygenator may also develop obstructions, which may lead to air emboli. Long-term use may wear the silicone membrane, resulting in blood and water in the gas phase.

Most ECMO circuits measure a pre- and post-oxygenator pressure. The difference in these two pressures, the DP, can help determine when an oxygenator is failing. An elevated pre-oxygenator pressure with a stable post-oxygenator pressure, thus elevated DP, likely means that there is an obstruction to blood flow in the oxygenator, often from thrombus. There is no absolute DP value that mandates replacement of an oxygenator. However, a rapid increase in this value with the anticipation of continued ECMO support should alert the practitioner to the need for replacement of the oxygenator. In addition, a larger oxygenator may also be required if the gas and blood flow rating of the old oxygenator are exceeded in order to maintain adequate perfusion.

In increased use are hollow-fiber oxygenators, such as the Quadrox-iD† oxygenator (Jostra Medizintechnik AG, Hirrlingen, Germany) for neonates. The oxygenator uses less priming volume (80 mL) and has a smaller surface area. The decreased surface area allows for more efficient gas exchange and reduces the potential for thrombus formation [16]. Additionally, the resistance across the oxygenator is smaller than the silicone oxygenator, less than 50 mmHg. This may cause less disruption of red blood cells.

21.5.5 Volume Management

While on ECMO, maintenance fluids for a term newborn under a radiant warmer are estimated to be 100 cc/kg/day. Water loss through the oxygenator may approach 2 cc/m^2/h. For a baby weighing 3 kg, this would be about 10 cc/day. Fluid losses from urine, stool, chest tubes, nasogastric tubes, ostomies, mechanical ventilation, radiant fluid loss, and blood draws should be carefully recorded. Fluid management may become difficult in the baby on ECMO as fluid extravasates into the soft tissues during the early ECMO course. Therefore, strict measurement of the net fluid balance on ECMO should be maintained. Classically, the weight increases in the first 1–3 days as the patient becomes increasingly edematous. On the third day of ECMO, diuresis of the excess edema fluid begins, and can be facilitated with the use of furosemide. This diuretic phase is often the harbinger of recovery. In the event of renal failure on ECMO, hemofiltration or hemodialysis can be added to the ECMO circuit for removal of excess fluid and electrolyte correction. In a retrospective comparison of neonates on ECMO, use of hemofiltration was associated with shorter duration on ECMO and time on mechanical ventilation [17].

While on ECMO, the baby's hemoglobin is maintained at 13–15 g/dL to maximize the oxygen carrying capacity of the blood. Platelet destruction during ECMO is anticipated and is secondary to the flow through the oxygenator and exposure to plastic surfaces. In order to reduce the risk of bleeding during ECMO, the platelet count should be kept above 100,000/mm^3 [18]. The authors recommend using 'hyperspun/concentrated' platelets to avoid the excess administration of fluid, and thus preventing further problems with volume overload and edema.

21.5.6 Ventilator Management

Once the desired oxygen delivery is attained, the ventilator should be promptly weaned to avoid further oxygen toxicity and barotrauma. The optimal rest settings remain unclear [19]. At the authors' institution, the FiO_2 is decreased to 0.21, PEEP to 5 cmH_2O, PIP to 20–25 cmH_2O, a rate of 12 breaths/min and inspiratory time of 0.5 s if the infant's arterial and venous oxygenation are adequate.

If the baby remains hypoxic despite maximal pump flow, then higher ventilator settings may be temporarily required. Alternatively, hypoxic neonates on VV ECMO may need to be converted to VA ECMO for full cardiorespiratory support. On occasion, the chest x-ray will worsen in the first 24 h independent of ventilator settings and improve after diuresis. As the patient improves on ECMO and the pump flow is weaned, ventilator settings are then modestly increased to support the baby off ECMO. At our institution, if the oxygen saturation is greater than 93%, then an FiO_2 of 0.4, PIP < 28, PEEP of 5, and a rate < 30 as adequate settings for a trial off ECMO.

In addition, during the course of ECMO, pulmonary toilet is essential to respiratory improvement and includes gentle chest percussion and postural drainage. Special attention should be made to the ECMO catheters and keeping the head and body aligned. Endotracheal suctioning is also recommended every 4 h and as needed based on the amount of pulmonary secretions present.

21.5.7 Medical Management

After the initiation of ECMO, vasoactive medications should be quickly weaned if the blood pressure remains stable. In the event of seizures, phenobarbital is usually given and maintained to prevent further seizures. In addition, gastrointestinal prophylaxis with an H_2-blocker, such as ranitidine, is instituted. Fentanyl and midazolam are usually administered for mild sedation, however the use of paralytics should be avoided. Paralysis is avoided because muscle activity plays a vital role in fluid mobilization, preventing edema and loss of compliance. Neonates also tolerate ECMO well without paralysis and it prevents an accurate neurologic exam.

Infectious prophylaxis is provided by cefazolin, if no other antibiotics have been started at the author's institution. However, many neonates who are placed on ECMO are already on broad-spectrum antibiotics. If these are discontinued than cefazolin ore equivalent should be initiated. Due to the indwelling cannula and manipulation of the circuit at stopcocks, the risk of infection is a constant concern; therefore, strict observance to aseptic technique when handling the ECMO circuit should be maintained. Routine blood, urine, and tracheal cultures should be obtained to monitor for infection.

The caloric intake on ECMO should be maximized using standard hyperalimentation. For a newborn, total parenteral nutrition (TPN) should be started at 100 kcal/kg/day. Normally, this should be supplied as 60% carbohydrates (14.6 g/kg/day) and 40% fat (4.3 g/kg/day). Intralipid infusion may be used as a fat source, although there is some controversy with its use in the setting of severe lung disease. As a result, the percentage of fat in the hyperalimentation may be lowered. Amino acids may be added but must be considered in the setting of poor renal function and increasing blood urea nitrogen (BUN) levels. With normal renal function, approximately 2.5 g protein/kg/day should be provided in the TPN mixture.

Enteral nutrition is gaining acceptance in some centers. Initial concerns with feeding enterally on ECMO were that there was inadequate gut perfusion from the initial insult, which could lead to necrotizing enterocolitis when feeding was begun [20]. However, a retrospective study of 67 neonates supported with VA ECMO who were fed enterally, did not show any significant adverse effects [21]. While septic complications of enteral feeding appears to be low, many of these patients will have a gastrointestinal ileus. Of the previously mentioned 67 neonates, 21% had enteral feeding temporarily discontinued due to high gastric residuals.

In the setting of cardiopulmonary failure and large volume shifts it is essential to closely monitor electrolytes with potassium, calcium, and magnesium repleted as necessary. Sodium and phosphorus are usually not repleted as they are often provided in blood products and volume expanders.

21.5.8 Coagulation Management

Heparin is initially administered as a bolus (100 units/kg) followed by a constant heparin

infusion (30–60 units/kg/h) to maintain a thrombus-free circuit. The level of anticoagulation is monitored by the activated clotting time (ACT). The heparin infusion is adjusted to maintain an ACT of 200–240 s. After decannulating, the heparin infusion is stopped and not reversed with protamine sulfate.

21.5.9 Hemodynamic Management

Hypotension and hypertension are both seen in neonates on ECMO. Hypotension is common in both respiratory and cardiac failure requiring the use of inotropes even after being placed on ECMO. Cause can be hypovolemia as well as myocardial dysfunction from pre-ECMO hypoxia. Inotropes are readily weaned after correction of hypoxia and acidosis in conjunction with volume resuscitation and hemoglobin at 15 mg/ld. Hypertension is also common and should be aggressively treated after reversible causes such as pain, hypercarbia and hypoxia are ruled out. Hypertension increases risk of ICH and its sequelae.

21.5.10 Temperature Management

Thermoregulation is controlled by adjusting temperature of blood returning to patient. Selective hypothermia for cerebral ischemia/hypoxia may improve neurologic outcome. It is not yet clear if whole body or cap cooling provides significant improvement in outcomes on ECMO. It is possible to maintain temperature of 34 °C for 45 h on ECMO without increasing morbidity [22]. The largest study to date is underway in the UK. The Neonatal ECMO Study of Temperature (NEST) is a multicenter prospective randomized control trial of mild hypothermia versus normothermia in neonates with respiratory failure [23].

21.5.11 Pharmacology Management

ECMO alters pharmacologic management secondary to increased volume of distribution and drug absorption due to the circuit. While antibiotic, analgesia and sedation is calculated by age and weight, it should be noted that drug absorption by the oxygenator can be significant with lipophilic agents most extremely effected. Sedatives such as fentanyl and midazolam have extremely short half-lives, in the order of minutes, when administered to patients on ECMO.

21.5.12 Surgical Procedures on ECMO

ECMO may be used to stabilize patient prior to surgical repair of reversible diseases, i.e. CDH or TGOV. Operative procedures may be safely preformed while the child remains on bypass. However care must be taken to obtain meticulous hemostasis to avoid hemorrhagic complications. Pre-operatively hemoglobin should be transfused to 15 g/dL and platelets to 100,000/mm^3. Intraoperatively ACT level should be reduced to 180–200 s. The fibrinolysis inhibitor aminocaproic acid is administered as a 100 mg/kg bolus 1 h prior to incision with a continuous maintenance drip at 30 mg/kg/h for up to 72 h postoperatively.

21.5.13 ECMO Weaning and Decannulation

As the patient improves during the ECMO course, the flow of the circuit is weaned, based on improving postductal arterial and venous oxygenation. Neonates supported with VV ECMO should be weaned using the patient's SaO_2 as the SvO_2 will be artificially high from recirculation. Neonates supported with VA ECMO should be weaned maintaining the patient's SvO_2 with a target of 65–75 mmHg. From full flow support of 150 cc/kg/min, the flow is decreased to 30 cc/kg/min while maintaining adequate perfusion. As flow decreases it will be necessary to increase ventilator support. The ACT should be maintained at 220–240 at lower flows to prevent thrombosis. If the baby tolerates the low flow, then the ECMO cannula (VV) or cannulas (VA)

may be clamped while the ECMO circuit recirculates. During a clamping trial, the child is observed for up to 4 h to ensure hemodynamic stability and adequate saturation without acidosis. The authors prefer to wean patients onto moderate conventional ventilator settings, i.e. IMV 20, FiO_2 0.4, PIP 25, and PEEP 5. Higher ventilator settings, though, may be tolerated if the risks of continuing ECMO outweigh those of discontinuing ECMO.

If the recirculation is tolerated, then decannulation is performed. As with the insertion, decannulation should be performed as a sterile surgical procedure. Muscle paralytics should be administered to prevent air aspiration into the vein. Prior to decannulation, vasoactive medication and hyperalimentation should be switched from the ECMO circuit to other vascular access. Once the catheter is removed, the vein is ligated and not repaired. This is also true for the artery in the case of VA ECMO.

21.6 Complications on ECMO

21.6.1 Hemorrhagic and Thrombotic Complications

The most common complication during ECMO is bleeding and coagulopathy. Bleeding can occur at cannula site, surgical site, intracranial, intestinal, tracheal or urinary. Coagulopathy occurs due to activation of coagulation cascade by contact with foreign surface of catheters and ECMO circuit. Platelets are consumed by the circuit as discussed previously. Treatment includes transfusion of blood products as well as coagulation factors if necessary.

Oxygenator failure and thrombus formation within circuit tubing is common. Venous or pre-oxygenator clot can be observed unless pressure drop is excessive and adequate flow cannot be maintained. Segments of tubing or oxygenator can be replaced as necessary. Arterial or post-oxygenator clot are of significant concern as they can emblaze with pulmonary and neurologic complications. Post-oxygenator clot is an indication for replacement of the entire circuit.

21.6.2 Mechanical Complications

While hypovolemia is an important cause for poor venous return to the circuit and subsequent poor pump flow, other causes must be eliminated prior to volume infusion. These may include small venous catheter diameter, excessive catheter length, catheter kinks, improper catheter position, insufficient hydrostatic column length (i.e. patient height), and improper calibration or set-up of the venous control module system. In addition, pneumothorax, cardiac tamponade, and abdominal compartment syndrome may need to be considered if there is no readily appreciated mechanical reason for poor venous return.

Air embolism should be rigorously guarded against. Air can enter the circuit via connectors, stopcocks as well as at cannulation and decannulation. Pre-oxygenator air can be aspirated via stopcocks but arterial or post-oxygenator air is an emergency. ECMO should cease until the air is aspirated. If there is an air embolus becomes systemic, the patient should be placed in Trendelenburg and embolus aspirated via the arterial cannula.

After these causes have been excluded, small amounts of isotonic fluid (5–20 cc/kg) may then be introduced into the circuit to support higher pump flow rate. However, a large amount of volume infusion in conjunction with long-term muscle relaxants and venodilators can lead to anasarca, which in turn, can lead to poor chest wall compliance, compromised gas exchange and oxygen delivery. In some conditions, such as sepsis, there may be endothelial damage and capillary leakage, in which case anasarca may be unavoidable.

21.6.3 Neurologic Complications

The most serious long-term complications of the ECMO patient have been neurologic (e.g. learning disorders, motor dysfunction, cerebral palsy) and appear to be due to hypoxia and acidosis prior to ECMO. Neurologic complications on ECMO include ICH, stroke and seizures. Seizures are common among ECMO neonates but are associ-

ated with prior hypoxic insult. The incidence of ICH in neonates is 14% on ECMO and increased in premature infants. During the ECMO course, frequent neurological examinations should be performed, and paralytic agents should be avoided. The examination consists of evaluation of alertness and interaction, fullness of the fontanelles, reflexes, tone, spontaneous movements, eye findings, and presence of seizures. Intracranial hemorrhage is the most devastating complication on ECMO. Therefore, careful attention must be made to the rate of ECMO flow, rate of exchange of PCO_2, fluctuations in the ACT, and platelet count. Cranial ultrasounds should be performed every day to monitor ICH and after any major event, such as equipment malfunction, sudden worsening in oxygenation status, and pneumothorax. Electroencephalography (EEG) may also be helpful in the neurologic evaluation of the neonate. As previously discussed studies are underway to evaluate the benefits of selective hypothermia on ECMO to mitigate neurologic sequelae of hypoxia. Progression of ICH or worsening of neurologic status may require cessation of anticoagulation and removal from ECMO support.

21.6.4 Renal Complications

Infants on ECMO may sustain acute tubular necrosis (ATN) marked by oliguria and increasing BUN and keratinize levels. ATN may extend into the first 24–48 h of ECMO before improvement in urine output is seen. This may be attributed to decreased renal perfusion secondary to nonpulsatile flow in VA ECMO or capillary leak at ECMO initiation. If the renal condition does not improve, poor tissue perfusion should be considered. A combination of inadequate ECMO flow rate, low cardiac output, and intravascular volume depletion from diuresis may lead to decreased renal function. If after adequate volume resuscitation oliguria does not resolve, pharmacologic diuresis with furosemide may be utilized. If the infant remains in complete anuric renal failure and requires dialysis, a hemofiltration module can be added in series to the ECMO circuit to remove excess fluid and stabilize electrolyte abnormalities.

21.7 ECMO and Congenital Diaphragmatic Hernia

Neonates with CDH have abdominal viscera in the thoracic cavity, most commonly on the left side. This often leads to significant pulmonary hypoplasia and pulmonary hypertension. Pulmonary insufficiency can ensue, leading to hypoxemia, hypercarbia, and acidosis soon after birth; this can then lead to a vicious cycle of pulmonary vasospasm, pulmonary hypertension, right-to-left shunting of blood and worsening hypoxemia, hypercarbia, and acidosis. This cycle must be broken, if not medically, then with the assistance of ECMO. Medical management has improved greatly with the use of pulmonary vasodilators such as inhaled nitric oxide.

If a fetus is antenatally diagnosed with a CDH, plans should be made for delivery in a medical center with ECMO capabilities in case of potential rescue therapy. There is no surgical indication or benefit to early delivery by Cesarean section. In the delivery room, intubation should be performed immediately after birth. The baby should then be transferred to a neonatal intensive care unit and started on mechanical ventilation to stabilize oxygenation and hemodynamics.

21.7.1 Surgical Repair CDH

In the past, newborns with CDH have undergone repair as a surgical emergency. However, respiratory mechanics frequently worsen postoperatively, perhaps as a result of early repair [24]. In the 1980s, however, surgeons reported improved results with delayed surgery after postnatal medical stabilization [25–30]. A strategy of delayed repair in CDH patients after stabilization of respiratory and hemodynamic parameters with or without ECMO is the current standard of care.

21.7.2 CDH and ECMO Selection

Patient selection of newborns with CDH for ECMO support is particularly difficult. Neonates with CDH who present with overwhelming pulmonary hypoplasia that precludes gas exchange

should not be offered ECMO. This group is characterized by the inability to sustain a preductal oxygen saturation ≥ 90% for at least 1 h, a PaO_2 of 100 on a FiO_2 of 1.0 or a PCO_2 < 50. Their degree of pulmonary hypoplasia is incompatible with life and they would not be able to be weaned from ECMO. Appropriate candidates for ECMO will go through a 'honeymoon' period where they will maintain a PaO_2 > 100 on FiO_2 of 1.0 or a $PaCO_2$ < 50 for a period of time. Should they develop sustained hypoxemia (PaO_2 < 40), acidosis (pH <7.2) or an alveolar arterial oxygen gradient >600 for 10 h, then ECMO should be instituted. This period of adequate gas exchange followed by deterioration suggests that these patients have a degree of reversibility of their pulmonary hypertension. Applying this criteria, 85% patients with a CDH supported on ECMO survived to discharge [31].

21.8 Results and Outcomes

21.8.1 Survival

Mortality statistics for neonates supported by ECMO are increasing according to the ELSO registry [32]. The ability for critically ill babies to be managed medically has improved significantly over the last decade. Use of inhaled nitric oxide (pulmonary vasodilator), surfactant, high frequency oscillating ventilation, permissive hypercapnea and spontaneous ventilation have all contributed have increased the severity of illness of neonates placed onto ECMO. Despite advances in medical management, mortality has remained specific to the primary diagnosis prior to ECMO [32]. For example, ECMO patients with the diagnosis of CDH have a 51% survival rate while meconium aspiration syndrome has a survival rate of 94% [32, 33]. Neonates supported by ECMO for respiratory failure have higher rate of survival to discharge (75%) than for cardiac failure (39%) [32] (see Tables 21.1, 21.2 and 21.3).

The leading cause of infant mortality on ECMO, is due to severe hemorrhagic or coagulopathic complications. Prematurity and low birth weight, <2 kg, are another risk factor for mortality. It should be noted that newborns <2.5 kg still have a higher mortality. A retrospective study reviewed 300 newborns supported with ECMO, and the infants who weighed <2.5 kg, although meeting the criterion of 2 kg, had a relative mortality risk of 3.45% compared to ECMO neonates with birth weights >2.5 kg [34].

21.8.2 Feeding and Growth

ECMO survivors often faced delayed discharge from the neonatal intensive care unit due to poor enteral feeding. As many as one-third of post-ECMO neontaes struggle to attain goal feeds [35–37]. The root cause of feeding failure varies; possibilities include interference from tachypnea, generalized central nervous system (CNS) depression, poor hunger drive, soreness in the neck from the surgical procedure, sore throat from intubation, poor oral motor coordination, and manipulation or compression of the vagus nerve during the cannulation procedure [37, 38]. Pre-ECMO diagnosis points to different causes. Infants with CDH have a higher incidence of feeding difficulty than infants with MAS and RDS [38–40]. The CDH infants have a field defect, one aspect of which is foregut dysmotility, which leads to significant reflux, delayed gastric emptying, and feeding difficulties. Respiratory compromise and severe chronic lung disease also interfere with feeding. These babies may require prolonged nasogastric feeding or even a gastrostomy, fundoplication, and pyloroplasty to maintain adequate growth. However, ECMO infants generally do not have major long-term feeding complications.

Though the majority of post-ECMO children demonstrate normal growth, this population of infants has a higher incidence of growth problems compared to normal controls.

Head circumference below the fifth percentile occurs at a higher rate (10%) in post-ECMO children. Furthermore, poor head growth is associated with a major handicapping condition with a risk greater than 75% at 5 years of age [41]. Although controversial, there have also been reports of macrocephaly, which follows a pattern of venous obstruction secondary to internal jugular vein ligation observed on neonatal neuroimaging [41, 42].

Growth problems are most commonly associated with ECMO children who had CDH or residual lung disease [39].

21.8.3 Respiratory

Respiratory sequelae are a significant cause of long term morbidity in ECMO survivors with corresponding high rate of hospitalization in the first 2 years of life related to pre-ECMO care or PPHN [43, 44]. Approximately 15% of ECMO survivors require supplemental oxygen beyond the neonatal period. This cohort is twice as likely to be hospitalized for pneumonia as control children by age five (25% versus 13%) with a half of these hospitalizations occurring within the first year of life.

Of the ECMO-treated neonates, the primary diagnosis of CDH, in particular, has been found to be associated with chronic lung disease, defined by the need for bronchodilators, diuretics, or supplemental oxygen for the management of pulmonary symptoms. Specifically, the use of supplemental oxygen at discharge from the hospital has been reported in 22–80% of CDH patients [40, 45–47]. Aggressive ventilator management and lung injury prior to initiating ECMO leads these children to develop bronchopulmonary dysplasia. Persistent oxygen requirements are due to pulmonary hypertension.

The duration of aggressive mechanical ventilation prior to initiating ECMO is associated with supplemental oxygen requirement beyond 28 days [3]. Neonates with severe respiratory failure had an 11.5-fold increased risk of bronchopulmonary dysplasia if ECMO was initiated at later than 96 h of age correlating with duration of ventilation. Additionally, ECMO infants with birth weights of 2–2.5 kg have a greater risk for chronic lung disease than larger ECMO infants [34].

21.8.4 Neurologic

The most serious morbidity post-ECMO is neurologic. Multiple institutions have published sensorineural, neuromotor and developmental handicap at 1 year after birth.

The average incidence of sensorineural handicap such as cerebral palsy, blindness and hearing impairment is 6% [41, 48–60]. Auditory deficits are reported in more than 25% of ECMO neonates at the time of discharge [61]. The majority consists of mild-moderate deficit by brainstem auditory evoked response (BAER) testing which generally resolve over time. Iatrogenic injury may play a role secondary to alkalosis, furosemide administration or gentamicin ototoxicity. As a result, hearing screening is recommended at the time of NICU discharge. Overall sensineural hearing loss occurs in 5% of ECMO children [41, 53, 55, 57]. This rate is comparable to non-ECMO PPHN children [62–65].

Visual deficits in ECMO neonates are usually limited to infants <2 kg associated with immature retina in premature patients. This is uncommon in ECMO neonates weighing >2 kg. Concern about retinopathy of prematurity due to the hyperoxic condition of ECMO has not been borne out.

Severe developmental delay among ECMO survivors is 9% on average, comparable to other critically ill neonates. Extremely low birth weight neonates (<750 g) have a 15% rate of having major sensorineural handicap with 21% testing in the mentally retarded range [66]. Additionally, newborns with PPHN not supported with ECMO have an average sensorineural handicap rate of 23% [62–65, 67–70].

At 5 years of age, 50% of children supported with ECMO as neonates had a normal neurologic outcome as defined by lack of a developmental delay, epilepsy, or cerebral palsy [41, 48, 50, 53–60, 71, 72]. The disabilities of the remaining children fall on a spectrum with most being mild to moderate. Consistent with ICH complications, low gestational age and low birth weight were significantly associated with a negative neurologic outcome. At discharge home, most ECMO neonates will exhibit signs of general CNS depression, including lethargy, hypotonia, and weak primitive reflexes, an indication of moderate hypoxic ischemic encephalopathy. By 4 months of age, ECMO infants typically function in the normal range, though residual hypotonia and asymmetry persists in about 25%. Severe

neuromotor are found in approximately 10–15% of affected individuals and by age three, learning disabilities, particularly with language and perceptual functioning appear [37, 73–75].

The increased morbidity and mortality of low birth weight and gestational neonates supports the theory that factors present prior to a course of ECMO are the cause of negative neurologic outcomes rather than ECMO itself. The pre-ECMO diagnosis correlates with poor cognitive development. At 2.5 years, children with CDH who underwent ECMO were at greater risk of having an abnormal cognitive status as compared to non-CDH ECMO survivors [58].

Seizures, both clinical and electroencephalographic, occur in 20–70% of EMCO neonates [76–79]. Neonatal seizures are associated with neurologic disease and poorer long-term outcome, including cerebral palsy and epilepsy [80]. According to one study, the handicap rate following neonatal seizures is 8% [81]. Abnormal EEG are predictive of developmental delay. Only 18% of ECMO infants with normal EEGs have developmental delays; 35% with one abnormal EEG and 58% with two or more abnormal EEGs [77].

Reconstruction of carotid artery post-ECMO ligation and cannulation remains controversial. ECMO infants post carotid artery ligation compared to those with right common artery reconstruction show no significant differences in neurodevelopmental delays [82, 83]. An additional study of neonates with CDH supported by ECMO showed a 72% incidence of occluded or highly stenotic right common carotid artery, following reconstruction at 2 years of age. Similarly to previous studies, there was no significant difference in neurologic development when compared to controls [84].

21.9 Summary

Since 1974 the role of ECMO in the treatment of neonatal respiratory and cardiac failure has been clearly established. During that time, new methods of medical management have allowed many infants to recover without ECMO, yet numerous babies still benefit. As knowledge has been garnered and disseminated through the ELSO registry and centers gained experience and data, neonatal selection criteria and indications have been elucidated. Any patient with reversible cardiopulmonary disease meeting criteria should be considered. ECMO is an excellent supportive modality after the failure of medical therapy with a proven reduction in mortality. The selection criteria maximize neonatal survival while minimizing unnecessary ECMO for irreversible disease.

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Congenital Lung Malformations

22

Emily R. Christison-Lagay and Peter C. Kim

Abstract

The development of the foregut, including the division of the esophagus from the tracheobronchial tree and the patterning and differentiation of the pulmonary anlage remains incompletely understood. Nonetheless, the last decade has made remarkable progress toward developing a more sophisticated model of the dynamic interactions of endoderm and mesoderm that give rise to the tracheobronchial tree, lung, and esophagus. Congenital cystic lesions such as congenital pulmonary airway malformation (alternatively congenital pulmonary adenomatoid malformation) (CPAM), bronchopulmonary sequestration (BPS), bronchogenic cysts, foregut duplications, and congenital lobar emphysema (CLE) arise from discrete perturbations within this interaction.

Keywords

Pulmonary sequestration • Congenital pulmonary airway malformation Congenital pulmonary adenomatoid malformation • Congenital cystic adenomatoid malformation • Congenital lobar emphysema • Foregut duplication

22.1 Introduction

The development of the foregut, including the division of the esophagus from the tracheobronchial tree and the patterning and differentiation of the pulmonary anlage remains incompletely understood. Nonetheless, the last decade has made remarkable progress toward developing a more sophisticated model of the dynamic interactions of endoderm and mesoderm that give rise to the tracheobronchial tree, lung, and esophagus. Congenital cystic lesions such as congenital pulmonary airway malformation (alternatively

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_22

congenital pulmonary adenomatoid malformation) (CPAM), bronchopulmonary sequestration (BPS), bronchogenic cysts, foregut duplications, and congenital lobar emphysema (CLE) arise from discrete perturbations within this interaction.

Historically, most cystic pulmonary lesions were discovered postnatally in the first weeks to months of life when they became infected or caused obstructive symptoms; now, however, they are diagnosed with increasing frequency by sonography during routine prenatal care. This early diagnosis not only provides an opportunity for improved prenatal surveillance, perinatal care, and a more comprehensive understanding of postnatal natural history, but also has posed some dilemmas surrounding the management of asymptomatic, incidentally discovered lesions whose behavior over time remains incompletely understood [1, 2].

22.2 Embryology

The human respiratory tract and primitive foregut begins development between 3 and 4 weeks of gestation and undergoes six separate stages: the embryonic stage (4–7 weeks), the pseudoglandular stage (5–17 weeks), the canalicular stage (16–26 weeks), the saccular stage (24–38 weeks), the alveolar stage (36 weeks to 2 years of age), and the microvascular maturation stage (birth to 3 years of age) [3].

Following the completion of gastrulation, the endoderm begins a complex reorganization to form the primitive respiratory and gastrointestinal tracts. Tracheal and lung bud precursors derive from different populations of cells. It is the lung buds that generate the bronchi and respiratory tree. Dynamic interactions of the endoderm (which will become the epithelium of the trachea, bronchi, and alveoli) with its surrounding mesoderm (which will give rise to muscle and cartilage) influence the location and pattern of branching. Paratracheal mesoderm inhibits branching while parabronchial mesoderm induces and supports the process. Aberrations in this process can lead to abnormal tracheal branching or the pulmonary agenesis [4].

More than 50 molecules have been implicated in lung morphogenesis. The process begins with the establishment of gradients of fibroblast growth factor (FGF) and FGF receptor mediated signaling that induce expression of the transcription factor Nkx 2.1 (thyroid transcription factor 1, TTF1) during the fourth week of gestation. The zone of expression of Nkx2.1 marks the future location of the thyroid gland and site of the midline laryngotracheal groove, the cranial extent of the respiratory system [4, 5]. Caudal extension of this groove forms the rudimentary trachea. The transcription factors T-box 4 and 5 (TBX4, TBX5) along with retinoic acid and its conjugate receptors RARα and RARβ induce FGF10 and transforming growth factor beta (TGFβ) stimulate lung bud development and initiate branching. Deficiencies in retinoic acid (vitamin A) and RAR signaling have been implicated in pulmonary agenesis, diaphragmatic hernia, lobar agenesis and tracheoesophageal fistula [6]. FGF-10 acts a tropic stimulus for epithelial cell proliferation while the secretion of BMP-4 initiates branching morphogenesis in the apical epithelial cells. Just beyond the elongating branch tip, sonic hedgehog (shh) stimulates mesenchymal proliferation and induces TGFβ1 which helps to stabilize the growing matrix and provides feedback inhibition of shh and FGF10. This inhibition allows at the tip allows epithelial proliferation lateral to the expanding bud to promote further branching. Subsequent formation of epithelialized ducts involves such molecules as Hoxb5 (larger bronchioles) and epimorphin (respiratory bronchioles and alveoli) [7]. Furthermore, the precisely controlled expression and interaction of the integrin family of transmembrane receptor proteins with E-cadherin and extracellular adhesion proteins such as laminin, fibronectin, and tenascin C contribute to tissue stability and homeostasis and organ morphogenesis [8].

22.3 Etiology and Animal Models of Cystic Lung Lesions

Because of the complexity of lung and foregut development, the spectrum of congenital cystic lung lesions likely results from innumerable local perturbations of the normal pattern of embryonic development. Studies of human resected CPAM

and BPS tissue have found that both Hoxb5 and an aberrant isoform of α2-integrin levels are abnormally increased [8, 9]. TTF1 and FGF9 overexpression and FGF7 underexpression have also been implicated in CPAM development without concomitant changes in FGF10 or FGFR2 expression [10]. Microarray analysis of resected CPAM specimens identified Clara cell marker 10 (CC10) and fatty acid binding protein 7 (FABP-7) to be much higher than in age matched controls, although any putative mechanism for their roles in lung dysmorphogenesis remains purely speculative [11]. Most authors feel that sequestrations arise from anomalous lung buds dorsal to the normal lung bud between the fourth and eighth week of gestation [12].

Animal models have found that overexpression of FGF7, 9, and 10 is associated with abnormal pulmonary morphogenesis and the development of cystic lung malformations [13–16]. Induced expression of the transcription factor Sox2 has also been shown to result in pulmonary cysts, "bronchialization" of alveoli, and "muscularization" of the airways and vasculature [17]. The adriamycin-induced model of foregut malformation also demonstrates abnormal lung budding with frequent anomalous connections between the respiratory and GI tract [18]. Recent research has noted increased platelet derived growth factor PDGF-B gene expression and protein production in in utero rapidly expanding CPAMs compared to normal lung or term CPAM specimens [19].

22.4 Prenatal and Neonatal Diagnosis and Imaging

The routine use of antenatal ultrasound has increased the frequency of prenatal diagnosis of congenital lung lesions. CPAM and BPS are now often sonographically diagnosed between 20–24 weeks gestation. Following diagnosis, antenatal surgical opinion is commonly sought. Most CPAM and BPS may be expectantly managed with planned term delivery followed by neonatal intervention if clinically warranted. It is not unusual for lesions identified during the second trimester to decrease in size over the remainder of gestation with some resolving altogether [20, 21]. The mechanism for this regression is not completely understood. One possibility is that the lesions outstrip their blood supply and involute. Another possibility is that the lesions decompress through small communications with the normal adjacent lung. Management of lesions which appear to regress is a source of controversy and will be discussed in detail below [22]. In the context of cystic lung lesions, the presence of nonimmune hydrops is the most important indicator of fetal distress and is strongly correlated to the incidence of fetal demise [23, 24]. Polyhydramnios, mediastinal shift, and a low fetal lung to thorax ratio are also markers for poor outcome [25]. A minority of CPAM cases present with antenatal fetal distress or with neonatal respiratory compromise. More commonly, infants with prenatally diagnosed CPAMs who do not undergo resection during infancy, present later in childhood with infectious complications.

Antenatal sonographic features of CPAM depend upon the size of the associated cysts. Multiple cystic lesions greater than 5 mm in diameter appear as an hypoechoic mass, microcystic lesions tend to be echogenic. Extralobar sequestrations tend to appear as well-defined, hyperechoic, homogeneous lesions similar to the appearance of a microcystic CPAM. In this case, the identification of a systemic blood supply can be crucial in making an appropriate diagnosis. MRI can be a useful adjunct to better delineate "hybrid" cases with features of both CPAM and BPS.

Subdiaphragmatic (intraabdominal) extralobar sequestration may appear as an echogenic suprarenal mass with a systemic blood supply and may be confused with a neuroblastoma or mesoblastic nephroma. Fetal adrenal neuroblastomas are frequently cystic, a feature which may be helpful in interpreting prenatal sonography [26]. On antenatal ultrasound, it is impossible to distinguish intrathoracic intralobar from extralobar sequestration.

An anteroposterior and lateral chest X-ray (CXR) is the often the first obtained postnatal imaging of CPAM and BPS. The lesions can be obscured by atelectasis or pneumonia if present. A CPAM most commonly appears as a radiolucent area on CXR. Large CPAMs and BPS can cause

mediastinal shift or esophageal displacement on barium swallow. Extralobar sequestrations are typically small and difficult to detect on CXR, they may be appreciated on chest or abdominal ultrasound to work up other organs. Intralobar sequestrations may appear as a triangle-shaped mass in the base of the lung. An air-fluid level may be present, suggesting either bronchial communication in hybrid lesions or the congenital bronchopulmonary foregut malformation (CBPFM) variant (see below). The latter diagnosis can be confirmed through demonstration of a communication of the pulmonary cyst with the esophagus or stomach by barium swallow. Ultrasound is the best screening tool. Sequestrations appear as echo-dense lesions on either side of the diaphragm with an identifiable systemic blood supply. CT imaging best defines the type of cystic lesion and its associated anomalies, although MRI is superior to CT in identifying systemic blood supply.

22.5 Congenital Pulmonary Airway Malformations

Congenital pulmonary airway malformations (CPAM), previously referenced in the literature as congenital cystic adenomatoid malformations (CCAM) are hamartomatous lesions of the lung characterized by terminal bronchiolar proliferation into cysts of various sizes (Fig. 22.1a). They are the most common congenital cystic lesions of the lung accounting for approximately 30–40% of developmental lung bud anomalies with an historically reported incidence of 1:25,000–1:35,000 live births [2, 27]. This is likely a substantive underestimation of true incidence. Macroscopically CPAMs appear as a multicystic intrapulmonary mass. Cysts are typically localized to a single lobe, with lower lobes more frequently affected than upper lobes and an equivalent left-right distribution. Bilateral disease is rare and is more likely to result in con-

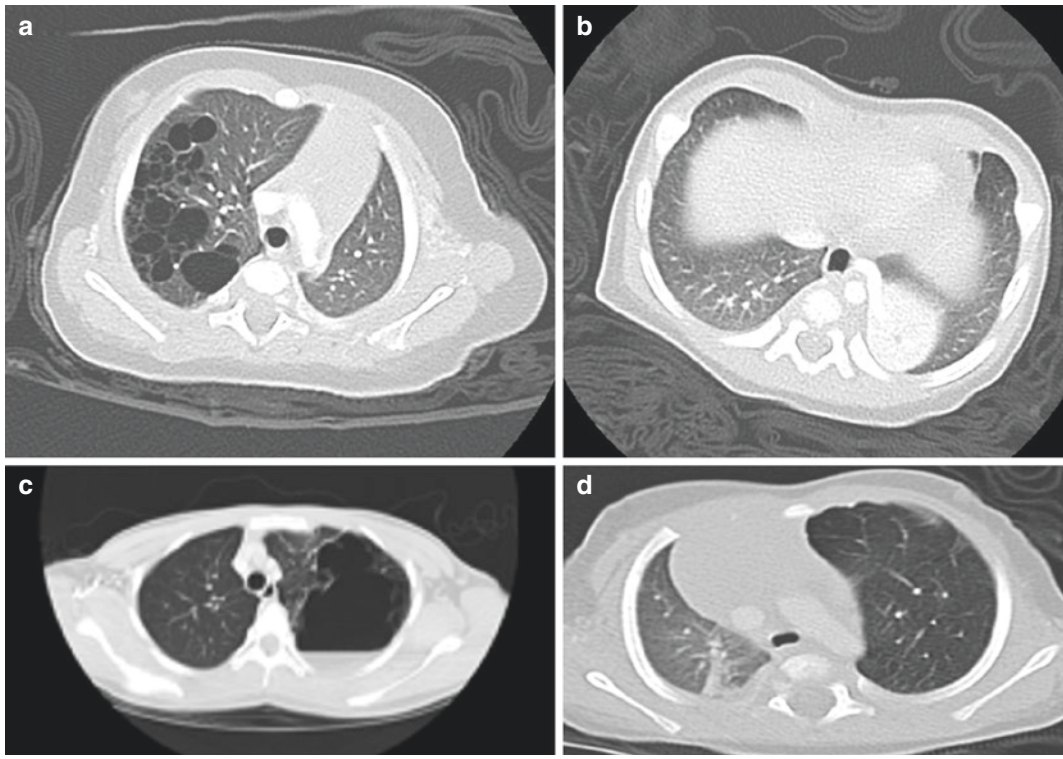

Fig. 22.1 (**a**) Right lower lobe CCAM; (**b**) left lower lobe pulmonary pleuroblastoma; (**c**) left lower lobe extralobar sequestration with a large aortic feeding vessel; (**d**) congenital emphysematous lung with left hyper lucent lung field is shown

genital high airway obstruction syndrome (CHAOS) [24]. Cysts can range in size from less than a millimeter to greater than 10 cm. Although many cystic lung lesions have been loosely encompassed under the moniker of CPAM, microscopically, CPAMs can be distinguished from other cystic lung lesions by five characteristics:

(1) Increased deposition of smooth muscle and elastin within the cyst wall, (2) the absence of cartilaginous remnants within the mass itself, (3) the presence of polypoid mucosal projections into the cyst, (4) the presence of mucus secreting cells with the cyst walls, and (5) a lack of associated inflammation [28]. CPAMs are not commonly associated with other congenital or genetic anomalies, although infants who are stillborn with CPAMs reportedly have a higher incidence of associated abnormalities including heart, renal, and neural tube defects as well as facial dysmorphia [2].

The historical classification of CPAM by Stocker based upon postnatal lung resections or autopsy results of stillborn infants divided the lesion into three types: macrocystic (Stocker I), microcystic (Stocker II), and solid (Stocker III) [28]. More recently this classification has been expanded to include tracheobronchial dysgenesis (type 0) and distal acinar dysgenesis (type 4, with an accompanying change from Roman to Arabic numbering) to encompass the complete spectrum of pathologic airway malformations extending from tracheobronchial to distal acinar malformations (see Table 22.1 and Fig. 22.2) [29]. Type 1 lesions account for the majority of cases (50–65%) and consist of a single or multiple large cysts surrounded by smaller cysts and compressed pulmonary parenchyma. The epithelium of larger cysts is pseudostratified and ciliated, while smaller cysts are lined by cuboidal to columnar epithelium [2, 29]. Type 2 CPAM are characterized by small cysts (0.5–2 cm) lined by cuboidal epithelium with an underlying fibromuscular layer. Occasionally, associated chromosomal or developmental anomalies may be seen with a Type 2 lesion. Type 3 lesions are rare (<10% of postnatal cases). They are often mixed solid-cystic adenomatous lesions, although on gross examination they appear solid. On histologic examination, the lesion resembles immature lung with an absence of bronchi. Cuboidal epithelial cells line irregular airway-like structures surrounded by alveolar ductules and saccules. Large type 3 lesions can exert a mediastinal

Table 22.1 Expand stocker classification of CPAMs

Stocker classification	Anatomic description
0	Acinar agenesis
I	Macrocystic (>5 mm)
II	Microcystic (<5 mm)
III	Solid
IV	Mixed solid-macrocystic

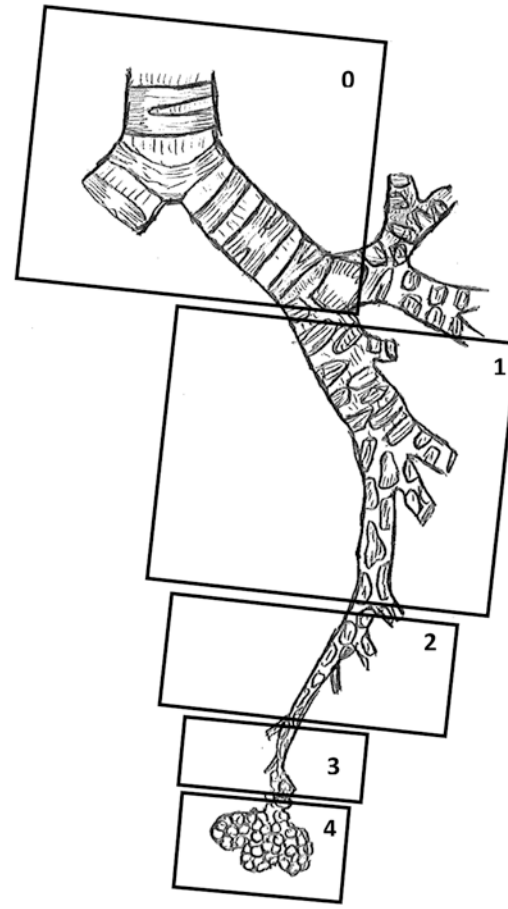

Fig. 22.2 Stocker reclassification of CPAMA based upon the presumed site of development of the malformation. 0 = tracheobronchial, 1 = bronchial, 2 = bronchiolar, 3 = bronchiolar/alveolar, 4 = distal acinar

mass effect causing contralateral lung hypoplasia or hydrops. Type 0 lesions are rare and are incompatible with life. Infants present with cyanosis at birth. There is an associated incidence of cardiovascular abnormalities and dermal hypoplasia [2]. Type 4 CPAMs are found 10–15% of the time and presents as a hamartomatous malformation of the distal acinus. Large thin-walled cysts are found peripherally and are lined by type I and II pneumocytes. They most closely approach Type I lesions and were previously classified as such.

Stocker's initial classification of CPAM reported a stillborn rate of 14%. Of those infants surviving to birth, approximately 80% presented with symptoms of infection or respiratory distress in the perinatal period through the first month of life [30]. Pulmonary hypoplasia in this population can contribute to cardiorespiratory compromise. Presentation later in childhood is rare, accounting for fewer than 10% of all presentations. Pulmonary hypoplasia is not a feature of these lesions which most commonly present with recurrent or persistent pneumonia, but may also present with lung abscess, pneumothorax, failure to thrive, and malignant transformation [2].

While Stocker's initial classification also attempted to attach prognostic value to these subtypes, clinically, it may be more practical to divide CPAMs on the basis of cyst size into macrocystic (>5 mm) and microcystic (<5 mm) categories. Macrocystic lesions tend to communicate with proximal airways and may lead to early air-trapping as the cysts fill but do not empty and compress adjacent normal lung. On the other hand, when diagnosed prenatally, it is rare for them cause hydrops. They are generally asymptomatic at birth and become symptomatic as amniotic fluid is exchanged for air. Microcystic and solid CPAMs are associated with anatomic abnormalities of the tracheobronchial tree including bronchial atresia and stenosis. They are more frequently associated with prenatal hydrops and pulmonary hypoplasia. It is the complications of hydrops and hypoplasia rather than the type of lung lesion alone that determine prognosis.

22.5.1 Prenatal Management and Fetal Surgical Considerations

Large fetal lung lesions can affect fetal development in several reproducible ways. Esophageal compression can cause polyhydramnios. Vena caval and cardiac compression results in fetal hydrops and death. While all prenatally diagnosed lung lesions should be approached with gravitas, they have a variable natural history. Approximately 15% of prenatally diagnosed CPAMs and up to 70% of BPS shrink during late gestation [31]. Several authors report complete sonographic regression [32, 33]. Crombleholme, Adzick and colleagues have developed a formula for the prediction of the development of fetal hydrops which uses a ratio of CPAM volume normalized against fetal head circumference [34]. CPAM volume is estimated as (length × width × height × 0.52). A cystic adenomatoid malformation volume ratio (CVR) greater than 1.6 is predictive of a greater than 80% chance of the development of hydrops. CVR reaches a plateau at approximately 28 weeks of gestation. For fetuses less than 28 weeks, twice weekly US surveillance is recommended to assess for hydrops. For fetuses with CVR <1.6, surveillance can be done weekly. Hydrops in this group occurs less than 2% of the time. An exception to this rule can occur in the event of a single dominant cyst. Such a cyst is at risk for acute enlargement and consideration should be given to shunt placement in if the CVR is less than 1.6.

Options for fetal intervention include shunt placement and resection. Fetal thoracentesis used as solo therapy is ineffective for treatment because of rapid reaccumulation of cyst fluid but it may serve as a temporizing measure prior to definitive therapy [35]. CPAMs presenting with a dominant large cyst without a solid component may undergo shunt placement. Successful delivery near term is possible in 75–80% of fetuses undergoing shunt placement with fetal loss occurring in approximately 10% [36]. Shunt placement prior to 20 weeks GA may result in an increased risk of chest wall abnormalities [37].

For patients with CVR >1.6 demonstrating evidence of hydrops, the firstline treatment of choice is a course of maternal steroids (betamethasone or dexamethosone) which has been shown to limit CPAM growth and diminish hydrops [38, 39]. Only after this option has been unsuccessful should any fetal intervention be entertained. Options for fetal intervention include shunt placement and resection. Fetal thoracentesis used as solo therapy is ineffective for treatment because of rapid reaccumulation of cyst fluid but it may serve as a temporizing measure prior to definitive therapy [35]. CPAMs presenting with a dominant large cyst without a solid component may undergo shunt placement. Successful delivery near term is possible in 75–80% of fetuses undergoing shunt placement with fetal loss occurring in approximately 10% [36]. Shunt placement prior to 20 weeks GA may result in an increased risk of chest wall abnormalities [37].

Open fetal surgery is an option at specialized centers for fetuses with microcystic CPAMs, a normal karyotype and no other abnormal anatomy on fetal sonography. Survival in the Children's Hospital of Philadelphia (CHOP) series is reported as 13 of 24 cases with resolution of hydrops at 1–2 weeks following resection, restoration of the mediastinum to midline and compensatory in utero lung growth [1]. In this series the majority of fetal deaths (6 of 11) occurred intraoperatively after the delivery of the mass from the chest. Maternal morbidity has been low and mostly related to uncomplicated wound infections. Occasionally, progressive hydrops can result in the "maternal mirror syndrome" in which illness in the fetus is reflected in the condition of the mother. Progressive symptoms of pre-eclampsia including vomiting, hypertension, peripheral edema, proteinuria and pulmonary edema can occur [40]. The only successful treatment of the mother is delivery of the fetus.

If significant respiratory distress is anticipated at birth, the Ex Utero Intrapartum Therapy (EXIT) procedure utilizes "placental bypass" during thoracotomy and lobectomy and may be considered in centers equipped to perform it.

22.5.2 Postnatal Management and Surgical Considerations

It is generally assumed that surgical resection is the management of choice of most pediatric surgeons today for symptomatic congenital cystic lesions. The management of asymptomatic lesions, however, is a clinical conundrum without broad consensus. The traditional argument favoring early resection cites avoidance of the long-term risk of pulmonary infection, an increased operative ease in the non-infected field, the potential benefit of long term compensatory lung growth and avoidance of the potential difficulty and expense of long-term patient follow-up. An opposing view is taken by surgeons who cite that operation on an asymptomatic patient poses significant and potentially morbid risks without clearly defined benefit. One study found that 10% of perinatally diagnosed patients undergoing excision of an asymptomatic CPAM experienced perioperative complications [31]. Moreover, several studies have suggested that resection of a complicated CPAM is not associated with any significantly higher morbidity than elective resection of an asymptomatic CPAM (although other studies have come to the opposite conclusion) [20]. Nor is there any definitive data suggesting that pulmonary function is improved in patients undergoing early resection (allowing a greater opportunity for compensatory growth) than later [21, 41].

More recently evidence has emerged that the risk for malignancy within the population of children with radiographically diagnosed CPAM may be higher than historically suspected. There is a known association between bronchoalveolar carcinoma and rhabdomyosarcoma and CPAM with over 25 case reports documented in the last three decades [42–45]. Ozcan reported 33 cases of primary pulmonary rhabdomyosarcoma; nearly 50% of these had cystic lung malformations and a quarter were associated with CPAM [46]. Furthermore, malignant transformation has been observed in incompletely resected CPAM [47]. Perhaps most concerning and convincing are the recent reports suggesting that

radiographic imaging is unable to accurately differentiate CPAM from pleuropulmonary blastoma (PPB) a high grade malignancy associated with a poor prognosis in advanced stage disease with little observed efficacy of adjuvant chemo- or radiotherapy (Fig. 22.1b) [22]. In our recent retrospective analysis of 129 CPAM resections, we identified three patients (2.3%) who had pathologically confirmed but clinically unsuspected PPB at the time of surgical resection [20, 22]. When counseling families at our institution, we approach discussion of the management of asymptomatic CPAM with these findings and now recommend surgical excision over expectant management. Patients who had previously elected to be followed conservatively are also now informed of these new recommendations.

22.5.3 Surgical Approach

The surgical approach to CPAM resection is by either open posterolateral thoracotomy or, more recently, a video assisted thoracoscopic (VATS) approach at 2–6 months of age to avoid neonatal anesthesia. The two techniques offer similar results and have a similar complication profile. Cosmesis, post-operative pain relief, and hospital stay is improved with VATS which is typically accomplished through the use of three or four 3–5 mm port sites. One of these must be enlarged sufficiently to extract the specimen from the thoracic cavity. A chest tube is typically left in place and may usually be removed on the first postoperative day.

The objective of surgical management is complete surgical excision of the entire cystic lesion. Most frequently this is performed via segmentectomy or lobectomy, very rarely it requires pneumonectomy [22, 48, 49]. If the CPAM involves adjacent lobes, lobectomy can be used to excise the principal lesion with segmentectomy reserved for the less involved lobe. In general, pneumonectomy should be avoided as it can lead to disabling respiratory symptoms and long-term complications including chest wall deformity, scoliosis, and abnormal systemic venous return [50]. Postoperative pulmonary function is excellent and infants are at no increased risk for respiratory infection than other children. If an infant has a significant degree of pulmonary hypoplasia, many centers encourage prophylaxis against RSV during the first year of life [2].

22.6 Bronchopulmonary Sequestration

Sequestrations are benign pulmonary lesions characterized by a lack of direct bronchial communication to the tracheobronchial tree and by a systemic blood supply. They are classified on the basis of the presence of a pleural covering. An intralobar sequestration is contained within the substance of the adjacent lung tissue while an extralobar sequestration is enveloped in its own pleural lining and is anatomically separate from the pulmonary parenchyma. The reported prevalence of sequestrations ranges form 0.15–1.8% in the general population, and intralobar sequestration is reported three times as commonly as extralobar sequestration in most series [51]. Both intra- and extralobar sequestrations are more commonly located on the left, and an extralobar sequestration may be located within the chest, within the muscle of the diaphram, or in a subdiaphragmatic position (Fig. 22.1c) [52]. Extralobar sequestrations are three times as common in males [2]. Rarely, the entire lung can be an extralobar sequestration. Approximately 80% of BPS have an aortic arterial supply, although other, and sometimes multiple, systemic sources have been reported. Venous drainage of extralobar sequestrations is typically into the systemic circulation, but up to 25% of extralobar sequestrations drain into the pulmonary circulation. In contrast, almost all intralobar sequestrations drain into the pulmonary venous system. While most BSP are asymptomatic, a few may present with respiratory symptoms, cardiac failure, infection, hemoptysis, or in conjunction with other congenital anomalies including congenital diaphragmatic hernia (CDH), cardiac and musculo-skeletal abnormalities, and

enteric duplications. Developmental abnormalities are much more commonly associated with extralobar than intralobar sequestration. Five to fifteen percent of infants with CDH have an associated extralobar sequestration [53]. Intralobar sequestration is more likely to present in older children with symptoms related to compression of adjacent, atelectatic lung or by infection secondary to inadequate drainage of secretions from the sequestered lung.

Although traditionally considered a different pathological and clinical entity from CPAM, BPS and CPAM can present as a hybrid anomaly with histologic features of a CPAM (most commonly a Stocker 2 or solid lesion) but a systemic blood supply [54–56]. As the process of tracheobronchial differentiation, budding, and branching is a complex one with the necessary synchronization of multiple elements, it is not altogether unexpected that patterning anomalies may overlap. Further complicating the nomenclature and easy separation of cystic lesions by pathology, a new term has been invented to define rare extralobar or intralobar sequestrations that communicate with the esophagus or stomach. These anomalies are termed congenital bronchopulmonary foregut malformations (CBPFM) and they are classified into four types according to their location and the level of communication between the alimentary tract and the tracheobronchial tree [57]. These lesions are more often located on the right side and have with equal gender distribution. Often there are associated congenital anomalies of the VACTERL spectrum, most commonly tracheoesophageal fistula/esophageal atresia and skeletal anomalies.

Like CPAM, the mass effect of BPS can cause fetal hydrops through cardiac and vena caval compression. Moreover, it has been speculated that shunting between a systemic arterial supply and the pulmonary venous drainage of a BPS may cause high-output cardiac failure and nonimmune hydrops [58]. Fetal mortality reaches 100% in untreated hydrops and 80% in fetuses who have significant pleural effusions [59, 60]. Placement of thoracoamniotic shunts improves outcome. Rarely BPS can cause esophageal or gastric compression resulting in polyhydramnios. Polyhydramnios can cause preterm labor and BPS associated with polyhydramnios has a survival rate of only 30% [61]. The role of reduction amniocentesis in the setting has yet to be defined.

With the prenatal sonographic identification of sequestration, a comprehensive sonographic survey and fetal echocardiography should be performed to attempt to identify any associated anomalies. Prior to consideration of fetal intervention, fetal karyotype must be performed. Fetuses with hydrops presenting after 30 weeks of gestation are candidates for preterm delivery while those less than 30 weeks may be considered for fetal intervention at specialized centers. Fetuses with large sequestrations that are not causing hydrops should be referred to a tertiary care maternal-fetal unit with the facilities for aggressive neonatal resuscitation and access to urgent surgical intervention. Large pleural effusions mandate emergent tube thoracostomy [1].

Neonates with respiratory symptoms should undergo urgent surgical resection. The arterial supply to the sequestration requires special attention. In up to 20% of cases, arterial supply comes from a branch of the infradiaphragmatic aorta. Loss of control of this blood vessel with subdiaphragmatic retraction can result in uncontrolled hemorrhage. It has also been reported that as many as 60% of right sided intralobar sequestrations may have scimitar syndrome in which the pulmonary veins drain into the vena cava [61]. Care must be taken not to inadvertently ligate the main branches of the pulmonary vein and therefore cause venous congestion of an entire lobe or ipsilateral lung.

Resection of asymptomatic sequestrations is generally advocated to prevent the later development of infection or hemorrhage (rare). Some surgeons elect to follow intraabdominal BPS citing the absence of any respiratory benefit and the rare instances of infection. The challenge remains with regard to inconvenience and methodology of follow up and persisting question of differential diagnosis in ruling out any tumorous lesions.

22.7 Congenital Lobar Emphysema

Congenital lobar emphysema (CLE) is thought be a form of bronchomalacia in which dysplastic bronchial cartilage allows passage of air during inspiration but collapse during expiration leading to lobar hyperinflation (Fig. 22.1d). More rarely a similar picture may result from extrinsic compression from a vascular ring formed by abnormal pulmonary vessels or a large patent ductus arteriosus, or endobronchial obstruction from inspissated mucus. A third of cases remain idiopathic.

On prenatal ultrasound, CLE appears as an echogenic lesion without evidence of systemic blood supply. Fetal lung fluid trapping within the affected lobe may cause second trimester expansion of the lesion. Some cases of CLE regress during late gestation and become sonographically indistinguishable from normal fetal lung [62]. Despite sonographic regression, these lesions can still cause postnatal air-trapping and should be followed clinically.

The most dramatic presentation of CLE occurs when lobar hyperinflation causes compression of the normal ipsilateral lung and mediastinal shift leading to cardiorespiratory collapse. Emergency thoracotomy is lifesaving and the involved lobe often extrudes through the thoracotomy incision upon opening the pleural space. Less dramatically, CLE presents with increasing tachypnea progressing to ventilator dependence. A plain chest radiograph often demonstrates a hyperlucent lobe with mediastinal shift and compressive atelectasis of the contralateral lung. Resection of the involved lobe is curative and allows for restoration of mediastinal contents to the midline, lung reexpansion, and compensatory ipsilateral lung growth. Occasionally, CLE is detected radiographically and remains clinically silent. In this instance, a trial of expectant management may be appropriate, keeping in mind that the dysplastic bronchial cartilage may not allow normal clearing of secretions and the involved lung may be at increased risk of pneumonia.

Acquired emphysematous changes and parenchymal cysts may also result from long-term ventilator dependence of poorly compliant, premature lungs. If these changes cause mass effect then surgical management may be appropriate, with the caveat that most infants with acquired emphysema have marginal pulmonary function and may not tolerate resection. With time and growth of the child, most acquired changes resolve spontaneously.

22.8 Bronchogenic Cysts and Foregut Duplication

Bronchogenic cysts, foregut duplication cysts, and neurenteric cysts likely represent various presentations of aberrant patterning of the foregut anlage. These bronchopulmonary foregut malformations classically feature (1) a well-developed coat of smooth muscle, (2) a mucosal epithelial lining of either gastrointestinal or respiratory origin, and (3) an intimate attachment to some portion of the foregut [63]. Hybrid lesions with both respiratory and gastrointestinal epithelium and attachments have been described. Presentation may vary and depends upon the organ of origin and anatomic location of the malformation as well as the presence of mass effect or infection [64]. Newborn infants can present in respiratory distress secondary to bronchial obstruction or compressive mass effect of adjacent lung. In an older child, lesions are frequently detected on imaging conducted to evaluate nonrelated symptoms. Gastrointestinal duplications may have islands of acid secreting gastric mucosa leading to ulceration and hemorrhage.

Bronchogenic cysts are the most common cystic malformation of the mediastinum and are most commonly located near the carina or right mainstem bronchus although there are case reports of bronchogenic cysts presenting in the neck, pericardium, pulmonary parenchyma and intra-abdominally [65]. Histologically they have well defined wall of fibroelastic tissue, muscle and cartilage lined with ciliated respiratory epithelium. Often they share a wall with the tracheobronchial tree or esophagus, occasionally they arise as a saccular diverticulum off the airway and in this case may present with an air-fluid

level on imaging. Peripheral lesions are more likely to have a communication with the tracheobronchial tree and typically present with distal bronchial obstruction and pneumonia. More commonly however, a bronchogenic cyst appears as a spherical non-attenuating mass with Hounsfield units greater than water on CT. Once identified, bronchogenic cysts should be surgically resected via lateral thoracotomy or thoracoscopy due to their potential to become infected, or to present subsequently with obstruction or hemorrhage. Malignancy arising in a bronchogenic cyst has been reported in rare instances [66]. Care must be taken during the surgical dissection to avoid damage to any shared bronchial or esophageal wall. A direct communication can be ligated or repaired.

Most foregut duplication cysts are intrathoracic. Presentation may be indistinguishable from a bronchogenic cyst and is often secondary to mass effect. Compression of adjacent structures may cause respiratory (stridor, wheezing, cough, or cyanosis) or gastrointestinal (vomiting, dysphagia, obstruction) symptoms [64]. Gastric mucosa is found in approximately 30% of esophageal duplications and may cause hematemesis [67]. Imaging options include ultrasonography which may identify anterior duplications or be helpful in fetal imaging, CT, or contrast esophagogram. The latter may also help determine whether there is any communication with the esophagus and assist in surgical planning [68]. Like bronchogenic cysts, foregut duplications should be resected given their potential to present with secondary complications.

Neurenteric cysts are the least common of the foregut malformations. They are associated with vertebral anomalies (including scoliosis, hemivertebrae, and spina bifida) [64]. As with other congenital foregut malformations, an exact embryologic defect leading to the development of neurenteric cysts has yet to be uncovered, however it is commonly attributed to either a failure of normal separation of notochord and foregut or to aberrant herniation of foregut endoderm into the dorsal ectoderm [69]. Urgent surgical excision is indicated as complications include meningitis and paraplegia. Cystic communication into the spinal canal presents surgical challenges which must be addressed by a multidisciplinary team of pediatric surgeons and neurosurgeons. All children with posterior mediastinal masses should have adequate visualization of the spinal cord and canal. MRI is the preferred modality because of its ability to precisely define intraspinal anatomic relationships [68]. Surgical management often includes laminectomy or laminotomy with simultaneous surgical and neurosurgical excision of the cyst [63, 70].

Conclusion

Congenital pulmonary malformations comprise a clinically heterogeneous group of developmental anomalies with an overall favorable prognosis associated with expedient diagnosis and resection. Increasing evidence supports a role for early resection of asymptomatic lesions by experienced surgeons, which may often be accomplished safely through minimally invasive techniques.

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Esophageal Atresia and Tracheo-Esophageal Fistula

23

Paul D. Losty

Abstract

Surgery for esophageal atresia (EA) is regarded as one of the greatest landmarks in newborn surgery. Advances have now led to greater than 95% survival for EA babies managed in the current era with much interest now focusing on health outcome(s), morbidity and quality of life (QoL) of survivors. Classical operation with muscle sparing thoracotomy, axillary skin crease incision and minimally invasive surgery offer a selection of management strategies for the pediatric surgeon and enthusiast alike. Debate continues with regard best practice and expert management of pure [long-gap] esophageal atresia without fistula, medical vs surgical treatment of gastro-esophageal reflux disease (GER), therapies for anastomotic stricture and tracheomalacia. Developmental biology and molecular genetic studies provide fascinating insight into the etiology of EA—TEF, with many key contributions emerging from animal models sharing striking similarity to the human phenotype.

Keywords

Esophageal atresia • TEF fistula • H fistula • Esophageal replacement surgery • Long-term outcomes

> To anastomose the ends of an infant's esophagus, the surgeon must be as delicate and precise as a skilled watchmaker. No other operation offers a greater opportunity for pure technical artistry.
> Willis Potts (1950) [1]

23.1 Introduction

Surgery for esophageal atresia (EA) is regarded as one of the greatest landmarks in newborn surgery. Advances have now led to greater than 95% survival for EA babies managed in the current era with much interest now focusing on health outcome(s), morbidity and quality of life (QoL) of survivors. Classical operation with muscle sparing thoracotomy, axillary skin crease incision and minimally invasive surgery offer a selection of management strategies for the pediatric

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_23

surgeon and enthusiast alike. Debate continues with regard best practice and expert management of pure (long-gap) esophageal atresia without fistula, medical vs surgical treatment of gastro-esophageal reflux disease (GER), therapies for anastomotic stricture and tracheomalacia. Developmental biology and molecular genetic studies provide fascinating insight into the etiology of EA—TEF, with many key contributions emerging from animal models sharing striking similarity to the human phenotype [2, 3].

23.2 History

The history of EA-TEF is well documented in the literature [2, 3]. First survivors were not recorded until 1939 with Leven and Ladd achieving success with staged esophageal repair. Cameron Haight (an American surgeon working at Ann Arbor, Michigan) is credited with the first successful primary repair and survival of a 12 day old female newborn. Success in the UK followed with Franklin (1947) based at Hammersmith Hospital London, Denis Browne (1948) at Great Ormond Street Hospital For Sick Children, London and subsequently Peter Paul Rickham (1949) working at Alder Hey Children's Hospital Liverpool. By the 1980s pediatric surgery units in the developed world were achieving spectacular outcomes notably 85–90% survival with mortality falling to less than 10% defining the modern era of care [2].

23.3 Classification

In 1929 Vogt proposed an anatomical classification for EA and TEF based on radiology and post-mortem findings [4]. A variety of surgical classifications were thereafter suggested as treatment became more successful, the most frequently deployed system being that attributed to Gross [5]. The most detailed classification, however, is credited to Kluth and incorporates all the described anatomical variants of EA and TEF [6]. A working classification based on the frequency of each specific anomaly is of greatest practical value to the surgeon (Fig. 23.1).

23.4 Risk Categorization

Waterston's seminal paper describing the influence of pulmonary disease, birth weight and associated congenital anomalies on outcome of newborns with EA-TEF provided important contributions in the development of prognostic scoring systems [7]. Advances in neonatal intensive care have now rendered the Waterston classification outdated. In 1994 Spitz et al. proposed a new risk grading system based on birth weight and presence or absence of congenital heart disease that is widely applicable to the modern era [8] (Table 23.1). A Montreal classification places greater emphasis on preoperative ventilator dependence and associated major anomalies as survival determinants [9]. Many studies have recorded the negative influence of respiratory distress syndrome and pneumonia on outcome(s) with the burden of aspiration events contributing to morbidity and late death following operative repair [10, 11]. Variant anatomy also features as risk factor(s) for determining favourable outcomes. Babies with 'long gap' or 'pure' EA without fistula experience a high morbidity from anastomotic leak, stricture, fundoplication rate(s), 'failure'/'re-do' operations and esophageal replacement [10–12].

23.5 Epidemiology

In Liverpool and Mersey the incidence of EA and TEF is approximately 1 in 3300 live births [13]. Incidence varies widely across the world, e.g. 1 in 2440 Finland [14] to 1 in 4500 in Australia [15] and USA [16]. Sex ratio has been quoted as equal by many authors but some publications also refer to a male preponderance [17]. EA and TEF is more common in twin pregnancy. Exposure to teratogenic drugs during pregnancy has been implicated, these include thalidomide, progesterone and estrogens [18].

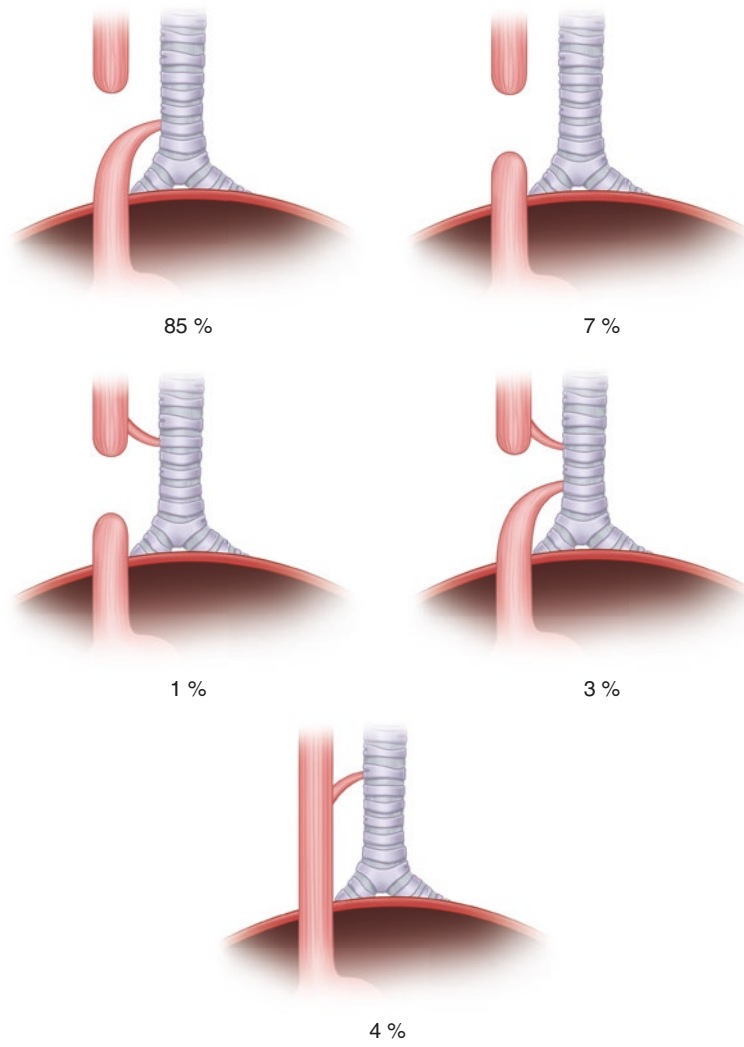

Fig. 23.1 Classification and frequency of esophageal atresia and tracheo-esophageal fistula. EA and distal TEF—85%; Isolated EA—7%; H-type TEF—4%; EA with proximal and distal fistulas—3%; EA and proximal fistula—1%

Table 23.1 Spitz prognostic classification scoring system [8]—Survival related to birth weight and congenital heart disease (CHD)

Group	Survival (%)
I birth weight > 1500 g without major CHD	97%
II birth weight < 1500 g or major CHD	59%
III birth weight < 1500 g and major CHD	22%

23.6 Genetics

Reports of familial cases of EA-TEF suggests a polygenic hereditary etiology. The best estimate of risk of recurrence for parents of a single affected child is 0.5–2.0%, rising to 20% if another sibling is born with EA. The vertical transmission risk is 3–4% [19]. A 10% incidence of non-specific chromosomal abnormalities (translocations, deletions and duplications) is recorded. Edwards syndrome (trisomy 18) and Down's (trisomy 21) are associated with the EA TEF phenotype. Recognition of a syndrome suggestive of a major chromosomal abnormality in EA and TEF should prompt urgent involvement of a clinical geneticist before corrective surgery is undertaken. EA-TEF has also been described in association with Feingold syndrome (autoso-

mal dominant), Holt–Oram syndrome, DiGeorge sequence, polysplenia, and in babies with Pierre Robin anomaly [19].

23.7 Animal Models

Contributions to understanding the embryology and genetic control of foregut development have evolved from laboratory research involving animal models of EA and TEF. The adriamycin rodent model was developed by Juan Tovar and colleagues in Madrid [20]. Timed pregnant rodents administered adriamycin (doxorubicin) in the prenatal period on gestational days 8 and 9, yield offspring with an EA-TEF variant phenotype [20]. These animals also have VACTERL spectrum anomalies—*v*ertebral, *a*norectal, *c*ardiac, *t*racheo-*e*sophageal, *r*adial/renal and *l*imb defects [21]. A murine model of the VACTERL syndrome has also been generated in mice with targeted deletions of the transcription factors Gli-2 and Gli-3 for the Sonic hedgehog (Shh) gene—pivotally linked with axial organogenesis. Gli-2−/−Gli-3−/−double mutants demonstrate the full phenotypic spectrum of VACTERL syndrome thus confirming a crucial role for Shh in genetic control of foregut development [21, 22].

23.8 Embryology

There is no unifying embryological theory which successfully explains all the anatomical variants of EA and TEF. In the developing embryo the ventral aspect of the primitive foregut is destined to become the tracheo-bronchial tree. A median laryngotracheal groove develops in the ventral aspect of the foregut of the 23 day old embryo. As the groove elongates with the growing esophagus it is postulated that lateral epithelial ridges fuse to bring about foregut septation. Whilst explaining the possible origins of tracheo-esophageal cleft and H type variant EA fistula, caudo-cranial separation of the ventral trachea from the dorsal esophagus by a mesenchymal tracheo-esophageal septum clearly cannot adequately explain all variants of EA-TEF.

The findings of an increased number of tracheal rings and a longer trachea in the adriamycin rodent model of EA-TEF, suggests localized abnormal proliferation and elongation of the ventral respiratory component of the common foregut tube. The preferential incorporation of tissue into the trachea may also result in esophageal discontinuity. The association of 13 pairs of ribs with long-gap TEF has also been postulated to strengthen the argument that abnormal forces, in this case hyper-somatization, results in a relative deficiency of tissue which is then preferentially absorbed into tracheal development at the expense of the esophagus [23].

Additional work in the adriamycin model has also shown that the notochord is implicated with signalling activity to determine the fate(s) of neighbouring cell populations. Shh protein, which is expressed in notochordal tissue is believed to be pivotal in this dynamic process [24]. Shh stimulates cell proliferation and inhibits apoptosis, via intermediary HOX gene expression. Shh binds to the cell surface protein 'Patched' (Ptc), which is upregulated by Shh, and thus limits the inductive capabilities of Shh. Ventral misplacement of the notochord may also result in an abnormal diffusion gradient for Shh and a localized imbalance of proliferation and apoptosis in the primitive foregut.

23.9 Associated Anomalies

Associated anomalies occur in over 50% of newborns with EA and TEF [2, 25, 26]. Although some of these are relatively insignificant, a high proportion can be life threatening contributing directly to the morbidity and mortality of this condition. The assessment of the newborn with EA-TEF should therefore be prioritised with some urgency to address social, ethical and surgical strategies relating to the co-existent anomalies. The incidence of co-existent anomalies appear to be highest in babies with EA without fistula and infants with oro-facial cleft defects [27]. Patients born with EA-TEF have a higher incidence of prematurity than that seen in the

normal healthy population. Congenital heart disease (27%) is the commonest co-morbid condition having the greatest impact on survival. Aortic arch anomalies occur frequently with 'long gap' EA-TEF variants. Other malformations include urogenital (18%), skeletal (12%), anorectal (12%) and gastrointestinal defects (9%) most notably duodenal atresia. The spectrum of associated anomalies encountered in 581 EA patients treated at Alder Hey Children's Hospital over four decades is shown in Table 23.2.

The VATER association [27, 28], now better referred to as the VACTERL sequence is defined by the presence of three or more anomalies. In a study from Liverpool, VACTERL associations were recorded in 19% of cases [26]. CHARGE association refers to—*C*oloboma, *H*eart disease, *A*tresia choanae, *R*etarded development, *G*enital hypoplasia and *E*ar deformities with deafness. EA-TEF is also apparent in the SCHISIS sequence—exomphalos, neural tube defects, cleft lip palate and genital hypoplasia [29–31].

Interestingly babies with EA and TEF have a higher than expected incidence of hypertrophic pyloric stenosis [32]. The almost universal association of gastro-esophageal reflux with EA may lead to delay in diagnosis if gastric outlet obstruction is not suspected from pyloric stenosis. Tracheomalacia of a variable severity is present in EA cases although the full spectrum of associated tracheo-bronchial and pulmonary abnormalities deserves closer scrutiny. Significant anatomical tracheo-bronchial variant anomalies can be seen in 47% of infants undergoing bronchoscopy [33]. Pulmonary agenesis, foregut duplication cysts, congenital cystic adenomatoid malformations, and sequestered lobe have all been described in association with EA and TEF. Other rare foregut pathology such as laryngotracheo-esophageal cleft and congenital esophageal stenosis may coexist with EA and TEF.

Table 23.2 Abnormalities associated with EA-TEF—Alder Hey Liverpool (1953–1997) [26]

Anomaly	1953–1997 (581 cases)
Cardiac	154 (27%)
Urogenital	105 (18%)
Skeletal	71 (12%)
Vertebral	64 (11%)
Anorectal	67 (12%)
Gastrointestinal	53 (9%)
Palate/Laryngotracheal	44 (8%)
VACTERL	25 (19%)

23.10 Antenatal Diagnosis

Fetal diagnosis is now possible in cases of EA and TEF [34]. This may be clearly advantageous, as delivery can be planned at or near a specialist centre with full neonatal surgical capability. Counselling by a skilled multidisciplinary team (obstetrician, paediatric surgeon, neonatologist) is essential. A careful search/screen for associated chromosomal or cardiac anomalies is important. The identification of a chromosomal abnormality may have potential implications for termination of pregnancy. Antenatal diagnosis of EA should theoretically reduce the likelihood of inadvertent newborn feeding and aspiration pneumonitis. Despite potential advantages of antenatal diagnosis, it is important to note that fetal sonography selects an 'at risk' group with a significantly worse prognosis [35–37]. Perinatal mortality (excluding termination of pregnancy) in a study from Newcastle, UK was reportedly 21% [35]. The classical sonographic features of EA and TEF in the fetus are absence of the stomach bubble and associated polyhydramnios [36]. Prenatal detection rates may vary widely in fetal medicine centres (9–24%). There is a high rate of false positive scans with almost 50% of all suspected cases on fetal ultrasound scanning later proven not to have EA after birth [35].

23.11 Clinical Presentation

Newborns with EA have difficulty clearing saliva. Episodes of coughing, choking and cyanosis may be witnessed shortly after delivery. Early attempts to feed an infant will result in respiratory distress. Diagnosis is confirmed by failure to advance a nasogastric tube into the stomach. A characteristic resistance is felt at the blind ending upper esophageal pouch and the tube cannot be introduced into the stomach. A plain X-ray film

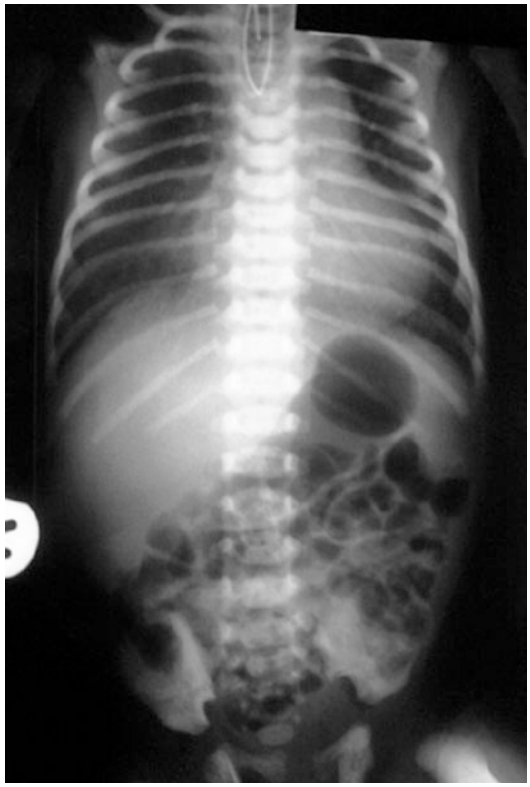

Fig. 23.2 Chest X-ray film of newborn with EA and TEF. Nasogastric tube is coiled in the blind-ending upper esophageal pouch. Gas filled intestinal loops below the level of the diaphragm confirms the existence of a distal TEF

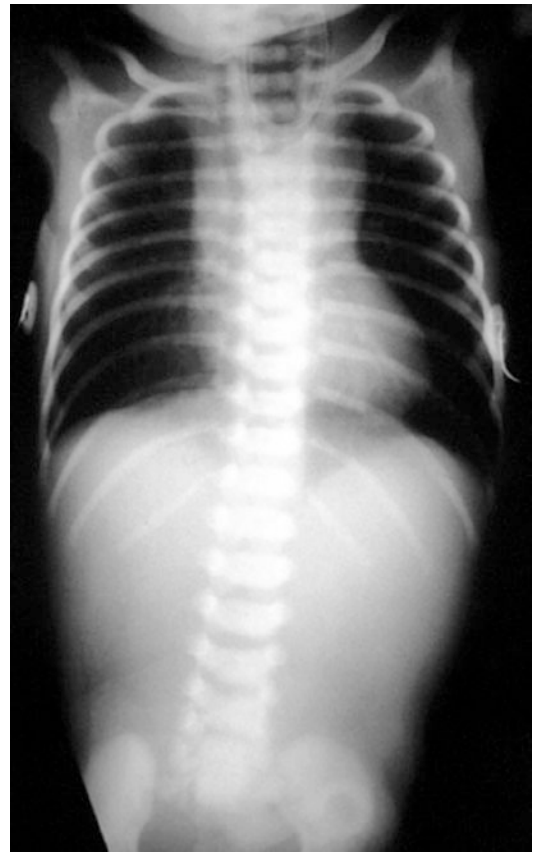

Fig. 23.3 Case of 'pure' EA without fistula. The nasogastric tube is lying in the upper esophagus pouch. Absence of air-filled abdominal intestinal loops suggests that there is no distal communicating esophageal fistula

should include the chest and abdomen demonstrating the nasogastric tube coiled in the upper pouch. The TEF is confirmed by the presence of gas-filled intestinal loops below the diaphragm (Fig. 23.2). In isolated or pure EA without fistula a featureless gasless abdominal X-ray is observed (Fig. 23.3). The presence of a double bubble on the abdominal plain film is highly suggestive of associated duodenal atresia (Fig. 23.4). A careful and thorough search for co-existent anomalies is essential specifically here also checking for imperforate anus. The cardiovascular system should be examined to exclude a major congenital heart defect whose treatment in some cases may take a higher priority over correction of the EA defect.

Having established a diagnosis of EA TEF intravenous fluids are started and a Replogle sump suction catheter inserted into the upper esophageal pouch to permit continuous suction of salivary secretions [38]. The infant should be nursed in a supine or lateral position. Arrangements should then be made for early newborn transfer to a specialist neonatal surgical unit. Surgery is best performed within the first 24 h after birth in an otherwise healthy baby, as pneumonitis is an ever-present risk from aspiration of saliva and reflux of gastric contents through the lower pouch TEF.

On admission to the newborn surgical unit, the infant should be fully re-examined and radiology reviewed. The X-ray study may be repeated with gentle downward firm pressure on the Replogle tube. On rare occasions a fine nasogastric tube may coil in the baby's oropharynx who has an otherwise normal patent esophagus. The successful

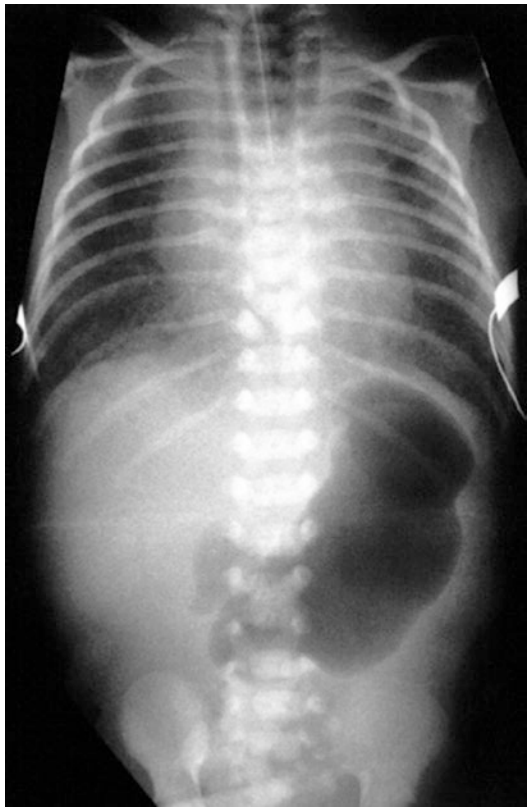

Fig. 23.4 EA and TEF with duodenal atresia. Nasogastric tube coiled in upper pouch. 'Double-bubble' appearance confirms duodenal atresia

passage of a Replogle tube into the stomach will prevent erroneous diagnosis and an unnecessary operation! When EA is diagnosed in the newborn an estimation of the length of the blind upper esophageal pouch seen on plain X-ray film can give the surgeon some useful clues as to the ease (or difficulty) of a primary anastomosis. Echocardiography should be performed before undertaking surgery as this will alert the surgeon and anesthetist of an underlying heart defect that may adversely influence prognosis and may importantly dictate operative approach by identifying the laterality of the aortic arch. Blood should be obtained for cross-match and a hematological and biochemical profile sorted preoperatively. Broad-spectrum antibiotics should be administered and intravenous fluids continued. Other investigations—whole-spine X-rays, renal and cranial ultrasonography can be deferred until after surgery. Contrast studies of the upper pouch to identify a rare upper pouch fistula have been superseded by preoperative bronchoscopy.

23.12 Surgical Management

Surgery for esophageal atresia is best usually performed in the stable newborn as a scheduled procedure during normal working hours [39]. Emergent operation in the middle of the night rarely benefits the baby unless the surgeon is confronted with a 'high risk' scenario, i.e. a ventilated patient with respiratory distress and gastric distension which indicates impending perforation. Here urgent transpleural thoracotomy with fistula ligation is life saving (see later). Most surgeons also like to perform bronchoscopy when planning elective repair of EA and TEF. We deploy flexible miniature bronchoscopy with scopes that can be steered through the endotracheal tube. Bronchoscopy allows precise confirmation of diagnosis and in most cases will demonstrate a common variant fistula just proximal to the carina. Occasionally the fistula may be seen arising at the level of the carina or higher in the main airway or from one of the main bronchi. Where possible a careful and thorough search should also be made to exclude a rare co-existent upper pouch fistula. The larynx should be examined to exclude a laryngotracheo-esophageal cleft lesion.

Following bronchoscopy the infant is positioned for operation. In the classical operation, a right thoracotomy is planned with the baby secured in a lateral position, with the right arm raised across the head so that the scapula can be easily manipulated (Fig. 23.5). The surgeon may find a working headlamp and optical loupe magnification greatly facilitate operation. A curved skin crease incision is made 1 cm below the angle of the scapula with a muscle sparing thoracotomy.

Bianchi has described an axillary skin crease incision, which gives excellent cosmesis, which we increasingly deploy at Alder Hey (Fig. 23.6) [40]. A retractor is used to lift the scapula off the chest wall and the ribs are counted down from the

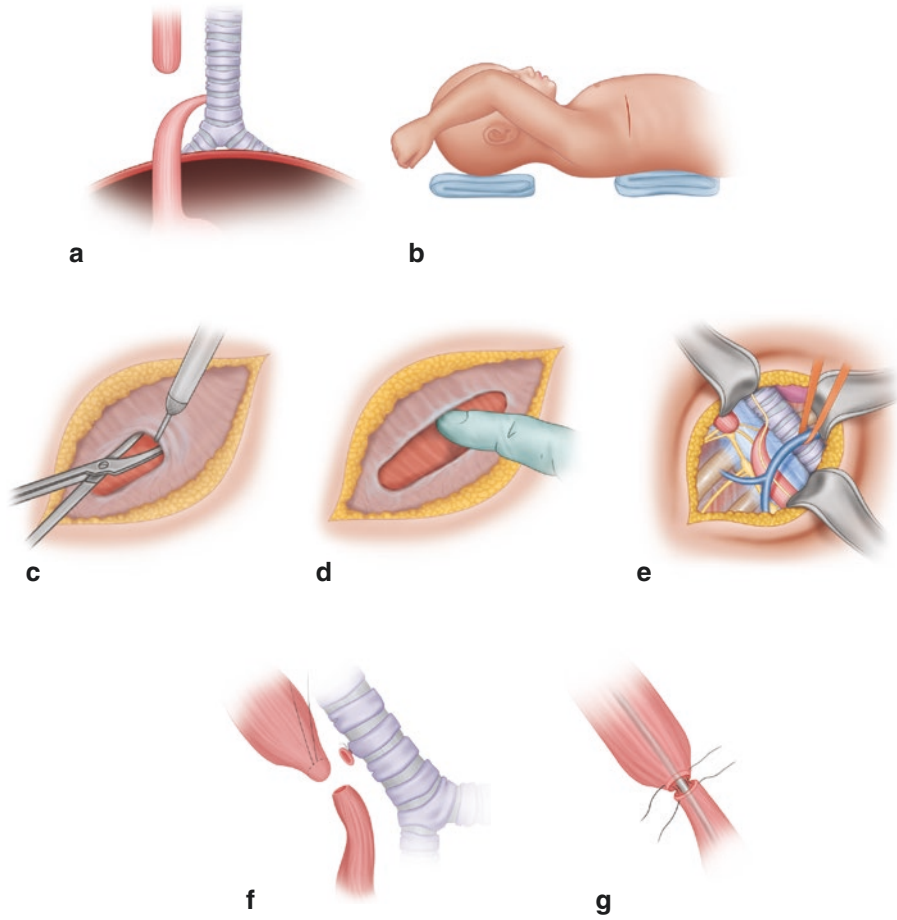

Fig. 23.5 (**a**) Operation EA TEF most frequent anomaly. (**b**) Newborn in lateral position with location of skin incision indicated. (**c**) Exposure of intercostal space with division of overlying muscles. (**d**) Gentle stripping of parietal pleura from chest wall to aid develop extrapleural space. (**e**) Operative field—lung with pleural membrane have been retracted medially. The azygos vein is easily visualized. Blind proximal esophageal pouch and the TEF fistula with distal esophagus and vagal fibers are seen lying on its exposed surface. (**f**) TEF fistula ligated and divided flush with trachea. (**g**) Lateral and posterior esophageal sutures in place and transanastomotic tube fed across anastomosis distally towards the stomach

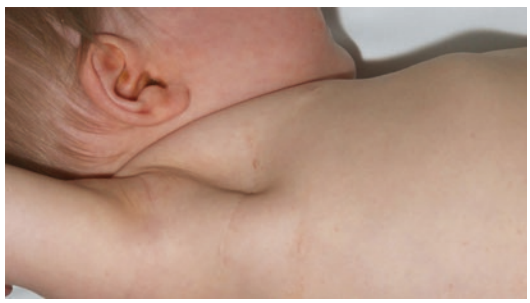

Fig. 23.6 Axillary skin incision in newborn some weeks after EA–TEF repair

second interspace. The thorax is entered through the fourth intercostal space with a blunt haemostat and bipolar diathermy separating the intercostal muscles to the level of the parietal pleura. The pleura is gently freed from the inner aspects of the rib cage to then facilitate an extra-pleural dissection and locate the TEF. This procedure is best usually commenced with moist pledgets and having developed the correct plane may be continued by inserting a moistened gauze swab into the extra-pleural space sweeping the pleura away

from the chest wall superiorly and inferiorly. Exposure is improved by introducing a Finochettio rib retractor. Great care is required with the dissection as it is particularly easy to create a pleural tear in the anterior aspect of the incision. If a significant pleural tear occurs during the dissection it is wise to open the pleura widely converting to a transpleural approach. The practical advantages of an extra-pleural over transpleural approach, include the possibility of avoiding chest drain insertion, and in the event of an esophageal anastomotic leak, the potential containment of any leak/soiling within the extra-pleural space. The extra-pleural exposure is achieved and completed by retracting the posterior mediastinal pleura forwards with a malleable retractor until the azygos vein is clearly visualized as it enters the superior vena cava in the depths of the wound.

The azygos vein is mobilized and controlled with vascular sloops. The author advocates temporary occlusion of the vein before ligation, as venous return to the heart may rarely be critically dependent on the azygos system. Provided this maneuver does not affect cardiac output, the azygos vein may be safely ligated and divided as it enters the superior vena cava. Alternatively some surgeons elect to preserve the azygos vein [41]. Once divided, the site of the TEF fistula communication between the trachea and the distal esophagus is usually apparent. Having confidently identified the distal esophagus, a vascular sloop is carefully passed around it. Traction on the sloop controls the fistula and enables its junction with the trachea to be located precisely. Although it is possible to suture ligate the fistula, the author prefers to divide the fistula in stages and apply interrupted 5-0 or 6-0 monofilament prolene sutures to the tracheal component of the fistula. The distal esophagus is secured with a stay suture. The integrity of the TEF repair is checked by instilling saline into the thoracic cavity and requesting the anesthetist to exert positive airway pressure to ensure that no air bubbles leak from the suture line. Rarely difficulty can be encountered in locating the distal esophagus, and it is quite possible to mobilize the descending aorta in the erroneous impression that it is the esophagus. The surgeon should recognize the distal esophagus by following the vagus nerve as it courses distally, and by observing its rhythmic distension with ventilation.

Attention is focused on the upper pouch—a bulbous structure—which is identified by requesting the anesthetist to push firmly on the Replogle tube. The upper pouch should be secured with a transfixion suture which can be driven through the Replogle tube and becomes useful then for traction. Bipolar diathermy is ideal for mobilising the upper pouch which should proceed upwards to the thoracic inlet unless the gap separating the esophageal segments is short. Dissection of the tissue plane between the upper pouch and airway requires great care to avoid injury to the trachea. With adequate mobilization of the upper pouch it is usually possible for the surgeon to judge whether a primary anastomosis is feasible. In most cases of EA with distal TEF a primary anastomosis is achieved although occasionally considerable tension is required to complete repair.

To undertake primary anastomosis the upper pouch is opened at its most distal extremity. The posterior wall of the anastomosis is commenced by placing two 5-0 or 6-0 PDS sutures through all layers of the lateral margins of the distal esophagus, taking great care to avoid excessive tissue handling and trauma with fine forceps. Sutures are completed by including all layers of the corresponding aspect of the upper pouch taking mucosa so that the knots comes to lie on the inside. Additional posterior wall sutures are inserted. All sutures are individually tied drawing the esophageal ends together commencing first with the laterally placed sutures. Having completed the posterior wall of the anastomosis, a 6–8 Fr. fine bore nasogastric tube (TAT tube) is passed by the anesthetist through the infant's nostril to the suture line, where it is grasped by the operating surgeon and carefully positioned distally along the lower esophagus into the stomach. The anterior layer of the anastomosis is completed by placing sutures with knots lying on the outside. When the gap defect length proves wide primary anastomosis may be facilitated by creating a Livaditis (1969) myotomy on the upper

pouch or with an esophageal flap as described by Gough. Anastomosis created under tension require a chest drain. For straightforward extrapleural primary EA TEF repair a chest drain may be unnecessary [42]. Ribs are loosely approximated with absorbable pericostal sutures and closure of the chest wall/skin then performed. A chest drain (if present) should be attached to under-water drainage. The baby is transferred to the intensive care unit for ventilatory support and postoperative monitoring. Should additional surgical pathology be present, such as duodenal atresia or imperforate anus, these should be dealt with accordingly under the same anesthetic in the stable infant.

23.13 Upper Pouch Fistula

Rarely the surgeon may also encounter a coexistent upper pouch fistula (1%–2% cases). Clues here to alert the surgeon of a 'second' upper pouch fistula are finding a short upper pouch more adherent than usual to the normal plane of dissection with the airway. Once identified the fistula tract should be divided carefully and repaired with 5-0 or 6-0 interrupted nonabsorbable prolene sutures on the tracheal airway side. The esophageal tissue defect is closed with 5-0 or 6-0 interrupted absorbable PDS sutures. Surgery then proceeds as discussed earlier to complete oesophageal atresia primary repair. Upper pouch fistula may well go unrecognised and become only evident on a postoperative esophogogram study which some surgeons routinely undertake to evaluate the primary anastomosis. Recurrent chest infections and aspiration on oral feeding in the early weeks after primary repair provide clues here also. A prone dynamic tube contrast esophography study performed in the radiology department may help localise the upper pouch fistula. If the lesion appears to be in a proximal location beyond the thoracic inlet a cervical approach (see H fistula later) may be indicated to achieve repair. The author here recommends NG tube feeding the infant and delaying the repair of the 'second fistula' for a number of weeks to allow time for the thoracic primary anastomosis to fully heal.

23.14 Long-Gap EA with Distal TEF

The surgeon will encounter situation(s) where the gap between the upper pouch and the distal esophagus is clearly too wide to permit primary anastomosis after division and repair of the TEF fistula having fully mobilized both the proximal and distal esophagus. Under such circumstances, it is probably wise to proceed to cervical esophagostomy as a 'spit stoma' and feeding gastrostomy, accepting the need for esophageal replacement surgery at a later date [2].

23.15 Right-Sided Aortic Arch

The optimum surgical strategy for management of babies with EA TEF and a right-sided aortic arch (RAA) is widely debated. The anomaly is most often undetected preoperatively and surgeon decision making to safely undertake EA TEF repair is required at thoracotomy. The incidence of RAA in association with EA is 1.8%–2.5% [43, 44]. Chest X-ray may provide some clues. Preoperative echocardiography is at best 20% accurate in identifying this anomaly [43, 44]. If the surgeon's suspicion remains high, magnetic resonance imaging should be arranged for definitive diagnosis. If a right-sided arch is identified from preoperative studies, experience from specialist centers advocate left side thoracotomy. The presence of RAA with right side thoracotomy does not preclude a successful anastomosis but the procedure is significantly more challenging as evidenced by a 42% leak rate reported from Great Ormond Street Children's Hospital, London [45]. A trial dissection with operative repair of the TEF with right thoracotomy is acceptable and feasible [46]. When the surgeon encounters significant difficulty left thoracotomy is advised to achieve esophageal anastomosis with division of the fistula through the right or left chest as circumstances dictate.

23.16 Premature Infant with RDS

In premature often very low birthweight (VLBW) babies with lung immaturity, emergency surgery is vital when ventilation is markedly compromised by the TEF with abdominal distension and diaphragmatic splinting. The surgical priority here is urgent ligation of the fistula deploying a transpleural thoracotomy to rapidly locate the TEF. Should the infant's condition stabilize sufficiently after TEF repair, primary anastomosis of the esophagus may then be appropriate. Otherwise delayed repair of the esophagus is undertaken when the baby is physiologically stable at a later date. Sudden deterioration with gastric wall perforation is also a 'high risk 'event in these fragile VLBW babies. In such situations, emergent ligation of the fistula is life-saving. Needle paracentesis to relieve tension pneumoperitoneum with laparotomy, repair of the stomach perforation and feeding gastrostomy should follow [47, 48].

23.17 Postoperative Care

Babies should be nursed in the intensive care unit following repair of EA TEF. Weaning from ventilation need not be unduly prolonged in the stable infant with a satisfactory anastomosis. Where the anastomosis is under considerable tension, elective paralysis and ventilation for a period of 3–5 days is practised [49]. It must be conceded however, that there is no strong evidence to support the claim that this technique favorably influences anastomotic healing [50]. There is some experimental data indicating that the level of tension in the anastomosis correlates with the severity of GER [51]. It is the authors practice to commence all patients on H_2-antagonists (e.g. ranitidine) as prophylactic therapy in an effort to reduce the risks of anastomotic stricturing potentiated by GER. A contrast esophagogram is optional at the discretion of the surgeon after 5–7 days to evaluate the anastomosis, although major anastomotic leaks are clinically evident before this time. Minor 'radiological' leaks may be noted on postoperative contrast studies. These are almost always of no clinical significance and do not preclude the infant from being offered feeds [52]. In most cases TAT tube feeding can be commenced after 48 h, and slowly increased as tolerated by the infant.

23.18 Surgical Management of Isolated ('Pure') Esophageal Atresia

The diagnosis of isolated EA without fistula (pure esophageal atresia) is confirmed by the inability to pass a nasogastric tube together with a featureless 'gasless abdomen' on plain film radiology (Fig. 23.3). The absence of intestinal gas below the diaphragm does not always however completely exclude the presence of a distal fistula, as a small proportion of babies may have a thin fibrous like connection between the lower pouch and the trachea, which does not readily permit the passage of air [48].

Surgical management of isolated EA is challenging and open to debate. Many pediatric surgeons consider delayed primary anastomosis of the native esophagus the best approach. This strategy demands meticulous nursing care with regular suctioning of the bind ending upper esophageal pouch, chest physiotherapy and careful attention to nutrition by supervised gastrostomy feeding. A prolonged period of hospitalization (6–12 weeks) is required to achieve this objective. Delayed primary esophageal anastomosis is associated with its own attendant morbidity with further ongoing care required to manage esophageal strictures and significant GER [53, 54]. The desire to preserve the infant's esophagus must be counterbalanced by the humility of knowing when to accept defeat and abandon the esophagus in favor of a replacement procedure. Initial management involves creation of a feeding gastrostomy with attention taken to avoid injury to the small stomach of these vulnerable babies with placement of the G-tube [55]. We do not advocate assessment of 'gap length' at the time of this operation deferring to a later session when the baby is more stable.

After a period of approximately 3–6 weeks, the extent of the gap defect can be assessed

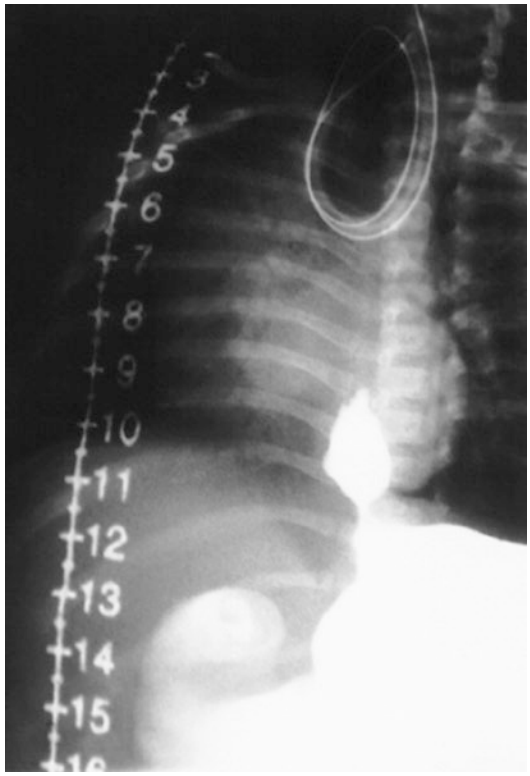

Fig. 23.7 Gap assessment in a case of isolated pure EA. The scale bar represents gap length (cm)

by fluoroscopy (Fig. 23.7). The radiopaque Replogle tube is advanced into the upper pouch and (1) contrast instilled via the gastrostomy or (2) a metal sound introduced through the gastrostomy site directed carefully towards the distal esophageal stump at the hiatus. This procedure can be repeated at 2–3 weekly intervals, to assess whether the ends of the esophagus are sufficiently close together to schedule delayed primary anastomosis [56]. Flexible endoscopy (under general anesthesia) can also be performed after several weeks when the G tube tract site is sufficiently mature to accept passage by steering the 'baby scope' to locate the blind esophageal stump. Images taken 'on table 'likewise provide an accurate gap length assessment with a radiopaque tube placed in the upper pouch. A distance of less than two vertebral bodies separating upper and lower pouches is ideal. However in practical terms there is little to be gained by the surgeon delaying attempts at surgery to reconstruct the esophagus beyond 12 weeks of age.

The operation of delayed primary anastomosis essentially involves the same meticulous approach by the surgeon. It is to be expected that the anastomosis may be created under considerable tension. The upper pouch should be fully mobilised proximally to the thoracic inlet. The distal esophagus is frequently a primitive stump not readily identified at thoracotomy without use of special aids. The surgeon can readily facilitate location of the distal esophageal stump by passing a flexible endoscope via the G-tube tract site towards the esophageal hiatus. A brightly illuminated stump is easily identified in the depths of the thoracotomy wound. A stay suture (5-0 or 6-0 prolene) should be secured on the distal esophageal segment to aid its mobilisation and dissection. Some surgeons still prefer passing metal bougies to identify the distal esophagus. The distal esophagus may be dissected to the diaphragmatic hiatus to help reduce tension on the anastomosis. A Livaditis myotomy or upper pouch flap may also be helpful [57–61]. The author prefers to perform a Livaditis myotomy over the inflated balloon of a Foley catheter passed by the anaesthetist via the mouth to the upper pouch. Extra length can also be obtained by proceeding to laparotomy and creating a lesser curve lengthening procedure as described by Scharli or a Collis gastroplasty [57–63]. If a primary anastomosis is still not possible using these techniques options are then proceed to cervical esophagostomy and schedule an esophageal replacement procedure when the infant is 18 months or older. A decision to convert to an immediate replacement of the esophagus is equally feasible provided the surgeon and team are sufficiently skilled. However caution is advised offering esophageal replacement to very young infants as risks of recurrent pulmonary aspiration are not insignificant in this young age group before walking and upright posture is established. Options for esophageal replacement include—gastric transposition, reverse gastric tube, colon replacement and jejunal interposition [2, 64]. Gastric transposition and colon graft interposition are the most popular operations currently.

Delays in restoring esophageal continuity have significant drawbacks. Firstly, there is the ever-present risk of aspiration pneumonitis, and secondly, the inability to feed the infant via the

normal oral route. Although the child's nutritional needs are met by gastrostomy feeding, the inability to establish oral feeds may lead to long-term aversive feeding behaviour. Spitz has recommended formally assessing the length of the gap when the gastrostomy is initially performed. A gap length > 6 vertebral bodies (6 cm), would prompt him to abandon the esophagus and perform a cervical esophagostomy [64]. This approach of early cervical esophagostomy and delayed esophageal replacement permits early sham feeding, which theoretically promotes neuronal maturation and development of the learning skills needed for feeding and later speech acquisition.

A number of other innovative approaches to the operative treatment of long-gap EA have been described. True primary repair has been performed with reported gap lengths exceeding 5 cm—the hypothesis tested by Foker was that a well-constructed esophageal anastomosis can withstand considerable tension [65]. The value added technique for esophageal reconstruction (VATER) operation involves mobilizing the gastric fundus and performing a limited Thal fundoplication. At thoracotomy the proximal stomach is drawn into the chest and a primary esophageal anastomosis is performed [66]. Staged neonatal colon esophagoplasty has also been described which involves the isolation of a short length of transverse colon based on the ascending branch of the left colic vessels at the time of open gastrostomy [67]. The conduit is positioned transhiatally in the posterior mediastinum to be retrieved at thoracotomy several days later, when continuity is restored.

Several well established operations are available to restore gastrointestinal continuity in long-gap EA, where the infant's own esophagus has been abandoned [64]. Colon replacement was originally popularized by Waterston. The colon conduit may be isoperistaltic (left colon based on the left colic vessels), or anteperistaltic (right colon based on the ileocolic vessels). The colon is best routed via the posterior mediastinum (via the hiatus), or through right or left chest cavities to the neck. Cervical esophago-colon anastomosis are prone to leak. Colon grafts also tend to dilate and kinking is not uncommon due to tortuosity. Respiratory problems are seen due to recurrent aspiration as the new food pipe created with colon is 'non refluxing'.

The stomach may be used to create an esophageal substitute graft. A gastric tube esophagoplasty can be fashioned from the greater curvature of the stomach, based on the left gastroepiploic (ante-peristaltic) or right gastroepiploic arcades (iso-peristaltic) preferentially using the posterior mediastinum as a route to the neck anastomosis. [68] The long suture line both of the tube created and greater curve suture line are susceptible to bleeding and leaking. Reflux is a problem and can predispose to anastomotic stricture formation. However, dilatation and kinking are not encountered with the graft. GER reflux may be controlled by performing a posterior partial wrap fundoplication.

Gastric transposition has been widely popularised by Spitz and has the merit of simplicity [64, 69]. The vascular supply is based on the right gastric and right gastroepiploic vessels, which allows full mobilization of the greater and lesser curvatures. After constructing a pyloroplasty, the stomach is routed through the posterior mediastinum via the diaphragmatic hiatus and the esophago-gastric anastomosis completed in the neck. Leakage from the neck anastomosis is reported in some 12% of cases and strictures requiring periodic dilatation in a similar percentage of patients [69].

Jejunal orthotopic interposition grafting re-emerged as a useful technique for esophageal replacement after the encouraging case series reports from the Netherlands by Klaus Bax and colleagues almost a decade ago [70]. Jejunal grafts do not dilate excessively and retain good peristaltic function which may explain why GER does not appear problematic for some of the patients [70, 71]. Use of jejunum substitutes has declined somewhat in recent years with gastric transposition and colon grafts now the popular choice of many surgeons worldwide today.

23.19 H-Type TEF

H-type TEF comprises 4% of all EA TEF variants [2]. It is perhaps more accurately termed N-type fistula as the track runs obliquely from

trachea to esophagus. Infants with H-type TEF usually present within the first few weeks after birth with a characteristic history of choking with feeds and cyanotic spells. Gross abdominal distension is an occasional presenting clinical feature which we have encountered as the belly 'accumulates wind' from the foregut fistula communication. Older children may have frequent chest infections with recurrent right upper lobe pneumonia(s) due to chronic aspiration.

Diagnosis may be readily established by a dynamic prone video esophagogram (Fig. 23.8). In this study, contrast is injected through a nasogastric tube which is slowly withdrawn from the esophagus. However, H-type fistula(e) may be missed in approximately 50% of contrast studies. Where suspicion remains, bronchoscopy should be scheduled. At bronchoscopy, a size 4 Fr. ureteric catheter is passed through the fistula into the esophagus to facilitate identification during subsequent neck dissection. A nasogastric tube is passed into the stomach, and broad-spectrum antibiotics commenced. A right transverse skin crease incision is marked a finger's breadth above the clavicle, before positioning the neck in extension with a roll placed under the shoulders. The sternomastoid muscle is split with the internal jugular vein and carotid artery mobilise laterally to expose the cervical esophagus and trachea. The ipsilateral recurrent laryngeal nerve should be identified and preserved. Flexible miniature bronchoscopy with a 2.2 mm calibre instrument (Olympus) can greatly aid precise localisation by brightly illuminating the site of the H fistula tract (Fig. 23.9) [72]. The esophagus is dissected at this point and slung with vascular sloops both above and below the fistula tract. Caution should be taken with the dissection as the contralateral recurrent laryngeal nerve is also vulnerable to injury. Traction on the esophagus enables the fistula to be secured with stay sutures. After withdrawing the ureteric catheter (and 2.2 mm bronchoscope if deployed), the fistula is divided and the tracheal component repaired with 5-0 or 6-0 interrupted non absorbable prolene sutures. The esophagus is closed with 5-0 or 6-0 PDS sutures. Some surgeons recommend tissue interposition between esophageal and tracheal suture lines to prevent recurrent fistula.

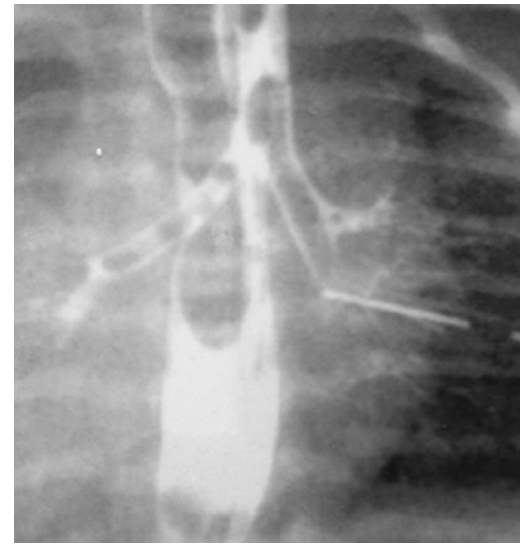

Fig. 23.8 Tube esophagogram study showing H TEF fistula

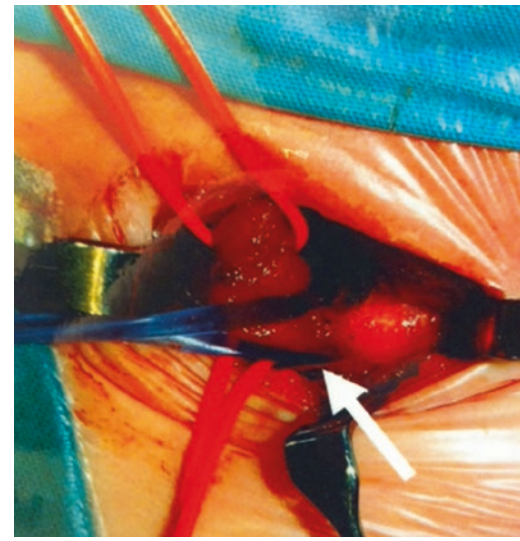

Fig. 23.9 Operative photograph showing a 2.2 mm flexible bronchoscope brightly illuminating a H fistula tract—[fistula marked with *arrow*]. Vascular sloops secure the mobilized esophagus clearly exposing the dissection plane between trachea and esophagus with H fistula

The infant should remain intubated and ventilated in the early postoperative period, as tracheal edema can result in a progressive stridor [73]. The vocal cords should be checked on extubation, given the significant risk of recurrent nerve palsy. Nasogastric tube feeding may commence after 48 h and oral feeds may be slowly introduced thereafter.

The Nd:YAG laser has also been successfully claimed to treat congenital H-type TEF. Repeated short duration pulses of laser light are used to coagulate the fistula [74]. Despite some success with this approach, the technique has not gained widespread acceptance and open repair remains the gold standard.

23.20 EA TEF—Complications and Special Considerations

23.20.1 Anastomotic Leak

The incidence of anastomotic leak following repair of EA and TEF ranges from 11%–21% [48, 75]. This is usually heralded with development of a pneumothorax and salivary drainage from the chest tube. It is rare for the anastomosis to be completely disrupted. Provided a trans-anastomotic tube (TAT) is in place, it is usually possible to control the leak with an adequately sized chest tube. With adequate drainage, broad-spectrum antibiotics and total parenteral nutrition, the esophagus will usually heal, although a prolonged period with a chest tube may be necessary. Some surgeons have used hyoscine patches in an attempt to 'dry up' the salivary leak. Others advocate early re-exploration (<48 h), with direct repair of the esophagus if possible, and the establishment of satisfactory chest drainage where a major leak is suspected [13, 75, 76]. When conservative management fails with uncontrolled sepsis establishment of a cervical esophagostomy and a feeding gastrostomy are essential. The child is then committed to esophageal replacement at a later date. A clinical anastomotic leak may predispose to the development of an esophageal stricture [77]. While this association seems entirely logical others contest such a correlation [75].

23.20.2 Gastroesophageal Reflux Disease—GERD

GER occurs in 40%–50% of babies following repair of EA TEF. GER may cause failure to thrive, predispose to recurrent aspiration episodes, and may lead to esophagitis and stricture formation [2]. Management of symptomatic GER initially requires aggressive medical therapy. Postural therapy and close attention to feeding regimes, with calorie supplementation may prove effective management strategies. Feed thickeners (e.g. Carobel), antacid preparations (e.g. Gaviscon), H_2-antagonists (e.g. Ranitidine), proton pump inhibitors (e.g. Omeprazole), and pro-kinetic agents (e.g. Domperidone), may be used in various combinations if vomiting is significant.

GER may contribute to recurrent pulmonary aspiration with frequent symptoms of respiratory distress including tachypnea, apneic episodes, cyanosis, and X-ray evidence of patchy pneumonic changes. Differential diagnosis in this clinical setting also includes swallowing incoordination, and respiratory distress from significant tracheomalacia. It is not uncommon to see infants in whom all of these factors are operating to a variable degree. It is important not to overlook the possibility of a recurrent TEF or ("double fistula "—see earlier) as a cause of repeated episodes of respiratory distress, although the history of choking and cyanotic episodes during feeding is usually much more evident in infants with a recurrent fistula. The selective use of esophageal pH monitoring, contrast studies, bronchoscopy, and assessment of swallowing by video fluoroscopy, may assist in evaluating the contribution of GER and other allied pathologies to respiratory symptoms. Failure to control GER despite full medical therapy is an indication for fundoplication.

Fundoplication rates following operation for EA vary widely between centers (6%–45%), reflecting the varied enthusiasm for anti-reflux surgery in the clinical setting of GER and esophageal dysmotility [2, 78]. There are several reasons for caution when considering fundoplication in EA patients. Dysphagia may be aggravated as a consequence of underlying foregut dysmotility. Fundoplication after EA repair has a higher failure rate (15%–38%) than is generally observed in otherwise normal healthy children with isolated GER [79]. Some authors recommend a partial wrap (Thal) fundoplication, because of the lower incidence of postoperative dysphagia [78].

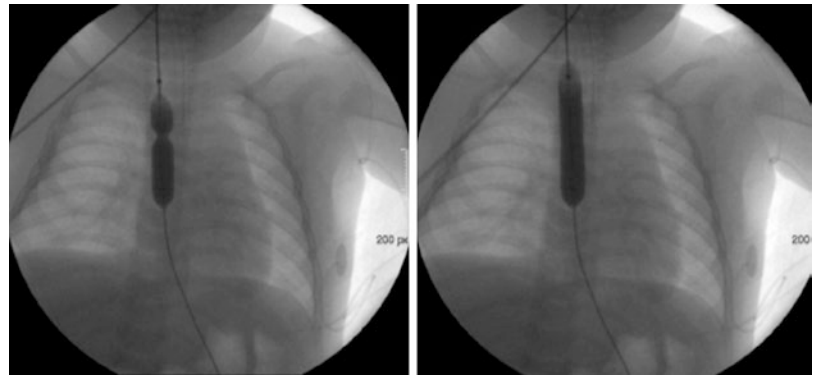

Fig. 23.10 Balloon dilatation of an esophageal anastomotic stricture—'wasting' appearance shows the region of stricture

Despite such concerns, many pediatric surgeons prefer a short (1.5–2.0 cm) 360° floppy Nissen wrap for its proven effectiveness in reducing GER [79]. The high failure rate of fundoplication and the significant complications associated with surgical treatment of GER, warrant careful follow-up in this group of patients.

23.20.3 Anastomotic Stricture

Definitions of esophageal stricture following repair of EA lack uniform consistency. The incidence of symptomatic strictures requiring therapeutic dilatation vary from 37%–55% [52, 77]. Some degree of anastomotic narrowing is invariably seen in all postoperative esophogram studies, but this is rarely of a sufficient degree to cause symptoms in the early period after operation. Parents should be counselled to report symptoms of prolonged feeding, incomplete feeding or associated respiratory difficulty to surgeons. Such symptoms prompt us to arrange surveillance endoscopy to assess the calibre of the esophageal anastomosis. Balloon dilatation is our preferred method of treating symptomatic strictures. The radial dilating forces generated during balloon dilatation are considered to be less traumatic than the longitudinal shearing forces caused by conventional esophageal bougienage [80, 81]. Balloon dilatation is performed under fluoroscopy imaging by passing a guide wire through the stricture over which a balloon dilator of appropriate size is introduced. Its accurate position is confirmed by partially filling the balloon with contrast medium, so that 'waisting' due to the stricture is centrally located with the device (Fig. 23.10). The balloon is then maximally inflated with volumes of dilute contrast to dilate the stricture. A contrast esophagogram is performed after removing the balloon catheter to ensure there has been no injury perforation. Some surgeons deploy steroid injections or mitomycin C to manage esophageal stricture(s). A tailored program of surveillance endoscopy/therapeutic dilatations may thereafter be scheduled for some patients. If a stricture requires frequent dilatation GER should be investigated by upper GI contrast, pH studies and endoscopy. Recalcitrant esophageal anastomotic strictures may require resection and fundoplication.

23.20.4 Tracheomalacia

Tracheomalacia is present to a variable degree in many patients with EA. It is thought to be responsible for the characteristically loud "barking" TEF cough [2]. Infants with severe tracheomalacia demonstrate expiratory stridor, which may result in episodes of desaturation, apnea, cyanosis and bradycardia (often associated with feeding), and life-threatening so-called 'dying episodes'. Tracheomalacia (if severe) may be evident in the early postoperative period when it proves difficult to wean the infant from ventilation.

Tracheomalacia can be assessed by bronchoscopy under conditions of spontaneous respiration. At endoscopy the tracheal lumen is

significantly compressed antero-posteriorly and assumes a narrow slit like appearance during expiration due to tracheal cartilage deficiency. Tracheo-bronchomalacia can extend beyond the carina into the main stem bronchi. As tracheomalacia may be self-limiting, surgical intervention is best indicated for patients with life-threatening symptoms [2]. Treatment options include continuous positive airway pressure (CPAP), aortopexy, tracheostomy and airway stenting [82, 83]. CPAP is a useful temporizing measure, but may be required for several weeks. Aortopexy is traditionally performed by anterior left thoracotomy through the third interspace. The left lobe of the thymus gland is excised to gain access to the root of the aorta taking care not to damage the phrenic nerve. A row of non absorbable pledgetted sutures are placed through the adventitia coat of the ascending aortic arch and then passed to the undersurface of the periostium of the sternum and tied hitching the aorta forwards and thereby relieving compressive forces on the trachea. Although this operation cannot resolve distal tracheobronchomalacia it often provides immediate dramatic symptomatic relief. Failure of aortopexy may be an indication for tracheostomy, although some authors advocate tracheal stenting in this situation [2, 82, 83].

23.20.5 Recurrent TEF

Recurrent TEF is estimated to occur in 5%–15% of cases [84]. Recurrent TEF may result from an anastomotic leak, but the possibility of a missed upper pouch fistula should always be considered. Symptoms include recurrent chest infections and choking attacks during feeding. A high index of suspicion is required if the diagnosis is not to be overlooked. Chest X-ray may sometimes reveal an air esophogram. The initial investigation of choice is prone video esophagography. If this study fails to demonstrate a fistula and the diagnosis remains strongly suspected, combined esophagoscopy and bronchoscopy should be performed. Rigid bronchoscopy is performed initially, and the site of the original fistula carefully examined. The fistula is gently probed with a ureteric catheter and methylene blue dye carefully instilled into the fistula pit. Synchronous flexible esophagoscopy is performed to see if blue dye can be seen entering the esophagus. Should this fail to demonstrate the fistula, an 'air/water test' is a useful supplementary investigation. The esophagus is filled with water and positive pressure ventilation applied to the bronchoscope. Occasionally, bubbles of air can be seen emanating from the fistulous opening into the esophagus.

Several strategies are detailed to manage recurrent TEF. The traditional approach is a formal 're-do' operation via right thoracotomy. At bronchoscopy, an attempt should be made to pass a fine ureteric catheter through the fistula into the distal esophagus. A flexible bronchoscope (2.2 mm—Olympus) may be useful to navigate, cannulate and brightly illuminate the fistula tract. The fistula is repaired using a similar strategy to that deployed for the H-type variant, i.e. isolation/slooping the esophagus repairing the fistula as described earlier. Tissue interposition between suture lines is sometimes advisable in an attempt to reduce the chances of further fistula formation. A 10%–22% risk of re-fistulation has been reported [84]. Other approaches described to treat recurrent TEF include diathermy fulguration of the fistula tract [84]. This technique has also been refined using the Nd:YAG laser to obliterate the epithelial tract communication. Sclerosing agents, Histoacryl, and fibrin glue(s) have all been injected subepithelially to occlude fistulae. A recent review of endoscopic therapies reported an overall success rate of 55% with several sessions required to effect permanent cure. A study from Oxford stated that surgical re-exploration should remain the treatment of choice [85, 86].

23.21 EA TEF Advances

Minimally invasive surgery is now feasible in EA-TEF. Rothenberg reported endoscopic repair in a personal series of eight newborns with EA-TEF ranging in weight from 2.1–3.4 kg. [87] This publication followed the first pioneering operation of EA in a 2 month old infant in 1998. Collaboration from members of the International

Pediatric Endoscopic Surgery Group (IPEG) led to a 2005 outcomes study which evaluated thoracoscopic repair from international centers located in the USA, Europe and Hong Kong [88]. One hundred and four babies with common variant EA and TEF (excluding H-type and long gap without fistula) were included. Of these, there were 5 (4.8%) conversions to open thoracotomy and a staged repair in one baby due to unforeseen long gap EA-TEF. Twelve infants (11.5%) developed early leaks and strictures and 32% required esophageal dilatation(s). Survival in this selected population was 97% with three deaths recorded of which one was directly related to the EA-TEF repair on the 20th postoperative day. Additional operations were required for associated anomalies. These included duodenal atresia repair, imperforate anus surgery, aortopexy and cardiac procedures. Twenty-five babies (24%) also underwent laparoscopic fundoplication for GER. In 2009, MacKinlay (Edinburgh) reported good outcomes in a study of 26 infants—88% survival, 27% leak rate—all minor not requiring operation and 35% acquired strictures needing dilatation(s) [89]. Long term benefits cited from minimally invasive surgery include a reduction in musculoskeletal morbidity notably winged scapula and unsightly skin scarring. MIS repair requires advanced technical skills in endoscopic surgery. For many centers not offering MIS repair, the axillary skin crease incision—(Fig. 23.6) popularised by Bianchi provides an excellent option with good aesthetic outcomes and comparable reductions in skeletal morbidity with all the benefits of classical open repair techniques [40]. MIS EA TEF vs open classical operation continues to remain widely debated in pediatric surgery and is perhaps best reserved for the MIS master enthusiast.

23.22 Quality of Life and Long-Term Outcome

The excellent survival of EA TEF babies born in the modern era has prompted detailed analysis of morbidity with emphasis on long-term outcomes [2, 90]. Several studies have examined respiratory function in EA children [91–94]. Symptoms of asthma and bronchitis are frequent, especially in the young child, and may persist into adolescence. Almost half of all children require future hospitalization due to ongoing respiratory morbidity. In a large Melbourne series comprising 334 EA children, episodes of pneumonia were seen in 31% of children under the age of 5 years, compared with 5% of those over 15 years [91]. The prevalence of annual attacks of bronchitis in these two age groups was 74% and 41%, respectively, with asthmatic symptoms reported in 40% of patients from each age range [91]. Spirometry studies have demonstrated both obstructive and restrictive abnormalities in over half the patients, and a similar proportion had a maximal working capacity below the normal range [92]. Tracheobronchial inflammation and airway narrowing have been demonstrated by bronchoscopy in one-third of patients, with histological evidence of inflammation in a further third [93]. It is plausible that abnormalities of bronchial anatomy, which are common in EA TEF, may contribute to respiratory morbidity. Clinical assessment by a respiratory physician with use of prescribed inhalers to manage reactive airway disease and antibiotics/physiotherapy for chest infections is recommended. The contribution of aspiration episodes, whether due to esophageal dysmotility or GER, to respiratory symptoms, should be actively investigated. Recognition of the long-term respiratory morbidity associated with EA patients, prompted the establishment of a specialist EA TEF clinic at Alder Hey Children's Hospital Liverpool almost 20 years ago staffed by pediatric surgeons, respiratory physicians, physiotherapists and dieticians. This multidisciplinary team approach ensures vigilant health surveillance is focused on all aspects of the child's welfare including the smooth transition to adult medical/surgical services [94, 95].

Esophageal dysmotility is a significant factor in long term patient morbidity [96]. It is clearly implicated in many cases of food bolus impaction when endoscopy reveals no significant anastomotic narrowing. Less severe symptoms of dysphagia have been reported in up to 20% of adolescents [96] and 48% of adults on long term follow up. Esophageal manometry and

fluoroscopy studies will demonstrate degrees of dysmotility in nearly all patients [92]. The dysmotility associated with EA may reflect intrinsic innervation abnormalities of the esophagus [97]. This may further contribute to respiratory morbidity through repeated 'silent' aspiration episodes.

GER may persist into adult life. Symptoms of heartburn and acid brash range from 18% to 50% in long-term follow-up studies [92, 93]. Clinical symptoms may underestimate the true incidence of GER as demonstrated by esophageal pH monitoring. An 8% incidence of Barrett's esophagus has been reported [98, 99]. The relative risks of esophageal cancer developing in the life time of a patient are uncertain though five cases have been recorded in the world literature [100, 101]. These findings further highlight the importance of comprehensive long term adult follow up [95, 102].

Various quality of life (Qol) scoring systems have been deployed to evaluate adult populations treated for EA and TEF. Using the Spitzer Index and a Gastrointestinal QoL Index, it has been shown that adults having primary anastomosis as newborns enjoyed an unimpaired quality of life. Quality of life metrics were also more favourable in patients who had native esophageal repair compared to colonic interposition [90]. Psycho-social studies show more learning, emotional and behavioral difficulties in EA adults than the healthy general population. Cognitive performance(s) were also significantly impaired in a high-risk patient group characterized by associated major congenital anomalies and/or the requirement for prolonged ventilation in the neonatal period [93, 103].

An energetic support group (TOFS)—a UK based charity was founded in 1982 for the benefit of children and parents. The organisation with over 1000 members (www.tofs.org.uk) provides a useful networking group for families together with a valuable handbook—'The TOF Child' [104]. With regular annual conferences attended by health care professionals and families opportunities therefore exist for knowledge exchange and practical advice. TOFS UK also raises valuable funds for research [2]. Similar support networks exist in other European countries, e.g. KEKS, Germany.

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Congenital Esophageal Pathology

24

Steven W. Bruch and Arnold G. Coran

Abstract

Congenital esophageal stenosis is an intrinsic stenosis of the esophagus, present at birth, which is caused by congenital malformation of the esophageal wall architecture. Three forms of congenital esophageal stenosis exist: a membranous web or diaphragm occluding the esophageal lumen, fibromuscular hypertrophy of the esophageal wall, and tracheobronchial remnants embedded in the esophageal wall (Nihoul-Fekete et al., Pediatr Surg Int 2:86–92, 1987). The membranous web or diaphragm, the rarest of the three forms, consists of a partially obstructing lesion with an eccentric opening covered on both sides with squamous epithelium. These are located in the mid to distal esophagus. Stenosis due to fibromuscular hypertrophy exhibits normal squamous epithelium overlying a proliferation of smooth muscle fibers and fibrous connective tissue similar to that seen in hypertrophic pyloric stenosis, leading to narrowing in the mid to distal esophagus. This tapering is more gradual than the narrowing seen with tracheobronchial remnants. Tracheobronchial remnants, the most common congenital esophageal stenosis, results from abnormal separation of the esophagus and tracheobronchial tree during embryologic development resulting in cartilaginous remnants ectopically located in the esophageal wall. The narrowing occurs in the distal esophagus, is covered by normal mucosa, and is often abrupt in appearance due to a ring of cartilage in the esophageal wall. The cartilaginous remnants may or may not form a complete ring.

Keywords

Congenital esophageal anomalies • Congenital esophageal stenosis Surgery • Outcomes

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_24

24.1 Congenital Esophageal Stenosis

24.1.1 Introduction

Congenital esophageal stenosis is an intrinsic stenosis of the esophagus, present at birth, which is caused by congenital malformation of the esophageal wall architecture. Three forms of congenital esophageal stenosis exist: a membranous web or diaphragm occluding the esophageal lumen, fibromuscular hypertrophy of the esophageal wall, and tracheobronchial remnants embedded in the esophageal wall [1]. The membranous web or diaphragm, the rarest of the three forms, consists of a partially obstructing lesion with an eccentric opening covered on both sides with squamous epithelium. These are located in the mid to distal esophagus. Stenosis due to fibromuscular hypertrophy exhibits normal squamous epithelium overlying a proliferation of smooth muscle fibers and fibrous connective tissue similar to that seen in hypertrophic pyloric stenosis, leading to narrowing in the mid to distal esophagus. This tapering is more gradual than the narrowing seen with tracheobronchial remnants. Tracheobronchial remnants, the most common congenital esophageal stenosis, results from abnormal separation of the esophagus and tracheobronchial tree during embryologic development resulting in cartilaginous remnants ectopically located in the esophageal wall. The narrowing occurs in the distal esophagus, is covered by normal mucosa, and is often abrupt in appearance due to a ring of cartilage in the esophageal wall. The cartilaginous remnants may or may not form a complete ring. The first description of this disorder was by Frey and Duschel in 1936 when at autopsy they found cartilaginous remnants in the distal esophagus of a 19 year old woman who died with the diagnosis of achalasia [2]. Congenital esophageal stenosis occurs rarely throughout the world with an incidence of one in every 25,000–50,000 live births [3]. In Japan, however, the incidence is higher for unknown reasons [4], with the fibromuscular form appearing more commonly. Most often, congenital esophageal stenosis occurs as an isolated malformation, but in up to 47% of the time it is associated with other congenital anomalies the most common being esophageal atresia with or without a tracheoesophageal fistula [5]. Other common associated anomalies include cardiac defects, intestinal atresias, malrotation, anorectal abnormalities, malformations of the head, face, and limbs, and chromosomal abnormalities, most commonly Down's syndrome [6]. The association between congenital esophageal stenosis and esophageal atresia with or without tracheoesophageal fistula was first described by Dunbar in 1958 [7]. The incidence of this association varies among reports from a low of 0.2% to a high of 14% [1, 8–12]. In a review of 187 tracheoesophageal fistula repairs, 21% of the H-type tracheoesophageal fistulas had an associated congenital esophageal stenosis [13]. The combination occurs often enough that distal esophageal narrowing should be looked for on the post-op esophogram obtained before feeds are started. In fact, many pediatric surgeons pass a tube through the distal esophageal segment before proceeding with an anastomosis in esophageal atresia patients.

24.1.2 Presentation

Children with congenital esophageal stenosis present in one of two ways. 10–20% will be identified on an esophogram obtained after a tracheoesophageal fistula repair [5, 14]. The other children are usually asymptomatic as infants until solid or semi-solid foods are introduced into the diet. They then develop dysphagia, vomiting, and solid food refusal. On occasion, a child with congenital esophageal stenosis will present with respiratory symptoms presumably from aspiration [5], or with foreign body obstruction [3]. In a review of 36 children with congenital esophageal stenosis, the average age at symptom onset was 7.4 months [5]. Since these symptoms occur commonly, there is an understandable delay in diagnosis. In the previous review, the average age at diagnosis was 1.8 years of age.

24.1.3 Diagnosis

With the clinical presentation of dysphagia and vomiting, a contrast study of the esophagus is often part of the initial evaluation. The stenosis is identified, but often attributed to other pathology. The initial thought is often a distal stricture due to reflux. If the symptoms have been more chronic, the proximal esophagus may have dilated making the radiographic picture similar to achalasia. The stenosis is usually in the distal portion of the esophagus just proximal to the gastroesophageal junction. With stenosis due to tracheobronchial remnants there is a thick abrupt narrowing as opposed to a smooth tapering "bird's beak" seen with achalasia, and it is almost always seen in the distal esophagus. The narrowing seen with fibromuscular hypertrophy may be somewhat more proximal but still in the distal esophagus and is a more gradual tapered narrowing as seen in Fig. 24.1. The radiologic picture of a web is a thin constricting band that may be in the mid or even upper esophagus [15]. Often other studies are required to differentiate congenital esophageal stenosis from a reflux stricture, or achalasia. Upper endoscopy with biopsy can be used. The endoscopy will show a distal narrowing with normal appearing mucosa as opposed to the inflammatory mucosa seen with a reflux stricture. The biopsies will not show inflammation with a congenital esophageal stricture. A 24 h pH probe may also help making this distinction. In a child with achalasia, the endoscope will fall through the distal esophagus in distinction to the congenital esophageal stricture which will exhibit significant resistance. More recently, endoscopic ultrasound has been used to assist in the diagnosis and also to distinguish between fibromuscular hypertrophy and tracheobronchial remnants as the type of congenital esophageal stenosis [16].

24.1.4 Treatment

The optimum treatment of congenital esophageal stenosis depends on the type of stenosis present. The membranous web is treated with dilation combined with endoscopic excision of a portion

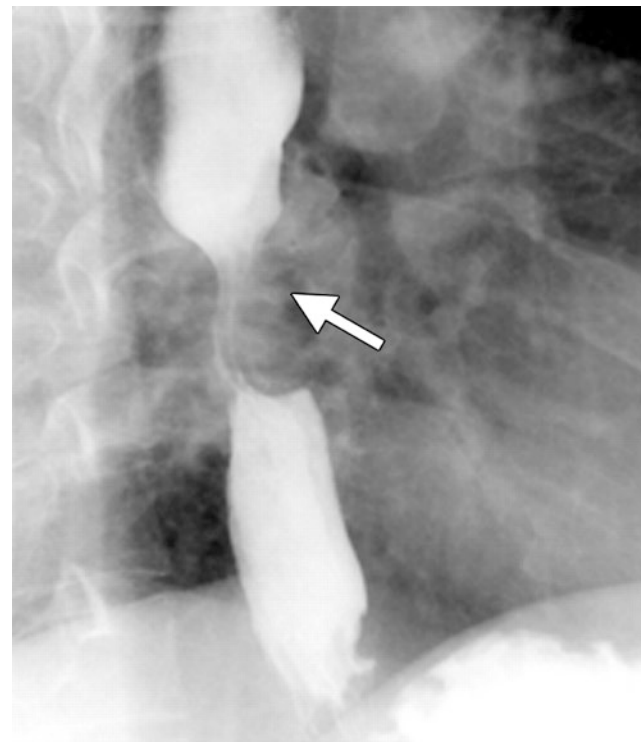

Fig. 24.1 Congenital esophageal stenosis secondary to fibromuscular hypertrophy in the mid esophagus

of the web. If dilation alone does not open the web adequately, the CO_2 laser may be used through the endoscope to excise the remainder of the web. In the previous review of 36 children, five had membranous webs and two required endoscopic CO_2 laser excision [5]. Fibromuscular hypertrophy is also amenable to dilation. The dilations can be performed with either hydrostatic balloon dilators or with bouginage. Theoretically, balloon dilators deliver the dilating force directly to the stricture and are therefore more effective and safer. However, in a retrospective series of 47 children with congenital esophageal stenosis who were all dilated using hydrostatic balloon dilators or Savory bouginage, the perforation rate was higher with balloon dilators (9.3%) compared to Savory dilators (1.7%). If dilation fails, there are two surgical options. The stenosis can be resected with a primary anastomosis, or a myotomy may be performed opening the hypertrophied esophageal muscle longitudinally and closing it transversely [5]. In general, the stenosis due to tracheobronchial remnants requires surgical resection. Often, dilations are initiated, fail, and then the child is brought to the operating room for esophageal resection. The stenosis is most often in the distal esophagus, thus requiring a left thoracotomy. A right thoracotomy is utilized for mid-esophageal stenosis. If the stenosis is just above the gastroesophageal junction, the best approach may be through the abdomen. It is often difficult to identify the stenosis visually or by palpation. Two techniques can be used to assist in finding the extent of the stenosis. A lighted endoscope may be passed from the mouth to the stenotic area. The other option is to pass a balloon catheter from the mouth past the stenotic area, inflate the balloon, and pull it back to find where it hangs up on the stenosis. The esophagus can be opened at that point, and the balloon catheter placed through the stenosis and pulled back to demonstrate the proximal extent of the stenosis [17]. In most cases the stenosis is less than 3 cm in length. A full thickness resection of the stenosis with a primary end-to-end anastomosis returns continuity to the esophagus. A circular myectomy has been described where the muscle wall of the esophagus is resected for the length of the stenosis removing the tracheobronchial remnants and leaving the mucosa intact. The two ends of the remaining muscle are then brought together in an end-to-end fashion [18]. Both of these techniques have been successfully described thoracoscopically [18, 19]. In any of these techniques care must be taken to avoid damage to the vagus nerves. In resections involving the area near the gastroesophageal junction, gastroesophageal reflux often results. Consideration should be given to adding an antireflux operation in these circumstances. In reality, unless the endoscopic ultrasound is utilized, it may be difficult to discriminate between the types of stenosis prior to initiating therapy. Often, dilations are begun and if they fail, it is suspected that the stenosis contains tracheobronchial remnants, and therefore requires resection. With this approach, some of the stenoses with tracheobronchial remnants may be treated with dilation alone, most likely the ones without circumferential cartilage. In a series of 47 children with congenital esophageal stenosis who all underwent dilation therapy, only two required operative intervention. They used predominately Savory dilators, dilated every 15 days until a caliber of 9–12.8 mm was achieved and then dilated as needed. Six of their children later in the study period had endoscopic ultrasounds showing tracheobronchial remnants. The mean number of dilations required was 3, with a range from 1–9. There were five perforations out of 147 dilations. Two of the perforations developed mediastinal abscesses, one was treated with CT guided drainage and antibiotics, the other required exploration, cervical esophagostomy, and eventual esophageal replacement. The other three were treated with antibiotics alone [14]. The algorithm for treating congenital esophageal stenosis begins with endoscopy and dilation for all stenosis with endoscopic CO_2 laser resection if needed for membranous webs. Only after a series of dilations fails should esophageal resection be undertaken [20].

24.1.5 Outcome

Overall the long term outcome for children with congenital esophageal stenosis treated with either dilations or resection is very good [6]. The complications associated with dilation are perforation and need for multiple dilations. A series of ten children were successfully dilated with 4.7 dilations over an average of 2.6 years [5]. Perforation rates vary from 10% in two series [5, 14], to 33% [10] and 44% [12] in two others. Following resection, complications include anastomotic leaks, stricture, and the development of gastroesophageal reflux if the resection is close to the gastroesophageal junction and not accompanied by an anti-reflux operation. Those children who had esophageal resection averaged 2.2 dilations over 2.1 months following the operation [5].

24.2 Esophageal Duplication Cysts

24.2.1 Introduction

Esophageal duplication cysts were first reported in 1711 by Blasius [21]. These duplications can occur in the cervical or thoracic esophagus, and on occasion the thoracic duplications will extend into the upper abdominal cavity. Cervical esophageal duplications are very rare. The first duplication cyst of the cervical esophagus was reported in 1964 by Bishop and Koop [22]. In an autopsy study by Arbona, the incidence of esophageal duplication cysts was 1 in 82,000, with a 2:1 male to female predominance [23]. Esophageal duplication cysts are defined by three characteristics: a cyst attached to the esophageal wall, covered by two layers of muscle and epithelium that represents some level of the gastrointestinal tract [21]. The epithelium contained in the duplication is most often esophageal, but up to one third contain gastric mucosa which may lead to ulceration, bleeding, or perforation. The majority of the esophageal duplication cysts, up to 80–90%, do not communicate with the esophageal lumen. Most, 60% are located in the distal esophagus [24]. Some esophageal duplication cysts referred to as neuroenteric cysts connect to the spinal canal and are associated with vertebral anomalies [25]. In addition to their association with vertebral anomalies (scoliosis, hemivertibra, and fusion), esophageal duplication cysts have also been described with small intestinal duplications, esophageal atresia and tracheoesophageal fistula, pulmonary abnormalities such as congenital cystic adenomatoid malformations, and pericardial defects [26, 27]. A recent literature review identified 12 cases of esophageal duplication cysts associated with esophageal atresia. Of those 12, five were not identified at the original repair [28]. The embryology of esophageal duplication cysts is unknown. Several theories have been presented including the failure of recanalization of the esophagus during the fifth to eighth week of embryonic life [29], and split notochord theory [30].

24.2.2 Presentation

Esophageal duplication cysts present in a number of different ways depending on their location and the type of mucosa that lines the cyst. Some, especially those of small size, remain asymptomatic. Of those that become symptomatic, the majority, 70–95%, are diagnosed before age 2 years [31]. The rare cervical esophageal duplication cysts most commonly present with respiratory symptoms due to tracheal compression [25]. However, they can also present with feeding difficulties or an enlarging neck mass due to infection, hemorrhage, or a build-up of secretions [29]. Thoracic esophageal duplication cysts can present with symptoms varying from respiratory symptoms, to dysphagia, to symptoms secondary to acid production of the gastric mucosa lining the cyst. The cysts in the mid to upper thorax generally cause respiratory symptoms due to tracheal compression. Cysts that lie in the vicinity of the mainstem bronchus can cause compression leading to

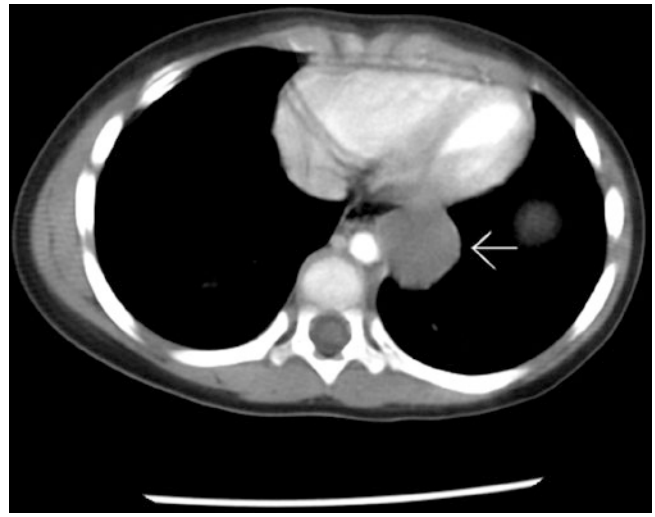

Fig. 24.2 Esophageal duplication cyst seen extending into the left chest from the posterior mediastinum

hyperinflation of the ipsilateral lung often requiring resection in the neonatal period [32]. Most of the cysts are located in the distal third of the esophagus and of these, 70% presented with dysphagia, 20% with epigastric discomfort, and the remaining 10% with retrosternal pain [25]. Gastric mucosa is found in up to one third of esophageal duplication cysts and can be responsible for a myriad of symptoms. Acid production from the gastric mucosa leads to ulcer formation. The ulcer can either bleed or perforate causing different symptoms depending on the location of the cyst. If the bleeding occurs in the esophagus it may present as hematemesis or as melena. Bleeding in the trachea leads to hemoptysis that may be life threatening. If the ulcer perforates into the pleural space it can cause a chemical pleurisy, an empyema, or a pneumothorax [33]. Esophageal duplication cysts are more and more frequently now being discovered prenatally with ultrasound or fetal magnetic resonance imaging [34].

24.2.3 Diagnosis

Imaging studies confirm the diagnosis of an esophageal duplication cyst. Plain films may reveal deviation or compression of the trachea or esophagus by a soft tissue mass. The esophageal deviation may be better seen with a nasogastric tube in place. Esophageal contrast studies reveal extrinsic compression of the esophagus from the mass effect and may show a communication between the cyst and the esophagus on the rare occasion when it is present [29]. With the diagnosis suspected from the plain film and contrast studies, further information regarding the size, exact location, and the anatomic relation to other mediastinal structures is useful prior to operative intervention. Ultrasound, computed tomography, and magnetic resonance imaging provide this information. The ultrasound exam reveals a cystic mass with a typical gut signature of the walls consisting of inner hyperechoic mucosa and outer hypoechoic muscle. It may also identify debris inside the cyst suggesting infection or hemorrhage. Computed tomography, as seen in Fig. 24.2, and magnetic resonance imaging better identify the location and extent of the cyst, such as extension into the abdominal cavity and mass effect on the airways. Recently, more magnetic resonance imaging rather than computed tomography is utilized to avoid radiation. Magnetic resonance imaging is favored if one suspects a neuroenteric cyst [32].

24.2.4 Treatment

Treatment of esophageal duplication cysts consists of complete excision. The cysts must be separated from structures in the mediastum, and

then dissected away from the common wall with the esophagus. The esophageal muscular wall is opened, and an extramucosal dissection is performed to remove the entire cyst while leaving the native esophageal wall intact. This may be performed through an open thoracotomy, or minimally invasively using thoracoscopy [35–37] or the surgical robot [38]. One of the difficulties when performing this operation in a minimally invasive fashion is ensuring the esophageal mucosa remains intact during the dissection. The use of intraoperative endoscopy with insufflation during the procedure helps prevent esophageal injury during the dissection [36]. The decision to remove the duplication cyst in a minimally invasive fashion should be up to the surgeon, but some situations that may require a thoracotomy include compressive subcarinal cysts with secondary lung hyperinflation and mediastinal shift and previously infected duplication cysts [34]. If for some reason the entire cyst cannot be removed it is important to remove all of the mucosa so the cyst cavity does not recur.

24.2.5 Outcome

With proper treatment, children with esophageal duplication cysts should have excellent surgical outcomes and overall quality of life.

24.3 Esophageal Perforation

24.3.1 Introduction

Boerhaave was first to describe a spontaneous perforation of the esophagus in 1724 [39]. In 1952, Fryfogle described a spontaneous perforation of the esophagus in a neonate [40]. In 1961, Warden reported the first iatrogenic perforation of the esophagus in a neonate [41]. The majority of esophageal perforations in children are iatrogenic in origin versus other etiologies such as spontaneous perforation and traumatic perforations from foreign bodies, caustic ingestion, and blunt and penetrating trauma. In a review published in 2006, spontaneous perforation or Boerhaave's syndrome has been described in 26 pediatric patients with half of these occurring in neonates [42]. Unusual causes of esophageal perforation include the ingestion of an eel [43] and of a shard of glass in a pancake [44], erosion of mediastinal necrotic tuberculous lymphadenopathy [45], and spontaneous perforation in a child with eosinophilic esophagitis [46]. Combining several pediatric series of perforated esophagi, 76.5% of perforations result from iatrogenic injury [47–49]. Most of the iatrogenic injuries occur during an endoscopic procedure in the older children, and with placement of naso- or oro-gastric tubes, endotracheal tubes, or the use of suction catheters in infants. In a series 39,650 endoscopies in children and adults, the incidence of perforation was 0.006%. When a therapeutic measure was added to the endoscopy, the incidence of perforation increased to 0.6% [50]. The most common therapeutic measure leading to perforation is stricture dilation, with strictures resulting from caustic ingestion being most at risk [51]. Other interventions leading to perforation include removal of foreign bodies, esophageal varix injection leading to focal necrosis [47], and perforation by a transesophageal echocardiogram probe during a cardiac surgery procedure [52].

24.3.2 Presentation

Signs and symptoms of esophageal perforation can sometimes be vague and nonspecific requiring a high index of suspicion to ensure early diagnosis and institution of treatment. Symptoms depend on the location and extent of the perforation. The most common area of perforation is the thoracic esophagus. These children develop dyspnea, chest pain, fever and vomiting most commonly, and may develop subcutaneous emphysema. Hammon's sign, a systolic crunching sound, can be heard over the cardiac apex and left sternal boarder and represents the heart beating against air filled tissues. With extensive soilage, tachypnea, tachycardia, and further signs of sepsis develop. Mackler's Triad classically represents spontaneous rupture of the esophagus and

includes emesis, chest pain, and subcutaneous emphysema [53]. Abdominal esophageal perforation leads to signs of peritonitis often associated with referred shoulder pain and dysphagia. Perforation of the cervical esophagus leads to cervical pain, subcutaneous emphysema, and pressure symptoms on the esophagus and trachea. The esophageal attachments to the prevertebral fascia limit the soilage following cervical esophageal perforation leading to localized retropharyngeal abscesses. Iatrogenic perforations in the neonatal population often take place in the cervical esophagus just proximal to the cricopharyngeal muscles. The nursing staff often has difficulty placing a nasogastric tube prompting a chest X-ray which identifies the abnormal course of the nasogastriac tube leading to the diagnosis of a perforation. If the perforation is not identified in that way, signs to be concerned with are respiratory distress, increased salivation, choking, cyanosis with feedings, blood in the nasogastric aspirates, and hypotonia [54, 55].

24.3.3 Diagnosis

When a perforation of the esophagus is suspected, work up should be expeditious. Plain films begin the evaluation. Findings depend on the etiology of the esophageal perforation. In a series of neonates with iatrogenic pharyngoesophageal perforations, plain film abnormalities included pneumothoraces, usually right sided, an abnormal position of the nasogastric tube, or pleural effusions [55]. In older children with iatrogenic or spontaneous perforation the findings on plain film include pneumomediastinum, pleural effusions, pneumothoraces, subcutaneous emphysema, and pneumopericardium [47, 54, 56]. A strong clinical suspicion and a normal chest X-ray should prompt further evaluation as 12–33% of esophageal perforations will have a normal initial chest radiograph [57]. The next step in the evaluation is a contrast esophagram. Initially, water soluble contrast is used to avoid the inflammatory response created in the mediastinum or pleural space if barium extravasates. The water soluble contrast exam has a 10% false negative rate [58], so barium should be used to pick up subtle perforations that the water soluble study can miss. Three abnormal patterns can be seen on the esophagram. The first is a retropharyngeal collection resulting from a cervical esophageal leak. The second is a contained submucosal perforation that results in contrast tracking parallel and posterior to the esophagus. The third pattern is a free perforation into the pleural space [54]. Computed tomography can be useful to define and drain intrathoracic fluid collections. Findings seen on computed tomography scan in children with esophageal perforation include mediastinal air and/or fluid and esophageal thickening. Computed tomography guides drain placement if fluid collections are present. The use of endoscopy is controversial in the diagnosis of esophageal perforation. When the perforation occurs during dilation, it is often first diagnosed with endoscopy. If this is the case, care should be used to minimize the amount of air insufflated into the mediastinum as it may cause pressure issues with mediastinal movement in the small children resulting in loss of venous return from vena caval obstruction. The use of endoscopy should be limited in the diagnosis of esophageal perforation as it is accurate in only 50% of cases, and may worsen the perforation [54].

24.3.4 Treatment

In the pediatric and neonatal setting, the majority of esophageal perforations can be treated successfully in a conservative manner. The principals involved include minimizing proximal flow of material through the esophagus, controlling contamination, maintaining downstream patency, and optimizing both clinical and nutritional status [59]. Patients are kept nothing per os, with placement of a nasopharyngeal or nasogastric tube to control secretions. Broad spectrum antibiotics covering gram positive, gram negative and anaerobic bacteria are used along with drainage of pleural effusions or mediastinal abscesses if necessary to control contamination. Mediastinal drainage can be performed with radiologic guidance or with the use of thoracoscopy [48].

Esophageal intraluminal stents have been used in pediatric patients but are usually not necessary [60, 61]. Nutritional status is optimized with total parenteral nutrition, or enteral feeds via a gastrostomy or jejunostomy tube. If these measure fail, the esophageal leak should be isolated with an cervical esophagostomy and gastrostomy placement which eventually leads to an esophageal replacement procedure.

24.3.5 Outcome

The outcome of esophageal perforation in the pediatric population is surprisingly good especially when compared to the adult population. In most cases conservative management allows the perforation to heal with little sequelae. Factors that predict a good outcome include early diagnosis and treatment, an iatrogenic origin, young age and absence of underlying disease [47]. Of these, the early diagnosis and treatment appear to be the most important with a 92% survival noted when treatment begins within 24 h of the perforation compared to 67% survival if treatment is initiated after 24 h [56]. In the most recent published series of pediatric esophageal perforations, all the perforations healed with conservative management and there was no mortality. After the perforation, the average antibiotic course was 10 days, the average time from perforation to an esophogram showing no leak was 10.2 days, the average time spent with nothing by mouth was 11.5 days, and the average hospital stay was 15 days [59]. A representative series of 19 esophageal perforations from multiple causes were initially all treated conservatively with nothing by mouth and antibiotics. Eighteen healed with conservative management. The one child who required esophageal diversion had portal hypertension and developed necrosis of the esophagus following sclerotherapy of an esophageal varix. Nine of the 18 did not require invasive management. There were 12 thoracic drains placed with some children receiving more than one, one pericardial window, six gastrostomies and two jejunostomies. One child required occasional dilations after the healing process was complete and two eventually went on to transhiatal esophagectomies due to their pre-perforation disease, but had no issues resulting from the perforation or its healing.

24.4 Achalasia

24.4.1 Introduction

Achalasia is an esophageal motor disorder resulting in increased lower esophageal sphincter resting pressure, incomplete relaxation of the lower esophageal sphincter after swallowing, and the absence of esophageal peristalsis. This leads to a dilated nonfunctioning esophagus with a functional obstruction at the gastroesophageal junction. Achalasia occurs infrequently in all ages, but only 5% of achalasia occurs in childhood. The incidence of achalasia in children has been on the increase. Large population studies of the incidence of achalasia in children have noted an increase from 0.11 to 0.18 cases per 100,000 children per year from 1988 to 2008 [62, 63]. In children, achalasia usually occurs in isolation during the teenage years, but has been associated in younger children with Trisiomy 21, Allgrove (triple A) syndrome consisting of achalasia, alacrima, and adrenal insufficiency and with familial dysautonomia [64]. Under the microscope an esophagus affected with achalasia will have a decrease in myenteric neurons, especially the inhibitory nitric oxide-releasing neurons in the distal esophagus and lower esophageal sphincter [65]. This is thought to result from an autoimmune mediated destruction of these inhibitory neurons in response to an unknown insult in genetically susceptible individuals [66].

24.4.2 Presentation

Although infants have been identified with achalasia, the symptoms most often develop in the early teen years. Several recent studies recorded the average age at diagnosis between 7.8 and 13 years of age with the earliest diagnosis at 1 month of age [63, 67–71]. Symptoms often

continue for a prolonged period prior to diagnosis with average times from symptom onset to diagnosis varying from 7.2 to 30 months [67–70]. Symptoms include dysphagia, vomiting and regurgitation most frequently. In addition, retrosternal chest pain, recurrent respiratory symptoms including cough or dyspnea after meals, nocturnal cough, failure to thrive or weight loss, drooling, and food sticking have been reported. In a review of 40 children with achalasia, 72.5% presented with dysphagia, 60% with emesis, 30% with food sticking, 27.5% with cough and 52.5% with weight loss [72].

24.4.3 Diagnosis

Achalasia is evaluated with a contrast esophogram, upper endoscopy and esophageal manometry. Most often all three examinations are obtained to cement the diagnosis, but some obtain manometry only when a question arises after the esophagram and endoscopy [67]. The contrast esophogram, seen in Fig. 24.3, reveals a dilated esophagus with retained contrast, smooth tapering of the distal esophagus accounting for the "bird's beak" appearance and lack of peristalsis in the body of the esophagus. These are classic findings, but a normal esophagram does not necessarily exclude early achalasia [64]. Endoscopy reveals a distended esophagus with retained food or secretions, but no obstruction at the gastroesophageal junction. Endoscopy can also be normal in up to 44% of cases of achalasia [66]. Esophageal manometry has the highest sensitivity of the three diagnostic studies [66]. Manometry reveals aperistalsis of the smooth muscle portion of the esophagus, incomplete lower esophageal sphincter relaxation, and an elevated lower esophageal sphincter resting pressure. Recently, esophageal high-resolution manometry, which displays manometric data as pressure contour plots, provides functional anatomy of the esophagus and can be obtained in children without sedation [73].

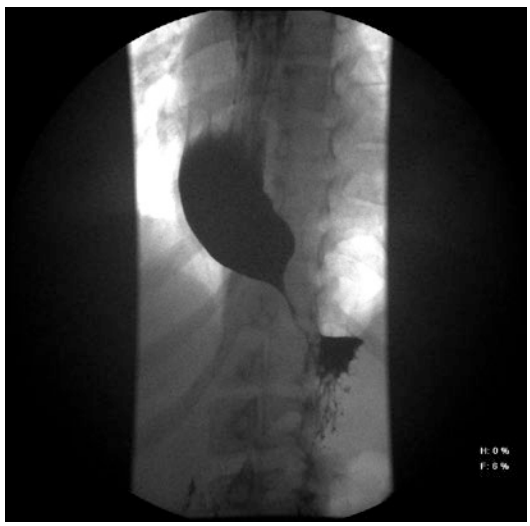

Fig. 24.3 Esophageal contrast study reveals dilated proximal esophagus and bird's beak appearance of the distal esophagus in achalasia

24.4.4 Treatment

Treatment for achalasia attempts to relax or disrupt the lower esophageal sphincter. There are three modalities commonly used: pharamacologic, endoscopic which includes dilation and injection of botulinum toxin, and surgical myotomy with or without a fundoplication to protect against gastroesophageal reflux. The pharamacologic agents used to achieve a reduction in lower esophageal sphincter pressure include calcium channel blockers, nitrates, and phosphodiesterase 5 inhibitors. These agents provide initial improvement in 50–90% of patients, but are short acting and have a significant side effect profile [74]. Pharmacologic treatment should be limited to patients unwilling or unable to undergo other procedures. Pneumatic dilation involves placing a dilating balloon in the lower esophagus and expanding the balloon to rupture the muscle fibers of the lower esophageal sphincter. The main risk of dilation is perforation which occurred in 1.6% of patients studied in a meta-analysis [75]. The long-term success ranges from 40–60% over 15 years [66]. Predictors of failure of dilation include younger age, male gender, pulmonary symptoms, failure to respond to 1 or 2 initial dilations, and manometric findings of a high initial lower esophageal sphincter pressure

(>15–30 mmHg), or reduction in lower esophageal sphincter pressure less than 50% of baseline after the first dilation [66]. Botulinum toxin is a neurotoxin that blocks the release of acetylcholine from excitatory motor neurons thus relaxing the lower esophageal sphincter. Occasionally, the initial injection does not provide relief, and if this occurs, future injections rarely if ever are effective. Repeat injections are often needed as the recurrence rate at 1 year is 50%, and patients are universally symptomatic at 2 years [66]. Given the need for long term results in children, surgical myotomy is often the first approach in this population. A Heller myotomy consists of division and dissection of the muscular wall of the esophagus from the mucosa for a distance of up to 4 cm from the gastroesophageal junction onto the esophagus, and 2–3 cm onto the stomach. This disruption of the lower esophageal sphincter may lead to postoperative gastroesophageal reflux and its complications, so a partial or complete fundoplication is often added to the myotomy. The operation can be completed in both an open or minimally invasive fashion from either the abdomen or the chest. The preferred approach is the laparoscopic abdominal approach. Adult data show that the risk of subsequent intervention for pneumatic dilation is 56% compared to 26% for surgical myotomy. Comparing pneumatic dilation to Heller myotomy with a Dor partial fundoplication at 5 year follow up, those treated with a myotomy had a good result in 95% compare to 65% for pneumatic dilation. However, the surgical success rate decreased to 75% at 15 years follow up. Of the patients treated with a myotomy that had a poor result 92% developed reflux symptoms and they were the cause of the poor outcome, not an incomplete myotomy [66]. The addition of a Dor partial fundoplication to the Heller myotomy decreased the incidence of postoperative reflux from 47.6% to 9.1%. Comparing a Dor partial fundoplication to a Nissen complete fundoplication, the reflux was similar, but those treated with a Nissen developed dysphagia 15% of the time compared to a 2.8% dysphagia rate with the Dor partial fundoplication [66]. At the time of surgery, endoscopy can be used to evaluate for a perforation and the completeness of the myotomy. The endoscope is placed, the distal esophagus is inspected, and gentle insufflation is used to open the lower esophageal sphincter. If the sphincter fails to open, a longer myotomy onto the stomach is required. Using this method, three of five patients required an extension of the myotomy after the endoscopy, and none of the five required further surgeries for achalasia [71]. Postoperative manometry may help predict which patients will develop postoperative symptoms. If the lower esophageal sphincter pressure was less than 12 mmHg after the myotomy, patients had no recurrent symptoms, while those that had postoperative pressures greater than 12 mmHg tended to develop symptoms [74]. When these modalities fail, esophagectomy and gastric pull-up remains an option.

24.4.5 Outcome

Less than acceptable outcomes with achalasia stem from three sources, the natural history of the disease, treatment related complications, and late consequences of successful therapy. The natural history of achalasia leads to problems related to aspiration, megaesophagus, and squamous cell cancer of the esophagus. Structural pulmonary disease thought to emanate from microaspiration occurs in 33% of patients with achalasia. A megaesophagus will develop in 10% of achalasia patients 18–21 years after the onset of symptoms. This may be related to a delay in either diagnosis or treatment. Treatment related complications include perforation with pneumatic dilation and with laparoscopic Heller myotomy. A large meta-analysis found that pneumatic dilation carries a perforation rate of 1.6% with a range of 0–8% in various series. Laparoscopic Heller myotomy had a 0.7% perforation rate with a similar range of 0–8%. The overall postoperative complication rate with the myotomy was 6.3% with a mortality of 0.1% [75]. Late consequences of successful therapy also lead to morbidity. Overall, 10% of patients with achalasia undergoing either pneumatic dilation or laparoscopic Heller myotomy will develop reflux esophagitis. Overall, 43% of patients following treatment for achalasia require acid sup-

pression therapy. Post procedure reflux is more common in those treated with a myotomy, 14% versus 5% in those undergoing pneumatic dilation. Of these patients who develop post procedure reflux, one half will develop late complications of reflux, most commonly a stricture [66]. Two types of esophageal cancer develop in achalasia patients, squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma occurs more commonly, and is thought to develop from stasis that leads to bacterial overgrowth, production of nitrosamines, chronic inflammation, dysplasia, and eventual cancer. Adenocarcinomas are thought to result from long standing reflux. A prospective study following achalasia patients for a mean of 15 years found a 3.3% incidence of esophageal cancer in the population. These cancers developed a mean of 11 years after the diagnosis of achalasia, and a mean of 24 years after the onset of symptoms. The hazard ratio for achalasia patients to develop esophageal cancer was 28 [76]. Using a pediatric quality of life instrument, children with achalasia were found to have a quality of life after being treated with a Heller myotomy that was lower than healthy children and children with inflammatory bowel disease, but comparable to children with chronic constipation [77].

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25 Gastroesophageal Reflux in Newborns and Premature Infants

Juan A. Tovar

Abstract

Gastro-esophageal reflux (GER) is defined as the retrograde passage of gastric contents back into the esophagus where it does not belong. Food and gastric juice may damage the mucosa, interfere with respiratory function and impair nutrition. This phenomenon, which follows a failure of the anti-reflux barrier, is particularly frequent in infancy, a period during which it is considered a near-normal event. Episodes are usually short, occur after feeds and tend to decrease with the passage of time. When GER becomes bothersome, gastro-esophageal reflux disease (GERD) develops.

In this chapter, only GER and GERD in newborns and young infants are addressed. The mechanisms, symptoms, associated conditions, diagnostic procedures and treatment recommendations are summarized.

Keywords

Gastroesophageal reflux • GERD • Investigations • Fundoplication Gastrostomy • Outcomes

25.1 Introduction

Gastro-esophageal reflux (GER) is defined as the retrograde passage of gastric contents back into the esophagus where it does not belong. Food and gastric juice may damage the mucosa, interfere with respiratory function and impair nutrition. This phenomenon, which follows a failure of the anti-reflux barrier, is particularly frequent in infancy, a period during which it is considered a near-normal event. Episodes are usually short, occur after feeds and tend to decrease with the passage of time. When GER becomes bothersome, gastro-esophageal reflux disease (GERD) develops.

In this chapter, only GER and GERD in newborns and young infants are addressed. The mechanisms, symptoms, associated conditions, diagnostic procedures and treatment recommendations are summarized.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_25

25.2 History

Interest in GERD is relatively recent. Only 100 years ago, reflux was linked to esophagitis and heartburn for the first time in adults when barium contrast studies were developed. A gastroesophageal barrier able to prevent retrograde passage of the bolus from the stomach was shown but its failures could not be investigated until the appropriate diagnostic tools became available. Esophagitis and Barrett's esophagus were characterized after development of endoscopy, esophageal manometry, pH-monitoring and miniaturized intraluminal impedance (MII), permitted understanding of the motor events involved in swallowing, GER and clearance. The number of publications on GERD increased enormously and it became a frequent diagnosis and a source of abundant medical consultation [1].

Unfortunately, knowledge on GER in infants and children in whom it is more frequent progressed more slowly, mainly because of the difficult application of these relatively invasive techniques to small individuals. Equipment size, lack of collaboration and ultimately, ethical problems for establishing normal values, made investigation difficult in them. In the fifties and sixties, GERD became a well-known pediatric disease in Europe whereas it was almost unheard of in North American children. When the current diagnostic tools were applied, this situation reversed and a flow of studies generated much interest and active, and sometimes hyperactive, therapeutic attitudes worldwide. GERD is currently considered as a highly prevalent condition in children, particularly in newborns and young infants, in whom medical and surgical treatments are often indicated.

25.3 Embryology

The esophagus and the stomach derive from the embryonal foregut [2] which is surrounded by mesenchymal cells that differentiate and arrange themselves into two concentric muscular layers, the internal or circular and the external or longitudinal ones. These muscle fibres are smooth except in the proximal end in which striated ones predominate. There are no anatomically defined muscle sphincters in the esophagus but the circular layer at both ends of the organ act as such. Early in embryonal life, neural crest cells invade the esophageal wall to form the submucosal and intermuscular plexuses of the enteric neural system that are widely interconnected. Sympathetic, parasympathetic and nitrergic elements mediate inhibition, stimulation and relaxation of muscle contractions and regulate gland secretion.

Embryogenesis of the diaphragm is related to that of the esophagus and stomach. Separation of the thoracic and abdominal spaces is effected by development of this muscle that maintains open orifices for the passage of the inferior vena cava, the aorta and the esophagus. The arrangement of the muscle fibres around the esophagus as a powerful sling contributes to the anti-reflux barrier.

25.4 Functional Anatomy of the Anti-Reflux Barrier

The stomach is located in the abdomen where positive pressures are maintained during the respiratory cycle even at rest. Recumbence, crying and movement further increase this pressure particularly during infancy, and so does gastric peristaltic activity. Conversely, the esophagus is located in the thoracic environment in which inspiratory negative pressures create a powerful pressure gradient between the abdomen and the thorax (and also between the stomach and the esophagus) that favours GER. Since the esophageal mucosa is not prepared for prolonged contact with digestive juices, an efficient anti-reflux barrier fights this phenomenon in normal individuals.

The components of this barrier are: (1) The infra-diaphragmatic location of the distal esophagus, that exposes it to permanently positive closing pressures; (2) The lower esophageal sphincter tone that maintains it permanently closed except during deglutition; (3) The diaphragmatic sling, that occludes the gastroesophageal junction during inspiration, when pressure gradients are stronger; (4) The gastric fundus that maintains

compression on the distal esophagus in the standing position and; (5) The distal rosette of mucosal folds, that contributes to cardial closure. This barrier is effective most of the time, but spontaneous non-deglutory relaxations or incoordination of its components allows reflux. Delayed gastric emptying might facilitate this failure.

Esophageal peristalsis acts as a second defensive line against GER. The normal esophagus is able to mount progressive peristaltic waves during deglutition that push the bolus into the stomach. These *primary* waves run all along the organ. Similar waves that occur when reflux has taken place and do not necessarily involve the upper level of the esophagus are *secondary* waves. In normal individuals, a few *tertiary*, simultaneous, non-progressive contractions, that are unable to clear the lumen, occur as well. Peristaltic activity is complemented by the permanent tonic closure of the upper esophageal sphincter that protects the respiratory tract from GER. During deglutition, both sphincters relax and primary waves propulsate the bolus. After reflux, salivary and esophageal gland secretions help primary and secondary waves to clear the lumen. In erect human individuals, gravity helps to achieve esophageal clearance, but this does not apply to recumbent newborns and infants.

25.5 Epidemiology

Regurgitation due to GER is recognized in more than one third of normal newborns and young infants, medical advice is sought in about one fifth of these cases and only a few of them have actually GERD [3]. All races and both genders are equally affected. Apparent differences in geographic distribution are probably due to variable degrees of interest in this condition that may look more prevalent in some areas than in others depending on the intensity of the diagnostic efforts.

25.6 Genetics

There is some evidence of the involvement of genetic factors in GERD because there are families in which several sibs suffer it. It was suggested that a genetic locus could in chromosome 13q14 and that a high-penetrance autosomal dominant mode of inheritance was likely in families with several members affected by severe GERD phenotype [4], but this was not fully confirmed [5].

25.7 Clinical Presentation and Diagnosis

Reflux can be visualized in the course of antenatal ultrasonography but it is doubtful that this can be of any clinical interest since it is a normal phenomenon. However, intrauterine esophagitis with haemorrhage responding to acid suppression has been reported [6].

Regurgitation and vomiting are the main symptoms of GERD in infants. They take place after feeds and are often partial and rarely explosive. Arrest of weight gain and growth may occur in a few cases, restlessness and nocturnal crying and, less often ground-coffee stained vomiting, are other expressions of esophagitis at this age. Occasionally, refusal to feed, dystonia or extreme irritability express esophageal sufferance [7]. Other symptoms, like repeated cough or recurrent atelectasis and/or pneumonia may be also due to GERD and several other respiratory symptoms like crises of asphyxia and cyanosis or difficulties for extubation in ventilated babies may have the same origin.

In the vast majority of infants, symptoms improve spontaneously or with some postural and dietary interventions during the first year. By 18–24 months most regular refluxers outgrow this condition and only a small proportion remain symptomatic.

The particular prevalence of GER in newborns and young infants and the trend of this phenomenon to improve were explained by the shortness of the intra-abdominal segment of the esophagus at this age and by the alleged immaturity of the anti-reflux barrier [8]. However, refined manometric studies demonstrated that the barrier and the esophageal peristaltic pump are operative since birth [9–12] and only partially undeveloped

in prematures [9, 13]. Spontaneous, transient, non-deglutory lower esophageal sphincter relaxations that account for GER in older patients are also their main mechanism in neonates [10–12, 14, 15]. Probably the relative large volume intake for weight, the crying pressures and the relative shortness of the esophagus in relation to gastric volume facilitate GER during this period of life, and the acquisition of the erect position could help to achieve the so-called maturation.

25.8 When to Perform Diagnostic Tests

This is particularly relevant in newborns and prematures in whom GER is so frequent and benign that the relatively invasive procedures used for its assessment tend to be avoided. All infants have episodes of reflux and therefore, demonstrating its presence only does not ensure its pathologic nature. Quantitation of acid exposure and assessment of mucosal damage become necessary whenever something more than symptomatic treatment is required and this means performance of more than one test.

Barium meal is still widely used for detecting GER but there is little doubt that it is scarcely specific or sensitive for this purpose [16]. In exchange, it is useful for ruling out malrotation and for assessing anatomical displacements (hiatal hernia) and gastric emptying (Fig. 25.1). Endoscopy and biopsy are possible with the thin fiberscopes currently available [17], but they are not routinely used, probably because mucosal damage does not always determine the severity of GERD at this age. Extended pH-monitoring remains the gold-standard for quantitating acid exposure [18–22] provided that some precautions are taken, like using double gastric and esophageal electrodes for detecting post-prandial gastric pH-buffering able to mask esophageal acidity [23, 24] and application of "normal" values that are different at this age are (normal reflux index close to 10% rather than the accepted 4% (22)) (Fig. 25.2). Prolonged multiple intraluminal impedance measurement (MII) coupled with pH-monitoring is rapidly replacing pH-monitoring alone because it informs about both acidic and non acidic episodes of reflux [25–27]. However, the equipment is expensive, interpretation of the tracings difficult and time-consuming and computerized analysis somewhat simplistic. Stationary and pull-through manometry with modern thin multi-lumen extruded catheters with high-pressure-low compliance perfusion is expensive, difficult to perform and requires specialized staff [9–15]. Scintigraphy is rarely used at this age and has its

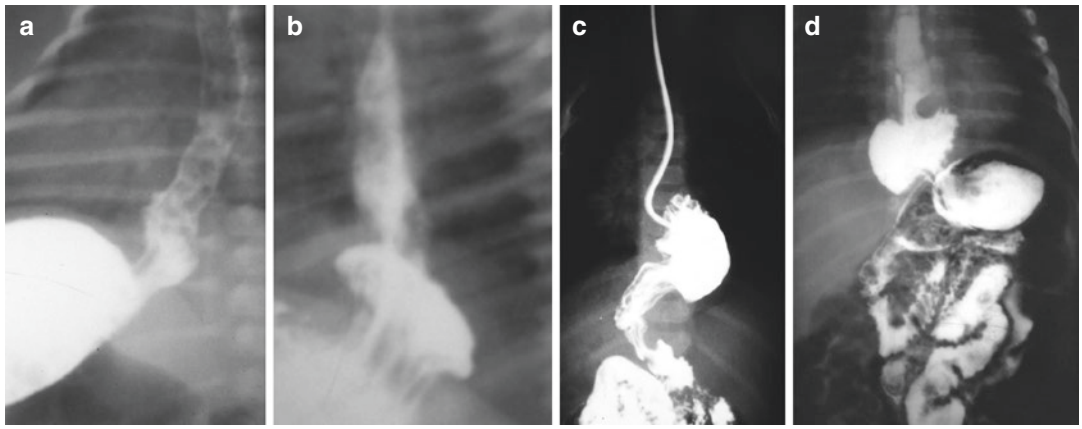

Fig. 25.1 Barium meal is a scarcely specific diagnostic method for GERD because in most cases, it only shows reflux that is to some extent a normal phenomenon (**a**). However, small displacements of the stomach into the thorax (**b**) or major hiatal hernia (**c**, **d**) are well illustrated by this widespread diagnostic method that also informs on duodenal position and gastric emptying

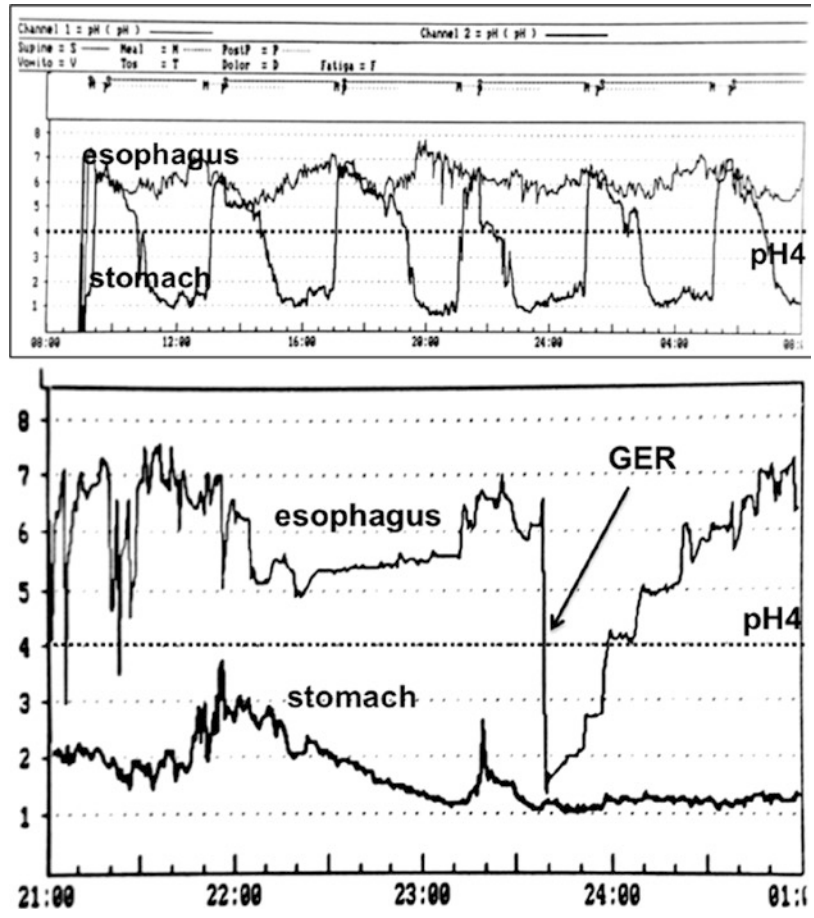

Fig. 25.2 Prolonged pH metering is the best method for quantifying acid esophageal exposure if gastric juice is acid. *Upper tracings*: With an electrode in the stomach and another one in the esophagus, it can be seen how postprandial buffering or alcalinization of the gastric juice for 2 h "blinds" the esophageal electrode six times in 24 h in this non-refluxing baby. *Lower tracings*: An episode of esophageal pH drop below 4 (*arrow*) while gastric pH remains low is indicative of an acid reflux episode

own limitations [28–30] and ultrasonography is probably under-used for this purpose. Indirect forms of relating symptoms to GER (search of either lipid-laden macrophages [31] or pepsin [32, 33] in broncho-alveolar lavage) may also be useful in cases with respiratory tract disease.

In the vast majority of refluxing newborns, diagnostic tests are deferred until demonstrated failure of postural, dietary and antacid treatments prescribed to assist the natural tendency of GER to improve with the passage of time. This failure takes place particularly often in babies with co-morbid conditions (severe respiratory disease, neurologic impairment, previous operations for esophageal atresia, congenital diaphragmatic hernia and abdominal wall defects) in which the anti-reflux mechanisms are damaged, as it will be shown later.

In these cases, and whenever surgery is contemplated, GER has to be convincingly quantitated with either pH-monitoring or MII. Damage caused by reflux has to be documented with endoscopy-biopsy and the anatomy investigated with a barium meal.

25.9 Co-Morbidities in Newborns and Prematures

25.9.1 Severe Respiratory Tract Disease and GERD

Delayed maturation, recumbence, upper airway obstruction, respiratory assistance with positive airway pressure [34, 35], xanthine medication [36], nasogastric tubes [37] and probably other

reasons, make GER particularly frequent and clinically relevant in premature babies and in those with neonatal broncho-pulmonary conditions. Conversely, microaspiration of gastric contents or esophago-bronchial reflexes caused by acid exposure [38] can cause the respiratory disease. Weaning off ventilator may be impossible until GER ceases and broncho-pulmonary dysplasia, that has other origins, is aggravated by GER [39].

On the other hand, apparent life-threatening events (ALTE), like pauses of apnea or cardio-respiratory arrests, are particularly common and dangerous in these tiny young infants. The relationship of GER with such events is difficult to demonstrate making this issue controversial. pH-tracings, poly-somnographic recordings [40, 41] and MII coupled with pH recordings [26, 42] clarified in part the extent of this relationship. Non-acidic reflux episodes are considerably more frequent than expected at this age on the basis of pH recordings alone [43]. ALTE could be related to both acidic and non-acidic reflux [44] although this interpretation is widely contradicted [45–47].

25.9.2 GERD in Neurologically Impaired Babies

Neurologically impaired (NI) infants have often GER. Abnormal neuro-enteric control, spasticity and constipation generate unfavourable conditions that exaggerate the GER-driving pressure gradient. Moreover, there is experimental [48] and clinical [49] evidence of lower esophageal sphincter pressure weakening after brain injury. Non-deglutory sphincteric relaxations are probably less determinant than sphincter insufficiency as a cause for GER in NI patients than in other refluxers [50]. For these reasons, NI children respond poorly to medical treatments and they are often candidates for surgery. Moreover, nutritional problems are common in this particular group of infants and a gastrostomy is often indicated in them in order to facilitate feeding. Gastrostomy itself has been shown to facilitate GER [51, 52] and some technical tips have been offered to prevent this [53]. NI infants constitute the group that requires more often surgical treatment for GERD during this period of life.

25.9.3 GERD After Treatment of Esophageal Atresia and Tracheo-Esophageal Fistula

Babies who survive neonatal repair of esophageal atresia (EA) and tracheo-esophageal fistula (TEF) have GER so often, that this is considered as a component of the original condition. This frequent association is explained by several reasons: (1) The esophagus is structurally abnormal and its extrinsic [54] and intrinsic innervations [55, 56] are deficient. (2) The hiatus and the position of the gastro-esophageal junction can be distorted as a consequence of the malformation [57] and/or of its repair [58] (GER is more frequent in long-gap cases [59–61]). (3) Some patients have upper airway obstruction due to tracheomalacia or tracheobronchial stenosis. (4) Innervation and function of the stomach are abnormal as well [62]. All these conditions create an environment in which the anti-reflux barrier fails while the peristaltic pump in charge of compensating for these failures is scarcely operative. Functional studies repeatedly demonstrated non-propagated peristalsis, weak propulsive force, particularly of the distal esophagus, and decreased lower sphincteric pressure [63–66]. Some of these dysfunctions were present prior to surgical repair [67]. Gastrostomy is occasionally used in the treatment of EA-TEF, and particularly in long-gap and in pure EA cases. This procedure by itself seems to facilitate GER [51, 52, 68].

EA-TEF patients have usually barking cough, often repeated atelectasis or pneumonia and sometimes chronic respiratory tract disease that may last for life. High proportions of survivors have restrictive, obstructive (or both) respiratory tract diseases that may interfere with school frequentation and impair their quality of life [69]. GER has been demonstrated to account in part for these symptoms.

Occasionally, recurrent anastomotic stenoses become refractory to bougie or balloon dilatation probably due to a peptic component [70]. This situation becomes manageable only after reflux is cured by fundoplication.

In EA-TEF survivors, GER tends to be clinically more expressive in the first months of life, but the actual incidence is difficult to estimate because it varies with the diagnostic tests employed reaching figures above 50% [71, 72] and tends to vary with time. In some series, it was almost constant in infancy and tended to decrease over time [73], whereas in others, it definitely increased [74]. It should be pointed out that the mechanisms that facilitate GER after EA-TEF persist for life and therefore, that little spontaneous tendency to improve should be expected. Esophagitis [65] and eventually Barrett's esophagus [75, 76] are found in a number of adolescent and adult patients after repair of EA-TEF and esophageal cancer has been reported in a few of them [77, 78] demonstrating that GER remains a long-standing problem.

Whenever symptomatic GER is shown in these patients, active treatment should be undertaken. Prospective assessment of reflux status and appropriate immediate post-operative medical treatment have been conducted in EA-TEF survivors with only limited proportions of anti-reflux procedures [73]. However, surgical correction of reflux is a widely accepted option [79, 80].

25.9.4 GERD After Treatment of Congenital Diaphragmatic Hernia (CDH)

CDH, a postero-lateral diaphragmatic defect that permits prenatal herniation of abdominal contents (bowel, liver, stomach, spleen or kidney) into the thorax, occurs in 1:3000 newborns. It is accompanied by lung hypoplasia with persistent pulmonary hypertension and often, by other malformations that cause mortality of up to 50% in population-based studies. However, 70–80% of babies treated in specialized units survive and many of them suffer subsequently respiratory tract disease, neuro-developmental deficiencies, hearing loss and GERD. The association between CDH and GERD was pointed out years ago [81] after a dysfunctional, dilated esophagus was described in some babies with CDH [82]. GERD was found more frequently in patients requiring ECMO [83, 84] and in those with large hernias [85]. It persists beyond childhood, causes problems in up to 54% of cases [74, 86] and produces esophagitis in more than 50% of patients and Barrett's esophagus in some of them [87].

There are several explanations for this: (1) The hiatus is under tension due to closure of the diaphragmatic orifice and/or by its replacement by a prosthetic patch. (2) Esophageal extrinsic and intrinsic innervations are abnormal, as shown in animals with CDH [88, 89] and in human autopsies [90] and consequently, the gastro-esophageal barrier and the esophageal peristaltic pump might fail. (3) The small lung, the flattened diaphragm [91] and the tight abdominal closure exaggerate the aboral pressure gradient that facilitates GER [92]. (4) Gastric emptying may be delayed [85] or the small bowel partially obstructed due to non-rotation or malrotation. (5) Gastrostomy is sometimes used for overcoming the nutritional difficulties that these patients experience post-operatively [93].

GER is frequent during the first year after CDH repair [94, 95] but it tends to taper-off in the ensuing years [74] unless chronic respiratory disease and/or neurologic impairment maintain it. Recent pH and manometric studies show that only a small proportion of patients maintain sphincteric and peristaltic dysfunctions over the years [96]. However, the severity of the respiratory disease in CDH patients and the difficulties for feeding make simultaneous performance of gastrostomy and fundoplication a relatively common indication.

25.9.5 GERD After Treatment of Anterior Abdominal Wall Defects (AAWD)

AAWD are developmental anomalies in which the body wall is incomplete or abnormal. In

omphalocele or exomphalos, the periumbilical wall is replaced by a gelatinous sac that contains the bowel and, sometimes, the liver. In Gastroschisis or Laparoschisis, there is a parietal orifice located on the right side, in the vicinity of the umbilical stalk, that allows the bowel, and sometimes other organs, to eviscerate. In both cases, the abdominal space is reduced at birth, and surgical reintegration of the viscera is invariably accompanied by increased abdominal pressure [97]. This, together with the difficulties for re-establishing intestinal transit after the operation and with the constant presence of non-rotation or malrotation, creates a pressure environment that facilitates GER and may even produce hiatal hernia [98]. The location of the hiatus itself, that is very anterior, sometimes substernal, may also facilitate some dysfunction of the anti-reflux mechanisms. Most often GER is a transient situation in this context that tapers off when abdominal contents re-accommodates itself into a progressively enlarged abdominal space but, in a number of cases, this does not happen. GER often accompanied by esophagitis has been found in 43% of omphalocele and 16% of gastroschisis patients [99]. Once again, some of these patients require gastrostomies for overcoming the first and sometimes long postoperative phase of gastrointestinal dysfunction and this may either aggravate GER.

25.10 Treatment

The concept of GER having a naturally-limited course in infants must guide all therapeutic actions except in those with co-morbidities in whom it may not apply. Orthostatic positions in prone [100] or left-lateral decubitus [101] have some limited effect although the alleged increased risks of sudden-infant death in prone position temperate this indication [102]. Formula thickening with rice starch or bean gums [103, 104] has been used with various degrees of enthusiasm although the cumulative evidence of its successes is scarcely convincing [105]. Prokinetics like Cisapride were extensively used [106] and then abandoned after some reports on their cardiac risks [107] that were probably exaggerated [108], but the evidence on their benefits in infants [109] and prematures [110] is weak. H_2-receptor inhibitors like Cimetidine [111], ranitidine [112] or famotidine [113] have also been extensively used for suppressing acid secretion until proton-pump inhibitors became the preferred medication. Omeprazole [114], esomeprazole [115] and pantoprazole [116, 117] are effective for acid suppression.

The need for randomized clinical trials for better defining the therapeutic guidelines in infants with GER has been repeatedly pointed out [118, 119] and the combined recommendations of the NASPGHAN [120] and ESPGHAN [3] on the management of GERD in children examine in depth all aspects of diagnosis and non-operative treatment of GERD limiting surgical indications to cases refractory to optimal treatment, those with intractable erosive esophagitis, intractable asthma or cases of ALTE with convincing evidence of temporal relationship between the episodes and reflux. However, these recommendations, that are less critical with some non-operative measures than with anti-reflux surgery [121], barely take into consideration some of the above-mentioned co-morbidities that are particularly relevant for pediatric surgeons.

Anti-reflux operations (Fig. 25.3) are based on reinforcement of the elements of the barrier. Some pretend to be more physiologic, like the anterior gastropexy designed by Boerema [122] or the anterior or Thal [123] fundoplication popularized by Ashcraft [124] and Boix-Ochoa [125]. In both cases the angle of His is exaggerated by elongation of the intra-abdominal segment of the esophagus and, in the anterior plication, half a fundal valve is sutured in front of this segment. However, the gold standard of anti-reflux operations remains the complete fundoplication devised by Nissen in which the fundus is wrapped around the lengthened intra-abdominal segment to act as a one-way pneumo-hydraulic valve [126, 127]. Provided that the wrap is loose enough, difficulties for burping are transient and the anti-reflux effect is powerful and achieves decrease of transient non-deglutory relaxations [128]. A minor modification is the posterior hemi-fundoplication

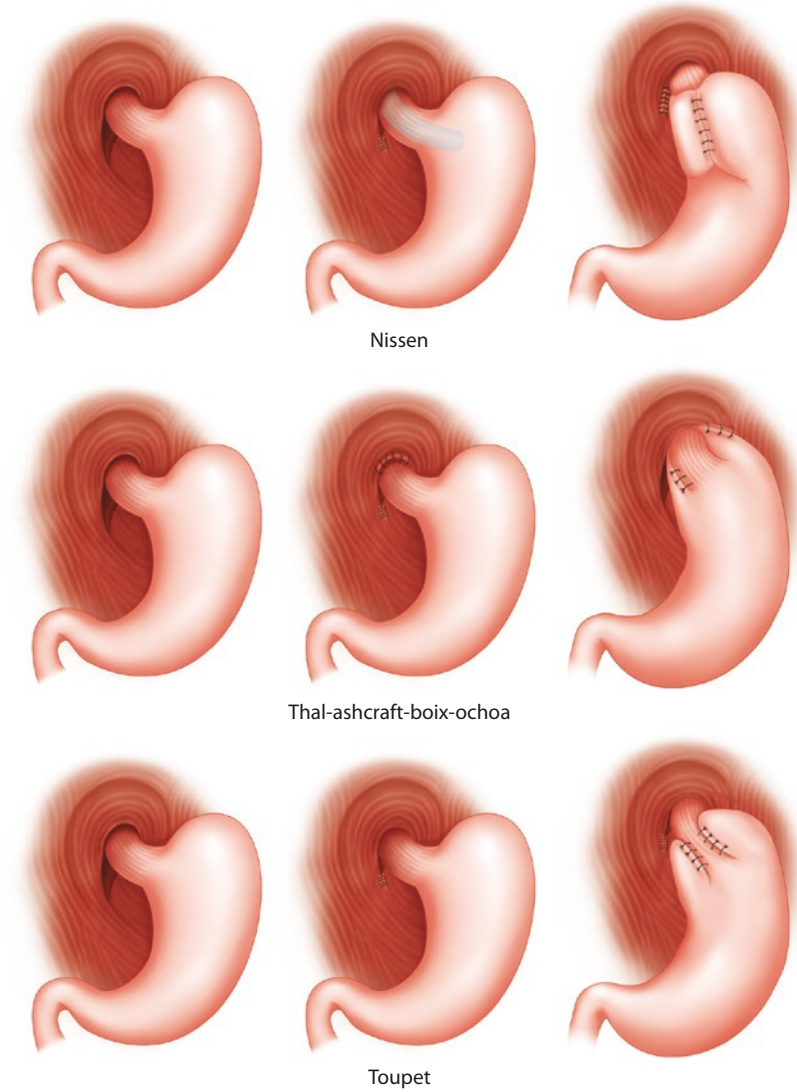

Fig. 25.3 Nissen fundoplication remains the gold-standard of surgical treatment of GERD. It consists (*upper drawing*) in replacing the distal esophagus below the diaphragm, passing the posterior wall of the fundus around the esophagus and suturing it to the anterior one in front of it. This one-way pneumo-hydraulic valve should be loose (a thick dilator is placed inside the esophagus during plication). Thal-Ashcraft-Boix Ochoa anterior plication (*middle drawing*) or Toupet posterior plication (*lower drawing*) may be as effective

of Toupet that achieves the same effect with only half a wrap [129, 130]. All these techniques can also be performed laparoscopically [131–143] and this approach is preferred in many cases.

It has been repeatedly shown that anti-reflux procedures work well in regular refluxers in whom the valve remains functional for long periods of time [142, 144]. However, this is not always the case when reflux-favouring conditions are present. In these patients, a full wrap is definitely stronger and is probably advisable [145].

Most surgeons agree on that anti-reflux operations are indicated only in cases in which symptoms cannot be managed by non-operative measures and when the naturally benign course of the disease is not any more a realistic perspective. However, pediatric surgeons are confronted with refluxing infants that were previously treated surgically for other conditions and this changes considerably their view of GERD for these specific groups [146].

The concurrent need for a gastrostomy in NI patients, and in some treated for EA-TEF, CDH or AAWD may also have some influence on the decisions since it facilitates reflux by itself [51] while at the same time can fight it by correcting malnutrition [147]. The performance of both

procedures during the same anesthesia motivates some indications. However, it should be taken into account that there is little evidence of the rationale for this attitude.

Fundoplication may be beneficial and even life-saving for infants with persistent respiratory tract disease in which GER has been demonstrated, particularly in those with broncho-pulmonary dysplasia and difficulties for extubation after prolonged mechanical ventilation [39, 148–151]. However, demonstration of the involvement of GER in the respiratory condition is difficult, and it is necessary to find better selection criteria for those eventually benefitting from anti-reflux surgery [42]. Operative decisions are particularly hard in infants with ALTE and apnoeic spells or cardio-respiratory events. Polysomnographic recordings have demonstrated that both these events and GER occur often in this particular population and are not necessarily related [47, 152] and that there are other causes for ALTE. This somewhat cooled a surgical indication that apparently stands by itself given the actual risk for life of these particular situations.

Anti-reflux surgery during infancy is relatively often indicated in NI individuals in whom dysfunction of both the barrier and peristalsis are irreversible and cause permanent regurgitation, malnutrition and respiratory tract disease. In addition, they often benefit from a feeding gastrostomy performed previously or concurrently [132, 153–155]. One third of fundoplications during this period of life are performed in NI infants and most have a gastrostomy [143]. However, it has been shown that a "protective" anti-reflux procedure is not necessary in all NI patients having a gastrostomy [156–158]. Complications and mortality after fundoplication are twice as frequent in them as in regular refluxers [155, 159, 160]. This is an important issue because the rates of fundoplication failure in NI patients range from 7% to 25% [159, 161, 162] in the long term.

After more than one failure of the anti-reflux procedure in NI children, alternative operations, like total esophago-gastric dissociation [163–165] or feeding jejunostomy [166, 167] can be offered as reasonable alternatives.

Infants with EA-TEF require anti-reflux surgery quite often and the operation in them may be more difficult than in regular refluxers. The esophagus (particularly the intra-abdominal portion) is shorter, the fundus is small, the angle of His is obtuse or non-existing and a gastrostomy might be already on site or else be required at the time of surgery. On the other hand, the compromised peristalsis in this condition makes any potentially obstructive manipulation less tempting. For these reasons, partial anterior (Thal, Aschcraft, Boix-Ochoa) [168, 169] or posterior (Toupet) [168] hemi-fundoplications are sometimes preferred to the classical Nissen. Anterior gastropexy has also been shown to be beneficial [122]. However, complete, loose fundoplication has been preferred by most authors [126, 144, 168, 170, 171] and there should not be reason for concern provided that it is actually non-obstructive. Lengthening of the intra-abdominal esophagus by Collis plasty followed by Nissen fundoplication has been found useful by some authors [172, 173].

The success of fundoplication in abolishing the GER of EA-TEF patients is, unfortunately, transient in a considerable proportion of cases ranging from 15% to 40% [79, 169–171, 174] due to wrap herniation or loosening. The persistence of all the causes for this dysfunction after fundoplication explains why it fails. In some cases, the severe consequences of GER have already been outgrown by the patient and, in others, redo plication is attempted. Chronic proton-pump inhibitors (Omeprazole) are indicated in these cases [175, 176] and, in some rare instances, more radical operations like esophago-gastric dissociation can be elected [177, 178].

Infants operated upon for CDH require anti-reflux surgery less often, but some cases with large defects and requiring ECMO support clearly benefit from it [85]. Abnormal hiatus, prosthetic patch, malposition or malrotation of the intestine and adhesions due to the previous operation can seriously interfere with the performance of an otherwise straightforward operation. A gastrostomy may be in place or is required at the same time. To circumvent these difficulties, prophylactic fundoplication during CDH repair

has been offered [179–181]. Hiatal refashioning and/or reconstruction may require prosthetic mesh patches in an attempt to reduce the incidence of recurrent reflux [182]. This may amount to 20% or more of operated patients [144].

Babies operated previously for AAWD like omphalocele and gastroschisis have sometimes GERD requiring surgical repair [98, 144]. Once again, this may be particularly difficult in them due to the abnormal arrangement of the intestine and the hiatus, adhesions and sometimes, to the need for a gastrostomy. In these conditions a prophylactic fundoplication during the initial operation has been proposed [183]. The approach to the hiatus can been found so difficult that a thoracic approach has been advised for these cases [184].

In summary, indications for anti-reflux surgery are scarce in newborns and infants, but they are clearly beneficial whenever non-operative treatment fails and especially when co-morbidities interfere with a favorable outcome. The higher number of complications and long-term failures in these particular patients should not discourage operative indications that may permit to overcome severe GER complications. Laparoscopic approach is indicated when feasible, and re-operation is necessary quite often.

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Congenital Diaphragmatic Hernia and Eventration

26

Paul D. Losty

Abstract

Congenital diaphragmatic hernia (CDH) has an incidence of 1 in 2500 live births in the UK. CDH is a defect in the fetal diaphragm which allows the contents of the abdominal cavity to protrude into the thorax. CDH may be associated with other major anomalies. The defect may be diagnosed in the fetus, newborn or older child. Some forms of CDH may remain 'asymptomatic' for several years and not present until later life or adulthood. CDH is most often a sporadic and isolated birth defect (70%) though a number of gene mutations have been identified, e.g. chromosome 4p, 8q, 15q. Links have been made to environmental factors such as thalidomide, nitrofen and vitamin A deficiency. CDH may also be associated with the chromosomal disorders trisomy(s) 13, 18 and 21 including the inherited conditions—Fryn's and Pallister Killian syndromes.

Keywords

CDH • Fetus • Pulmonary hypoplasia • Pulmonary hypertension • Associated anomalies • Surgery • Fetal surgery • Outcomes

Congenital diaphragmatic hernia (CDH) has an incidence of 1 in 2500 live births in the UK [1, 2]. CDH is a defect in the fetal diaphragm which allows the contents of the abdominal cavity to protrude into the thorax. CDH may be associated with other major anomalies. The defect may be diagnosed in the fetus, newborn or older child. Some forms of CDH may remain 'asymptomatic' for several years and not present until later life or adulthood. CDH is most often a sporadic and isolated birth defect (70%) though a number of gene mutations have been identified, e.g. chromosome 4p, 8q, 15q. Links have been made to environmental factors such as thalidomide, nitrofen and vitamin A deficiency. CDH may also be associated with the chromosomal disorders trisomy(s) 13, 18 and 21 including the inherited conditions—Fryn's and Pallister Killian syndromes [1, 2].

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_26

26.1 Pathology

The precursors of the human diaphragm begin development during the fourth week of gestation in the form of the septum transversum and lateral folds of mesenchymal tissue(s). These partition the abdominal and thoracic compartments with the formation of the pleuroperitoneal membrane occurring by the eighth week. As development continues muscle fibres migrate into this membrane. Aberration(s) of these critical phases in early human development will result in a 'true' diaphragmatic defect (CDH) or a complete, yet hypoplastic, poorly muscularised diaphragm, i.e. diaphragmatic eventration. Closure of the right hemidiaphragm typically occurs before the left, which likely accounts for the higher incidence of left sided diaphragmatic defects (84%). Right diaphragm defects comprise some 13% of lesions and 2% cases are bilateral defects. Rarer forms include complete diaphragmatic agenesis. The commonest lethal form of CDH in humans is the defect occurring in the posterolateral regions of the developing diaphragm referred to as a Bockdalek's hernia [2]. Other variants encountered in clinical practice are the anterior diaphragm or sternocostal defect, i.e. Morgagni hernia.

Outcomes in CDH are highly variable with regard to prognosis in comparison to other major index neonatal surgical conditions, with reported mortality rates varying from 20%–60% across centres worldwide [1, 2]. Outcome data are here integrally link with the 'hidden mortality' of CDH when taking into account in utero deaths and perinatal fatalities. Morbidity and mortality in CDH is principally related to mechanical compression of the developing lung(s) by herniated intrathoracic abdominal viscera (gut, liver and spleen) resulting in pulmonary hypoplasia which also affects vasculature biology. Histological changes seen at human post mortem studies in the underdeveloped ipsilateral lung on the affected side of the hernia defect are also closely mirrored in the contralateral lung suggesting that whatever insult is responsible for the failure of the diaphragm to develop normally also potentially has wider impact on primordial development of the respiratory system. A primary anomaly affecting early human lung development is postulated [3]—the 'first hit' insult occurring with a 'secondary hit' resulting from later intrathoracic herniation—'dual hit hypothesis' [4].

26.2 Antenatal Diagnosis

Although CDH is not always diagnosed in the prenatal period—all cases detected antenatally must be referred early to a specialist centre. Antenatal diagnosis permits counselling by an experienced multidisciplinary team—paediatric surgeon, neonatologist and obstetrician—as well as allowing treatment and delivery planning [1, 2]. Antenatal diagnosis is reported as early as the 11th week of gestation, however, in the UK region, CDH is more often detected at a 20 week fetal anomaly scan. Within the wider European region—a multicentre study found that 60% of cases of CDH were identified antenatally at an average gestational age of 24.2 weeks [2].

26.3 Associated Anomalies

Antenatal detection should always make effort to identify other associated anomalies, to permit accurate parental counselling [1, 2, 5–7]. Survival of newborns with associated severe malformations (e.g. cardiac) remains dismally poor. Amniocentesis is recommended to identify chromosomal anomalies e.g. Trisomy(s) 13, 18 and 21, Donnai-Barrow, Fryns and Pallister Killian syndromes. Echocardiography is utilised to screen for cardiac anomalies, present in up to 18% of cases A thorough sonographic evaluation of the urinary, gastrointestinal and central nervous system should also be performed to detect further structural malformations (33%).

26.4 Predicting Outcome

Defining reliable antenatal predictors of outcome in CDH have been the subject of intense study over the last few years. Most current methods

rely on indirect techniques, e.g. US/MRI to make an assessment of fetal lung volume. Measurement of the contralateral fetal lung area to head circumference ratio (LHR), using 2D ultrasound (US) imaging, as a potential predictor of outcome was first proposed by Mike Harrison's group at UCSF in the mid 1990s [8]. LHR gained early popularity as a prognostic marker and indeed was incorporated into the NEJM randomised clinical trial to guide decision-making for fetal intervention in CDH—see later. A systematic review and meta-analysis study published from Liverpool (2007) showed absolute measurement of LHR was flawed and it was recommended better refinement was needed with procurement of comparative data in the normal healthy developing fetus [9]. LHR criteria have now been improved by fetal medicine specialists taking into account the fourfold relative increase of lung area to head circumference that occurs between 12–32 weeks in the normal developing fetus. The observed to expected predicted (O/E) LHR is now believed to be a better prognostic scoring tool [10].

Aside from determining fetal lung volume(s) with ultrasound other useful markers guiding prognosis antenatally include the presence or absence of liver herniation (designated 'liver up' CDH), and an emerging role for fetal MRI lung metrics. In a further systematic review study published from Liverpool it was later shown that fetuses with an increased volume of liver within the thoracic cavity—('liver up' cases) defined cases with (a) larger hernia defects, (b) a greater need for prosthetic patch repair and (c) worse survival [11]. Further studies to accurately predict survival have included real-time sonographic measurement of pulmonary artery dimensions to estimate risk(s) of postnatal pulmonary hypertensions [12].

26.5 Fetal Intervention

Fetal intervention for CDH was promoted and pioneered by Michael Harrison's group at UCSF, California, initially focusing on open surgical repair of the diaphragmatic defect deploying maternal C-section hysterotomy [13]. Early trials which evaluated open surgical repair of CDH were later abandoned due to problems with maternal preterm labour and adverse fetal outcome(s). Wilson's (1993) laboratory work explored and showed the dramatic changes seen in lung growth by occluding or 'plugging' the fetal trachea in the surgical CDH lamb model that led to the evolution of new fetal surgical approaches for CDH [14, 15]. Harrison then undertook the first randomised clinical trial in humans which explored the potential of fetal endoscopic tracheal occlusion. The trial showed equivalent survival outcomes in a treated cohort who underwent occlusion versus a control group of fetuses managed with conventional postnatal care in specialist centres [16]. For fetal surgery to have future clinical application selection of CDH fetuses with better prognostic 'high risk scoring' was needed. With the deployment of new LHR (O/E) and 'liver up' entry criteria (i.e. defining fetuses considered to have the very worst prognosis), fetal medicine programmes have now begun to explore the potential of FETO (a new minimally invasive operation 'fetoscopy guided balloon occlusion') in a prospective randomised clinical trial [17, 18]. The FETO trial outcome is eagerly awaited with findings expected to be published in the next few years.

26.6 Newborn Management

26.6.1 Delivery

With an increasing antenatal detection rate of CDH expert opinion regarding the mode of newborn delivery remains a subject of debate. In 2007 the International CDH study group reported a marginal (not significant) survival benefit for elective delivery by caesarean section [5, 19]. Further well designed randomised studies are required to draw any definitive conclusions here.

In order to maximise pulmonary development, delivery of the baby with CDH should be planned as near to term (more than 37 weeks) as

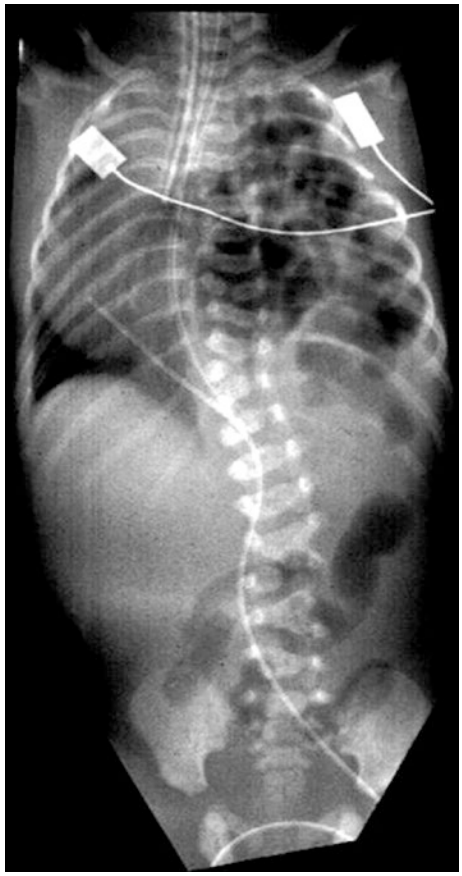

Fig. 26.1 Chest X-ray of newborn with left side CDH Bochdalek defect. Note bowel contents in left thoracic cavity, mediastinal shift and dextrocardia

possible [1, 2]. Delivery should be co-ordinated in a specialist centre equipped with full neonatal intensive care facilities and ready access to a multidisciplinary CDH team. Elective intubation following birth and 'gentle' ventilation (avoiding barotrauma) is recommended. All babies should have a nasogastric tube inserted to avoid gastric distension impairing ventilation and vascular access promptly secured to aid delivery of fluids and pharmacological/vasoactive agents. After initial stabilisation full clinical examination is essential to exclude associated anomalies and dysmorphism. Chest X-ray (Figs. 26.1 and 26.2) confirming the diagnosis and echocardiography is arranged screening for associated cardiac anomalies.

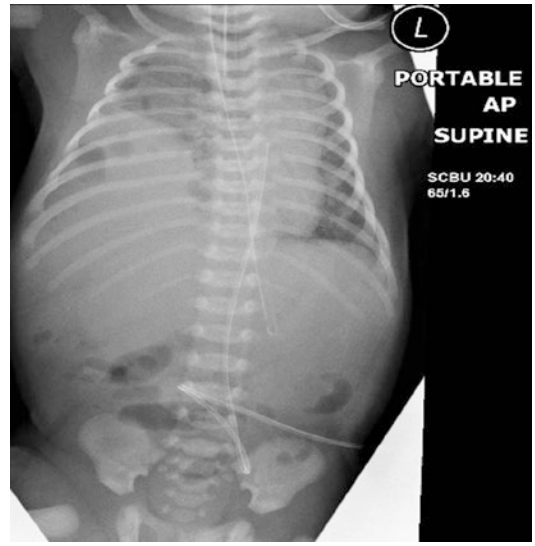

Fig. 26.2 Chest X-ray of newborn with right side CDH defect. Note marked opacification of the right hemithorax region as the liver and intestines (focal areas shown by gas shadows) were displaced in the thoracic cavity

26.6.2 Postnatal Diagnosis—'Late Presenting CDH'

Despite antenatal imaging almost 30% of patients with CDH may remain undetected until after delivery [2]. These cases may present emergently in the immediate newborn period or the first few days after birth whilst others may remain 'asymptomatic' until later life. Symptoms may include mild respiratory distress or laboured feeding problems. Delayed CDH presentation may occur with small diaphragmatic defects in which there is little or no herniated bowel at birth. Herniation of intestinal viscera into the chest may then occur as a later event following the introduction of feeds or accompany a respiratory tract infection. Clinical examination may reveal bowel sounds on chest auscultation. There may also be signs of decreased air entry on the affected side of the defect and mediastinal shift. Diagnosis is readily established by chest X-ray but occasionally may require an upper gastrointestinal tube contrast study to confirm the diagnosis of 'gut in the chest'.

26.6.3 Stabilisation

26.6.3.1 Permissive Hypercapnea/'Gentle' Ventilation Strategy

A major advance in the management of CDH particularly in the last 20 years has been the adoption of 'gentle ventilation' strategies (permissive hypercapnea) to reduce iatrogenic lung injury from barotrauma. Wung and Stolar—New York, introduced this therapy strategy which is characterised by preservation of spontaneous ventilation with permissive levels of hypercapnea ($paCO_2$ 60–65 mmHg or 9 kPa) and avoidance of high inspiratory airway pressures (ideally not exceeding 25 cm H_2O) [20]. Specialist centres worldwide are reporting improving survival (>80%) outcomes in CDH using this strategy with a declining utilisation of ECMO. High frequency oscillatory ventilation (HFOV) has also been deployed in management of CDH as a 'rescue therapy' prior to ECMO and as a primary ventilatory modality in an effort to reduce pulmonary barotrauma. Whilst several reports document improved survival of CDH using HFOV the recently published VICI trial has shown better outcome(s) with conventional ventilation in a prenatally detected CDH population as defined by (1) shorter duration of ventilation, (2) a reduced need for ECMO, (3) lesser requirements for iNO therapy also including (4) vasoactive agents notably sildenafil [21].

26.6.3.2 ECMO, Nitric Oxide, Sildenafil

ECMO (refer to Chap. 21) was introduced in the 1970s and used with modest success to treat cardio-respiratory failure in newborns not responding to conventional life support measures. ECMO was then later utilised in CDH to treat pulmonary hypertensive crisis. Pulmonary hypertension (PHT) associated with CDH is due to adverse physiologic events triggering abnormal pulmonary vascular resistance with right to left shunting, worsening severe hypoxemia and persistent fetal circulation. In the 1980s and early 1990s ECMO therapy expanded across intensive care units in clinical management of CDH. A 1990s UK multicentre randomised clinical trial and a Cochrane review later showed that no significant survival benefits were shown with ECMO use in CDH [22–24]. These findings have to some extent led to a steady decline in ECMO practice in many centres. Methods currently deployed for managing pulmonary hypertension associated with CDH now include use of inhaled nitric oxide (iNO) and the phospho-diesterase inhibitor sildenafil [25, 26]. A large multicentre randomised controlled trial (NINOS) and a Cochrane review failed to demonstrate significant sustained benefits with iNO therapy in CDH. In the studies that were published nitric oxide (iNO) therapy did not reduce (a) requirement for ECMO support or (b) improve CDH survival [25]. Sildenafil has emerged as a promising pulmonary vasodilator with some success recorded in CDH. Drug bioavailability and therapeutic efficacy from erratic gut absorption can be a problem. Intravenous sildenafil has been tested with encouraging early reports from Australia [27]. Randomised controlled trials are required.

26.6.4 Surgery

CDH was once regarded as a surgical emergency with operative repair performed early after delivery in an effort to improve ventilation by reducing the herniated viscera from the thoracic cavity [1, 2]. Currently preoperative stabilisation of labile physiology is paramount with delayed surgery scheduled during 'normal working hours' which permits optimisation of respiratory and cardiac status. A coordinated team approach is crucial with vital roles provided by cardiologists, intensivists and surgeons in selecting best therapies—(serial echocardiography monitoring of PHT, ventilator strategy(s)—CMV, HFO, iNO, ECMO) and timing of operation [1, 2, 22].

Classical operation is performed using a subcostal incision with the herniated contents returned to the abdominal cavity from the thorax and the defect in the diaphragm repaired with interrupted non-absorbable Ethibond sutures. A subcostal slide incising the upper margins of

the diaphragm defect can also be helpful to achieve primary closure—Figs. 26.3 and 26.4. In some 10–15% of babies a hernia sac will be evident at operation and this requires excision prior to diaphragm closure. In 20–30% patients with a large defect a prosthetic 'patch' must be deployed to achieve closure—Fig. 26.4. There are a number of different materials currently available to the surgeon e.g. GORETEX or biosynthetic substitute(s)—SURGISIS. Varied reports have cited poor outcomes with patch repair with up to 50% patients in some centres requiring re-operation for recurrent CDH from prosthesis failure with patient growth [28]. Experience from 'high volume' CDH centres, e.g. Philadelphia, USA and Liverpool, UK have however reported better patient outcome(s) showing low rates of patch failure (5–10%) principally using GORETEX material [22, 29]. Biosynthetic patches are theoretically appealing to use though have been linked with early recurrence(s) and revisional operation. We (like others) believe prosthetic patch failure reflects a likely technical problem with its implantation at primary CDH repair by the surgeon. Innovative techniques combining the skills of plastic surgery may also achieve effective repair of large diaphragm defects with deployment of latissimus dorsi or rectus abdominis for muscle flap closure [2].

Minimally invasive techniques (MIS) can be used for CDH repair. Benefits potentially include reduced post-operative pain and improved cosmesis though physiological derangement(s) during operation may prove hazardous in fragile newborns. The diaphragm defect is visualised thoracoscopically, the hernia contents are repositioned in the abdominal cavity and endoscopic repair then undertaken with or without patch insertion. A systematic review from Liverpool showed that higher rates of hernia recurrence are a problem with MIS repair vs. classical open operation [30]. To address such concerns surgeon case selection incorporating 'lower risk' patients with smaller size diaphragmatic defects should see high recurrence rates decline. Surgeons rarely deploy the routine placement of an intercostal pleural drain after CDH repair. There are also few (if any) indications for a Ladd's operation in the

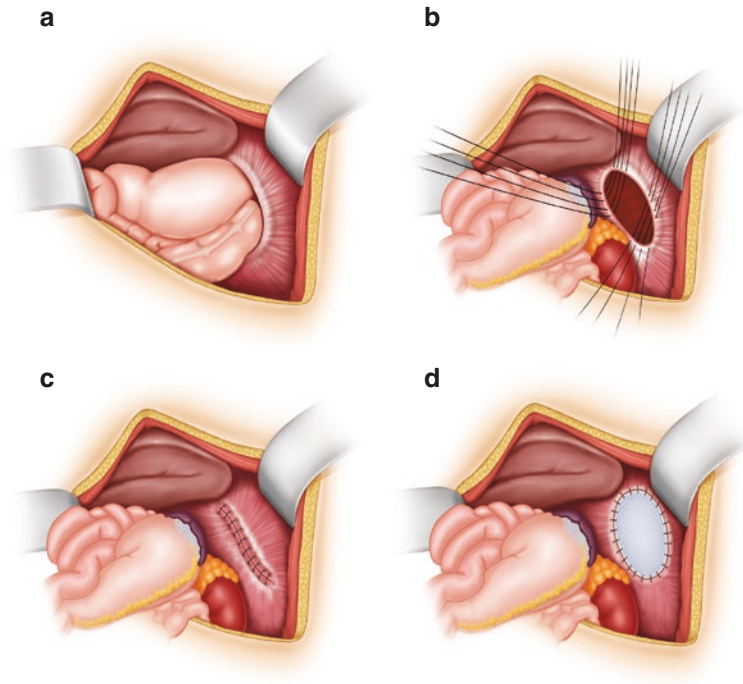

Fig. 26.3 Classical operative repair CDH—(**a**) stomach, intestines and spleen are displaced in the thorax through a Bochdalek posterolateral diaphragm defect. (**b**) Hernia contents including spleen have been reduced into the abdomen. A row of interrupted non-absorbable sutures have been placed to secure primary diaphragm closure. (**c**) Primary repair completed, (**d**) prosthetic patch material deployed to secure closure for large left side defect

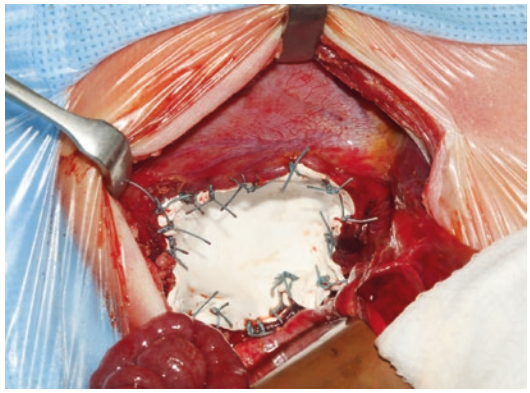

Fig. 26.4 Goretex prosthetic patch repair for large right side CDH defect

'non-rotated' gut frequently seen in the CDH patient. Such additional (and unnecessary) procedures increases patient morbidity with the risk(s) for adhesive intestinal obstruction [1, 2].

26.6.5 Morbidity

Pneumothorax will present with sudden deterioration in the cardiac and respiratory status of the postoperative ventilated patient too often with fatal outcome. Rapid needle thoracocentesis and chest drain insertion may be life saving. Diagnosis of pneumothorax on a routine post-operative chest X-ray in the physiologically 'stable' patient should be made with extreme caution. The lung, on the ipsilateral side of the repaired CDH defect is hypoplastic, and will not fill the whole hemithorax, giving the false impression of a pneumothorax to the inexperienced clinician [1, 2]. Post-operative effusions are not uncommon e.g. chylothorax (28%) in some series. The majority of effusions are small transient collections which resolve. Large effusions respond adequately to needle thoracocentesis. A recurrent troublesome chylothorax may require a pleural drain, octreotide, a period of withholding oral feeds together with parenteral nutrition and graded introduction of medium chain triglyceride (MCT) formula [31]. Refractory pleural collections in the sickest infants should also alert the surgeon to the possible co-existence of the very rare disorder—congenital pulmonary lymphangioectasia—a uniformly fatal condition [32]. Treatment here is often futile. Diagnosis may be confirmed by high resolution CT imaging and/or lung biopsy.

Abdominal compartment syndrome (ACS) must be considered a risk in CDH patients particularly where the volume of herniated abdominal contents returned to the abdominal cavity is large often requiring patch repair and/or when the primary diaphragm repair is under tension. The risk of developing ACS can be minimised considerably by reducing intra-abdominal pressure with the liberal insertion and use of an abdominal wall patch—'abdominoplasty' [1, 2, 22].

Risk factors for recurrent CDH include—(1) large defect size (2) need for patch repair. Studies have reported revisional surgery in some 50% of patients. Technical factors with primary repair and particularly with prosthetic patch usage likely equate with recurrent herniation and early patch disruption [22, 29].

26.7 Outcome(s) and Long Term Follow Up

Survival data for CDH show outcomes widely ranging from 40%–80% success rate(s) in different countries likely reflecting variability in accurate reporting of birth defect registries and omission of 'hidden mortality' metrics [1, 2, 22, 23, 33]. Population-based studies criticize positive reports (>80% survival) as often not including the full spectrum of antenatal losses and terminations/perinatal CDH deaths. However 'high volume' centres have convincingly shown modest improvement(s) in outcomes with Alder Hey for example achieving 85% CDH survival with hospital discharge vs 50% survival rate seen in an early 1990 era [22, 34]. Improving survival has yielded a 'new population' with the most vulnerable 'high risk' patients, i.e., ECMO or FETO survivors experiencing a high morbidity. CDH patients require regular health care surveillance and long-term follow up best provided in specialist multidisciplinary CDH clinics [2, 22, 35, 36].

26.7.1 Respiratory Function

Respiratory function in survivors may be impaired as a result of (a) pulmonary hypoplasia biology and (b) postnatal lung injury—secondary to aggressive mechanical ventilation. Chronic lung disease (CLD) has been recorded in up to 50% of CDH survivors requiring intensive resuscitation and ECMO support. CLD and recurrent respiratory infection(s) contribute significantly to failure to thrive. A number of well conducted long-term outcome studies now show though that pulmonary function can improve in survivors as they reach adolescence and adulthood [2, 35].

26.7.2 Gastroesophageal Reflux

The development of GER is common in CDH survivors, the impact of which is not just limited to feeding difficulty and reduced caloric intake but may affect respiratory health from recurrent aspiration. GER is managed with feed thickeners—carobel, anti-reflux medication,—H_2 antagonists,—ranitidine/proton pump agents,–omeprazole. A significant number of CDH patients may ultimately require fundoplication for medical therapy resistant GER. Studies from Canada and Belgium have defined cohort populations at greatest risk here which include (a) ECMO survivors (b) patients with large CDH defects requiring patch repair and (c) FETO treated 'liver up' cases [37–39]. In Liverpool with multidisciplinary GER management led protocols some 10% of our CDH population have required fundoplication [22]. Mechanisms and theories postulated to explain the high prevalence of GER in CDH patients notably include defective diaphragm crura distorting the anatomy of the normally protective GE junction barrier and oesophageal foregut dysmotility—a concept first proposed by Stolar in the 1990s [39].

26.7.3 Neurodevelopmental

Motor and cognitive deficits are encountered in CDH survivors. Long term follow up studies report neurodevelopmental delay in some 30%–70% of patients [40, 41]. A North American study examining CDH survivors in a multidisciplinary clinic at 3 years of life found up to 73% of patients had variable degrees of motor delay (most commonly hypotonia and motor asymmetry), 60% had language problems and 10% sensory/hearing problems. It is believed neurological morbidity is linked to neonatal hypoxic events. Ventilator time and use of ECMO have also been found to be statistically significant predictors of future neurological impairment (70% of patients with neurological delay had ECMO support in one study). Aminoglycoside therapy has also recently been strongly linked with sensorineural hearing loss [42].

26.8 Lesser Variants—Morgagni Hernia, Pentalogy of Cantrell

Diaphragmatic defects such as the anterior sternocostal Morgagni defect (2% of congenital diaphragm defects)—allow herniation of intestinal viscera into the thoracic cavity through failure of fusion of the sternal component of the diaphragm [2]. There can be associations with chromosomal disorders notably trisomy 21 and congenital heart disease. Morgagni defects may be detected incidentally on chest X-ray. Some patients present with intermittent feeding or respiratory problems. Operative repair can be accomplished with a subxiphoid upper abdominal incision where a congenital hernial sac often present in such cases will require excision with primary closure or prosthetic patch insertion. MIS approaches are also feasible [2].

Cantrell's pentalogy resulting from failure of development of the septum transversum is a severe anomaly comprising exomphalos [major or minor], sternal cleft(s), pericardial and diaphragm defects, ectopia cordis with congenital heart disease. Survival and outcome is linked to severity of heart disease. Operation involves closure of the diaphragm defects (±prosthetic patch), abdominal wall defect repair and correction of cardiac status [2].

26.9 Diaphragm Eventration

Eventration of the diaphragm may be a congenital or acquired anomaly [2]. The involved diaphragm is elevated and moves paradoxically with respiration which can be visualised readily on fluoroscopy screening imaging. Chest X-ray reveals an elevated hemidiaphragm—(Fig. 26.5). Disturbance in functional performance of the diaphragm interferes with lung function such that some babies may have profound respiratory problems from birth requiring ventilatory support. In its congenital form nerve and muscle precursors cells fail to populate the developing diaphragm. Acquired diaphragm palsy may result from birth injury to the phrenic nerve/brachial plexus with Erb's paralysis or follow cardiac or oncological surgery operations where the phrenic nerve has been inadvertently injured or sacrificed to achieve mediastinal tumour resection. Infants unable to wean from ventilation should undergo operative repair which involves serial plication or 'reefing' of the floppy diaphragm to make it flat and taught with a row of interrupted braided non absorbable sutures. This manoeuvre immobilises the weakened diaphragm reducing paradoxical movement and improves respiratory mechanics. Where the eventration is a very thinned out section of diaphragm excision and primary repair is sometimes possible (as for CDH) with or without prosthetic patch incorporation. Operation can be undertaken using classical open surgical techniques laparotomy/thoracotomy or minimally invasively by thoracoscopy [43, 44].

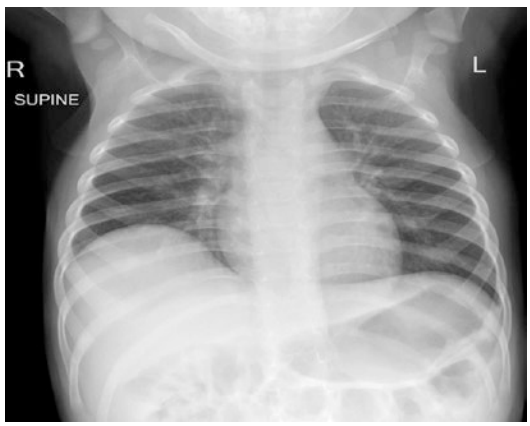

Fig. 26.5 Right side diaphragm eventration. The baby had recurrent chest infections and had a diaphragm plication

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Chylothorax and Other Pleural Effusions

27

Paul Cullis and Graham Haddock

Abstract

A pleural effusion is the accumulation of fluid in the pleural space, and may represent chyle, pus, blood, transudate or other fluid. This chapter covers the pathophysiology, presentation, diagnosis and management of pleural effusions in neonates, with particular reference to the accumulation of chyle. Chylothorax is the commonest explanation for a pleural effusion in the first few days of life. It may be congenital or acquired with numerous causes. Laboratory fluid analysis, ultrasonography and plain radiography are the most important diagnostic modalities. Once diagnosed, an initial period of intestinal rest and parenteral nutrition is warranted accompanied by pleural drainage, followed by a low fat enteral feeds containing medium chain triglycerides. Nevertheless, emerging pharmacological and interventional therapies are being introduced, but surgery is reserved for when medical management fails.

Keywords

Chylothorax • Pleural effusion • Thoracic duct • Respiratory distress

27.1 Introduction

A pleural effusion is the accumulation of fluid in the pleural space. A small volume of physiological fluid is naturally present between the two pleural layers; however, changes in fluid dynamics may result in accumulation. Alterations in lymphatic pressure, hydrostatic pressure of the pulmonary venous system, circulatory oncotic pressure or local inflammation can contribute. Fluid accumulation may however arise from other sources, such as chyle from the thoracic duct

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_27

transected unknowingly during thoracic surgery (chylothorax), blood from a damaged intercostal vessel as may occur during traumatic chest drain placement (haemothorax), or parenteral nutrition leaking from a central venous catheter [1, 2].

27.2 Epidemiology

Data on the incidence of pleural effusions and its subtypes in the neonatal population are limited. Most recent estimates suggest that 50 per 100,000 neonates are admitted to neonatal intensive care units for investigation and management of pleural effusion. Two-thirds have an acquired form and the remaining third have congenital effusions [1, 2]. A recent British Paediatric Surveillance Unit study determined that the UK incidence of infantile chylothorax is approximately 16 per 100,000 children <12 months per year ('neonatal' and 'cardiac surgery' were the most frequent subcategories) [3], whilst a recent Australian study (albeit of a retrospective nature) estimated an incidence of congenital chylothorax at around 17 per 100,000 live births [4].

27.3 Anatomy and Physiology

Intestinal and lumbar lymphatics draining the intestines and posterior abdominal wall coalesce to form the cysterna chyli. This structure is located close to the second lumbar vertebrae behind the aorta. The thoracic duct drains from the cranial end of the cysterna chyli and enters the thoracic cavity through the aortic hiatus of the diaphragm between the 10th and 12th thoracic vertebrae (T10–T12).

The thoracic duct ascends initially to the right of the vertebral column extrapleurally. It crosses behind the oesophagus and pericardium at the level of the fourth to sixth vertebrae to reach the left side of the vertebral column. It ascends behind the thoracic aortic arch passing into the root of the neck anterior to the anterior scalenius muscle. It enters the venous circulation at the junction of the left subclavian and left internal jugular veins.

The anatomy of the thoracic duct is prone to variation. Up to 50% of the population exhibit such variation [5–7]. Collaterals are common which may account for the risk of leakage of chyle after thoracic surgery.

The thoracic duct drains lymph from the abdomen and the left side of the upper trunk, head and neck. Lymph from the other parts of the body drain into a right lymphatic duct but this does not contain chyle.

The pleura comprise mesothelium over a connective tissue bed that houses its lymphatics, nerves and vasculature. The visceral pleura receives its blood supply from the bronchial circulation and drainage is to the pulmonary vasculature, whilst the arterial and venous supply of the parietal pleura is systemic. Both the parietal and visceral layers filter fluid into the pleural space and fluid reabsorbation is principally via lymphatics [1, 2].

The thoracic duct is the main conduit for transport of chyle from the intestine to the circulation. Chyle is an alkaline fluid composed mainly of long chain triglycerides, cholesterol (in the form of chylomicrons), lymphocytes, glucose and albumin, which can reach 4 L per day in adults. This figure varies depending on dietary composition, intestinal function, drugs and physical activity. The electrolyte composition is similar to serum, whilst the protein content is between 0.2–0.6 g/L, total fat between 4–6 g/L and lymphocyte count (mostly T cells) between 400 and 6800/mm^3 [8]. Chylomicrons pass through the intestinal wall into intestinal lacteals and thence into the lymphatic system including the thoracic duct. This explains chyle's milky appearance. Chyle can appear turbid in the fasting state because lipid content is reduced (Fig. 27.1).

27.4 Aetiology

Pleural effusions result from the accumulation of chyle (chylothorax) or other fluids. The aetiology of each is myriad.

The causes of chylothorax fall into five main groups (Table 27.1) [8] with injury or obstructed drainage of the thoracic duct underpinning many. Trauma however probably accounts for the most frequent surgical encounters of chylothorax (and haemothorax). Interventions associated

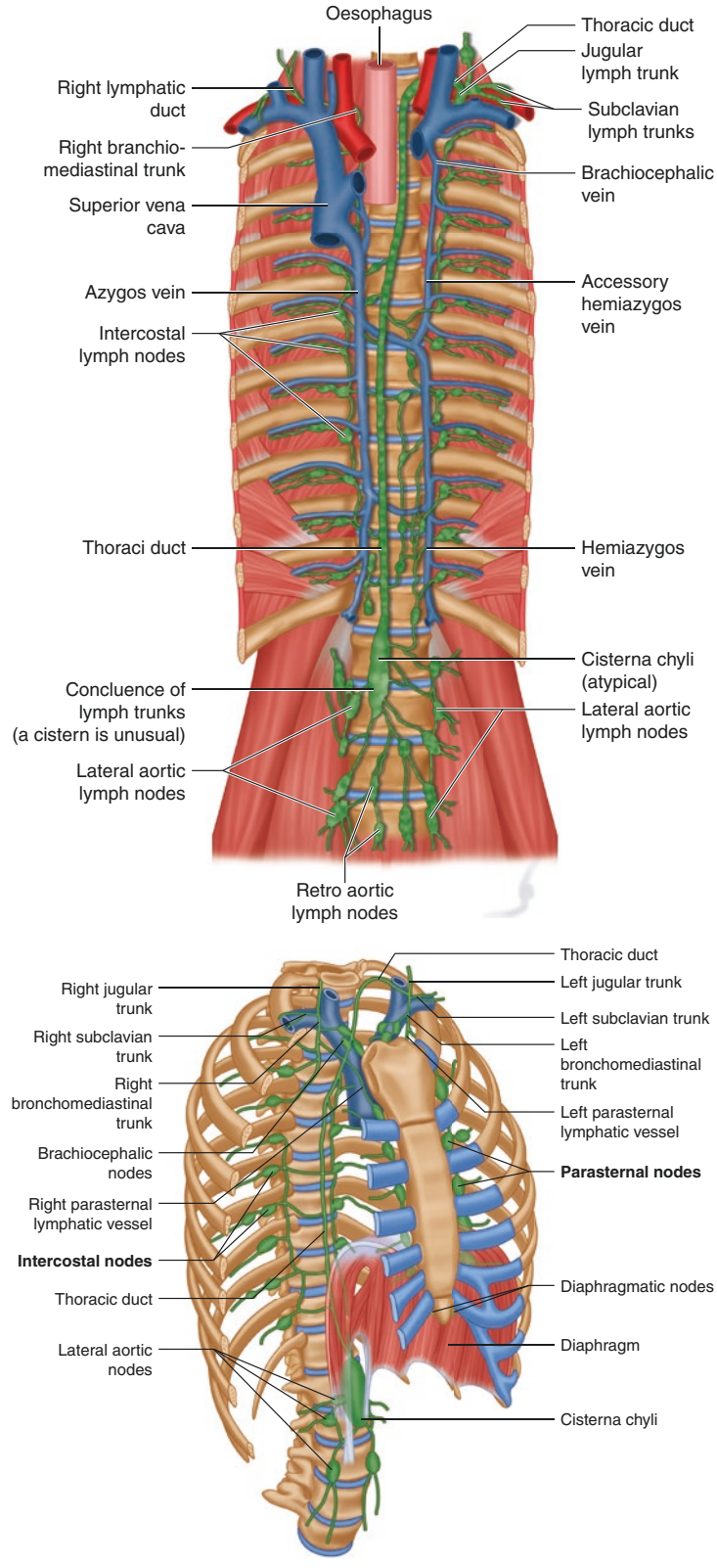

Fig. 27.1 Anatomy of the thoracic lymphatic system

Table 27.1. Aetiology of chylothorax in children [8]

A. Congenital	1. Lymphatic malformations	(a) Lymphangiomatosis (b) Lymphangiectasia	
	2. Thoracic duct atresia		
	3. Syndromic associations	(a) Down's syndrome (b) Turner's syndrome (c) Noonan's syndrome	
B. Traumatic	1. Surgical	(a) Cervical	1. Lymph node excision
		(b) Thoracic	1. Surgery for congenital cardiac disease 2. Surgery for mediastinal neoplasms 3. Surgery for congenital lung malformations 4. Other
	2. Other invasive procedures	(a) Catheterisation of the subclavian vein	
	3. Non-iatrogenic trauma	(a) Hyperextension or stretching of the thorax	
		(b) Forceful coughing or emesis	
		(c) Child birth	
C. Elevated central venous pressure	1. Central venous thrombosis (superior vena cava/ subclavian vein)		
	2. After Fontan procedures		
D. Neoplasm	1. Lymphoma		
	2. Teratoma		
	3. Sarcoma		
	4. Neuroblastoma		
E. Others	1. Benign tumours		
	2. Tuberculosis		
	3. Histoplasmosis		
	4. Sarcoidosis		
	5. Chylous ascites transmitted per diaphragm		

Adapted from Soto-Martinez M, Massie J. Chylothorax: diagnosis and management in children. Pediatric Respiratory Reviews 2009;**10**:199–207

with its development include chest drain insertion for pneumothorax, angiography and surgery for congenital heart disease, repair of tracheo-oesophageal fistula and oesophageal atresia (5% cases [9]), repair of diaphragmatic hernia (4.6% cases [10]), and cannulation or maintenance of patients on extracorporeal membrane oxygenation who may also have an iatrogenic coagulopathy.

Similar to chylothorax, a hydrothorax may also be congenital or acquired. The congenital type is often associated with hydrops or ascites, but may also occur in isolation. Congenital pleural effusions may be associated with transient tachypnoea of the newborn, pneumonia secondary to group B *Streptococcus* spp. or various chromosomal anomalies, such as Turner and Down syndromes. Acquired hydrothoraces may arise secondary to pneumonias (e.g. *Stapylococcus* spp., group B *Streptococcus* spp., *Acinetobacter calcoaceticus*, and *Bacteroides fragilis*), after procedural interventions (e.g. diaphragmatic hernia repair, fluid leakage from a central venous catheter), respiratory distress syndrome, birth asphyxia, meconium aspiration syndrome, congenital heart disease, hypoproteinaemia, or acute kidney injury [1, 2, 8].

27.5 Antenatal Presentation

Pleural effusions may present antenatally on ultrasonography. Polyhydramnios may be visualised, which has been suggested as the result of

raised intra-thoracic pressure that may interfere with swallowing *in utero* [11]. Large effusions can result in cardiac failure and pulmonary hypoplasia in the developing foetus. Chylothorax can be associated with fetal hydrops, cystic hygroma and lymphatic, pulmonary venous and other malformations. It can also be a feature of Turner's and Noonan's syndromes [1]. Familial cases have been reported affecting males suggesting that X-linked inheritance may be implicated [12, 13] and affecting girls suggesting that an autosomal recessive inheritance may be involved [14–16]. Antenatal chylothorax can impair lung growth and development resulting in lung hypoplasia. Occasionally, in severe cases, antenatal drainage of the chylothorax using a pleuroamniotic shunt may be warranted [17, 18]. In a series of 54 fetuses treated antenatally for large pleural effusions using a thoracoamniotic shunt, all of the 31 survivors had chylothorax suggesting that antenatal chylothorax has a better prognosis than other causes of foetal pleural effusion [18].

27.6 Postnatal Clinical Presentation

Chylothorax is the commonest explanation for a pleural effusion in the first few days of life. In half of cases, patients with congenital chylothorax are symptomatic from birth [14]. Boys are more commonly affected than girls for reasons unknown, and probably because of its anatomical course, the right hemithorax is affected more often. The majority of cases of chylothorax are seen as a complication of surgery. Any procedure which involves surgery in or near the thorax can cause chylothorax to develop including repair of congenital diaphragmatic hernia, oesophageal atresia, ligation of a patent ductus arteriosus and excision of a thoracic duplication cyst. Major surgery in the neck, obstruction of the superior vena cava, and tumours of the thorax are other less common causes of acquired chylothorax.

Clinical presentation depends on the size of the accumulation of fluid and the rate of such accumulation. Symptoms and signs of respiratory distress may be seen as the size of the accumulation of chyle in the chest increases. Clinical signs of a pleural effusion including dullness to percussion, diminished breath sounds and tracheal deviation will also depend on how much fluid has accumulated in the pleural space. Signs of superior vena caval obstruction should also be sought.

27.7 Diagnosis

An antenatal diagnosis may be made on ultrasonography, or postnatally on either plain chest radiography where the ipsiltaeral hemithorax is obscured by a 'white out' or ultrasonography, which permits direct visualisation of fluid, and may contribute to the determination of its aetiology by assessing its characteristics.

Nevertheless, a definitive diagnosis is based on biochemical, microscopic and microbiological analysis of the fluid obtained by pleural aspiration. In chylothorax, the fluid will contain high levels of chylomicrons (in a fed neonate), a triglyceride concentration in excess of 1.1 mmol/L, an absolute cell count in excess of 1000/μL and a lymphocyte fraction greater than 80% (as long as the baby is receiving at least minimal fat intake) [18]. Böttiker's criteria are commonly cited as the definitive diagnostic method [19]. The fluid may be milky in a fed patient but may be clear if the patient is fasted. If the diagnosis is unclear, a trial of feeding using a high fat milk formula may confirm the clinical suspicion.

Parapneumonic effusions and empyemas will display a high proportion of neutrophils, may contain causative microbes, will exhibit increased protein levels and will appear turbid or purulent.

27.8 Management

Initial management of neonates with pleural effusions should follow the same principles as any neonate with respiratory distress. In significant congenital effusions, intubation and ventilation may be required to achieve adequate chest wall expansion.

For chylothorax, the principles of initial management in all cases include a period of intestinal rest and parenteral nutrition accompanied by pleural drainage by single or repeated

needle aspiration or chest drain insertion [2, 8]. Thereafter, the administration of a low fat formula feed containing medium chain triglycerides (MCT) is recommended. This approach relies on reducing the flow of chyle through the thoracic duct in the hope that any leak will heal spontaneously. MCTs are absorbed directly into the portal circulation from the intestine, and as such, do not require transportation in the lymphatic system of the thoracic duct. The consequent reduction in flow of chyle increases the chance of spontaneous healing of the damaged thoracic duct. There is emerging evidence that fat-modified breast milk may provide similar benefits. A recent albeit small Canadian trial of MCT versus fat-modified breast milk in neonates with chylothorax following cardiac surgery suggested both feeds were similarly efficacious [20].

It is not clear for how long this approach to management on its own should be continued. In general terms, a reduction in the amount of chyle draining from the pleural cavity each day indicates that the treatment strategy is working. Some suggest that a period of parenteral nutrition which should be continued for at least one week after chyle drainage has ceased followed by a period of MCT feeding of up to three weeks before treatment success should be determined [2].

In recent years, somatostatin and, in particular, its long acting analogue octeotride, have been reported in the treatment of chylothorax [21–26]. Routes of administration and dosage schedules have varied.

Octeotride administration intravenously to a neonate successfully stopped chyle drainage after three days of treatment [21]. Bloody stools accompanied octeotride administration but this continued after the drug was discontinued raising the possibility that the bleeding was not related to drug administration.

In an early review of the available published evidence, 35 children (including neonates with spontaneous chylothorax and post-operative cases) were identified to have been treated by somatostatin or octeotride [22]. Ten received somatotstatin and 25 octeotride. The ten who received somatostatin received a median infusion dose of 204 μg/kg/day for a media duration of 9.5 days. The 25 children who received octeotride had either a median intravenous infusion dose of 68 μg/kg/day for a median of 7 days or subcutaneously at a median dose of 40 μg/kg/day for a median of 17 days. Reported side effects included cutaneous flush, loose stools, transient hypothyroidism, abnormal liver function tests, transient hyperglycaemia and necrotising enterocolitis.

In a more recent Cochrane Database Review [27] the authors reported that they were unable to identify any randomised controlled trials on the use of octeotride in this clinical setting. They identified 19 case reports of 20 neonates where octeotride had been used either subcutaneously or intravenously. In 14 of the case reports, the chylothorax resolved; in four there was no resolution and in five, the impact of the ocetotride was said to have been equivocal. Gastrointestinal intolerance, necrotising enterocolitis and transient hypothyroidism were reported as side effects.

The mechanism of action of somatostatin in the context of the treatment of chylothorax is unclear. It has been suggested that reductions in splanchnic blood flow, gastric, intestinal and pancreatic secretion or intestinal motility may be the explanation. Alternatively, a reduction in the absorption of triglyceride from the intestine may be implicated [23]. In one animal study, one group of investigators reported that the intravenous infusion of somatostatin attenuated the flow of thoracic duct lymph flow [28].

In the small number of cases where initial management has failed to resolve the chylothorax, surgical options may have to be considered. This is particularly challenging in the neonatal patient. While there is no consensus about the timing of surgery most clinicians would consider that a trial of at least three to four weeks of conservative treatment would be appropriate before surgical approaches to treatment are employed [8].

Surgical ligation of a leaking thoracic duct is only practical where a leak site has been clearly identified. This is almost impossible in neonatal patients, although thoracoscopic methods may make this more likely in the future [29]. Ligation of the cisterna chyli has been suggested as an alternative therapy, but has yet to be confirmed in neonatal setting [30].

Pleurodesis using a variety of substances can also be considered. Talcum powder and iodine solutions have been used successfully, although

less common substances have been reported. The sclerosing substance can be administered via a chest drain, but the procedure is usually more successful of the sclerosant is administered at the time of open thoracotomy, or thoracoscopy and as an accompaniment to surgical pleuridectomy. Fibrin glue has also been employed at operation in an attempt to seal a chylous leak [29].

Pleural shunts, which drain the chyle from the thoracic cavity into the peritoneal cavity, have also been reported in older children [31, 32]. This approach has the advantage that the chyle is not lost to the patient. While this technique has been reported in older children, it has not been used in neonates.

Antenatal management of primary foetal chylothorax and hydrothorax are out with the scope of this chapter.

Systematic antibiotics are essential in the management of pneumonia and empyema, with therapy focusing on microbial growth yielded from pleural fluid and blood cultures. A prolonged course may be required. Chest drain placement is often required in the setting of fibropurulent pleural space disease. There is limited experience of thoracotomy and debridement, video-assisted thoracoscopic techniques and fibrinolytic therapy in this setting amongst the neonatal population with the latter two proving increasing popular therapies in older children [11, 33]. Traditionally open techniques were used for neonates where medical management failed.

27.9 Prognosis

The outcome of pleural effusions depends on the underlying cause, the co-morbidities and the severity of the effusions.

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Congenital Cardio Thoracic Surgery

28

Prem Sundar Venugopal and Harikrishna Doshi

Abstract

The word congenital derives its meaning from Latin word 'Congenitus' where 'con' means 'together' and 'genitus' means 'born'. Congenital heart disease refers to any defect of the heart present from birth. It includes structural defects, congenital arrhythmias, and cardiomyopathies. At least eight in every 1000 babies are born with a heart or circulatory condition and only a quarter of these are detected by ultrasound scans.

Keywords

Congenital heart disease • Cardiac surgery • Outcomes

The word *congenital* derives its meaning from Latin word 'Congenitus' where 'con' means 'together' and 'genitus' means 'born'. Congenital heart disease refers to any defect of the heart present from birth. It includes structural defects, congenital arrhythmias, and cardiomyopathies. At least eight in every 1000 babies are born with a heart or circulatory condition and only a quarter of these are detected by ultrasound scans [1].

Although geographical variation exists, the rate of congenital heart disease remains more or less the same globally, however there are wide variations in its burden, for example countries with higher fertility rates will have to bear higher burden of disease. Unfortunately there are other wider issues (Table 28.1).

Besides, there is even wider imbalance on availability of cardiac surgeons (Table 28.2).

Each year over 1000,000 babies are born worldwide with a congenital heart defect. 100,000 of them will not live to see their first birthday and thousands more die before they reach adulthood. Almost half of all children and adults with complex congenital heart disease have neurological and developmental disabilities. There are an estimated 2,000,000 CHD survivors in the United States. For the first time, more than 50% of the CHD survivors are adults. The cost for inpatient surgery to repair congenital heart defects exceeds $2.2 billion a year.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_28

Table 28.1 Comparison of money spent in children with CHD between two countries

Country	CHD/million population	CHD/million wage earners	GDP per capita	GDP/CHD
Singapore	~100	~120	$63,000	$525
Niger	~500	~850	$1000	$0.85

From: J Hoffman. The global burden of congenital heart disease: Cardiovascular Journal of Africa 2013; 24; 4: 141–145; used with permission

Table 28.2 Ratio of cardiac surgeons to population in different continents

North America	1:3.5 million
Europe	1:3.5 million
South America	1:6.5 million
Asia	1:25 million
Africa	1:38 million

From: J Hoffman: The global burden of congenital heart disease: Cardiovascular Journal of Africa 2013; 24; 4: 141–145; used with permission

In United Kingdom, 1:180 babies are born with congenital heart disease and data from British heart foundation suggests that between 1979 to 2008, absolute number of deaths from CHD in children declined by 83% whereas number of operations performed for CHD increased by 60% between years 2000 to 2010. NICOR data shows that in the year 2012–2013, 10,170 procedures were carried out in UK which involved 5815 surgical procedures [2].

28.1 Critical Congenital Heart Disease

Congenital heart disease is the most common congenital disorder in the newborns. Critical congenital heart diseases are those, which requires intervention in the first year of life and occurs in around 25% of babies with CHD. Many newborn with critical CHD are symptomatic and are identified soon after birth others however are not diagnosed until after discharge from birth hospitalisations. In infants with critical CHD, risk of mortality and morbidity increases when there is delay in diagnosis and or intervention.

Early serious or life threatening presentation. These are the most urgent cases which may present as neonatal shock, cyanosis or pulmonary oedema.

Causes of neonatal shock may be:

- Loss of systemic perfusion as seen in neonates with hypoplastic left heart syndrome, critical aortic stenosis, interrupted of aortic arch or coarctation of aorta.
- Restriction of pulmonary blood flow as seen in Total anomalous pulmonary venous connection (TAPVC), tricuspid atresia (TA), mitral atresia (MA).
- Lack of mixing between systemic and pulmonary circulation when they are running in parallel as seen in transposition of great vessels with intact ventricular septum (TGA with IVS).

Causes of cyanosis may be:

- In critical right sided obstructive lesions such as critical pulmonary stenosis or atresia, the patent ductus arteriosus may be the only source of pulmonary blood flow. In these neonates as the PDA closes, progressive cyanosis ensues.
- In patients with critical left sided obstructive lesions like HLHS, PDA may be the only supply to systemic circuit flowing from right to left side and when the PDA closes the peripheral perfusion suffers and progressive cyanosis follows.
- In patients with parallel circulations like TGA, PDA may be the only source of mixing of blood to provide a route of oxygenated blood entering the systemic circuit. Closure of PDA in them will lead to profound cyanosis.

Profound cyanosis in these patients can lead to shock, acidosis and end organ damage. Timely commencement of prostaglandin E1 may allow the duct to reopen and improvement and temporary stabilisation of clinical situation to allow for

transport and intervention in a timely manner. There are some non duct dependent circulations like obstructed TAPVC where emergency surgery is the only option. Fall in pulmonary vascular resistance may allow rapid non restricted increase in pulmonary blood flow which may flood the lungs and lead to congestive heart failure as seen in PDA in premature infants. Identifying the high risk group of neonates and early infants allows corrective or palliative interventions but remains a challenging proposition since the clinical findings in some may remain subtle or even absent immediately after birth and in prenatal screening [3].

28.2 Introduction to Embryology and Functional Classification of Cardiac Lesions

Development of heart is a complex process. Recently, rapid advancement in molecular biology and research has added huge amount of knowledge into cardiac morphogenesis.

Basic Principles:

At day 20 in human embryo development, cells in lateral mesoderm adopt a cardiogenic fate [4]. The cells in endoderm are actively involved in signalling for this process. These cardiogenic precursor cells are preordained to have information about their positional identity and cell fate, for example caudal cardiogenic cells contribute to future atria and rostral cells to ventricles [5]. Bilaterally symmetrical primordia fuse in the midline to form Primitive heart tube in the ventral midline of early embryo. This tube starts contracting at around 4 weeks of foetal development. The primitive cardiac tube becomes five chambered heart tube with bilateral symmetry at venous and arterial poles. This tube undergoes complex three dimensional looping involving all three axes to form multichambered heart. The rightward looping is essential for orientation of chambers to one another and appropriate connection of inflow and outflow. This process is regulated by Henson's node and other complex array of signalling proteins [6, 7]. In fact the whole body's left to right positional orientation especially in terms of viscera, is based on molecular hierarchical information and any interruption with this process can lead to heterotexy syndrome. Defects in left to right establishment of visceral organs, is known as heterotaxy syndrome, a word derived from Greek word heteros which mean other arrangement. Thus in simple terms, there may be bilateral right or left sidedness. The concept of atrial isomerism and atrial appendage isomerism has been contentious [8] and several genes or its expressions are involved in establishing the left-right symmetry. Thus, even single gene mutation can lead to polysplenia or asplenia syndrome which was previously thought to arise due to distinct etiology.

28.2.1 Cardiac Septation

Following looping and alignment of cardiac chambers, septation allows division and connection of systemic and pulmonary chambers. Inter atrial septum formation separates right from left atrium. Similarly, interventricular septum allows separation of right and left ventricles. Formation of atrioventricular junction separates atria from ventricles and infundibular septation allows separation of aortic from pulmonary flows. Deficiency of septation leads to various congenital defects including, atrial or ventricular septal defects and Cono-Truncal anomalies.

Conal segment of primitive cardiac tube connects ventricles to aortic sac. Aorticopulmonary septum grows into the outflow tract to lead to formation of Aorta and pulmonary artery. Remodelling of subaortic conus leads to establishment of continuity between aorta to left ventricle and pulmonary artery to right ventricle. CATCH phenotype (cardiac defects, abnormal facies, T cell deficit, cleft palate, hypocalcemia) is associated with Di-George syndrome, Takao (conotruncal anomaly face syndrome) and Shprintzen (velocardiofacial) syndrome and shares common molecular lesion which is deletion of 22q11. The 22q11 deletion is the most common deletion in humans, occurring in 1 of 4000 live births [9].

28.3 Cardio Pulmonary Bypass in Congenital Patients

History of use of extra corporeal circulation for repair of congenital heart defects is as old as the first use of bypass machine in humans by Gibbon for repair of atrial septal defect in 1953. Since then, we have come a long way in advancement of technology, perfusion and myocardial protection techniques. In the realms of congenital surgery, intricate play with bypass and various uses of perfusion techniques with much advanced circuit components, have allowed us to successfully treat even the most complex of the congenital heart defects at very low mortality rates. Congenital population is inherently prone to cardio pulmonary bypass related dysfunction on account of relative deficiency of contractile protein mass in myocardium, immature calcium cycling and fewer mitochondria [4].

28.3.1 Technology

Most paediatric circuit use roller pumps where flows are governed mainly by revolutions per minute and diameter of the tubing. The surface area of the bypass circuit is relatively large compared to surface area of small infants and neonates. Similarly, the prime volume can lead to significant haemodilution. To minimize the complications, the size of tubing, circuit size and amount of prime are kept as minimum as possible. Oxygenators need special attention since they have to adapt to a wide range of flow rates and temperature. Most centres currently use membrane oxygenators. Oxygen delivery to oxygenator is controlled with gas "sweep speed" (flow rate). Thermistors measure temperatures of perfusate and the water bath. They also measures temperature of arterial and venous blood.

Bypass circuit now comes with abundance of monitoring aids and filters. Bubble monitor, reservoir level monitor are some amongst many more. Gas inflow line filter, cardiotomy suction inflow line filter and arterial line filter are some commonly used filters in circuit. There are also huge advances in patient monitoring techniques. Continuous arterial gas and mixed venous oxygen monitoring during bypass in addition to conventional monitoring tools like pulse oximetry, end tidal CO_2 monitors and core as well cutaneous temperature monitoring in addition to invasive monitoring lines have added immensely to improvement in patient safety. NIRS-based cerebral oximetry is a noninvasive and easily applied monitoring technology that has been shown to trend the oxygen saturation of haemoglobin in the frontal cortex [10].

28.3.2 Technique

In congenital population especially in small infants and neonates, placement of cannula for venous drainage or arterial flow can be deciding factor in terms of smooth conduct of surgery. Complex anatomy, surgical approach should guide the choice of placement of cannula thus each case offers a unique challenge. For example our institutional preference is to selectively cannulate innominate artery using gore-tex tube graft for arterial cannulation in stage I Norwood procedures whereas many centres prefer to cannulate the duct for establishing the flow to the lower half of body.

The cannula sizes are small and pose special problems of placement, kinking and obstruction to the vessels. Due to smaller chest cavity sizes, sometimes it becomes necessary to optimise the operative field and thus, deep hypothermic circulatory arrest became a common adjunct. Although recently, its use is on the decline and it is only used sparingly. Many cardiac malformations are approached now using normothermic bypass even in neonatal period.

During conduct of bypass application of cross clamp leads to ischaemic arrest of heart which requires application of principles of myocardial protection. Hypothermia is conventionally thought to be one of the mainstay of myocardial protection. Full beating heart at normothermia consumes 9 ml per 100 g of myocardial tissue as opposed to empty still heart at 32 °C temperature consumes only 0.4 ml of O_2 per 100 g of myocardial tissue.

Modified ultrafiltration (MUF) is a technique increasingly adopted by many centres during congenital heart surgery. Systemic inflammatory response to bypass induces extravasation of fluid into extra capillary third space due to release of various inflammatory mediators and vasoactive compounds. MUF removes extra fluid along with removal these inflammatory mediators and vasoactive compounds thus reducing tissue oedema and better haematocrit. There are various reports of achieving better lung compliance, reduced duration of mechanical ventilation, improved left ventricular function and decreased pulmonary vascular resistance following MUF [11, 12].

28.4 Pre and Peri Operative Management of Congenital Heart Disease Patients

28.4.1 Pre Operative Multi Disciplinary Team (MDT)

Congenital heart surgery has evolved a long way from an individual making decisions to a complex multidisciplinary team approach along the entire process of patient pathway. Pre operatively, the cases are presented in MDT meetings consisting of cardiac surgeons, cardiologists, radiologists and a variety of other allied staff including liaison nurses. Decisions are taken after all relevant information and imagery are deliberated and documented. Patients are admitted directly on the day of surgery if they have attended the pre assessment clinic or they come a day before if they haven't attended the clinic.

Pre operative planning includes:

Consent: Detailed informed consent constitutes a major chance for detailed and frank discussion between the parents and surgical team. The importance of detailed consent process can't be overemphasised since longer time spent at this stage may avoid a lot of anxiety to the parents at various stages of these complex surgeries where post op recovery may be delayed or post op period is likely to be stormy for many days to come.

Other things to consider are:

- Blood and blood products
- Prosthetic materials and homografts that may be required and are kept ready for use in various sizes.

Pre operative huddle on the day of surgery between the surgeon, anaesthetists, perfusionist and nursing team makes sure that detailed operative plans are understood by the entire team and materials and various instruments or prosthetic material are prepared well in advance.

Post operative transfer from theatre to intensive care unit and handover to intensive care team constitutes one of the most important event in patient management and one which gets neglected many a times. Our current strategy for handover involves:

- Transfer under direct anaesthetic and surgical supervision.
- Initial transfer in to bed space with attachment to ventilation and routine monitoring.
- For handover, mandatory presence of consultant anaesthetist, cardiac surgeon, intensivist along with intensive care registrar allocated to the patient and the named nurse looking after the child.
- Handover includes detailed anaesthetic and surgical progress of patient in theatre along with any anticipated complications and detailed post op plan.

28.4.2 Unique Features for Management of Congenital Cardiac Surgical Patients in ICU

- Infants or neonates are more prone to barotrauma and are more sensitive to develop hypoxia or pulmonary hypertensive crisis. Pressure limited ventilation are commonly used in children.
- Small size of airways means smaller size endotracheal tubes which are more prone to obstruction. Nasal intubation is commonly used in this age group.

- Although PEEP may help in recruiting collapsed alveoli and alleviate chances of hypoxia, it may also lead to increased pulmonary vascular resistance, shunting and reduced venous return.
- Traditionally weaning is considered slower in children as small changes in ventilation may lead to massive changes in patient volumes and thus blood gases. Currently many centres have started routine use of paravertebral blocks for analgesia in children leading to a strategy of early extubation in children.
- Small size of vessels in children do not allow routine use of Pulmonary artery catheter, thus many a time direct measurement lines like left atrial lines are routinely used for post operative intra cardiac pressure monitoring. SvO_2 is also used as a surrogate marker for cardiac output in children.
- Chest may be left open especially in neonatal patients following complex cardiac procedure to enable stable haemodynamics and to allow for myocardial and tissue oedema following cardio pulmonary bypass to subside.

28.5 Pathophysiology of Congenital Heart Surgery Patients

Neonates respond more quickly and extremely to physiologically stressful circumstances which they may express in terms of rapid changes in pH, lactic acid, glucose or temperature. Besides, pre term or full term neonates have high metabolic rate and oxygen demand which is two or three times compared to an adult which may be compromised during period of stress, due to limited cardiac and respiratory reserves.

Myocardium in neonates and immature children are different to adults in that it has only 30% myocardial muscle made up of contractile tissue versus 60% in mature myocardium [4]. It has reduced ability to respond to afterload stress, and reduced compliance of myocardium along with relatively fixed stroke volume thus making cardiac output heart rate dependent.

Ventricular interdependence is important in neonates and infants. It refers to shift of interventricular septum to other side in case of increased ventricular end diastolic volumes and pressures. This leads to reduced size and compliance of opposite ventricle leading to biventricular dysfunction. Volume overload can be seen in intracardiac shunts or valve regurgitations whereas pressure overload can be seen in cases with outflow tract obstruction or increased vascular resistance. The effects may last even after the surgery, for example in cases of tetralogy of fallot with right ventricular outflow tract obstruction, diastolic dysfunction of left ventricle and increased LVEDP will take weeks or months to recover since myocardial recovery takes time. In this respect, the recovery may be delayed or hampered markedly if there is persistent overload of ventricle as may happen with a residual VSD [4].

Diaphragm and intercostal muscles of neonates have fewer type I muscle fibres which are slow contracting, high oxidative fibres for sustained activity leading to early fatigue in case of increased work of breathing. Intra-abdominal pressure increase may significantly compromise diaphragmatic function for example from hepatic congestion, gastric distension or ascites.

Minute ventilation in neonates is rate dependent thus with other limitation on respiratory mechanics they maintain resting respiratory rate of 30–40 per minute needing significant part of their energy expenditure for maintaining adequate ventilation. If work of breathing is increased for any reasons like, cardiac failure or increased pulmonary blood flow, large proportion of total energy will be needed to maintain adequate ventilation leading to failure to thrive or easy fatigability [4].

Caloric requirement in neonates especially pre term is high up to 100–150 kcal/kg/day due to high metabolic rate. Fluid restriction needed for certain post operative management makes task of delivering nutrition very challenging requiring concentrated or hyperosmolar feeds [4]. This comes at a price of increased risk of necrotizing entero colitis (NEC). This is more so in children with left sided obstructive lesions.

28.5.1 Physiology of Congenital Heart Disease

If there is complete mixing of blood within the heart chambers, the SpO_2 will be in the range of 85% on air. This level of mixing is mandatory for survival in cases with right or left atrioventricular valve atresia as in tricuspid or pulmonary atresia or hypoplastic left heart syndrome, it may also be mandatory in parallel anatomic circuits as in TGA. Left to right intra cardiac shunt can cause increased pulmonary blood flow, which if left untreated lead to development of pulmonary vascular obstructive disease. This is more so in cases where there is volume and pressure overload as is the case with VSD as opposed to only volume overload in ASD.

Increase in end diastolic volume of LV in patients with increased pulmonary blood flow may leave behind irreversible effects if the lesion is left uncorrected for a prolonged period of time. Residual dysfunction is uncommon if the surgical intervention is undertaken within the first 2 years of life.

PVR can be manipulated by various iatrogenic maneuvers. It may be increased by lowering the FiO_2 or increasing $PaCO_2$ within a range or vice versa. Post op changes in lungs in the form of atelectasis and reduced lung compliance leads to significant elevation of PVR [4].

PVR can be reduced by:

- Vasodilatation: Some examples are Nitroprusside, PDE inhibitors like Milrinone, Eicosanoids like PGE1 and Isoprenaline. They may also reduce the systemic pressure and perfusion.
- Inhaled Nitric oxide selectively dilates the smooth muscles of small pulmonary vessels and lowers the PVR. It is generally more effective in patients with pulmonary vascular obstructive disease, for example in patients with obstructed TAPVD as opposed to patients with pre-existing left to right shunt.
- Drugs like PDE Type V inhibitors Sildanefil and endothelin I blocking agents like Bosentan.

28.6 Classification of Congenital Heart Disease

Three broad categories can be defined as:

- Conditions with Normal pulmonary blood flow: For example; Transposition of great vessels
- Conditions with Excessive pulmonary blood flow: For example; ASD, VSD, PDA
- Conditions with restricted pulmonary blood flow: For example; TOF

The broad lines of discussion for common and significant lesions will be as enumerated below:

- Introduction
- Embryology and genetics
- Classification or types
- Natural history
- Clinical features and diagnosis
- Management including surgical principles
- Follow up and outcome

28.7 Atrial Septal Defects (ASD)

28.7.1 Introduction

It is one of the most common congenital cardiac malformations present in 10–15% of patients with congenital heart disease. Only around 1% patients born with large ASD will have symptoms during the first year of life. Majority would develop symptoms into later decades mainly in the form of reduced effort tolerance and early fatigability which later may lead to symptoms and signs of frank congestive heart failure.

28.7.2 Embryology and Genetics

Septum primum is a true septum which starts developing from the roof and posterior wall of primitive atrium by fourth week of embryonic life. Endocardial cushions septate the atria from the ventricles. In Ostium Primum defects the primum septum does not reach the endocardial

cushions, leaving behind a gap. Resorption of superior aspects of primum septum leads to closure of ostium primum and formation of superior ostium secundum. Septum secundum forms by infolding of atrial wall parallel and to the right of primum septum. It obliterates the primum septum and circumscribe a fossa called Fossa Ovalis. There is a flap valve covering on the left side of fossa ovalis and thus it provides unrestricted right to left shunt during intranatal period.

The cardinal veins drain to two sinus horns which drain into the posterior aspect of the common atrial wall called sinus venosus. The common pulmonary venous opening later invaginates into the sinus venosus portions leading to normal pulmonary venous drainage into left atrium. An abnormal persistence of the right-sided anlage of the common pulmonary vein might be the embryologic basis for the development of direct connections of pulmonary veins to the right atrium.

Around 10% of all ASDs are familial with autosomal dominant inheritance penetrance [13]. Involvement of various expression factors and genetic defects into genes coding for sarcomere contractility are amongst many reported in patients with ASD.

28.7.3 Types

1. Patent Foramen ovale (PFO): Failure of septum primum and secundum to fuse.
2. Ostium secundum ASD (OS ASD): Defect within the boundaries of fossa ovalis.
3. Primum ASD: Discussed with Atrio ventricular septal defect (AVSD).
4. Sinus venosus ASD: Located in sinus venosus area more commonly superior but less commonly inferior variety. Usually they are associated with partial anomalous drainage of pulmonary vein into Right atrium.
5. Coronary sinus ASD: Associated with complete or partial unroofing of coronary sinus. This variety may be associated with persistent left superior vena cavae.
6. Iatrogenic ASD: Most of these variety are less than 1 mm and 95% resolves spontaneously. Most of them are following catheter but true traumatic ASD are extremely rare.

28.7.4 Natural History and Pathophysiology

Secundum ASD occur in 1:1500 live births with male to female ratio of 1:2 [14]. Maternal rubella, alcohol, hydantoin and valproic acid are some substances used during pregnancy predisposes to development of ASD [4]. More than 50% ASD diagnosed in infancy and measuring up to 5 mm close spontaneously whereas closure is rare after 3–4 years of life. Degree of Right ventricular volume overload remains asymptomatic during childhood but during adolescence and adult life it leads to reduction in exercise capacity and evidence of right ventricular failure. Untreated ASD can lead to reduction in life expectancy with average life expectancy of 40–50 years [15].

28.7.5 Clinical Features and Diagnosis

ASD rarely produces symptoms in infancy and childhood unless it is associated with a large shunt. They may present with excessive tiredness, shortness of breath on exertion and frequent chest infections. More often they are referred for specialist attention due to heart murmur found during examination. They rarely develop symptoms before third decade.

Pulmonary vascular disease may develop by fourth decade of life. Pulmonary hypertension can develop early in premature babies and in children with trisomy 21 [16].

28.7.6 Diagnosis

Clinical examination reveals prominent Right ventricular impulse with precordial heave. Auscultation reveals pulmonary artery systolic flow murmur due to excessive blood flow and the second heart sound show wide and fixed split.

The second heart sound may be loud with pulmonary hypertension.

Chest X-ray will reveal prominent pulmonary vascular markings with enlarged pulmonary artery at the hilum. ECG will reveal increase P-R interval, right ventricular hypertrophy and incomplete Right bundle branch block. Trans thoracic echocardiogram is diagnostic and will reveal the drop out in septum along with colour flow Doppler revealing direction of shunt. Bubble contrast is most acceptable way of diagnosis. MRI may help delineate the anatomy.

28.7.7 Management

Elective closure of ASD is commonly undertaken at pre-school age between 2 to 5 years. Early repair leads to normal life expectancy whereas delayed closures are associated with reduction in long term survival [17]. Excessive pulmonary artery pressure with pulmonary vascular resistance between 8 to 12 woods units per m^2 along with reduction of Qp:Qs to <1.2 despite pulmonary vasodilator therapy suggests contraindication to surgical therapy. Surgery is also indicated in certain anatomically located ASD like sinus venosus ASD.

Surgical principles includes:

- Confirming the anatomy and ruling out coexisting anomalies like partial anomalous pulmonary venous return on opening the pericardium.
- Aorto-bicaval cannulation and normothermic bypass.
- Cardioplegic arrest and approach through right atrium.
- Direct closure or patch closure using autologous pericardial patch.
- No long term medication or need for Infective endocarditis prophylaxis.

28.7.8 Outcome and Follow Up

Most children in whom ASD closure is performed later than 5 years of age tend to have some evidence of RV dilatation in their later years [18]. In adults with ASD, the advantages of surgical or device closure are more pronounced in population younger than 40 years of age with improvement in NYHA functional class, reduction in RV volume, improvement in exercise capacity and clear survival advantages [19]. Although controversial, but in asymptomatic patients who are older than 40 years, some reports have suggested advantages of surgical or device closure over medical management [20]. Long term follow up data have suggested that sick sinus syndrome or atrial arrhythmias are uncommon in children who underwent ASD closure [21].

28.8 Ventricular Septal Defect

28.8.1 Introduction

It is the commonest of congenital cardiac malformation which may be isolated or occur in association with complex heart lesion such as tetralogy of Fallot.

28.8.2 Classification (Fig. 28.1)

1. Inlet VSD
2. Peri-membranous VSD: 80% of all VSD
3. Outlet or conal VSD
4. Muscular VSD

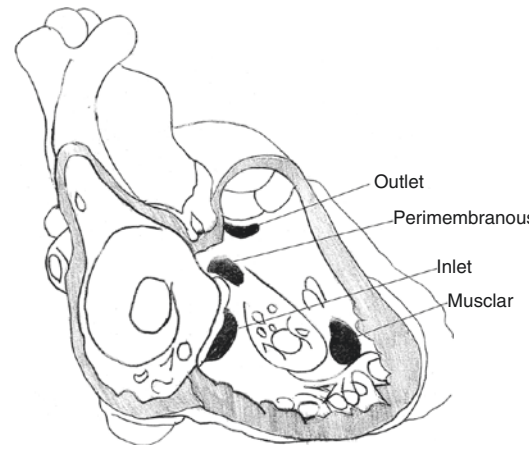

Fig. 28.1 Types of VSD

28.8.3 Pathophysiology

VSD leads to excessive flow from high pressure left sided systemic circuit to low pressured right sided pulmonary circuit. This leads to left to right intra cardiac shunt which eventually returns to left ventricle leading to left ventricular volume overload. Small sized VSD will provide some resistance to left to right shunt and development of pulmonary artery hypertension is rare. Amount of pulmonary blood flow may exceed systemic flow but their ratio (Qp:Qs) remains less than 2. Whereas large sized VSD allows unrestricted blood flow across the defect leading to marked volume overload in pulmonary circuit and LV. Over time pulmonary resistance increases in order to protect lungs from being flooded and this process may eventually lead to pulmonary vascular obstructive disease. This may lead to irreversible histopathological changes in the pulmonary vasculature and pulmonary hypertension.

28.8.4 Natural History

Around 70% of infants who present with intractable cardiac failure or failure to thrive can be managed medically since natural history of VSD suggests that around 50–70% of VSD presenting at 1 month of age will close spontaneously by 1 year of age. This means that around 30% of infants will still need surgery for closure of VSD [4]. Certain anatomic variety like malaligned or inlet variety will need to be closed and this should be undertaken soon after establishment of diagnosis due to the possibility of early development of pulmonary hypertension and pulmonary vascular obstructive disease.

28.8.5 Clinical Features and Diagnosis

VSD usually remains asymptomatic in the early weeks of life due to high PVR but as the PVR falls, left to right shunt increases and the pulmonary blood flow increases. If the VSD is smaller in size, it may offer resistance to flow making it a restrictive VSD which may be better tolerated than large unrestrictive VSD. These infants may just present with systolic murmur. Large or unrestrictive VSDs may allow volume and pressure overload of right side and the LV may enlarge due to excessive pulmonary venous return leading to early development of congestive heart failure. Large numbers of small VSD's remain asymptomatic and are picked up as incidental murmurs whereas large VSD may present with symptoms of congestive heart failure and failure to thrive. Clinically they have a pansystolic murmur and signs of congestive heart failure like enlarged liver.

Although X-ray may show evidence of higher pulmonary blood flow and cardiomegaly and ECG may show evidence of biventricular hypertrophy, the cornerstone of diagnosis remains echocardiography. It reveals the type, anatomy, associated defects and flows across the VSD with measurements of pressure gradients and estimated RV and PA pressures. It may also reveal other concurrent VSD's and functional status of heart valves including aortic valve.

Cardiac catheter is only indicated in cases with pulmonary hypertension to quantify shunt, calculate PVR and its reversibility with 100% O_2 and/or nitric oxide.

28.8.6 Surgical Management

Surgical principles include:

- Aortic and bicaval cannulation with cardioplegic arrest.
- Normothermia or at the most mild hypothermia.
- Approach through right atrium and across tricuspid valve as opposed to certain VSDs like doubly committed sub arterial variety, which are best approached through MPA distal to pulmonary valve. Heart is vented across the inter atrial septum.
- VSD's are ideally closed using various prosthetic materials like Dacron or bovine pericar-

dium using either continuous or interrupted technique and making sure to carry out rigorous deairing of the left heart before releasing the cross clamp.

28.9 Tetralogy of Fallot

28.9.1 Introduction

Tetralogy of Fallot affects approximately 3 in 10,000 people and constitutes 7–10% of all congenital cardiac defects. It accounts for almost one in ten cases and thus it is one of the common congenital cyanotic heart diseases. It is the most common cardiac cause of cyanosis beyond the neonatal age group. It has some male preponderance.

28.9.2 Embryology and Genetics

TOF is commonly associated with trisomy 21 and microdeletion at 22q11. It is associated with Velocardiofacial syndrome, Di-George syndrome and trisomy 18 and 13 along with others [22].

28.9.3 Anatomy and Pathophysiology

The classic four characteristic pathologies associated with tetralogy are:

- VSD
- Overriding of aorta
- Pulmonary stenosis
- Right ventricular hypertrophy

They are largely explained by the leftward and anterior displacement of infundibular septum which produces malaligned VSD along with narrowing of Right ventricular outflow tract (RVOT). This part of septum also has aortic valve directly located behind it and thus it produces overriding of aorta. Unrestrictive VSD and narrowed outflow tract produces hypertrophy of RV. The main pulmonary artery is usually short with stenotic pulmonary valve which is often bicuspid and with dysplastic cusps. Branch pulmonary artery stenosis is less common but can be seen in around 10% cases [4]. VSD is large, unrestrictive and malaligned with a degree of aortic override. Around 15% cases also have additional VSDs.

28.9.4 Natural History

In non-corrected patients mortality is very high within the first few years of life with only 10% surviving up to 30s and only 3% chance of surviving into their 40s [23]. The commonest causes of mortality in these patients are hypoxic spells, cerebrovascular accidents and brain abscesses [2].

28.9.5 Clinical Features and Diagnosis

The main presenting symptom is cyanosis. Patients with TOF may present from normal saturations at room air to the other end of spectrum of severe cyanosis early in infancy. Hypercyanotic spells are frequent occurrence which may be precipitated by dehydration or viral illnesses and usually managed medically. Frequent spells are one of the indications for expedited surgery. Early diagnosis and treatment has lead to the reduction in number of children with delayed manifestation of long term cyanosis like polycythemia or brain abscesses.

Mid-systolic murmur and single second heart sound may be heard during clinical examination. Chest X-ray may reveal boot shaped heart with oligemic lung fields, reduced hilar pulmonary prominence and vascularity. Echocardiography is diagnostic for TOF with increasing emphasis now shifting towards foetal echocardiography and antenatal diagnosis.

28.9.6 Management Including Surgical Principles

Ideal age of repair is still debated but in patients with relatively stable symptoms, surgery is usually undertaken at the age of 4–6 months of life. Neonates and young infants with severe symptoms may either be managed by early total correction or in two stage repair with definitive surgery following earlier systemic to pulmonary artery shunt. The principles of repair include:

- Cardiopulmonary bypass including cannulation of aorta for arterial return and bicaval cannulation for venous drainage.
- Normothermic to mild hypothermic bypass.
- Cardioplegic arrest of heart before approaching the VSD first through right atrium.
- Closure of VSD using Dacron or pericardial patch using continuous or interrupted non absorbable sutures like polypropylene.
- Resection of right ventricular outflow tract obstruction through right atrium and later completing it through pulmonary artery or in cases with severe pulmonary annular hypoplasia with valve 'Z' scores less than −3, using transannular incision and enlargement of the RVOT using transannular patch of pericardium or prosthetic material.
- Junctional ectopic tachycardia is common complication following TOF repair attributed to RVOT muscle resection or excessive stretch of RA during retraction. It is commonly treated using core cooling or by pharmacological measures like Amiodarone infusion. Residual lesions affect outcomes as any residual left to right shunt are poorly tolerated following surgery due to reduced RV compliance and pulmonary regurgitation.

28.9.7 Follow Up and Outcomes

There are many series now describing 20 years outcomes following TOF repair with survival in excess of 95–96% and freedom from re-intervention and symptoms at the end of 20 years [24, 25]. Main issue in long term management of patients operated for TOF repair is the timing of pulmonary valve replacement due to pulmonary insufficiency. General consensus today is to proceed for pulmonary valve replacement once right ventricular volume exceeds 150 ml/m^2 especially in association with RV dysfunction and significant tricuspid regurgitation [26].

28.10 Atrio Ventricular Septal Defects

28.10.1 Introduction

Main pathology in AVSD is due to the abnormal development of endocardial cushions which leads to defects in atrio ventricular septum and valves. 50% of patients with AVSD are associated with trisomy 21. In simpler terms, patients with AVSD will have primum type atrial septal defect and ventricular septal defects with common atrio ventricular valve between all four chambers of heart.

28.10.2 Embryology and Genetics

AVSD is commonly seen in association with Down' syndrome and less commonly with Noonan syndrome and Ellis-van Creveld syndrome. Isolated AVSD have shown autosomal dominance with incomplete penetrance. CRELD 1 gene located on chromosome 3 is shown to be associated with AVSD [27].

28.10.3 Classification

Two major types have been reported. Partial AVSD is associated with only atrial defects and none to very small ventricular component with two well formed atrioventricular valve orifices. Complete AVSD on the other hand is more common and shows primum ASD, unrestrictive VSD and free floating atrioventricular valve. As can be imagined, due to free floating valve, there is wide

spectrum of presentation of patients with AVSD starting from balanced two ventricles to only one dominant and other rudimentary ventricle or unbalanced type of AVSD. There are various classification of AVSD like Rastelli classification which takes into account the superior leaflet of AV valve and its bridging across IVS whereas Bharati and Lev's classification is about balance of the two ventricles.

28.10.4 Pathophysiology

Due to atrial and unrestrictive ventricular septal defects, children with AVSD will have large intracardiac left to right shunt. After birth, pulmonary vascular resistance falls leading to increase in intra cardiac shunt leading to volume overload of ventricles and congestive heart failure, poor weight gain and eventually failure to thrive. Any leak of AV valve leads to more volume overload and more shunting.

In patients with Down' syndrome, the pulmonary vascular resistance remains elevated for longer time after birth. They also have increased bronchial secretions, reduced number of distal bronchi along with inherent abnormality of lung parenchyma which leads to accelerated development of pulmonary vascular obstructive disease.

28.10.5 Natural History

Uncorrected patients with CAVSD have been reported to have 6 months survival of 50%, 2 years survival of 15% and 5 years survival of around 4% [28]. Another series showed follow up of un-operated patient with CAVSD and reported 65% mortality within first 6 years of life with most within first year. Most common cause of mortality was congestive heart failure, respiratory complications and Eisenmenger's syndrome. Remaining 35% patients did survive up to 17 years of follow up but remained in NYHA class III or IV and were declared inoperable by that time [29].

28.10.6 Clinical Features and Diagnosis

Within few weeks of life, as the PVR falls, the intracardiac shunt through ASD and/or VSD increases leading to marked volume overload of right ventricle and the returning blood to heart leading to dilatation of left side. Associated AV valve regurgitation can lead to increased left to right shunt markedly. CAVSD usually have unrestricted VSD which leads to a large intracardiac shunt and signs of congestive heart failure whereas PAVSD have only atrial component with absent or very small ventricular component and this leads to their presentation similar to secundum ASD.

X-ray chest may show evidence of increased pulmonary blood flow and cardiomegaly. ECG on the other hand may show striking feature of moderate to extreme left axis deviation. Echocardiography forms the mainstay of diagnosis. It can delineate the atrial and ventricular components, show status of AV valve, morphology and its competency, ventricular balance and status of LVOT and RVOT.

28.10.7 Management Including Surgical Principles

In 1952, Denis and Varco were trying to close an ASD on pump, unfortunately this patient did not survive and post mortem confirmed the diagnosis of PAVSD. Lillehei first reported successful closure of Ostium primum ASD using controlled cross circulation and CPB. Initially many advocated palliation but now surgery offers cure with excellent outcomes and long term results. The principles include:

- Optimum timing of surgery: In symptomatic infants with CAVSD, surgery may be needed at presentation, whereas in asymptomatic infants around 4 months seems be the appropriate age to operate. In asymptomatic children with PAVSD surgery should be carried out around 1–3 years of age whereas in symp-

tomatic patients expedited surgery may be indicated.

- For CAVSD, single or two patch techniques are commonly used for closure of atrial and ventricular components. PAVSD needs only single patch for closure of primum defect. The 'cleft' in left AV valve also needs addressing during the surgery.
- Bypass is instituted through aortic and bicaval cannulation. Approach is through right atrium across the AV valve. Extensive valve testing forms the basis for decision about where to septate the free floating AV valve. In two patch technique, normally, the ventricular component of the defect is closed first using prosthetic patch and the atrial component is closed using autologus pericardium. Both patches are anchored at the hinge point or midline raphae of the AV valve. Delineation of this midline raphae is crucial as any left ward movement can have severe implications in terms of compromising left AV valve orifice and narrowing left ventricular outflow tract. Single patch technique involves closing the VSD first and bringing the patch through the incised left AV valve and anchoring two sides and closing the ASD with the same patch. Both techniques have very good long term outcomes.

The coronary sinus and AV node are displaced inferiorly. Nodal triangle is bound inferiorly by extent of right AV valve annulus, coronary sinus and inferior edge of IAS. Bundle of His(BOH) passes superiorly and anteriorly from AV node to the crest of IVS. Consequently some surgeons prefer to include coronary sinus under the patch allowing it to drain in to the left atrium to avoid damage to BOH and accept a degree desaturation. With increasing knowledge and experience, many surgeons now prefer the coronary sinus to drain anatomically and pass stitches through the wall of coronary sinus to avoid damage to BOH.

28.10.8 Follow Up and Outcome

Outcomes in AVSD repair have improved dramatically in recent years due to better understanding of morphology and natural history of the disease, improved anaesthetic and bypass techniques and improved post operative management with more experience in managing this challenging group of patients. In a series from Children's hospital; Boston, 83% patients out of 365 cases, operated using single patch technique showed operative mortality of only 1.5% [30]. Another series of 100 consecutive cases with two patch technique has recently reported no perioperative mortality. Left AV valve regurgitation remains a problem on long term follow up of patients operated for CAVSD repair but in the 100 cases series quoted above, the freedom from reoperation at 10 years was 94% [31].

28.11 Transposition of Great Arteries (TGA)

28.11.1 Introduction

TGA is relatively common accounting for 9.9% of infants with CHD in one series [32] and 2:1 male preponderance [33]. It is an anomaly where aorta arises from RV and PA arises from LV indicating a ventriculo-arterial discordance. In congenitally corrected TGA on the other hand, RA is connected to LV which connects to PA allowing venous return from body to go to lungs. The LA on the other hand, is connected to RV which in turn is connected to aorta allowing blood returning from lungs to be channelled into the aorta. This is called atrio-ventricular and ventriculo arterial discordance.

28.11.2 Embryology and Genetics

TGA is classified as cono-truncal anomaly which entails anomalies related to deranged development of cardiac outflow tract. One of the theory for development of TGA is persistence of subaortic conus and absorption of subpulmonic conus [34].

TGA is very rarely associated with any other syndrome like Marfan's or Turner's syndrome and is practically never seen in patients with

Down's syndrome. Only syndrome strongly associated with TGA is heterotexy syndrome and less commonly with trisomy 8, trisomy 18, vacteral, charge and William's syndrome. Some non genetic causes like maternal diabetes, maternal infection, ionising radiation and drugs like ibuprofen and antiepileptic drugs have also been described [35].

28.11.3 Pathophysiology

The issue in TGA is the presence of two parallel circulations. Blood returning from body through SVC and IVC is channelled into RV and lead to aorta thus returning back to right atrium through vena cavae. On the other hand blood in the left system keeps circulating from left atrium to LV and into PA leading back into the lungs. This means that some sort of communication (shunt) between two system is obligatory for survival. This shunt allows for mixing of deoxygenated and oxygenated blood before being pumped into either circuit. With development of Rashkind atrial septostomy in 1966 the management of neonates with TGA has completely changed as atrial septostomy allowed for mixing of blood at atrial level and provides period of stability before corrective surgery is undertaken. The septostomy can now be performed under echocardiography guidance in ICU especially in patients who are too unwell to be shifted to cardiac catheter suite.

In normal neonates, the reducing PVR after birth leads to increased flow into left ventricle which starts ejecting into systemic circuit against peripheral vascular resistance which lead to rapid increase in LV myocardial mass [36]. However, the septostomy will also decompress the left ventricle which loses its pressure load and may quickly regress in size if corrective surgery is delayed for more than 4 weeks.

28.11.4 Natural History

In a study published in 1969 from the state of California, natural history of 290 cases of TGA was presented with an aim to help decision making about surgical risks in these patients. According to the study:

- The age of death for the whole group if not operated was 30% by first week, 50% by first month and 90% by first year.
- The average life expectancy at birth for simple TGA (without ASD or VSD) was 0.11 years, for TGA with VSD was 0.28 years whereas for TGA, VSD with PS was 4.85 years [33].

28.11.5 Clinical Features and Diagnosis

Patients of TGA with intact septum and inadequate mixing of blood, may present with marked cyanosis, signs of inadequate tissue perfusion, acidosis and neonatal shock. Patients with TGA and VSD will have higher pulmonary blood flow and thus higher saturations. ECG may be normal at the time of birth. Echocardiography constitutes the mainstay of diagnostic tool for these patients. In addition to diagnosis it may delineate the relationship of great vessels, coronary patterns, additional defects and volume and function of ventricles. Cardiac catheter is now largely reserved for balloon atrial septostomy.

28.11.6 Management Including Surgical Principles

Arterial switch is one of the most complex and technically demanding surgical procedure which is a single stage repair of the complex anomaly. It involves rerouting the RV into pulmonary artery and LV into aorta along with its coronary supply. The complexity of the procedure is due to smaller size of heart and great vessels, wide variation in relationship of these great vessels and coronary anatomy. Optimum time of repair is within first 2 weeks of life. The surgical principles include:

- Approach through sternotomy, harvesting of sizable pericardial patch.
- High aortic and single cannula in right atrium. Previous BAS makes the conduct of surgery

easier since excellent venous return can be obtained due to venting across unrestricted IAS.

- Transection of aorta at appropriate level and preparation of coronary buttons by cutting out of the coronary ostia from the aortic sinuses and mobilization of proximal coronaries enough to be able to implant them onto the neoaorta without any tension or kinking of the coronary buttons.
- The remnant of this aortic root will become the neo pulmonary root. The reconstruction of this neo pulmonary root is accomplished by using the harvested autologus pericardium.
- The pulmonary artery is transected at the level of its bifurcation and the coronary buttons are translocated to this neo aortic root. The coronaries are implanted in a trapdoor manner using reverse L incision.
- Bringing the pulmonary confluence anterior to aorta by Le'compte manoeuvre. Completing the distal aortic anastamosis. Once this anastamosis is completed the neo pulmonary artery is anastamosed to the pulmonary confluence.
- On completion of the procedure, once the patient is weaned off bypass, it is necessary to ascertain that all the regions of the heart are well perfused. This is usually indicated by isoelectric ECG tracing and ECHO showing no regional wall motion abnormality.
- It is not unusual for these neonates to be transferred to the ICU with their chest left open. Following a period of haemodynamic stability, the chest is closed in the ICU in 24–48 h.

28.11.7 Follow Up and Outcome

The current operative mortality for arterial switch operation is 2–3% with recent NICOR data showing a 30 days survival in the UK for the year 2012–2013 to be 97.3%. Gestation age less than 36 weeks, higher bypass time and single or intramural coronary anatomy are some risk factors for mortality. The long term outcomes after arterial switch surgery remains excellent with around 2% of patients needing aortic valve replacement at an average time of 11 years after the ASO.

28.12 Hypoplastic Left Heart Syndrome

28.12.1 Introduction

Hypoplastic left heart syndrome encompasses a severe and complex form of congenital malformations of heart which are fatal if untreated early in life. Management of hypoplastic left heart patients has evolved very rapidly in recent years leading to 5 years survival rate approaching 90% [37]. It is relatively common and estimated to occur in 0.16–0.18 per 1000 live births and has male preponderance. This accounts for 4–9% of children born with CHD [37–39]. Congenital heart surgery nomenclature database project has defined the HLHS as a spectrum of cardiac malformations characterised by a severe underdevelopment of the left heart-aorta complex consisting of aortic and/or mitral atresia, stenosis or hypoplasia with marked hypoplasia or absence of the left ventricle and hypoplasia of the ascending aorta and aortic arch [40] (Fig. 28.2).

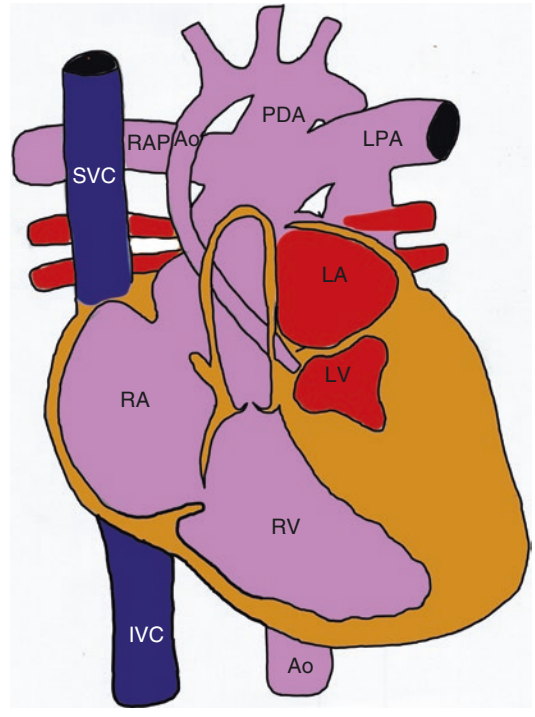

Fig. 28.2 Hypoplastic left heart syndrome

28.12.2 Embryology and Genetics

There is growing evidence that there may be genetic basis for development of HLHS. It has been shown to be associated with Trisomy 13, trisomy 18, Turner's syndrome (X0) along with others [41]. Mutations in four genes namely GJA1, NKX2–5, NOTCH1 and HAND1 have been implicated in patients with HLHS [42–46].

28.12.3 Pathophysiology

Neonates with HLHS are born with small or rudimentary left ventricle. This means that they have to be converted into single pump circulation for survival where right ventricle will take over the role of sole pump for the body and drive blood from aorta, through the body tissues and returning to heart via lungs bypassing the heart. In patients with HLHS, the blood is diverted through duct into descending thoracic aorta during foetal life but due to hypoplastic or atretic aortic valve, ascending aorta and arch, around 30% children show some neurological abnormality following birth and post natal MRI have confirmed ischemic brain lesions in 23% cases. Thorough neurological assessment must be carried out pre operatively to rule out major neurological abnormality and have a baseline study to compare with in the future.

28.12.4 Clinical Features and Diagnosis

At birth these neonates may be entirely normal due to flow through open duct however, very quickly they may present with respiratory distress, hypoxia and collapse with neonatal shock. Duct and interatrial communication may provide some areas of mixing and thus presentation depends largely on their adequacy; for example neonates with severely restrictive atrial communication will present immediately after birth with collapse and medical management alone is insufficient in this group. Echocardiography forms the mainstay in diagnosis. Advancement in foetal diagnostic capability have lead to better antenatal diagnosis and reduced incidence of neurological injury, better preoperative condition of these neonates. Cardiac catheterization is now largely reserved for borderline cases where biventricular repair is likely. CT and MRI imaging abilities have vastly improved leading to ability to reconstruct 3D anatomy to better plan operative strategies for these complex patients.

28.12.5 Natural History

If untreated it is uniformly fatal with 95% neonates dying within first month of life [3].

28.12.6 Management Including Surgical Principles

Current favoured surgical strategy for these patients is three stage Norwood procedure.

Stage I: Done within few days after birth. It involves repair of hypoplastic ascending aorta and its arch along with preparation of single pump by creating large atrial communication and connecting pulmonary artery to aorta using Damus-Key-Stansel anastomosis. Supply to pulmonary tree is generated using either systemic to pulmonary shunt (BT shunt) or RV to PA non valved conduit (Sano shunt).

Stage II: Usually performed by 4–6 months of age. Rerouting the head, neck and upper extremity venous drainage through superior cavo-pulmonary anastomosis where SVC is transected at its entry into RA and routed into RPA to off load the right ventricle which now only handles the blood directly coming from lower extremities through IVC and the pulmonary venous blood. The RV to PA conduit is now taken off to allow the RV to become the main pumping chamber.

Stage III: Performed at around 3–5 years of age. Completing the Fontan circulation by diverting the IVC blood directly into right pulmonary

artery which completely off loads the right ventricle of systemic venous return.

The surgical principles of Norwood stage I include:

- Approach through sternotomy. Anastomosis of 3–3.5 mm PTFE tube graft onto major head and neck branch of aorta and connect it to aortic cannula for arterial flow. Single right atrial venous cannula and cooling to 20° for profound hypothermia. Ligation and division of duct.
- Mobilisation of aorta and its head neck branches along with extensive mobilisation of descending thoracic aorta. Extensive mobilisation of both branch pulmonary arteries right up to hilum.
- Hypoplastic arch and aorta are reconstructed using a pulmonary homograft patch. MPA is transacted at the level of confluence and sano shunt is constructed from RV free wall on to PA confluence. 5 mm PTFE tube graft is used for the anastomosis.
- MPA proximal end is anastomosed onto ascending part of aorta in a Damus Key Stensel anastomosis.
- Atrial septectomy is carried out under total circulatory arrest. Aortic reconstruction is done using antegrade cerebral perfusion to protect brain from prolonged ischaemic time.

Post operative period of Norwood stage I can be stormy. Chest is left open till a period of hemodynamic stability is achieved.

28.12.7 Follow Up and Outcome

In a recent series of 267 cases over 6 years, from Boston children's hospital 27 patients died following stage I palliation (88.6% hospital survival). There was 10% interstage mortality. 93% of stage I survivors underwent stage II repair with no operative mortality and so far 40% of the initial patients have undergone stage III repair with no operative mortality. Seventy-two patients are still awaiting completion of the Fontan surgery [37].

28.13 Total Anomalous Pulmonary Venous Connection (TAPVC)

The pulmonary veins normally return the oxygenated blood into left atrium. TAPVC involves anomalous connection between the pulmonary vein and the right atrium. Blood enters the left heart through the ASD or more unusually through a VSD. It accounts for 1–3% of all CHD [47]. To survive, these patients must have mixing of oxygenated and deoxygenated blood or in other words some shunt at atrial (commonly) or some other level (less common like VSD). The common types of TAPVC includes:

- Supracardiac variety: Involves drainage of pulmonary venous return into a common chamber behind the left atrium. A vertical vein than drains the blood into systemic vein, commonly into innominate vein.
- Cardiac variety: Pulmonary veins drain into common confluence and then into coronary sinus or directly into right atrium.
- Infracardiac variety: Common chamber of confluence of pulmonary veins behind the heart communicate to portal venous system through a descending vein which passes inferiorly through the diaphragm. This variety is most prone to obstruction.
- Mixed variety: Any combination of above (Fig. 28.3).

Blood returning from the lungs enters into right atrium due to anomalous connection of pulmonary veins. Blood can only pass to left side of heart if there is right to left shunt for example through PFO. This shunt is obligatory for survival and its size will decide the presentation of these children who may present from neonatal shock and collapse to presentation after few months of birth with signs of mild cyanosis or

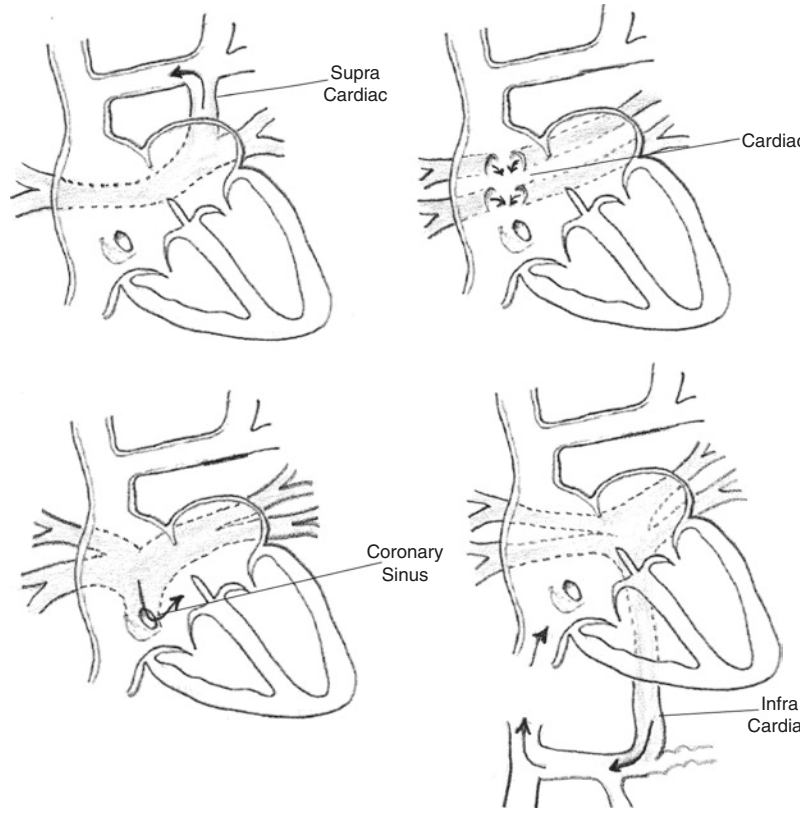

Fig. 28.3 Types of TAPVD

heart failure due to unobstructed shunt. Obstruction of this shunt (restricted PFO) or obstruction of vertical vein can present as a surgical emergency as there are no non interventional way of alleviating this condition. Obstructed TAPVC is one of the few cardiac emergencies presenting to congenital cardiac surgeons where immediate surgical intervention is warranted. Ecocardiography forms the mainstay of diagnosis.

During surgery, the common venous chamber is anastomosed to left atrium to allow for unobstructed passage of blood. Although surgery was advocated to be done under profound hypothermia and total circulatory arrest, there has been increasing trend toward performing these operation under normo thermic or mild hypothermic conditions. The guiding principle of the anastamosis is that, that the anastamosis should be larger than the diameter of the mitral valve. Hospital mortality has been reported between 5–10% and long term outcomes are excellent after the repair.

28.14 Truncus Arteriosus

This is a relatively rare anomaly comprising of common trunk originating from heart rather than aorta and pulmonary artery separately. This trunk in turn gives rise to pulmonary arteries as well as the coronary arteries. The anomaly has been classified based on origins of pulmonary arteries from the main trunk (Fig. 28.4).

Truncus arteriosus may be associated with interrupted aortic arch. Coronary variations are also quite common and around 30% patients are reported to have extra cardiac anomalies like Di-George syndrome [48].

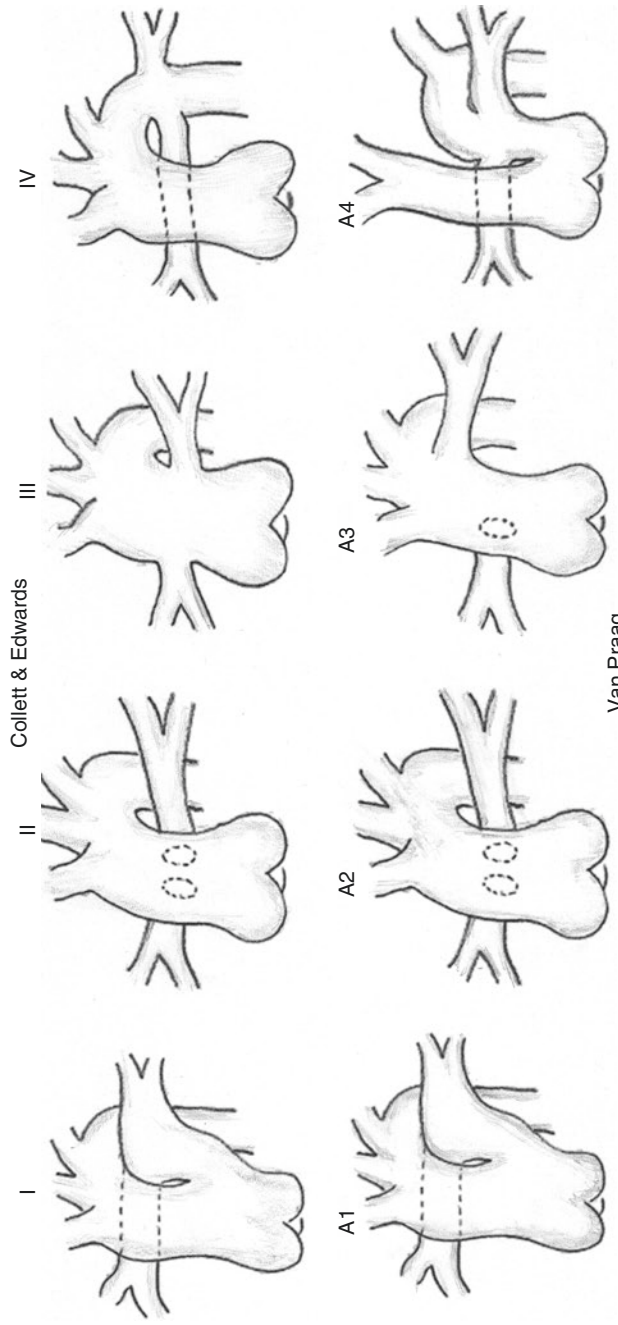

Fig. 28.4 Classification of truncus arteriosus

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Part IV

Gastrointestinal System

Inguinal Hernia

29

Antti I. Koivusalo

Abstract

Inguinal hernia is one of the most common surgical conditions in infancy. Practically all infant hernias are of congenital indirect type. Medical conditions causing increased intra-abdominal pressure and connective tissue weakness predispose to inguinal hernias. Close to 5% of infants undergo hernia repair before the age of 6 months and in every fourth of those infants an emergent repair for incarceration, strangulation or repeated difficult reduction is performed. Thus hernia repair is indicated whenever a diagnosis has been made. Incarcerated or strangulated hernia is a paediatric surgical emergency and requires either manual reduction and subsequent repair or immediate surgery if reduction is not achieved. Elective repair of uncomplicated neonatal inguinal hernia is scheduled not later than 2–4 weeks following the diagnosis. In premature infants complicated hernias are repaired before discharge from NICU. In small infants the risk of apnoea requires appropriate facilities for postoperative monitoring after hernia repair.

Neonatal inguinal hernia is repaired in the standard fashion of division and high ligation of the sac, but for a pediatric surgeon mastery of alternative incisions and laparoscopy is very useful. In a unilateral repair routine exploration of the asymptomatic contralateral groin is not recommended in any infant. Complication rate in the repair neonatal inguinal hernia is 1–5% including recurrence, testicular ascent, testicular atrophy, injury to vas deferens and injury to intestine, ovary, bladder and uterus. Neonatal hernia repair should have 0% mortality rate.

Keywords

Inguinal hernia • Newborn • Newborn surgery • Outcomes

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_29

29.1 Introduction

Inguinal hernia is one of the most common surgical conditions in infancy and consequently repair of the hernia is a common surgical procedure in neonates. The peak incidence of inguinal hernia is during the first months of life and approximately one third of children are aged less than 6 months at the time of the repair. The recent developments in paediatric anaesthesia and intensive care have enabled safe hernia repair in premature babies. The basic operation for an indirect inguinal hernia, high ligation and division of the hernia sac at the internal inguinal orifice, remains the mainstay of the surgical technique, but the introduction of laparoscopy in children has provided a new surgical approach also for neonatal hernia repair. Hernia repair in infants must take in consideration anaesthetic risks, appropriate postoperative care and the risk of inguinal hernia related complications. Proper timing, awareness of risks, mastery of proper techniques and the ability to treat complications are basic skills of a paediatric surgeon for safe and efficient neonatal hernia repair. These issues are discussed in this chapter.

29.2 Etiology

At the neonatal period practically all inguinal hernias are of congenital indirect type, whereas direct inguinal or femoral hernias are rare [1–3]. Indirect inguinal hernias are the result of failure of the processus vaginalis to close. Processus vaginalis is an outpouching of the peritoneum through inguinal canal identifiable from the third month of the gestation. Processus vaginalis elongates as it accompanies gubernaculum and testes during their descent, and it reaches the scrotum by the seventh month of gestation. Processus vaginalis obliterates after the descent of the testes, but the process of obliteration continues after birth. In the female, processus vaginalis accompanies the round ligament and reaches the labia major as the canal of Nuck. The rate of patency of processus vaginalis has been reported to sink from 89–94% in the newborn period to 57% in the 4–12 month age group and 20% in adulthood [4]. Patent processus vaginalis is a potential hernia but not an equivalent to an inguinal hernia. It has been estimated that although at the age of 2 years processus vaginalis may be bilaterally open in 40% of children, only 6–12% of those who have undergone unilateral hernia repair by the age of 2 years, develop a metachronous contralateral inguinal hernia [5–7].

29.3 Epidemiology

The incidence of indirect inguinal hernia in full-term neonates ranges from 3.5–5% [8]. The incidence in preterm infants commensurates with the patency of the processus vaginalis and highest incidence rates ranging from 16% to 30% are reported in premature infants [8–10]. During the birth hospitalization, the incidence of inguinal hernia for premature infants is reported to range from 3% to 9% and for infants weighing less than 1500 and 1000 g, 11% and 17%, respectively [10, 11]. Males are much more likely to develop hernias with a reported male-female ratio of 3:1 to 10:1 [8]. In both sexes, approximately 60% of the hernias are right-sided, 25–30% left-sided and 10% are bilateral [12, 13]. In premature infants the incidence of bilateral hernias may reach 50% [11].

Approximately 11.5% of patients have family history of inguinal hernia [8, 13]. The incidence of hernia is increased in twins as well [14, 15].

29.4 Associated Conditions with an Increased Incidence of Inguinal Hernia

There is an increased incidence of inguinal hernia in patients with the following conditions:

- Urogenital
  - Undescended testis
  - Bladder exstrophy
  - Cloacal exstrophy
- Increased peritoneal fluid
  - Ascites
  - Ventriculoperitoneal shunt
  - Peritoneal dialysis

- Increased intraabdominal pressure
  - Repair of omphalocele/gastroschisis
  - Meconium peritonitis
  - Necrotizing enterocolitis
  - Chylous ascites
- Chronic respiratory disease
  - Cystic Fibrosis
- Disorders of the connective tissue [16]
  - Marfan syndrome [17]
  - Loeys-Dietz syndrome [18]
  - Williams syndrome [19, 20]
  - Cutis laxa [16]
  - Costello syndrome [16]
  - Menkes disease and OHS [16]
  - Ehlers-Danlos syndrome [21]
- Mucopolysaccharidoses [16]
  - Osteogenesis imperfecta
  - Hurler syndrome, Hunter syndrome
- Disorders of sexual differentiation
  - Complete androgen insensitivity syndrome [22]
  - Persistent Mullerian duct syndrome [16]
  - Chromosomal disorders and gene defects such as XXYY males, Opitz syndrome Aarskog syndrome, Fragile X [16]
  - Etiology unknown: Velocardiofacial–syndrome
  - DiGeorge syndrome [16]

29.5 Clinical Presentation

Inguinoscrotal hernia may be diagnosed prenatally by ultrasonographic screening [23]. In the newborn the presenting feature is a firm bulge in the groin lateral to the pubic tubercle which increases size and extends toward or into the scrotum or in the female the ipsilateral labia major with crying and straining. In the female the bulge is less obvious and may contain often a nonreducible ovoid-shaped mass corresponding with the herniated ovary. The bulge may disappear spontaneously when the patient is relaxed or sometimes remain visible and palpable causing crying, discomfort and vomiting. The bulge can be reduced with gentle pressure. After reduction 'silk glove sign', thickening or silkiness of the spermatic cord as it crosses the pubic tubercle or, in the female on palpating the processus vaginalis over the pubic tubercle, may be felt on palpation. Silk glove sign has been reported to detect indirect inguinal hernia or patent processus vaginalis with as high as 93% sensitivity and 97% and specificity [24], but the accuracy of silk glove sign in the female is lower and probably varies between examiners. A positive silk glove sign together with a reliable clinical history is, however, highly suggestive of inguinal hernia. Stretching a supine infant on the bed with legs extended and arms held straight above the head may cause the infant to struggle and push out the hernia. When the physical examination with clinical history is not diagnostic a new evaluation should be arranged. Digital photographs of the hernia taken by the parents may confirm the diagnosis accurately and prevent repeated visits to the attending surgeon [25]. The diagnosis of neonatal inguinal hernia can be made by clinical history and physical examination and radiologic investigations are generally not needed. Groin ultrasound scan may disclose patent processus vaginalis, presence of mass in the inguinal canal or movement of an intestinal loop through the internal ring. In older children ultrasonographic diameter of the inguinal canal may be used to differentiate between patent processus vaginalis and a true inguinal hernia [26, 27]. Ultrasound scan may be also used in differential diagnostics to detect disorders of testis, abnormal inguinal lymph node, abscess or hydrocele.

29.6 Management

An inguinal hernia does not resolve spontaneously and because of the incarceration risk which is particularly high during the first months of life repair is always indicated. An irreducible incarcerated or strangulated hernia requires immediate surgery. A reduced incarcerated hernia should be repaired as soon as the patient is stable and the swelling in the sac has subsided usually by the second day after the reduction. Delaying the surgery 5 days or more after reduction carries a significant risk of reincarceration [28].

Most paediatric surgeons recommend that an uncomplicated inguinal hernia in full-term neonates and in infants under 3 months of age is repaired as soon as convenient not later than four but preferably within 2 weeks following the diagnosis. Undue delay of elective repair increases the risk of incarceration [29] and should an incarceration occur the parents must be informed where to take the infant for immediate paediatric surgical care. From a daily clinical point of view it is rational to plan a semi-emergent repair within a couple of days if an otherwise uncomplicated hernia has been difficult to reduce, or, if an infant is brought day after day to the emergency ward for the reduction of the hernia.

In premature infants timing of repair for hernias should follow same guidelines as in full-term infants. A complicated inguinal hernia or a hernia requiring repeated difficult reductions during birth hospitalization should be repaired before discharge from neonatal intensive care unit (NICU). Premature infants with uncomplicated inguinal hernias may be discharged and scheduled for a repair at an age when postoperative observation at NICU is not required. If, however, the hernia causes complications or repeated reductions, the need for overnight observation at NICU should not delay a semi-emergent repair.

29.7 Anaesthesia

General anaesthesia with endotracheal intubation, laryngeal mask or face mask is the method of choice. The use of regional techniques such as spinal, epidural or caudal anaesthesia, local anaesthetic instilled in the operative field reduce the need for postoperative analgesics. Neonates carry at least a 5% risk of postoperative apnoea and consequently they usually undergo a 24 h period of postoperative respiratory and circulatory monitoring. The risk of postoperative apnoea has been reported particularly high among preterm neonates but it is also associated with low postmenstrual age, anaemia, and a history of recurrent apnoea [30–32]. Use of regional or local anaesthetics may reduce but does not eliminate the risk of apnoea within the 24 h following the surgery [32, 33]. It has been estimated that the risk of postoperative apnoea does not drop below 1% until 56 weeks for a 32-week premature infant and 54 weeks for 34-week premature infant [30].

In the authors institution day surgery is performed to healthy infants with a minimum corrected age of 3 months (i.e. the estimated day of birth after full-term pregnancy plus 3 months), whereas infants with the corrected age less than 3 months stay overnight at paediatric surgical ward. Infants with gestation age a minimum of 37 weeks and aged less than 4 weeks and infants with gestation age of less than 37 weeks and postmenstrual age under 45 weeks are observed overnight in neonatal intensive care unit.

29.8 Operative Technique

29.8.1 Males

The operative technique aims for ligation of the hernia at the internal inguinal ring. The patient lies supine with the genitals included in the sterile operative field. The use of magnifying surgical telescope glasses is recommended. A short incision is placed with the medial end just superior and lateral to the pubic tubercle. Thus placed the incision lays a little superior to the external ring. The incision is carried through the subcutaneous fat and Scarpa's fascia until the level of aponeurosis of the external oblique muscle. Division of the epigastric vein above Scarpa's fascia should be avoided but if inadvertently divided careful haemostasis is required in order to prevent bleeding and postoperative haematoma. In small children the inguinal canal is short and external and internal rings overlap and the entire operation can be performed through the external ring without splitting the external aponeurosis unless more exposition is needed. The cremasteric muscle and fascia are grasped and raised with blunt forceps the hernia sac is exposed spreading and opening the cremasteric fibers. The hernia sac is grasped with forceps and elevated with the structures of the spermatic cord. The testicular vessels and vas deferens are identified and dissected from the

hernia sac without touching them by gently separating the thin tissue adhering them to the wall of the hernia sac. The dissection of the cord structures is carried to the level at or just above of the internal ring. The proximal hernia sac is freed of all adherent connective tissue and at this stage the hernia sac may be opened for checking its contents, and then divided between small clamps when at the same time the separated cord structures are gently kept out of harms way. No attempt is made to dissect further the distal sac because of the risk of ischemic orchitis or haematoma. If the dissection of the sac is complete, gentle traction on the scrotal skin should now take the testis into the scrotum without any traction felt in the proximal sac. The proximal sac is twisted on itself and suture-ligated at the internal ring with absorbable monofilament thread while again the cord structures are protected from twisting with the sac or from being inadvertently included in the ligature. Scarpa's fascia and the subcuticular layer are closed with absorbable monofilament thread and the cutis is closed with adhesive tape. Finally the position of the testis is controlled once more (Fig. 29.1).

29.8.2 Females

The surgical approach to the inguinal canal is same as in males. The hernia sac is identified and always opened for inspecting the contents or a sliding component. The wall of the hernia sac may contain the fallopian tube which can be found by following the round ligament. If the hernia sac is empty it is divided together with the round ligament between clamps, twisted on itself and suture-ligated with absorbable monofilament thread, and the distal end of the transected round ligament is cauterized with diathermy (Fig. 29.2).

If a sliding component such as fallopian duct, ovary, uterus or bladder is identified in the wall of within the hernia sac, the sac may be closed with purse string above the structure, inverted at the internal ring and then the internal ring is closed with interrupted sutures [34]. Alternatively a peritoneal flap procedure [35, 36] or laparoscopic approach [37] may be used.

29.8.3 Laparoscopic Repair

Laparoscopic repair of paediatric inguinal hernias have gained popularity especially in children past the neonatal age. The relative advantages of laparoscopic repair include the possibility to synchronous inspection and repair of the contralateral side or a bilateral hernia, easy diagnosis of a direct inguinal hernia, repair of a recurred hernia without renewed dissection of the cord structures and the possibility to identify sliding components of the hernia. In terms of pain, cosmetic appearance of the scar, length of hospitalization and the length of the required theatre time, paediatric laparoscopic repair has no significant advantages compared with the open procedure which in children is considerably less invasive than in adults.

In small infants weighing from one and a half to five kilograms laparoscopic hernia repair is reported feasible and technically simple when performed by expert laparoscopic surgeons [38, 39]. Adequate studies comparing open and laparoscopic hernia repair in neonates do not exist and presently no guidelines for the choice of operative technique, except surgeons' expertise and preference, can be given [40]. Laparoscopic hernia repair in children has carried a 2–3% recurrence rate but recently recurrence rates below 2% has been reported [41]. Although cord structures are not dissected in laparoscopic repair there is a reported rate of 4% of postoperative testicular ascent requiring subsequent orchidopexy [39]. For many surgeons the risk of injury to the cord structures and testicular perfusion have been of concern. In the hands of experienced laparoscopic surgeons, the risk of impaired testicular perfusion or testicular atrophy is, however, low [39, 41]. Some centres perform routinely all or most paediatric hernia repairs laparoscopically. In other centres, the authors centre included, laparoscopic hernia repair is performed in selected indications including incarceration, sliding hernia and recurrence. In premature low-weight infants open approach is preferable to laparoscopy because the small abdominal domain provides limited working space to handle friable tissues, and there is a risk for respiratory problems because of CO_2 pneumoperitoneum.

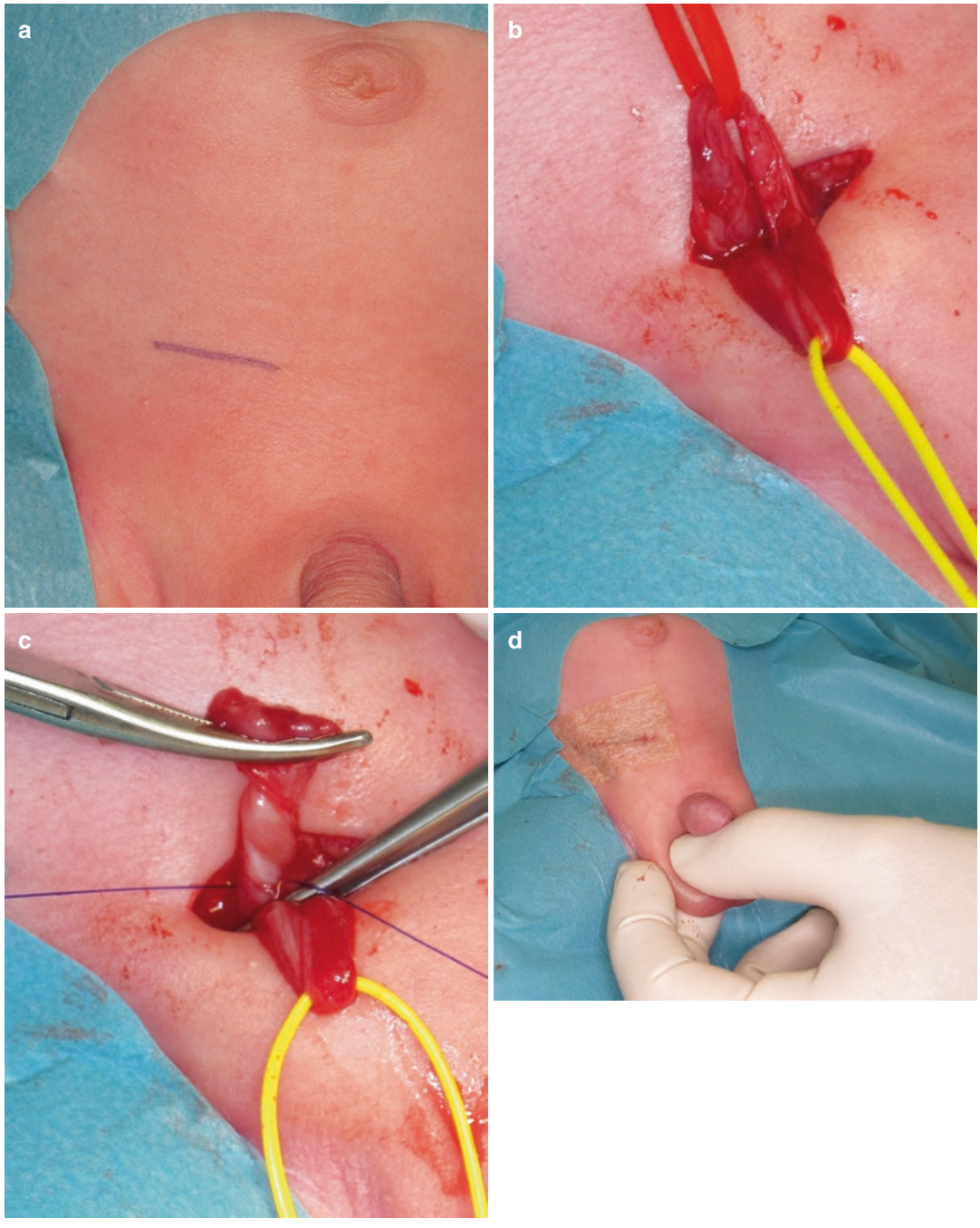

Fig. 29.1 Open repair in male. (**a**) Placement of the incision; (**b**) vas and spermatic vessels (surrounded by *yellow loop*) are dissected free from the sac (*red loop*); (**c**) sac has been diveded, proximal sac is twisted and ligated, distal part is allowed to retract; (**d**) after closure, location of the testicle is checked once more

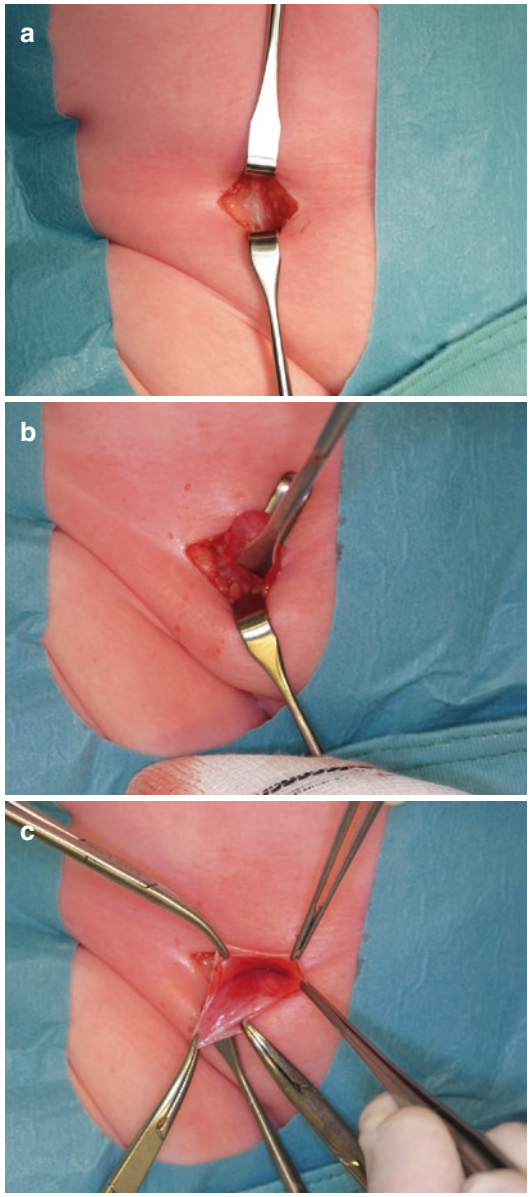

Fig. 29.2 Open repair in female. (**a**) Incision, Scarpa's fascia seen at the bottom of the incision; (**b**) a small retractor is passed below the sac and round ligament; (**c**) hernia sac is opened for examination of its contents

Laparoscopic techniques include closure of the peritoneum at the inguinal ring by a running suture or a purse string suture [41], use of peritoneal flap [42], or division of the periorificial peritoneum from inside, collapse of the sac and subsequent closure of the peritoneal margins [43]. Hernia repair may also be achieved with laparoscopically guided extraperitoneal suture closure surrounding the internal ring [44].

Authors preferred technique of laparoscopic repair in male infants and neonates is performed with the patient supine under general anaesthesia. Urinary bladder is emptied by compression method (Crede's manouver) or, alternatively, urinary catheter may be inserted. The patient must be securely attached to the operating table in order to allow Trendelenburg's position and turning to both sides. Five or three millimeter trocars and instruments are used. Alternatively, laparoscopic instruments can be inserted through stab incisions without trocars. A small incision is made in the infraumbilical fold for open placement of a trocar for videocamera and insufflation. After insufflation two small stab wounds in the left and right abdomen are made for two needle holders. A thread of appropriate length is then placed into abdominal cavity either through abdominal wall or through a trocar. The internal ring is closed with a suture taking general bites of the peritoneum including the medial aspect of the internal ring but excluding the cord structures. Absorbable or unabsorbable thread may be used. The thread is then tightened and tied intracorporeally. A second suture may be added if the course of the cord structures is clear. Trocar incisions are closed in layers and injected with local anaesthetic (Fig. 29.3).

In the female the procedure is similar except that round ligament may be included in the suture that closes the internal ring.

29.9 Incarcerated Inguinal Hernia

Incarceration occurs when the contents of the hernia sac cannot easily be reduced into the abdominal cavity. If there is delay in the reduction of the hernia, incarceration progresses rapidly to strangulation. Strangulation is characterized by irreducible mass, constant pain, vomiting, and in later stages signs of hypovolemic chock. The contents of the hernia sac, small bowel, appendix, omentum, ovary and the fallopian tube or even parts of uterus and urinary bladder become tightly constricted and swollen in the

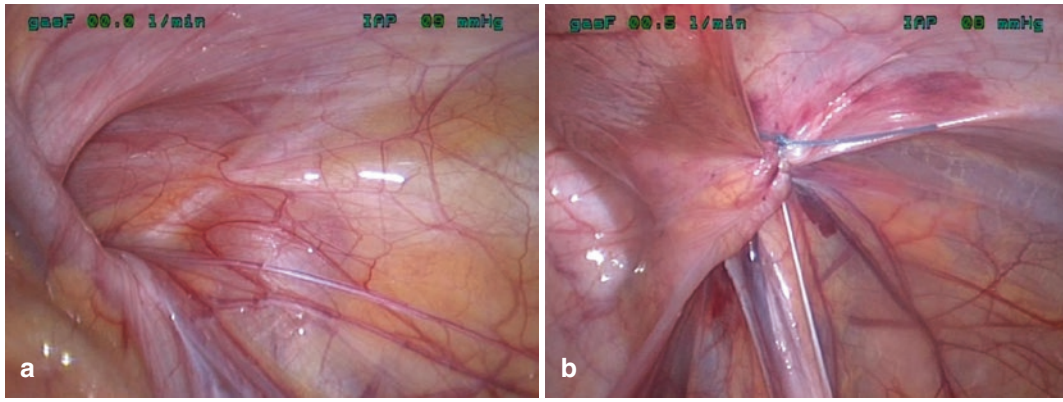

Fig. 29.3 Laparoscopic repair. (**a**) Open internal inguinal ring; (**b**) peritoneum at the internal ring has been closed with a purse string suture

inguinal canal rendering the hernia irreducible. After constriction occludes venous and arterial blood circulation the contents of the hernia sac become gangrenous and intestinal necrosis end even a faecal fistula may result [45, 46].

An incarcerated or strangulated hernia may occlude the testicular vessels located in the spermatic cord and in infants younger than 3 months testicular infarction or cyanotic testis has been reported in 30%. The rate of testicular atrophy after operation for an incarcerated hernia is however estimated to be lower from 9% to 17%. Neither operative or early postoperative testicular assessment correlates with testicular survival, and the pathology may become evident only after puberty. Unless a testis is frankly necrotic it should not be removed [47].

The incidence of incarceration in neonatal infants is relatively high, but due to different practices in reporting the numbers are variable and sometimes unreliable [48]. In infancy incarceration rates as high as 30% has been reported [45, 49], and among infants undergoing their hernia repair during the first year an incarceration rate of 28% has been reported [10]. During their birth hospitalization up to 16% of premature infants need surgery for the incarceration, and later on the incarceration risk approaches that of full term infants [10, 11, 48],

Approximately 5% of the infant female inguinal hernias contain a herniated irreducible ovary without signs of strangulation [50]. Of the irreducible ovaries a torsion rate of 19% has been reported [51] and a semi-emergent hernia repair within days is indicated.

29.10 Management of an Incarcerated Inguinal Hernia

An incarcerated or strangulated inguinal hernia is always a paediatric surgical emergency and treated without delay. In a clinically stable infant an incarcerated irreducible inguinal hernia should initially be managed nonoperatively. Firm compression with fingers on all sides of the mass concentrated to the external inguinal ring along the axis of the inguinal canal may reduce the incarcerated mass. Several minutes of patient compression may be required. The procedure causes discomfort and pain to the infant, and analgesia or sedation may be required. If sedative agents are used the infants must stay under appropriate observation because of the risk of respiratory depression.

After the reduction of a hernia the palpable mass should disappear. In the male with the ipsilateral testis normally descended, the testis should after reduction return downwards into the scrotum by gentle traction. If there is any doubt of successful reduction the manual compression should be continued to complete reduction, and the reduction ascertained by ultrasound examination.

After the reduction the infant is observed until clinically stable. Preferably the hernia repair should be performed during the same hospitalization. Open repair is usually performed 48 h after reduction when the swelling of the hernia sac and the spermatic cord has subsided. Laparoscopic repair may be performed soon after the reduction because there is less or no peritoneal swelling at the internal ring interfering with the closure.

If there are clear signs of strangulated hernia or an incarcerated mass cannot be reduced immediate operative treatment is indicated. Reduction under general anaesthesia without exploration is not recommended, because unrecognized gangrenous contents of the hernia sac may be returned into abdominal cavity. Antibiotic prophylaxis covering the microbes of both upper and lower gastrointestinal tract is given at the induction of the anaesthesia.

The standard surgical approach used in elective open hernia repair can be used, but the incision must allow ample exposure The first step is to free the herniated sac by opening the external oblique aponeurosis through and upwards the external ring or, if the constriction still exist, the internal ring must be freed. The hernia sac is opened and the contents inspected. If the small intestine looks cyanotic, enough length of viable intestine is drawn out to determine the length and condition of the ischemic segment. The ischemic segment is covered with warm saline moistened cloth and inspected after 5 min for colour, arterial pulsation and peristalsis and if deemed viable, returned into abdominal cavity and the hernia is repaired in the standard fashion. Nonviable intestine is resected and anastomosed end-to-end. If the resection cannot be performed through the hernia incision or if the suspectedly gangrenous contents of the sac are spontaneously reduced before the sac is opened a separate abdominal incision may be needed. Transperitoneal Pfannenstiel approach gives excellent exposure to deal with ischemic intestine, visualisation of contralateral inner ring and a cosmetically acceptable scar [52]. Alternatively, preperitoneal approach [53] may be used.

Repair of an incarcerated hernia can demanding because of the friable but thickened sac is difficult to separate from the cord structures. Laparoscopic approach enables inspection of the reduced contents and closure of the internal ring without dissection of the cord structures and the operation may be performed as soon as reduction is accomplished [54, 55]. In irreducible incarcerated strangulated hernias it is advisable to combine laparoscopy with open approach to free the sac [56] because pulling the constricted contents of the sac with laparoscopic instruments from inside may not be possible even with the help of synchronized manual compression of the mass from outside and tearing of the herniated tissue may result.

29.11 Sliding Hernia and Atypical Herniated Organs

Except the fallopian tube and ovary, the sliding component of the hernia may consist of large intestine, appendix, uterus, or the urinary bladder. If a sliding component is at risk of injury, the hernia sac must be opened and a purse string ligature placed at an appropriate level after which the sac is inverted and the internal ring closed. An inguinal hernia may contain appendix (Amyand's hernia), Meckel's diverticulum (Littre's hernia) or a wall of a viscera (Richter's hernia).

29.12 Direct Hernia and Femoral Hernia

Although rare in infants a direct inguinal or femoral hernias may be encountered and should be suspected if in an exploration for a clinically evident hernia the indirect sac cannot be found [1, 2]. In direct hernia a fascial defect medial to epigastric vessels may be palpated and in femoral hernia the bulge and hernia opening lie below the inguinal ligament. A direct hernia may occur together with an indirect hernia in a pantaloon fashion. A direct inguinal hernia and femoral hernia can be diagnosed reliably in laparoscopy [2,

57]. Although laparoscopic repair of direct hernia has been described, in open repair the anatomic landmarks are easier to recognize. Open repair is performed by suturing the internal oblique and transversalis fascia to Cooper's ligament.

29.13 Contralateral Exploration and Metachronous Hernia

Contralateral inguinal exploration and closure of the eventual patent processus vaginalis has been widely practised routinely in premature infants because the high incidence of bilateral hernia among them. Justification for this practise has been the supposed elimination of the renewed risks associated with repair of a metachronous contralateral hernia. More recently there have been a move away from this practice because the risk of a patent processus vaginalis to develop a metachronous clinical hernia is less than 15% [57–59]. In addition an open exploration may be harmful to the structures of the spermatic cord. At laparoscopic hernia repair exploration and closure of the contralateral inguinal orifice are safe and easy.

Alternatively, open hernia repair may be combined with exploration of the contralateral inguinal orifice with a videolaparoscope introduced through the opened ipsilateral hernia sac [60]. The hernia sac in small children may, however, be too narrow to allow this procedure. In addition, routine use of laparoscopy for the sake of contralateral exploration requires resources and increases the theatre time.

It is reported that the overall incidence of metachronous hernias up to the age of 19 years is 7.2% and incidence is below 11% from infants aged less than 6 months to children at 7 years of age, and thus 9–14 contralateral explorations are required to prevent one metachronous inguinal hernia [61, 62]. Without a medical condition that significantly increases the risk of inguinal hernia or high risk of complications of anaesthesia, routine contralateral exploration by any technique in an infant with unilateral inguinal hernia and a normal asymptomatic contralateral groin is not indicated.

29.14 Differential Diagnostics

29.14.1 Hydrocele

Hydocele develops when patent processus vaginalis allows accumulation of peritoneal fluid in the space surrounding the testicle between the layers of tunica vaginalis. Hydrocele presents as a non-tender swelling which may vary in size because its draining is dependent of the position of the infant. Usually it is possible to get above the swelling and palpate the cord structures. If hernia is doubted, ultrasound scan is preferable to transillumination to detect herniated intestine in infants. Hydrocele may contain a strip of herniated omentum. Repair is delayed to the age of 2–3 years.

29.14.2 Testicular Torsion

Testicular torsion presents as a tender mass in the scrotum. The testicle is located higher up than in the contralateral scrotum. In intravaginal torsion it is possible to palpate above the mass.

29.14.3 Inguinal Lymphadenitis

Vaccination site, infected wound or insect bite in the draining area of the inguinal lymph nodes may be found. Cord and testes are found to be normal.

29.15 Complications

Mortality rate in neonatal inguinal hernia repair should be 0%.The overall rate of major complications is 5.2% but after elective repair should be less than 1% [63, 64]. Complication rate increases in association with incarceration to [54] and prematurity [64].

Haematoma in the operative field or in the scrotum can be avoided with meticulous haemostasis. Only rarely is evacuation of the haematoma needed.

Wound infection occurs in 1% of patients and can be treated in most cases by irrigation and minimal drainage of the wound.

Recurrence rate in an uncomplicated hernia repair in children is usually 1% [65, 66]. In neonates or premature infants recurrence rate is 3–8% [67, 68]. Recurrence rate is increased in medical conditions which predispose to the development of inguinal hernia. Large hernia sacs and ruptured sacs with technically difficult closure [65] and incarceration [69] are associated with increased risk of recurrence. In rare instances the supposed recurrence turns out to be an undiagnosed direct inguinal hernia. By laparoscopy the nature of the recurrence is easily clarified and laparoscopic repair of the indirect recurrence is recommended [70].

29.15.1 Iatrogenic Ascent of the Testis

Iatrogenic ascent of the testis occurs in 1–4% of patients [39, 63, 67]. It is probably due to entrapment of the testis in the scar tissue, failure to pull the testis down into the scrotum at the end of the operation, or technical difficulties resulting in incomplete mobilisation and division of the hernia sac. Funiculolysis and orchidopexy should be done according to the same principles as in congenital undescended testis.

29.15.2 Injury to Reproductive Organs

Injury to vas deferens during hernia repair is estimated at 0.1–2% [63, 66, 71, 72] but injuries because of overzealous dissection may remain unrecognized. Injury to vas may result in obstructive azoospermia or formation of spermatic antibodies and cause male infertility. Apposition of the ends of a transected vas under magnification with 8-0 sutures should be attempted, but also secondary microsurgical repair even in adulthood may be successful [72]. Vascular compromise of the testicle or ovary are associated with irreducible or incarcerated hernias [67, 68]. Testicular manipulation in an elective repair should not compromise circulation [73].

Injury to urinary bladder is a rare but potentially severe complication. In infants the bladder lies in a relative superficial position and the lateral angles of the bladder may herniate into the inguinal canal and become injured during the division and closure of the sac. A recognized injury should immediately be repaired and an urinary catheter inserted. An unrecognized injury may lead to urinary peritonitis and subsequent scarring and dysfunction of the bladder and the ipsilateral ureter [74].

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Gastric Outlet Obstruction

30

Graham Lawrence Lamont

Abstract

Primary intrinsic obstruction to the outlet of the stomach in the neonate is a rare phenomenon, and in the previous edition of this book only five cases had been identified in the preceding 20 year period at the regional neonatal centre in Liverpool. The numbers are of course far outweighed by those children presenting with what is the most common surgically correctable cause of vomiting in the first few weeks of life—infantile hypertrophic pyloric stenosis (IHPS). The justification for including it in a textbook on neonatal surgery is two-fold. Not only do a percentage of the cases present within the true neonatal period, but given the numbers that present to regional neonatal units for management it is often the fledgling Paediatric Surgical trainee's first exposure to the skills required to successfully manage neonatal cases, both in diagnostic and in operative management terms. This chapter will mainly focus on the current state of knowledge around IHPS; its aetiology, diagnosis and management, before concluding with comments around the pathologies leading to intrinsic obstruction.

Keywords

Pyloric stenosis • Pyloromyotomy • Gastric outlet obstruction • Surgery Outcomes

30.1 Introduction

Primary intrinsic obstruction to the outlet of the stomach in the neonate is a rare phenomenon, and in the previous edition of this book only five cases had been identified in the preceding 20 year period at the regional neonatal centre in Liverpool [1]. The numbers are of course far outweighed by those children presenting with what is the most common surgically correctable cause of vomiting in the first few weeks of life—infantile hypertrophic pyloric stenosis (IHPS). The justification for including it in a textbook on neonatal surgery is two-fold. Not only do a percentage of the cases present within the true neonatal period, but given the numbers that present to regional neonatal

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_30

units for management it is often the fledgling Paediatric Surgical trainee's first exposure to the skills required to successfully manage neonatal cases, both in diagnostic and in operative management terms. This chapter will mainly focus on the current state of knowledge around IHPS; its aetiology, diagnosis and management, before concluding with comments around the pathologies leading to intrinsic obstruction.

30.2 Infantile Hypertrophic Pyloric Stenosis (IHPS)

The first recorded description of pyloric stenosis is thought to be from Hildanus who described a child with spastic vomiting in 1646 [1] but there were only further sporadic reports of the condition in the literature until Hirschsprung presented what is recognised as the first accurate depiction of the clinical features and pathological anatomy [2]. Though the condition initially was treated medically, the operation of pyloromyotomy was first introduced by Dufour and Fredet in [3] and further developed and popularised by Ramstedt [4] resulting in the procedure now commonly bearing this eponymous title.

30.3 Incidence

The incidence of pyloric stenosis has shown considerable variation over time, and quoted incidences have varied from as low as 1.5 per 1000 [5] to as high as 3 per 1000 [6]. Reported incidences are higher in Western countries than in Asian and African countries [7–10]. This trend towards a differing incidence in different racial groups is also seen within Western countries where a lower incidence is often found in non-Caucasian groups compared to Caucasian populations in the same geographic area [11].

It has also been well documented that there is a variable incidence of the disease in different areas over different time periods. There has however been little evidence of a consistent pattern of change. While some studies have shown increases in parts of the UK, [5, 6, 12, 13] other papers have identified a decrease over later time periods [14]. In the 1960s the rate in Belfast was identified as 3 per 1000 live births [6] but the later work from Scotland [14] had shown a decrease from 4.4 per 1000 live births to 1.4 per 100 live births between 1981 and 2004. A European wide study also identified variable patterns of increase and decrease over similar time patterns between different European regions with no consistency [15]. In searching for explanations of this change a number of risk factors have been studied. A paper from Scandinavia [16] reported a potential link between a decrease in the incidence of Sudden Infant Death Syndrome (SIDS) and a fall in the incidence of pyloric stenosis, suggesting this may be in some way linked to the success of campaigns to change sleeping posture. This area was further explored in a paper by Sommerfield [14] which showed similar decreases in the two conditions in Scotland yet identified that the fall in pyloric stenosis incidence preceded that of SIDS by at least 2 years. Further environmental influences will be discussed in the subsequent sections.

What has clearly come through on every review and paper is the influence of genetics on the disease. There is a marked male preponderance with a generally accepted ratio of four affected males to every female [17]. Of interest is one paper showing that a rise seen in incidence in a specific area of the USA was largely due to a widening of the gender ratio with a male to female ratio of over 6 to 1 in that series [18].

More recently we have been analysing Health Episode Statistic (HES) data at Alder Hey. The exercise has shown that the incidence in England over the latest 10 year period for which data was available (2000—2009) has been remarkably consistent, with a mean incidence over this time of 1.6 per 1000 live births. The male to female ratio over this time period was 5.4 to 1.

30.4 Aetiology

30.4.1 General Considerations

The variability in incidence described above and the well recognised risk of recurrence in

family members have pointed strongly to a multifactorial aetiology and led to numerous attempts to identify candidate causative factors over the years.

The aetiology of pyloric stenosis has received much attention over the years. As understanding of disease processes has progressed from the investigation of overall physiological and anatomical phenomena to investigation at the molecular level, so the search for the 'cause' for pyloric stenosis has become more focussed on abnormalities at the ultra-structural level. Clinical observational studies have given way to more sophisticated laboratory based techniques, and yet a single unifying theory for the aetiology of pyloric stenosis remains elusive.

It is recognised that the stenosis of the pyloric canal is secondary to hypertrophy of the smooth muscle of the pyloric sphincter [19], first postulated as the primary causative factor by Hirschsprung [2]. This has been supported by observational studies showing this occurring in both foetuses [20] and premature infants [21]. However given the more common occurrence of the condition at the end of the neonatal period and into early infancy, it is generally accepted that the hypertrophy is itself a secondary phenomenon as originally proposed by Thomson [22] as far back as the late nineteenth century. The more difficult question to answer relates to what are the triggers and, indeed, what are the underlying mechanisms that lead ultimately to the hypertrophy.

The pyloric region is recognised as the sphincter that controls the rate of gastric emptying and thus delivery of the stomach contents to the duodenum for further digestion and onward passage. The sphincter consists of thickened circular muscle that is tonically active giving a high pressure zone separating the stomach from duodenum. It exerts its' effect on the regulation of gastric emptying by the transient relaxation of the muscle in a co-ordinated fashion allowing stomach contents to pass in to the duodenum [23, 24]. This interplay involving muscle contraction and relaxation, and the associated neural signalling mechanisms has proven to be a fruitful area for investigation as our understanding of the complexity of these processes has increased.

30.4.2 Genetic Factors

From the earliest descriptions of series of pyloric stenosis occurring in families, [25] it has been clear that heritable factors play a part in the aetiology, and with the increased sophistication of analytical techniques it is now becoming possible to determine specific gene loci that seem to have a role in the causation [26]. It is well recognised that males are more likely to be affected than females in a ratio generally quoted as 4:1 [17, 27–30]. In addition, the risk to subsequent siblings is higher than in those children without a family history, a risk described as being as great as 15 times [31]. Indeed, as many as seven affected children were described in one family [32]. An increased risk is also passed down to the next generation, with sons of affected mothers being most at risk with as many as 5% developing the condition [28].

The possibility of a single gene being responsible for the condition was first proposed by Cockaigne and Penrose in their paper from 1934 [32], and though it is associated with other known genetic syndromes such as Smith-Lemli-Optiz [33] and Cornelia de Lange [34], there has been no convincing evidence of a single candidate gene. Though there have been described a small number of cases on whom the inheritance seems to follow a monogenic pattern [35, 36], the majority of cases follow a model of inheritance that is described as a multifactorial sex-modified threshold model [37]. In this model the risk of developing the disease is determined by the additive effects of various genetic and environmental factors.

In recent years the techniques used to study specific loci in different genes have identified areas that seem to be associated with the development of pyloric stenosis and include regions on chromosomes 16 (16p12-p13; 16q24) and on chromosome 11 (11q14-q22) as well as the X-chromosome [27, 38]. In addition, work on chromosome 12q has suggested that the gene

encoding neuronal nitric oxide synthetase is a susceptibility locus for pyloric stenosis [39, 40].

30.4.3 Environmental Factors

The role of environmental factors has been felt to be of importance and would help to explain the variability of incidence reported over time. As noted above, various candidate factors have been sought but none have been clearly identified. For example, a possible role for maternal smoking was highlighted in the Scandinavian literature [41] though it was unclear whether this would have been a pre- or post-natal influence. A further link sought to relate the fall in pyloric stenosis to the changing incidence of SIDS [16]. However, research on a Scottish population [14] identified that the decrease in incidence seen occurred prior to the change in incidence of SIDS.

Other potential environmental factors have been investigated but no consistent pattern has been found. While, in at least one study [42], breast feeding has been identified as a potential risk factor, this potential link has been challenged by work from Italy identifying that in a series in Naples it was more common among bottle fed babies [43]. Neither paper however made any claim for a direct causal link though both explored the potential physiological basis for their results. In other papers the influence of feeding has been explored with particular reference to the potential for transpyloric feeding tubes to be associated with an increase in the incidence of the disease [44, 45]. Again the exact mechanism is unclear though it is postulated that mechanical interference or at least an effect to disrupt the normal co-ordination of emptying may be responsible. No recent reports have looked at this issue, and it may be that the use of transpyloric tubes for feeding is not as widely used a technique as it once was.

An interesting insight into a possible aetiology was the recognition of the potential for erythromycin to lead to an increase in the incidence of pyloric stenosis [46]. This would appear to be specifically related to postnatal exposure and is presumed to work via a motilinomimetic effect [47]. While it has been identified in a number of studies the overall effect has been difficult to determine due to different methodologies used in the different studies especially around different dosage regimens that were used [48].

30.4.4 Hormonal Factors

A key feature in the proper functioning of the pylorus as a sphincter region is the interplay between the regulatory hormones that allow for the co-ordination of gastric emptying. The identified mediators are gastrin, cholecystokinin and secretin [49], and their various effects have been studied in pyloric stenosis. The main focus for research has been the role of gastrin, and the experiments of Dodge [50] in which he identified a key role of pentagastrin in an animal model for pyloric stenosis suggested that gastrin was a causative factor. It was postulated that this worked through driving pyloric contractility and thus led to a work hypertrophy of the muscle [49]. However investigations on the animal model could not be replicated [51] and in human studies of pyloric stenosis, results have been confusing with some authors showing an increase in pre-operative gastrin levels [52, 53], whereas others found no differences [54, 55] in pre-operative levels. Further theories advanced have sought to define a role for secretin and cholecystokinin through a response to higher gastric acid secretion [56]. Work reported in 1979 by the same group failed to show any increase in cholecystokinin activity [57]. More recently however [58] the central role for hyperacidity has been reframed postulating that a loss of the controlling role of gastrin has a part to play in the pathogenesis.

Another group of compounds that have been investigated for a role in pyloric stenosis are prostaglandins (PG). Both PGE2 and PGF2α have been shown to have an effect on gastrointestinal muscle contraction [59] and La Ferla [60] found elevated levels of these compounds in the gastric juice of infants with IHPS, suggesting a role for the compounds in the causation of the hypertrophy. Other studies however, [61, 62]

have shown that PGE2 can also mediate relaxation of muscle, throwing doubt on the place if any, of these compounds on the causation of pyloric stenosis.

30.4.5 Histological Anomalies

As noted earlier, the pyloric sphincter has an inbuilt contractility maintained by myogenic mechanisms [23]. Thus in the search for the cause or effects of the stenosis, the smooth muscle cells (SMC) themselves have been the subject of study to try to elucidate any causative mechanisms. Again any evidence of abnormality has proven contradictory. Dieler on reviewing pathological findings on 37 specimens [63] identified degenerative changes in both the SMC and associated neural network that led him to postulate the existence of two distinctive types of pyloric stenosis: myogenic and neurogenic subsets of the condition. Langer however failed to find such a distinction in the SMC describing them as morphologically normal [64]. This group did identify that there were significant differences in the neurological control of the sphincter in their study population, and also pointed to anomalies in cell-to cell adhesion. Other groups focussing on the structure of the cell and the arrangement of the junctions between them have sought anomalies in the different proteins involved. Again, results have been contradictory, with one group showing clear differences in the expression of desmin, a protein important in the organisation and function of muscle fibres between pyloric stenosis samples and normal controls [65], and others showing no difference [66]. This group did however find anomalies in the proteins talin and dystrophin, which are involved in the interaction between smooth muscle cells and the extracellular matrix. That anomalies have existed within the extra-cellular environment has been recognised from early light-microscopy studies showing increases in the 'connective tissue' elements from hypertrophied pyloric muscle [67, 68]. As the ability to investigate more fully the underlying structure of connective tissue proteins has increased, so the capability to more specifically define the anomalies seen in pyloric stenosis has also improved. Again a number of candidate proteins have been identified with studies showing increases in chondroitin sulphate, fibronectin, laminin and elastin [66, 69, 70]. In addition the described increase in collagen fibres is thought to be a direct result of enhanced synthesis by the abnormal muscle itself [71].

Though the exact changes seen at the cellular level in both the cells and supporting matrix of the pyloric sphincter remain a subject of debate, there is clear recognition that the hypertrophy is genuine and a significant feature of the condition. The mechanisms by which this hypertrophy is brought about have themselves been the focus for research at the cellular level. Growth factors have been shown to be important in the regulation of the growth of SMC in various tissues [72], and so similar relationships with the SMC of the pyloric sphincter again have been sought. An initial candidate peptide investigated was Insulin-like growth factor-I (IGF-I), which had previously been shown to be a mediator for many cellular activities including growth, replication and differentiation [73, 74]. Studies reported in 1998 [28, 75] identified increases in both IGF-I and IGF-I mRNA expression suggesting increased local synthesis of this growth factor plays a significant role in the causation of the muscle hypertrophy. Since then, other mitogenic growth factors have also been shown to be increased. Studies have reported increases in platelet-derived growth factor-BB [76], platelet-derived endothelial cell growth factor [77], transforming growth factor-α [78] and epidermal growth factor [79]. The finding of an increase in a wide range of growth factors suggests that no single factor acts directly but may be part of a cascade process that ultimately leads to the anomalies seen.

30.4.6 Pyloric Innervation

In keeping with the plethora of anomalies identified when looking at both hormonal control and intrinsic structural changes, the study of the neural control pathways has also turned up abnormal findings in many different aspects. Indeed more

or less every component of the neural pathways studied has shown some degree of anomaly, making it difficult to determine the relative strength of each effect and to determine which may be a primary causative effect or a secondary phenomenon.

Among the earliest parts of the neural pathway to be studied were the ganglion cells. The recognition that the absence of ganglion cells in Hirschsprung's disease was responsible for the motility disturbances led to the further investigation of their role in the causation of pyloric stenosis [80, 81]. However, while some studies have reported fewer number [64, 67] or a failure of maturation [82] of ganglion cells in biopsies, these findings have not been confirmed by other groups [83]. Further structural anomalies have been found both within individual nerve cells and the supporting cells that maintain the integrity of the neural cells. In addition to identifying potential anomalies in the ganglion cells, Langer's [64] group also identified a decrease in the number of nerve cells, while further degenerative changes in the axons of these nerves have also been identified [84]. The entire neural network depends on a class of supporting cells that help both in the spatial orientation of the cells and in the physiologic functions [85]. In pyloric stenosis a number of studies have shown both quantitative and qualitative abnormalities in the morphology and function of this supporting network [65, 86, 87] suggesting that this in turn can have a deleterious effect on the innervation of the pylorus.

Another major part of this neural network that has a marked bearing on the proper functioning of the enteric nervous system is the interstitial cells of Cajal. This class of cell is recognised as providing an important role in both the mediation of neurotransmission and acting as electrical pacemakers [88, 89]. Results of studies looking at the role of these cells have shown some concordance. Using electron microscopy Langer [64] has shown a reduction in the presence of these cells compared to control specimens, a finding confirmed by other groups using immunoreactive staining [90, 91]. Given the central role of this class of cell in the regulation of GI motility it has been postulated that these may be crucial to the motility disturbance seen in pyloric stenosis [29]. However, it has been argued more recently that while this network of cells is an important facet of the control of GI motility it is too simplistic to see one system as the key factor [89].

As well as structural anomalies within the GI tract neural network, further anomalies at the synaptic junctions between the nerve cells and muscle cells and disorders of the synthesis and release of neurotransmitters at these junctions have been identified. Such anomalies vary from a decrease in the total number of synapses [92], to an indicator of a decreased expression of neural cell adhesion molecule at the muscular level [93] possibly leading to impaired functioning of the synapse.

Finally, studies have demonstrated anomalies in the cholinergic, [86] adrenergic [76] and peptidergic innervation of the pyloric muscle. In particular, compounds that help in the regulation of other neurotransmitters have found to be deficient including enkephalin [94], substance P [95] and vasoactive intestinal polypeptide [96].

The role of nitric oxide (NO) has been well documented. This is the neurotransmitter particularly related to non-adrenergic, non-cholinergic neural transmission (NANC) that has a recognised role in the mediation of pyloric relaxation [97]. The synthesis of this transmitter has been shown to be reduced in pyloric stenosis [90, 93]). In a specific mouse knockout model [98] those lacking the ability to synthesise NO were shown to have marked enlargement of the stomach with hypertrophy of the pyloric sphincter. Further studies on the role of NO immunoreactivity have shown it be decreased or absent in most though not all cases of pyloric stenosis [67, 99–101], and have also linked lack of NO synthesis to anomalies in ICC distribution, identifying a possible interdependency [29].

In short, the aetiology of the condition remains elusive yet the wide identification of potential causative factors at a pathological, physiological and molecular level points ever more firmly to the interplay between genetic and environmental factors in the causation of this condition.

30.5 Clinical Features

The clinical presentation follows a well recognised pattern, with a previously well child being noted to suffer from increasingly frequent and forceful vomiting. The majority of children will present between 4 and 6 weeks of age, though as many as 3% have been noted to occur within the neonatal period [1], with even isolated cases in the first few days of life. The frequency of presentation peters out at the older age range, and the condition is rare after 12 weeks of age [102]. The incidence in children who are born prematurely is similar to those born at term [103] and at least one study suggested that premature infants may present at a later stage than those born at term [104]. One case report of premature twins however showed that the condition can present while the children are still in the premature age range [105].

The vomiting, while intermittent at first, is noted to increase in frequency until it is occurring after every feed. In a similar fashion, the intensity is described as becoming more forceful, until truly being recognised as projectile. It is this gradual onset and worsening of symptoms that can lead to several days delay in diagnosis of the child. It is the author's opinion though that if there is a family history of the condition, then the child should be reviewed earlier in the course of the condition.

The vomit consists of milk, which may appear relatively fresh if the vomiting occurs soon after feeding, or curdled, if the vomit occurs at a later time from the feeding episode. As the condition progresses and vomiting worsens the contents may contain more mucous than milk. Though occasionally being discoloured by altered blood especially if there is any occurrence of gastritis, the vomit never includes any bile.

The child feeds readily especially in the earlier stages. Delay in the recognition of condition can lead to an overall deterioration in the child's clinical condition, at which point they may become disinclined to feed as part of the spectrum of developing dehydration. While the majority of children present with only mild signs of dehydration, there will be those that present more severely affected, with noticeable decrease in skin turgor, sunken fontanelle and sunken eyes.

While weight loss is also seen in some cases, it is perhaps more recognised as a gradual falling off of the expected weight gain. Given this corrects quite quickly after successful treatment then this may be more related to the degree of dehydration rather than true loss of subcutaneous fat.

30.6 Diagnosis

30.6.1 Clinical Examination

The diagnosis is largely suggested by the occurrence of the history described above, and is supported by the findings on clinical examination.

The abdominal examination remains the keystone to the diagnosis of IHPS. If performed appropriately, the palpation of the pyloric tumor has been reported as having a highly positive predictive value [106, 107].

The description given in the previous edition of this book [1] succinctly describes the conditions required to achieve maximum diagnostic yield. The child should have the abdomen exposed so that the examiner can view the area from the lower chest to upper thighs (Fig. 30.1) and should be nursed comfortably, preferably on the mother's lap. There needs to be a good (and if

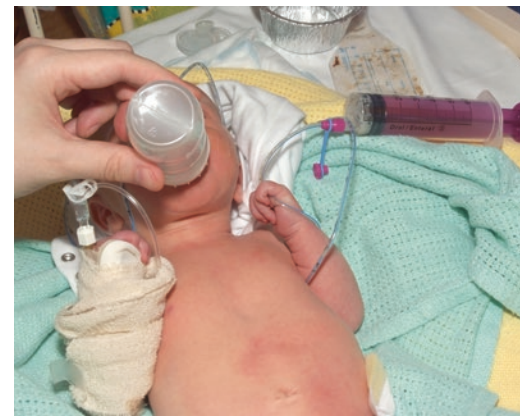

Fig. 30.1 Demonstration of required exposure of infant

possible) natural light shining tangentially on the abdomen. The feed would normally consist of clear fluid, though the actual contents may vary from dextrose to electrolyte solutions. Observation of how the infant feeds can provide the clinician with useful ancillary information, such as inappropriate feeding techniques or whether the infant is apathetic or feeds hungrily, possibly with the swallowing of excess air.

The clinician should inspect the abdomen from the left side looking for a developing fullness in the epigastrium, consistent with the filling stomach. As the stomach continues to distend, visible peristalsis will be seen to develop with the wave spreading from upper left toward the lower right side of the abdomen, before disappearing.

The pyloric tumor is described as having the size and shape as to be consistent with an olive and should be palpable to the right side of the rectus muscle. An initial palpation should start at the transpyloric plane (lying between the tips of the ninth costal cartilages). At this point, one is likely to feel the edge of the liver or possibly even the fullness of the caudate lobe. Working gently below the liver at this point will take the careful examiner to the area where the pyloric tumor can most easily be felt (Fig. 30.2).

It should be noted that this technique can take some time to complete, and indeed may even need to be repeated to confirm the diagnosis. Yet careful and persistent clinical examination will reward the clinician with a positive diagnosis. While it has been recommended that continuous nasogastric suction be employed to aid the diagnosis [108], the author has never found this to be necessary in his own practice.

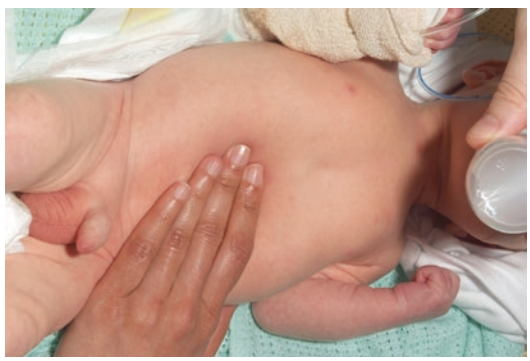

Fig. 30.2 Palpation for the pyloric olive

The pyloric 'olive' is reported to be palpable in approximately 80% of cases [109] and the finding of a palpable tumor has a positive predictive value as high as 99% [106, 107, 110]. There is growing evidence, however, that a rise in the routine use of ultrasound examination is diminishing the confidence with which clinicians will make the diagnosis on clinical grounds alone. In one study [111] the cases diagnosed by clinical means alone fell from 87 to 49% between two study periods separated by 11 years. Indeed in a review of cases from Alder Hey [110] as many as 39% did not have a test feed, the diagnosis being made solely on a positive ultrasound and clinical symptoms. This reported reliance on investigative modalities over clinical examination is not new however. Scharli, in reviewing a large single institution series [109], lamented the fact that of the 254 children undergoing contrast radiological examination, 154 did not require it as the clinical diagnosis was not in doubt. Indeed Cook [1] felt that the triad of visible peristalsis, a palpable pyloric tumor and projectile vomiting was proof positive of the diagnosis.

30.6.2 Biochemistry

A further mainstay in making the diagnosis is the search for specific biochemical abnormalities. As noted, these children present with a variable length of history of vomiting and poor feeding, both of which contribute to a deranged biochemical picture. The losses from the stomach will contain sodium, potassium and hydrochloric acid, leading to the typical picture of hypokalaemic, hypochloraemic metabolic alkalosis, though the individual values quoted may vary from centre to centre due to different reference ranges [7]. In the more severe cases paradoxical aciduria may also be observed as there is an attempt to conserve sodium at the expense of losing hydrogen ions despite metabolic alkalosis [1]. Though described as classic picture it is by no means universal and indeed in the series from this institution reported in 2008 [110] only 55% of cases had evidence of

metabolic alkalosis. It may be that a trend to earlier presentation and diagnosis is limiting the degree of biochemical derangement that occurs.

30.6.3 Radiology

In those cases where clinical examination leaves diagnostic doubt then the radiological investigation of choice is now an abdominal ultrasound examination. The routine use in the investigation of pyloric stenosis was first described by Teele and Smith [112], and, as has been alluded to above, it has become the first line investigation of choice for many clinicians. It is a safe, non-invasive technique that, with appropriately trained and experienced operators, can give figures for sensitivity and specificity approaching 100% [113–115]. Over the years different groups have tried to refine the diagnostic criteria moving from initial simple measurements of canal length [116], to the creation of a muscle index [117], but there is no one accepted method. In Alder Hey we use a combination of canal length ≥14 mm and a muscle thickness of ≥4 mm to consider the diagnosis to be positive and with this have demonstrated a positive predictive value of 99.1% for length and 98.7% for muscle thickness [110] (Fig. 30.3).

The place of contrast radiology has, by and large, been consigned to history, though as an investigatory modality it can still find a place in cases of diagnostic doubt to rule out other pathologies (Gastro-oesophageal reflux; other causes of outlet obstruction). Various features have been described as diagnostic including finding a large gastric residue, vigorous peristalsis and a 'string sign' [118]. Again the technique has been felt to be operator dependent but in experienced hands could give sensitivity as high as 95% [119]. This modality is now only used sparingly due to the large dose of radiation that is required and the fact that the results may be either unhelpful or frankly misleading [119, 120].

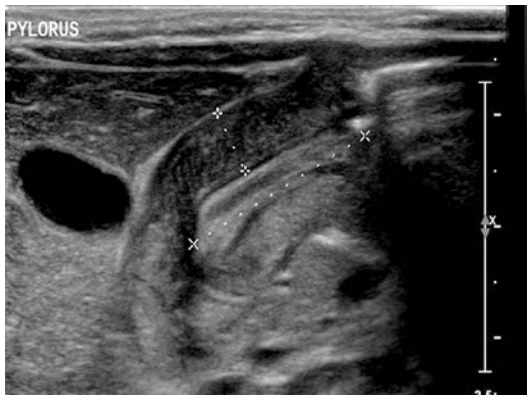

Fig. 30.3 Ultrasound of pyloric tumor

30.6.4 Other Diagnostic Testing

Despite the utility and accuracy of ultrasonographic diagnosis there are still cases when the diagnosis is in doubt and if repeated examination is still not diagnostic it has been the authors practice to undertake an upper GI endoscopy with a view to proceeding to pyloromyotomy if obstruction is confirmed. On two occasions, this has prevented a laparotomy by identifying marked antral gastritis. In both cases the symptoms resolved on medical management. Endoscopy is recognised in other series as a useful adjunct to making the diagnosis [121, 122].

Other modalities to look at the emptying of the stomach have been tried and a technique of measuring electrical resistance to derive an index of stomach emptying 'Applied Potential Tomography' (APT) was shown to provide comparable results to scintigraphy [123]. In one study [124] on a group of infants with pyloric stenosis it was able to demonstrate a significant delay in gastric emptying from a control group. However given the more widespread availability of ultrasound and the improvements over the years in scanning equipment this was never likely to find a widespread application.

30.7 Management

The mainstay of management of this condition remains operative correction following appropriate and adequate pre-operative preparation of the child.

30.7.1 Pre-operative

The condition of pyloric stenosis does not need emergency surgery and time spent adequately resuscitating the child will reduce the likelihood of anaesthetic complications, such as delayed recovery from anaesthesia or even post-operative apnoea [103, 125]. The purpose of resuscitation is to restore the extracellular fluid volume (ECFV) and restore the proper balance of Na^+ and Cl^- to allow for renal correction of the metabolic alkalosis [104]. The preferred fluid therapy in this institution is 0.45% saline with 5% dextrose for maintenance fluid. The actual rate is based on the estimated maintenance of 120 mls/kg/day with an upward adjustment made to correct for the estimated dehydration deficit. Potassium is added to the maintenance fluid, once it has been established that the baby is passing urine, at a maximum value of 3 mmol/kg/day. We would use normal saline to replace any further nasogastric loss, and, in the small number of cases in which dehydration is so severe as to require the use of fluid boluses.

Ongoing monitoring of the child includes an assessment of the state of hydration, evidence of urine output and 12 hourly measurement of blood gases until the alkalosis is corrected. When surgeon and anaesthetist are happy with the clinical state of the baby then arrangements are made for operative correction. Though it is recognised that many babies are now presenting with only minimal signs of dehydration and lesser degrees of biochemical derangement [110, 126], it may yet take 24—48 hrs of fluid therapy before the child is ready for theatre, and in some cases even longer. If there appears to be delayed correction of the abnormality despite adequate fluid therapy consideration should be given to whether there is underlying renal pathology contributing to the clinical picture.

30.7.2 Operative Considerations

The operative management of IHPS was described in 1892 by Cordua [127] who carried out a jejunostomy on a child, who unfortunately did not survive the procedure. The first successful operation described was a gastroenterosotmy carried out by Loebker in 1898, and the first description of a pyloroplasty followed closely in 1903 [128]. Pyloromyotomy was proposed by Dufour and Fredet in [3], but subsequently developed and implemented by Ramstedt in 1912 [4]. This approach of splitting the muscle layer, down to but not through the mucosa of the pyloric canal without suturing, is now the standard technique for operative intervention.

Historically, the initial approaches were either through high midline or pararectal incisions due to a fear of wound dehiscence in malnourished babies, but as pre-operative resuscitation improved the general condition of the children and improvements in anaesthetic techniques were introduced, so these concerns receded. The standard approach in many centres was the use of a transverse incision in the right upper quadrant directly overlying the pylorus [1]. In 1986 Tan and Bianchi [129] published their results of using a circumbilical incision to approach the pylorus, showing this to be an acceptable method of accessing the pylorus and producing a superior cosmetic result. Though in the original paper, the abdomen was originally opened in the midline through the linea alba, [130, 131] many surgeons (including the senior author on that original paper) utilise a transverse muscle cutting approach to enter the abdomen. This is currently the preferred approach at Alder Hey (Fig. 30.4).

Though the cosmetic results are acknowledged as superior, there have been concerns

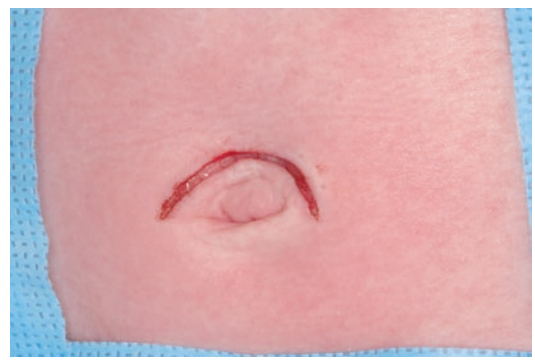

Fig. 30.4 Site of 'circumbilical incision'

raised about the possibility of increased rates of complications including wound infections, incisional hernias or mucosal perforations [132]. This concern has not been replicated in other studies [133–135].

Whatever the approach to the abdominal cavity, the basic tenets of the pyloromyotomy remain the same. The greater curve of the stomach is often the first aspect encountered and is carefully delivered in to the wound. This can then be traced distally to allow identification and extrusion of the pyloric tumor. Care must be taken in this delivery as over enthusiastic traction on the stomach can lead to damage to the antrum. A common cause of difficulty is trying to perform the operation through too small an incision, and enlargement of both skin and muscle incisions may be necessary to facilitate easy delivery of the tumor. It is straightforward to recognise the extent of the pathological thickening at the distal end as there is a sharp demarcation between the abnormal thickened pylorus and the duodenum, though at the proximal margin there may be a more gradual change from antrum to pylorus (Fig. 30.5).

A longitudinal incision is then made in the anterior border of the pylorus avoiding the blood vessels identified there. Distally this should stop at the sharp demarcation with the duodenum but proximally should be carried on to the antrum to ensure that the full extent of the pylorus has been identified. The incision is then deepened using blunt dissection to reach the level of the mucosa at the midpoint. There are various ways that this incision can be deepened and each surgeon has their own preference; use of blunt dissectors, arterial clips or even specially constructed pyloric spreaders. The ultimate aim however is to achieve disruption of the full extent of the pyloric muscle without causing a breach of the mucosa (Fig. 30.6).

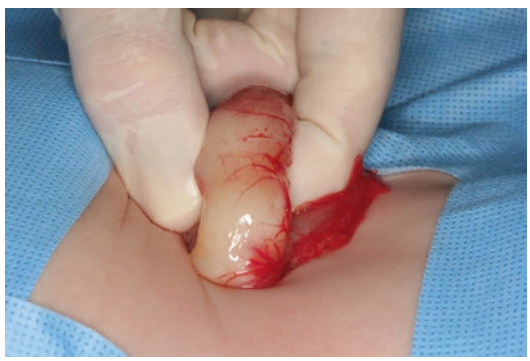

Fig. 30.5 Delivery of 'olive'

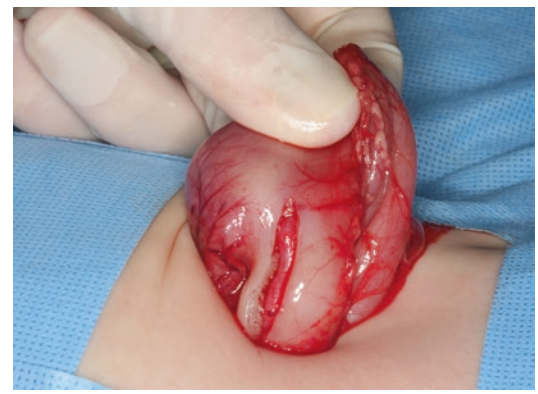

Fig. 30.6 Muscle split to demonstrate mucosa bulging

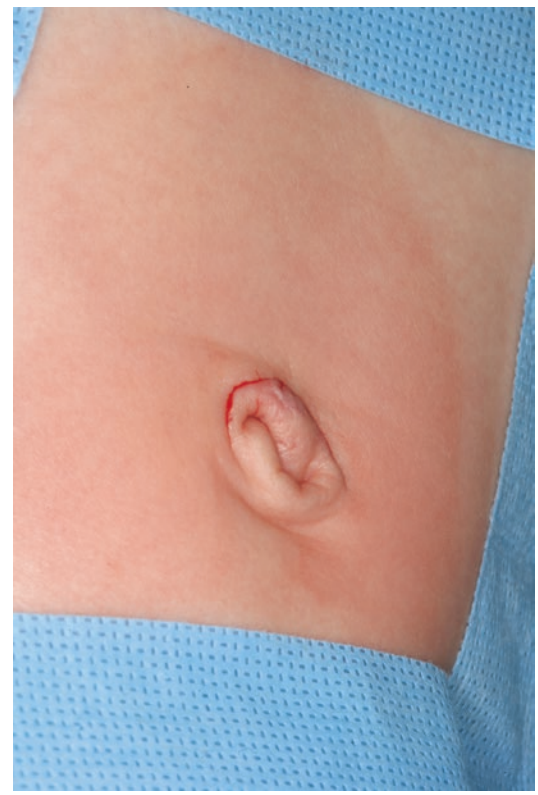

Fig. 30.7 Post-operative appearance

To ensure completeness of the procedure and confirm the integrity of the mucosa, a 'leak-test' can be performed. In this, the anaesthetist is asked to insufflate air into the stomach via the nasogastric tube, and the surgeon then causes the air to be passed form the antrum into the duodenum. The mucosa is inspected to watch for it bulging as the air passes and palpation of the duodenum confirms passage into the duodenum. Breaches in the mucosa can be spotted with this technique, though some surgeons will augment this by instilling saline to the cut surface of the pylorus and looking for bubbles being released during the passage of air.

After aspiration of any remaining air in the stomach, the stomach and pylorus are returned to the abdomen. Though there is occasionally oozing from the cut surface of the pyloric muscle this is usually minimal and will cease once the pylorus is returned to the abdomen.

Closure is carried out in a standard fashion, with my own practice being to close the muscle in two layers using continuous absorbable sutures, followed by a subcuticular absorbable suture for the skin (Fig. 30.7).

While open operation remains the standard practice in many centres, the growing use of laparoscopy has seen this become the standard approach for many. The first reported cases treated via a laparoscopic approach were published in 1991 [136], and subsequent larger series have shown both the efficacy and safety of this approach to pyloromyotomy [133, 134].

30.7.3 Postoperative Management

A further area where there is a divergence of opinion is around the use of a post-operative feeding regime. In many centres and going back some time, there was strict adherence to a specific feeding regime [1] and many units still have their own versions that people abide by. This may commence anywhere from a few hours to even a full day after surgery, and in these regimens there is a gradual increase in volume at every feed and a switch from clear fluid to milk over time. The rationale for this has previously been related to a concern over prolonged gastric stasis [137], with the belief that this graduated approach to feeding decreases the incidence of post-operative vomiting. However, one randomised controlled trial [138] identified that the risk of post-operative emesis was independent of the type of feeding. Observational studies [139, 140] have shown no or only little effect when an accelerated feeding regime is used. Overall there is little evidence to support the use of a specific restriction in post-operative feeding. Once full oral feeding is established the child is ready for discharge.

30.7.4 Outcomes and Complications

The outcomes for pyloromyotomy are generally good with most series reporting zero or minimal mortality and low morbidity for the procedure. This is in contrast to an historical series where, even as recent as the late 1930s, mortality rates as high as 25% were being reported [141]. In the series tracing a single institution's results over a prolonged time period [109], the mortality showed a steady decrease from 13.2% in the period between 1912 and 1930, to 0.5% in the period between 1961 and 1967. Many of the deaths in that series were attributed to infections not directly related to the children's underlying pathology, but in the earlier time period, 7 of 27 deaths were attributed to dehydration and shock. In the latter time period, this cause of death had been eradicated. A review of studies reported from both paediatric and general surgical centres [142] confirmed that this trend had continued, with only one death reported in almost 3500 cases.

This low rate of mortality has meant that most papers focus almost exclusively on the morbidity of various procedures, with quite wide variations in reported outcomes. How much of this variation is due to differences in definition of the evaluation measures used in the various studies is not clear, as it can be difficult to ascertain the parameters used in sufficient detail to allow a comparison between studies.

The complications most reported on in the short term can be divided into those occurring

intra-operatively and those in the post operative period.

30.7.5 Intra-operative Complications

The most significant intra-operative complication is that of duodenal perforation. This usually occurs at the junction between the thickened pylorus and the duodenal fornix where there is often a sharp demarcation between abnormal pylorus and normal duodenum. These are usually identified as a result of the 'leak-test' described above, but a number can be missed. The reported rates vary widely with Crabbe [142] calculating an average of 3.2% across specialist paediatric centres versus a rate of 15% in which the operations were performed by non-specialist surgeons. This variation has been highlighted in various studies [143, 144] and it has been postulated this is the effect of specific sub-specialty training. However at least one other study would suggest that it is more related to a case-volume effect [145]. In a review of 11,003 cases, this group identified a better outcome with both higher institutional case volume and higher individual surgeon case volume. This has re-inforced the notion that having protocols for management and ongoing review of surgical outcomes could provide equivalent results to transfer to a specific specialist centre for management. Furthermore, there are other studies showing that, provided the care is provided by appropriately trained staff, then services in district general hospitals can provide equivalent results to specialist centres [106]. This may be of particular importance where the provision of specialist service is limited or the distances for transfer are large [7].

There are only a few reported instances of perforation not being recognised at the time of the procedure [146, 147] that have led to adverse outcomes. It is accepted however, that while the approach to using a leak-test is widespread the test may provide false re-assurance [148]. It behoves the surgeon therefore to have a high index of suspicion for this complication in those cases that do not follow the expected post-operative course.

On recognition of a perforation there is general agreement that primary closure is the treatment of choice, though there is debate about the best way to approach this. The majority of studies, where an approach is identified, describe a primary suture of the perforation plus or minus the addition of an omental patch. An alternative is practised by some surgeons where the perforation is repaired by closure of the primary pyloromyotomy, and the operation completed by rotation of the pylorus and the performance of a secondary pyloromyotomy [149]. Both approaches were compared and contrasted in a series reported in 1995 [150]. No significant differences were found in the efficacy or safety of either procedure. It is the authors practice to opt for a simple primary closure with use of omentum if this is easily manipulated to the area.

There is a small but recognised risk of an incomplete pyloromyotomy being performed. Attention to the detail of the procedure described above should reduce this complication to a minimum, and ensuring free passage of air to the duodenum with observation of both distension of the mucosa of the pylorus and of the distal duodenum should help ensure an adequate pyloromyotomy. However in different reported series the rate varies from less than 1% [106] to as much as 5.6% [151]. In a survey undertaken in the UK in 1995 the overall incidence of incomplete pyloromyotomy was reported as 1% [152]. Though no specific studies of this complication have been undertaken, there are a number of factors that could lead to this, including failure to carry the incision sufficiently proximal onto the gastric antrum, concern over the risk of perforation at the distal extent of the thickened pylorus, or sufficient exposure of the full extent of the tumor either through an open or a laparoscopic approach.

A final intra-operative problem to consider is that of a negative laparotomy. Many studies have not specifically looked at this as an issue but a recent review of practice from our own institution [110] identified that four cases out of a total of 343 underwent a negative exploration. Three of the cases had a positive ultrasound diagnosis (albeit performed at different institutions prior to transfer), and one a positive contrast study.

Prompted by this review, our institutional policy has been revised to ensure that if there is not clear evidence of a positive test-feed and an in-house ultrasound examination identifying specific diagnostic criteria, then operation is not undertaken.

30.7.6 Post-operative

The most commonly reported post-operative complication is that of wound infection. The risk of post-operative infection varies markedly between series [142], with some reporting no post operative infections [153], to other series reporting rates as high as 15% [154, 155]. In the studies reviewed by Crabbe [142] there appears to be a lower rate of infection across all the series reported from paediatric surgical centres compared to series coming from non-specialist centres, with an average difference of 2.2 vs. 9.8%. Though this could be related to differences in the definition of wound infection and the reporting policies, this in itself is unlikely to account for such a marked difference. Of particular interest is those series from paediatric centres that have reported their institutional results comparing the traditional RUQ approach to a circumbilical approach [130, 132, 156]. Each demonstrated a rise in the infection rate when the circumbilical approach has been used. Overall, the collected series quoted [142] have identified a rise from 2.2% with the 'conventional 'approach to 9.2% with the circumbilical approach. It has been suggested that this rate can be reduced by the use of prophylactic antibiotics but one study [157] identified that there was no difference in rate of infection related to the use of prophylactic antibiotics. Moreover this study also showed that majority of infants had umbilical colonisation with gut and skin flora and thus contamination at skin level was not necessarily the source of the wound infections identified. The policy in our own institution is to use a single dose of prophylactic antibiotic at the time of induction, and in a postal survey of UK centres [158] 70% of surgeons who used the circumbilical route advocated the use of prophylactic antibiotics. It has been postulated that the higher rate of infection may be related to the difficulty that can be faced in delivering the pylorus through a wound that has not been made sufficiently large, [142] and indeed at least one published study has advocated taking an approach to manage the pyloromyotomy without delivery through the wound and shown a minimal infection rate [159]. In a review of results from our own institution [160] where the circumbilical route has been used since the mid-90s, the overall infection rate was 3.2%, though no infection led to an increase in hospital stay or delay to discharge.

In general, studies on the use of a laparoscopic approach have shown the same or slightly lower incidence of wound infection, but in the majority of reviews this has not shown a significant difference [161–163]. One review did show a reduction in wound infection that was felt to be significant [164], though a subsequent commentary on the methodology used [165] counselled caution in the interpretation of the results citing concerns over sample size and the quality of the overall process of analysis. A further study looked to analyse the impact of using prophylactic antibiotics in laparoscopic pyloromyotomy [166] but this showed no significant difference in the groups with an overall rate of infection of 3%.

As laparoscopy has become more widely available, much of the recent literature has focussed on looking for potential benefits to this technique over open approaches. Different studies have been carried out varying from reporting practice in single centres [162] to reviews of studies and even meta-analysis [161]. Early papers looking at the technique tended to show an increase in length of operation and the risk of incomplete pyloromyotomy, but more recent papers have shown no difference in these parameters. This suggests that once the learning-curve effect has been overcome the technique is both safe and effective. The overall evidence of benefit is lacking in that while some studies will show benefits in some of the parameters, others will not show any benefit from this approach. Though the evidence has so far failed to identify a convincing case for one approach over the other, the use of laparoscopy is both safe and effective and in centres that have both the appropriate

experience and available equipment, this will likely be the operative method of choice.

Vomiting is a common finding in the immediate post-operative period and, as previously noted, the risk of vomiting has been used as the rationale for instituting specific feeding regimes. A study on motility [137] had identified disordered gastric peristalsis that may last up to 5 days and proposed this as the reason for vomiting, while at the same time identifying that specific feeding regimes had no influence on the incidence of vomiting. A further risk factor may be a prolonged pre-operative phase of vomiting [140] though it is felt that with earlier presentation most infants should tolerate early and accelerated feedings [7].

The long term sequelae are an area less studied over the years but the most comprehensive recent review occurs in Crabbe [142]. The pylorus heals by the normal processes of wound healing and ultimately there may be little evidence of an operative procedure [167]. There are anecdotal reports of persistence of the hypertrophied muscle in those cases treated by alternatives to surgical approaches [1]. Both radiological [168] and ultrasonographic [169, 170] techniques have been used to study the pyloric muscle in the post-operative period and have shown a gradual resolution of the muscle thickness back towards normal, with most achieving this by 12 weeks. The increase in length of the pyloric canal can persist beyond this time.

A number of studies in adults have reported on the incidence of dyspeptic symptoms in groups who had undergone pyloromyotomy [171–173], though both methodological problems and a reliance on contrast studies to seek out peptic ulcer disease have mitigated against being able to give a true figure for the incidence of ulcers in this group. Indeed in the one study that systematically looked to compare those patients who had had medical treatment for the condition, and a control group there were no significant differences in the occurrence of symptoms [174].

It has been postulated that the occurrence of dyspeptic symptoms may be related to effects on gastric emptying, and indeed in those studies that have used contrast radiology [172, 173]) they have indeed found delay in some of their subjects. However the use of contrast radiology has been shown to give inaccurate results, and in studies using both scintigraphy and ultrasonographic methods, [175–177] no differences have been found as a result of pyloromyotomy.

There have however been case reports relating to prolonged retention of swallowed foreign bodies, particularly coins in children who have had pyloromyotomy [178]. Indeed the author has had a similar case himself and would concur with the advice to remove these coins endoscopically.

30.8 Other Treatment Options

The mainstay of management for almost 100 years now has been the successful use of an operative approach whether by an open or laparoscopic method. An alternative interventional approach has been reported on in studies from Japan [179, 180]. Here, balloon dilatation of the pylorus can be undertaken via an endoscopic technique, analogous to that with oesophageal strictures. However this may be associated with a higher perforation rate and non-resolution of symptoms, and so is unlikely to displace the use of traditional interventions.

Prior to the establishment of the Ramstedt procedure however, medical management was the main approach and is still reported on in some studies from more recent times. In the early twentieth century the treatment was based on trying to maintain feeding regimes until the eventual resolution of the condition [181, 182, 183] though the success was not great. The introduction of an oral form of atropine was reported to give improved success [183] though it was recognised that intensive and prolonged nursing care was required [184].

A number of studies from Japan have identified that the use of atropine as a primary treatment along with both fluid and nutritional support have been effective in managing the condition [186, 187, 188]. The studies have shown success with the use of a regime of intravenous followed by oral atropine. Here though, the in-patient stay was significantly longer than a comparable group

undergoing surgery [185] and the total course of treatment was on average 3 months after initial diagnosis. This alone would call into question the economic benefit of the procedure. Yet, given it can be successful and with no reported side-effects, it is a strategy that could be used in children who for varied reasons may not be appropriate for surgical intervention.

30.9 Other Causes of Outlet Obstruction

In contrast to the relatively common occurrence of pyloric stenosis, other causes of gastric outlet obstruction are rare and constitute a diverse and varied range of pathologies.

The most readily recognised pathology would be related to atresia of the pyloric canal. Like other forms of intestinal atresia three distinct types are recognised [188, 189]. Type 1 where there is continuity of the wall but a membrane or web obstructs the lumen, Type 2 in which the pyloric canal is replaced by a thickened cord or type 3 where there is complete separation of the ends.

The incidence is reported as 1:100,000 live births [190]. While many are sporadic cases, there is an association with epidermolysis bullosa (EB), [191] though it is difficult to be clear from the literature just what percentage of cases have the two conditions. Moore [192] published a review which identified 125 cases of gastric outlet obstruction, of which only 18 were also reported to have EB. Both these conditions are inherited with an autosomal recessive pattern [193–195]. Yet other isolated cases have been found to have other intestinal atresias, and congenital cardiac lesions [196, 197].

The exact aetiology remains unclear but the prevailing theories of recanalization of solid organs [197, 198] or neonatal vascular accident [199] have been proposed as being the basic aetiology. However further arguments that there is no evidence of the stomach having ever been occluded [200] or that re-canalisation commences within the duodenum rather than the stomach [20] would mitigate against the re-canalisation theory. A further theory has been postulated that slippage of the epithelial layer may be responsible for the initiation of a diaphragm [201], but again further evidence is felt to be lacking. Work on the association with EB has provided some indirect evidence for this as a possible aetiology [195]. In essence abnormalities of the mucosal layer of the developing intestinal tract lead to the initiation of fibrosis and thus obstruction in narrow areas of the gut such as the pyloric canal. Whether this is the whole story is unclear. However, while there are studies that have shown an inflammatory component to the atretic segment [202] others have not [203].

The presentation tends to be within the neonatal period unless the web is incomplete or perforated. The clinical picture can resemble pyloric stenosis though the onset of vomiting is often earlier in the post gestational period and more progressive. The condition is often diagnosed by a straight abdominal X-Ray with the finding of a ‘single bubble’, but although this could be viewed as diagnostic, confirmatory evidence can be sought with an upper GI contrast. Treatment consists of managing the pre-operative condition of the child by correcting any electrolyte anomalies as would be required in the management of pyloric stenosis. The type of surgery is dependent on the anatomic variation encountered, and may include a simple pyloroplasty with excision of web, to a formal antroduodenectomy with anastomosis of stomach to duodenum (Bilroth Type I). The use of bypass operative procedures such as gastrojejunostomy is reported to have high failure rates and should be avoided if possible [188]. Overall results for isolated pyloric atresia are good with prompt recognition and treatment of the condition [193]. Mortality seems to be related to associated conditions or a delay in the operative treatment. While the addition of EB as a co-morbidity seemed to herald an almost universally poor prognosis in early published work [192, 203] the recognition that EB itself can have a variable prognosis does not preclude the early recognition and aggressive surgical management of this condition.

A further sub-type related to atresia is the occurrence of a pre-pyloric membrane. Though

this often presents in later life [204] previous studies have identified that it is a true congenital anomaly. Family studies have identified this as having a pattern of autosomal recessive inheritance [205]. The condition is amenable to surgical treatment with good results in the cases reported. Any deaths, as in the family series from Libya [205] seem to be related to other comorbid conditions rather than as a result of the congenital anomaly.

Duplications of the stomach or pyloroduodenal canal are a rare cause of gastric outlet obstruction, which may present in the neonatal period or depending on site and size may present later in childhood [206, 207]. In a series from Philadelphia [208] they represented 8% of all intestinal duplication seen in that institution, though the majority presented beyond the neonatal period. The symptoms can be analogous to hypertrophic pyloric stenosis, but the condition can be distinguished on ultrasonographic and radiological examination by the lack of muscle hypertrophy and the finding of an obstructing lesion, often cystic in nature. In those children (and adults) who present beyond the neonatal period the symptoms more often relate to pain and vomiting or even hematemesis. In the series reported by Clement [206] six of the cases also had ectopic pancreatic tissue as part of the duplication cyst, and three of the cases in the Philadelphia series had a similar pathological finding [208]. The recommended treatment is surgical excision or resection depending on the precise anatomical arrangement of the cyst and the overall results of surgery are reported to be good.

An increasingly recognised cause of obstruction in neonates is related to bezoars. A review of the literature [209] noted that the majority were classed as lactobezoars and some 70% of the published cases occurred in the neonatal period. The aetiology was felt to be multifactorial but factors involved included prematurity and high medium chain triglyceride or casein concentrations in the milk formulae used. Prompt recognition was found to be helpful as it allowed conservative management to be successful, though in some cases, surgery was required secondary to gastric perforation, or non-resolution of symptoms. It should also be noted however that while the majority of reported cases are related to inappropriate milk formulation the use of apparently innocuous therapies can also lead to problems. Gaviscon is widely used for the treatment of reflux, even in neonates and there are reported cases of this also leading to symptoms of gastric outlet obstruction [210]. As with lacto bezoars, if this is promptly recognised then conservative management can be successful.

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Duodenal Atresia and Stenosis

31

Emily Partridge and Holly L. Hedrick

Abstract

Congenital duodenal atresia and stenosis is a common cause of intestinal obstruction in the neonate, with an incidence of 1 in 5000 to 10,000 live births and an increased prevalence in males. More than 50% of affected patients have associated congenital anomalies, including annular pancreas, intestinal malrotation, esophageal atresia, Meckel's diverticulum, imperforate anus, renal anomalies, lesions of the central nervous system, and biliary tract malformations. The most common anomalies associated with duodenal atresia include Trisomy 21, diagnosed in one third of patients, and isolated cardiac defects, which occur in approximately 30%. The presence of trisomy carries an increased risk for congenital heart defects requiring operative repair. Approximately 45% of patients are born prematurely, with one-third exhibiting failure to thrive and persistent growth retardation. Presently, laparoscopic or open duodenoduodenostomy has become the standard of care, with survival rates of greater than 95% and mortality primarily attributed to associated anomalies of other organ systems.

Keywords

Congenital duodenal obstruction • Prenatal diagnosis • Associated anomalies • Embryology • Surgery • Outcomes

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_31

31.1 Duodenal Atresia and Stenosis

Congenital duodenal atresia and stenosis is a common cause of intestinal obstruction in the neonate, with an incidence of 1 in 5000 to 10,000 live births and an increased prevalence in males [1]. More than 50% of affected patients have associated congenital anomalies, including annular pancreas, intestinal malrotation, esophageal atresia, Meckel's diverticulum, imperforate anus, renal anomalies, lesions of the central nervous system, and biliary tract malformations [2]. The most common anomalies associated with duodenal atresia include Trisomy 21, diagnosed in one third of patients [3], and isolated cardiac defects, which occur in approximately 30% [4]. The presence of trisomy carries an increased risk for congenital heart defects requiring operative repair [5]. Approximately 45% of patients are born prematurely, with one-third exhibiting failure to thrive and persistent growth retardation [6]. Presently, laparoscopic or open duodenoduodenostomy has become the standard of care, with survival rates of greater than 95% and mortality primarily attributed to associated anomalies of other organ systems [7].

31.2 Etiology

Duodenal atresia occurs due to a failure of recanalization of the fetal duodenum, resulting in complete obstruction. Early in the fourth week of gestation, the duodenum develops from the distal foregut and proximal midgut. During the fifth and sixth weeks of gestation, the duodenal lumen is temporarily obliterated due to proliferation of the epithelium. Subsequently, degeneration of the epithelial cells leads to recanalization of the duodenum by the eleventh week of gestation. Embryonic insult during this developmental window may result in an intrinsic web, atresia or stenosis. Unlike atresias distal to the Ligament of Treitz, vascular insult is not thought to play a role in the etiology of duodenal stenosis. Although no specific genetic mutation has been shown to correlate with duodenal atresia, the coincidence of the condition within sibling cohorts supports the likelihood of an underlying genetic predisposition [8].

31.3 Classification

Anatomically, congenital duodenal obstruction is classified as either an atresia or stenosis. Incomplete obstruction due to a fenestrated web or diaphragm is considered a stenosis, while atresias, or complete obstructions, are classified into three morphologic types [9]. Type I atresias account for more than 90% of all congenital duodenal obstructions, and contain a luminal diaphragm including mucosal and submucosal layers with an intact mesentery. A variant of type I duodenal atresia, the 'windsock' deformity, presents with distal dilation of the luminal diaphragm, and may pose particular challenges to surgical repair as a segment of dilated duodenum may persist distally to the point of true obstruction. Type II atresias account for less than 1% of all cases and are characterized by a segment of proximal dilation and distal decompression connected by a fibrous cord with an intact mesentery. Type III atresias account for approximately 7% of all cases, and are distinguished by a V-shaped mesenteric defect. There is no connection between the blind proximal and distal duodenal segments.

31.4 Postnatal Presentation

The postnatal presentation of congenital duodenal obstruction depends greatly on the grade of obstruction and its location in relation to the ampulla of Vater. Neonates classically present with bilious vomiting in the first hours of life, although in approximately 15% of cases the obstruction occurs proximal to the ampulla, resulting in non-bilious emesis [10]. The abdomen is generally scaphoid, and abdominal distension is rarely apparent [11]. Patients with incomplete obstruction, or stenosis, may have a delayed presentation dependent on the initiation of enteral feeds. Delayed diagnosis can result in aspiration, dehydration and the development of acid-base disorders.

Suspected cases of duodenal obstruction may be confirmed by a plain upright X-ray of the abdomen, with the classical finding of the "double bubble" sign generated by the proximal left-sided air- and fluid-filled stomach tapering at the pylorus and the distal dilated proximal duodenum to the right of the midline (Fig. 31.1). Generally the distal bowel is gasless, however in

cases of anomalous bifurcated bile duct with termination of one duct distal to the point of obstruction, distal gas may be visualized [12]. In the setting of neonates who have undergone placement of a nasogastric tube, 30–60 mLs of instilled air may reproduce the "double bubble" sign, or a limited upper gastrointestinal contrast study may be performed to confirm the diagnosis and exclude malrotation or volvulus.

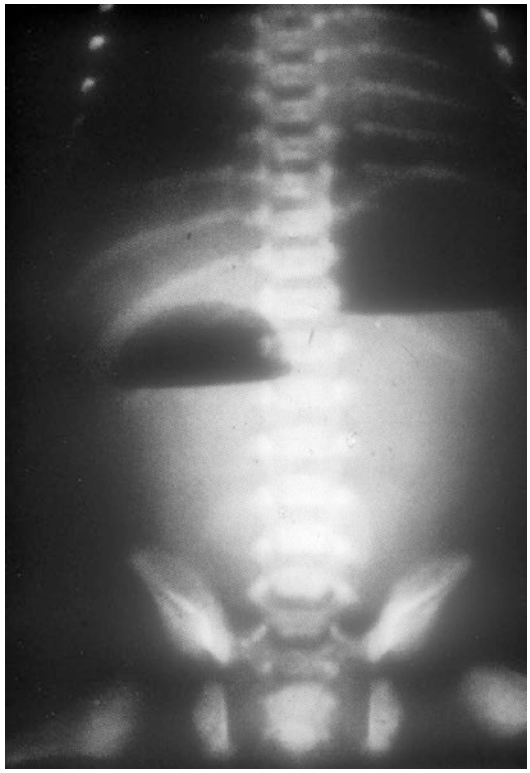

Fig. 31.1 Duodenal atresia showing classic 'double bubble 'sign features indicating proximal foregut obstruction

31.5 Prenatal Diagnosis

Advances in prenatal imaging have led to increased diagnosis of a number of anomalies of the gastrointestinal tract, including stenosis and atresias of the small and large bowel [13]. Prenatal diagnosis may be made in as many as 50% of cases of congenital duodenal obstruction [14]. Prenatal diagnosis is more common in the presence of other congenital anomalies, and is therefore associated with higher overall mortality rates [15]. Polyhydramnios is a frequent complication in the setting of congenital duodenal obstruction [16], and may prompt increased imaging surveillance leading to definitive diagnosis. Prenatal ultrasonography may detect two fluid-filled structures consistent with a double bubble sign (Fig. 31.2a). With the advent of fetal MRI, detailed delineation of soft tissue anomalies has become possible across a wide range of gestational ages, and may be useful in confirming the diagnosis and ruling out other anomalies (Fig. 31.2b). Low fetal and birth weight is also commonly observed, and may be attributed in part to reduced swallowing and transit of amniotic fluid through the fetal bowel [17].

Duodenal atresia is most commonly prenatally diagnosed in the second half of pregnancy [18], although cases of accurate diagnosis in the first of early second trimester have been reported [19, 20]. It has been hypothesized that the relatively late appearance of significant duodenal distension may be attributed to immature fetal swallowing and gastric emptying. Peristaltic movement of the small intestine may be appreci-

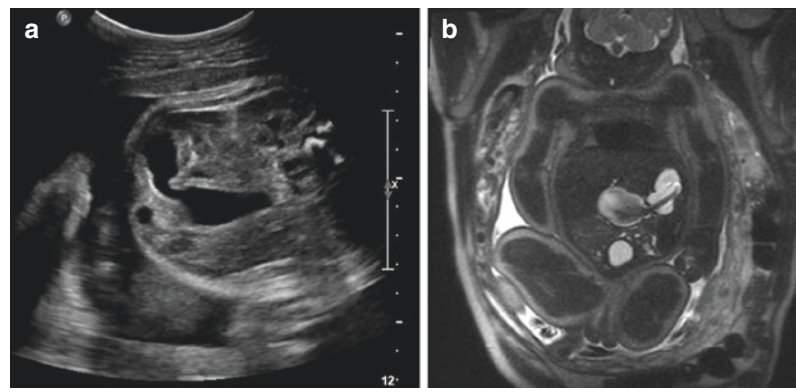

Fig. 31.2 Prenatal radiographic imaging of duodenal stenosis. (**a**) Duodenal stenosis imaged by ultrasonography of the fetus, with a "double-bubble" sign. (**b**) Appearance of duodenal stenosis by fetal magnetic resonance imaging

ated by ultrasonography as early as 6–7 weeks gestational age and may transiently mimic the appearance of dilated intestinal segments, leading to the possibility of a false diagnosis [19]. Importantly, in cases of true obstruction the dilation of the affected segment is observed constantly, therefore scans of several minutes duration are required to minimize the likelihood of false positive diagnoses.

31.6 Postnatal Management

In suspected cases of duodenal stenosis or atresia, placement of a nasogastric tube is an appropriate initial maneuver to achieve gastric decompression and reduce the risk of aspiration. After confirmation of the diagnosis by plain radiograph with or without contrast, a complete metabolic profile is obtained including complete blood cell count, electrolyte panel, blood gas, and coagulation studies. Appropriate resuscitation is required to correct any underlying fluid imbalance or electrolyte disorder. Due to the high risk of congenital heart disease in this patient population, cardiac investigations including an electrocardiogram and echocardiogram should be performed prior to surgical intervention. Generally it is only in the setting of an inability to exclude the possibility of malrotation or volvulus that emergent surgical intervention is undertaken.

Prior to the mid-1970s, duodenojejunostomy was the preferred approach for correction of duodenal atresia [21]. Rarely, gastrojejunostomy was performed as an alternative to duodenojejunostomy [22], but was found to result in a high incidence of marginal ulceration and bleeding [23]. Duodenojejunostomy was found to result in delayed anastomotic function often requiring use of parenteral nutrition or trans-anastomotic feeding tubes [24]. Blind-loop syndrome and megaduodenum also appear to result more commonly in patients treated with duodenojejunostomy, and may require reoperation and conversion to a duodenoduodenostomy to achieve satisfactory functional outcomes [25]. Weitzman and Brennan first reported the results of a direct side-to-side duodenoduodenostomy approach in 1974, with no anastomotic complications in their cohort of 14 patients [26]. The approach was widely adopted, although continued reports of complications including blind loop syndrome and duodenal dilation requiring tapering [27] or duodenoplasty [28] prompted continued technical modifications. In 1977, Kimura and colleagues reported an anastomotic technique with a side-to-side duodenoduodenostomy closed in two layers with the bowel incisions arranged to form a diamond-shaped anastomosis to achieve a larger stoma [29]. The technique was widely adopted with a favorable functional profile, and was further refined by Kimura to incorporate a transverse incision on the distal end of the proximal duodenum and a longitudinal incision in the distal duodenum (Figs. 31.3 and 31.4). By this technique, bowel function is recovered in a significantly shorter time period with a low incidence of complications and good long-term results [30]. The procedure of choice for duodenal atresia, irregardless of type, is presently duodenoduodenostomy with a proximal

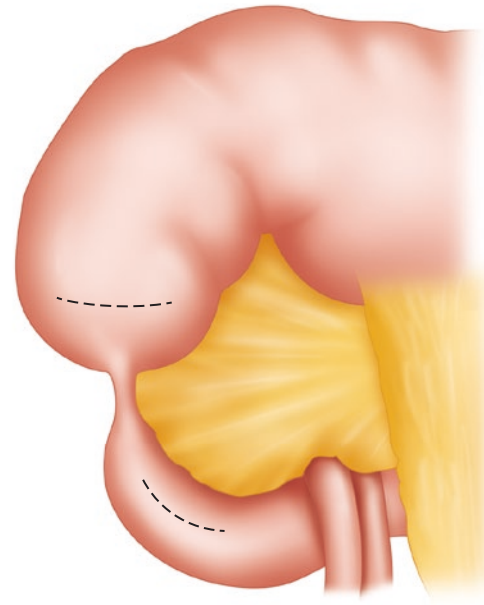

Fig. 31.3 Kimura technique operative duodenal atresia repair. A transverse incision is made in the distal portion of the proximal obstructed duodenum segment. A longitudinal incision is then created in the nearby portion of duodenum distal to the site of the atretic obstruction

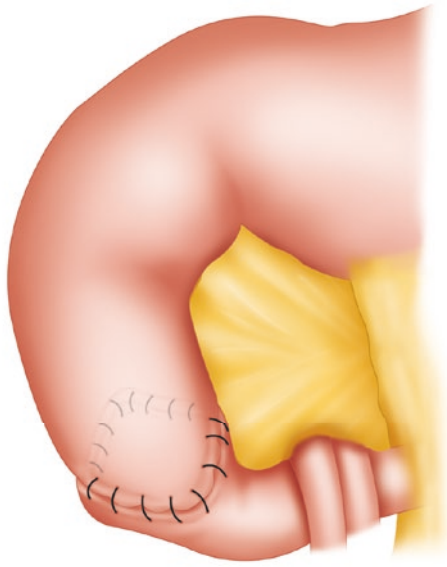

Fig. 31.4 A wide diamond shaped anastomosis is formed by joining the two duodenal segments

transverse to distal longitudinal, or diamond-shaped, anastomosis.

In the open approach, a right upper quadrant supraumbilical incision is made, and the ascending and transverse colon is mobilized medially to expose the duodenum. The position of the bowel should be assessed at this time, as malrotation may occur in up to 30% of cases of congenital duodenal obstruction [31]. Eviscerating and positioning the small bowel and colon cephalad and to the left of the incision achieves ideal exposure of the third and fourth duodenum. The decompressed duodenum is mobilized distal to the point of obstruction to permit a tension-free anastomosis. With the aid of tacking sutures, a transverse duodenotomy is made in the anterior wall of the distal portion of the distended proximal duodenum, and a vertical duodenotomy is made on the anti-mesenteric border of the distal duodenum. To rule out an additional web or windsock deformity, a catheter should be passed proximally into the stomach and distally into the jejunum and pulled back. The ends of the distal vertical duodenotomy incision are then approximated to the mid-portion of the proximal transverse duodenotomy incision with stay-sutures, and the posterior wall of the anastomosis is constructed by placing interrupted sutures using a repeating bisecting technique. The anterior row of the anastomosis is then completed in a similar fashion (Figs. 31.3 and 31.4). In the setting of gross dilation of the proximal segment, an anti-mesenteric tapering duodenoplasty may be performed as to expedite postoperative recovery of bowel function [32]. This may be performed by resection using a gastrointestinal anastomosis (GIA) stapler over a large red rubber catheter. Tapering is performed on the anterior or anterolateral portion of the proximal duodenum to avoid damage to the common bile duct and ampulla of Vater. Finally, the anastomosis is examined for patency, and the intestine is returned to the abdomen. In cases of malrotation, a formal Ladd's procedure is performed. Prior to closure of the abdomen, proper positioning of the nasogastric tube is confirmed. Placement of a transanastomotic feeding tube may hasten the time to tolerance of full oral feeding [33], although the literature on this approach is limited.

The laparoscopic approach to repair of congenital duodenal obstruction was first reported by Rothenberg in [34], with no complications and rapid initiation of oral feeds in the three patients described. The laparoscopic approach begins with insufflation of the abdomen through an umbilical port, with two additional ports placed in the right lower quadrant and the left mid-quadrant. A liver retractor may be placed via a fourth port in the right or left upper quadrant as indicated, or the liver may be retracted by placement of a stay-suture around the falciform ligament secured to the abdominal wall. The duodenum is exposed and mobilized, and rotational position of the bowel inspected. The proximal and distal duodenotomies are performed in a manner similar to that utilized in the open approach, with either running or single interrupted sutures used to anastomose the anterior and posterior walls. Alternatively, U-clips may be used to perform the anastomosis, with favorable outcomes reported in one series to date [35]. Results of an additional series of seventeen neo-

nates undergoing laparoscopic repair following Rothenberg's initial report noted no intraoperative complications, no conversions to open procedures, and no anastomotic leaks [36]. Due to the relatively recent advent of laparoscopic repair of duodenal stenosis, long-term outcomes are not yet reported in the literature. Reports of long-term complications and functional outcomes will facilitate a critical comparison of open versus laparoscopic repair of congenital duodenal obstructions.

Postoperatively, total parenteral nutrition is continued with monitoring of nasogastric tube outputs, and feedings are initiated when the volume of nasogastric output is diminished and non-bilious.

31.7 Outcomes

Early postoperative mortality for duodenal atresia is low. The most common complication encountered in the postoperative course is prolonged feeding intolerance. Prokinetic agents may have some benefit in this population, with one randomized controlled trial reporting shorter duration of TPN requirements, earlier achievement of full enteral feeding, and reduced length of hospitalization in a cohort of 30 neonates undergoing primary anastomosis for congenital small bowel atresias [37]. While some variability in return of bowel function is expected, feeding intolerance beyond the second week postoperatively should prompt concern for residual obstruction, anastomotic stricture, or a complicating motility disorder. An upper gastrointestinal series is helpful to rule out anastomotic stricture, although it should be noted that residual dilation of the proximal duodenum may be apparent for several months in the setting of a fully functional anastomosis.

Long-term complications reported after repair of duodenal obstruction include chronic severe gastrointestinal reflux, bleeding peptic ulcer, megaduodenum, gastritis, blind-loop syndrome, and adhesive bowel obstructions [38]. Patients with additional foregut anomalies, including esophageal atresia and gastroduodenal motility disorders, are the most likely to have gastroesophageal reflux disease [39]. Dysmotility in duodenal atresia may be attributed to smooth muscle cell injury secondary to ischemia or hypoplasia of the enteric nerves [40], while the dilated proximal segment may be associated with impaired transit and low contraction amplitude [41]. Megaduodenum may be diagnosed up to eighteen years postoperatively, and is associated with poor weight gain, frequent emesis, abdominal pain, and blind-loop syndrome [38]. An anti-mesenteric tapering duodenoplasty may be performed to manage cases of megaduodenum manifesting in the postoperative period [42]. Overall survival rates have improved over the past half-century from 45 to 95%, with the majority of deaths attributed to complications arising from associated congenital anomalies [43]. Long-term follow-up is essential for infants treated for congenital duodenal obstruction, with early diagnosis and management of late complications to achieve optimal outcomes.

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Malrotation and Volvulus

32

Spencer W. Beasley

Abstract

The term malrotation is used to denote the situation where the embryonic bowel, during the period when it herniates into the coelom of the body stalk between the 4th and 10th week of gestation, fails to rotate correctly. This means that when it returns to the abdominal cavity it is not correctly oriented, preventing the normal process of fixation of the midgut and its mesentery to the posterior abdominal wall. This results in a narrowed "universal" mesentery, which predisposes to volvulus. Volvulus is the term given to abnormal twisting of bowel (which, in the case of malrotation, involves most of the midgut) on its mesentery, and may have the consequence of cutting off its blood supply leading to ischaemia or infarction of the bowel.

Keywords

Malrotation • Gut rotation • Human embryology • Volvulus • Ladd's operation

32.1 Introduction

32.1.1 Definition

The term malrotation is used to denote the situation where the embryonic bowel, during the period when it herniates into the coelom of the body stalk between the 4th and 10th week of gestation, fails to rotate correctly. This means that when it returns to the abdominal cavity it is not correctly oriented, preventing the normal process of fixation of the midgut and its mesentery to the posterior abdominal wall. This results in a narrowed "universal" mesentery, which predisposes to volvulus. Volvulus is the term given to abnormal twisting of bowel (which, in the case of malrotation, involves most of the midgut) on its mesentery, and may have the consequence of cutting off its blood supply leading to ischaemia or infarction of the bowel.

32.1.2 Significance

The significance of malrotation relates to the potential for volvulus to supervene. Malrotation alone is usually asymptomatic, and may remain so

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_32

throughout life. Even when asymptomatic, malrotation is dangerous because of its predisposition to midgut volvulus. When volvulus causes ischemia and necrosis of small bowel, the consequences are dire and include death or short gut syndrome.

32.2 Embryology and Pathology

32.2.1 Normal Rotation and Fixation of the Midgut

In simple terms, the normal configuration of the small bowel is acquired in a five stage process (Table 32.1), although there is considerable overlap with some of the stages. For example, rotation commences at the time of herniation.

32.2.1.1 Development of Dorsal Mesentery

The prerequisite for rotation of the midgut is development of the dorsal mesentery at 3–4 weeks gestation [1]. This forms after division of the lateral plate mesoderm into its somatic and splanchnic components to create the coelom, a process facilitated by *Foxf1* [2], with activation of the homeobox gene *Irx3* restricted to the somatic mesoderm.

Table 32.1 Stages leading to the final configuration of the normal midgut

1.	Development of dorsal mesentery
2.	Herniation
3.	Rotation
4.	Return to the abdominal cavity with completion of rotation
5.	Fixation

Intestinal rotation itself is mediated by changes in the dorsal mesentery [3] where mesenchymal cells on the right side of the mesentery become more sparse and cuboidal, and on the left dense and columnar. This is controlled by the transcription factors, *Pitx2* and *Isl1*, which themselves are under the control of *Nodal*. Their effect is that the mesentery is tilted to the left (Fig. 32.1).

32.2.1.2 Herniation

In the fourth week of embryonic life, the midgut (which is primarily supplied by a single vessel, the superior mesenteric artery) starts to protrude ventrally to herniate into the coelom of the body stalk (Fig. 32.2a). This occurs because of the combined effects of the rapid elongation of the intestine and growth of the liver [4]. For convenience, the bowel of the midgut proximal to this vessel is called the "pre-arterial" or "duodenojejunal" segment; and the part distal to the main stem of the superior mesenteric vessel is called the caudal ("post-arterial" or "caeco-colic") segment [5]. Initially, the pre-arterial segment grows more quickly than the post-arterial segment (Fig. 32.2b).

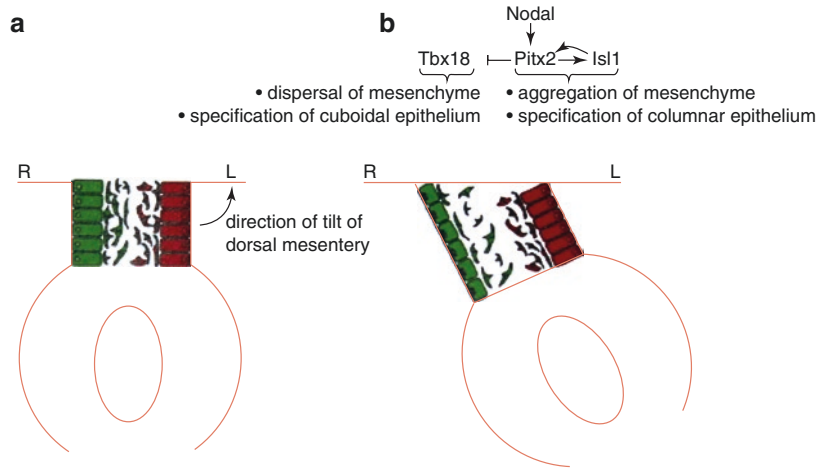

Fig. 32.1 Expression of the transcription factors Pitx2 and Isl1 (influenced by Nodal) occurs on the left side and Tbx18 on the right. The morphological changes to the epithelium and mesenchyme produced make the dorsal mesentery tilt to the left Modified from Davis et al [3]

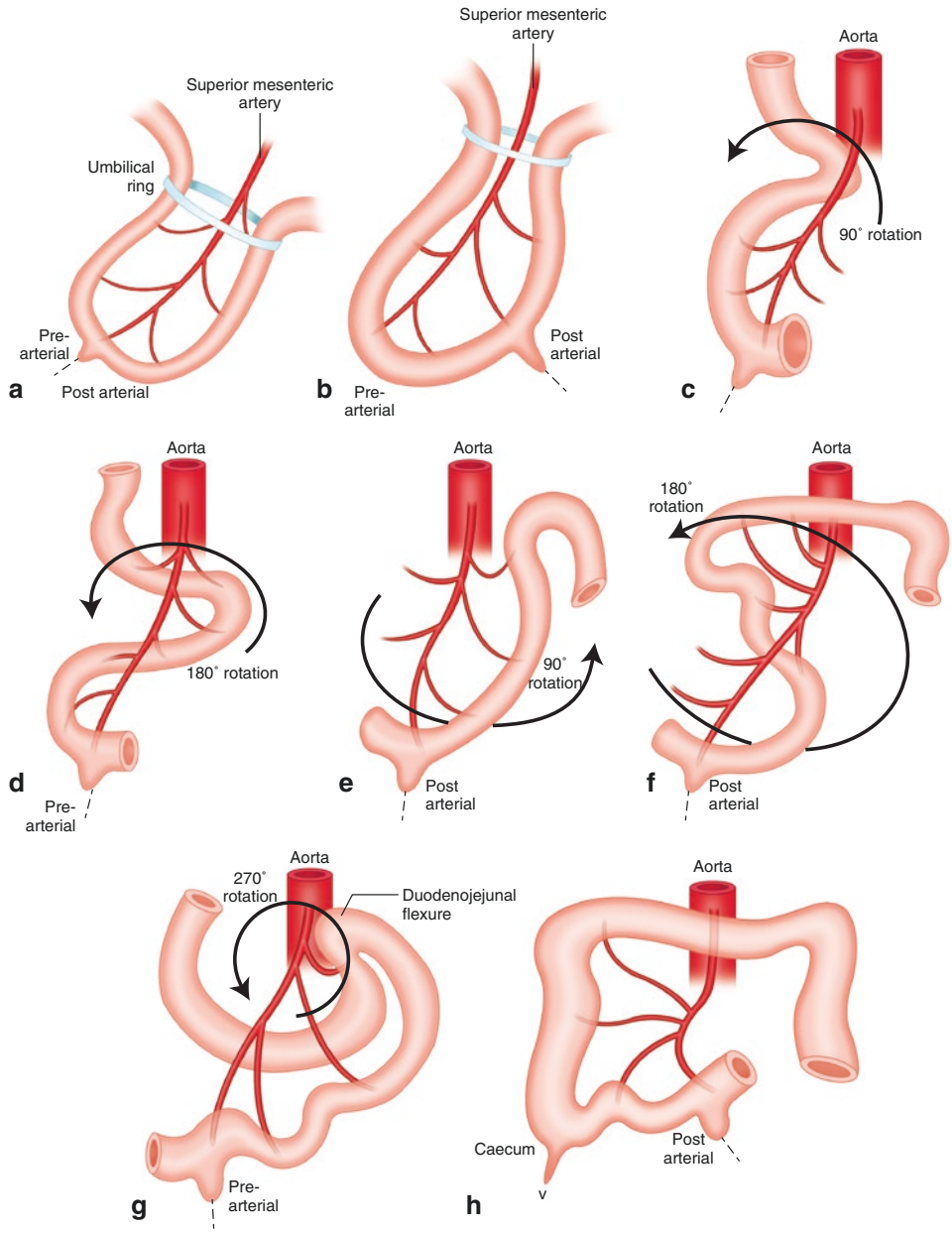

Fig. 32.2 In the fourth week of embryonic life the midgut grows rapidly and soon becomes too big for the space available to it in the abdominal cavity. It herniates through the umbilical ring into the coelom of the body stalk (**a**). The pre-arterial (duodeno-jejunal) segment initially grows more quickly than the post-arterial (ileo-colic) segment (**b**). The pre-arterial segment first rotates 90° counter-clockwise which places it to the right of the SMA (**c**) and then a second 90° (**d**) and in doing so the duodeno-jejunal junction comes to lie posterior to the SMA. Rotation of the post-arterial segment is in the same direction (counter-clockwise) as that of the pre-arterial segment (**e**), initially through 90° (a), followed by a second 90° (b). The 180 degree counter-clockwise twist of the SMA around its axis effectively drags the attached midgut with it. The final configuration of the pre-arterial segment of the midgut after completion of 270° of rotation means that the duodeno-jejunal flexure has altogether rotated 270° counter-clockwise from its original position to now lie to the left of the root of the superior mesenteric artery (**f**). Similarly, the 270° of counter-clockwise rotation brings the caecum down into the right lower quadrant after return of the midgut into the peritoneal cavity

32.2.1.3 Rotation

As the pre-arterial segment protrudes into the coelom, it rotates 90° counter clockwise so that it lies to the right of the SMA (Fig. 32.2c). And as it continues to lengthen it undergoes a further 90° rotation which pulls the duodenojejunal junction posterior to the SMA (Fig. 32.2d), a position it maintains throughout life and is a key feature on imaging by ultrasonography and CT.

Rotation of the post-arterial segment follows that of the pre-arterial segment, such that by the time it returns to the abdominal cavity it is lying ventral to the SMA, effectively having undergone a 180° counter clockwise rotation. The easiest way to understand the process is to imagine the SMA twisting 180° counter clockwise on its axis, drawing the attached midgut with it (Fig. 32.2e).

32.2.1.4 Return to the Abdominal Cavity

By the time the human embryo is about 40 mm in length (10th week) the midgut begins to return into the peritoneal cavity [5]. In doing so, the pre-arterial (duodenojejunal limb) segment completes an additional and final 90° rotation around the SMA, still rotating in a counter clockwise direction (Fig. 32.2f). Similarly, the post-arterial limb, is obliged to undergo a final 90° rotation which brings the caecum down into the right lower quadrant (Fig. 32.2g).

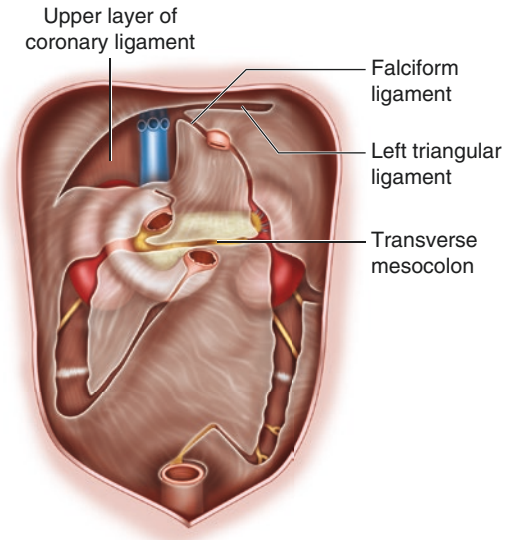

Fig. 32.3 The normal attachment of the root of the small bowel mesentery extends from the ligament of Trietz obliquely downwards and to the right as far as the caecum.

32.2.1.5 Fixation

Within a week or two of its return, the colon, particularly its ascending and descending parts, become adherent to the posterior abdominal wall, within the paracolic gutters. By now the duodenum is well attached to the posterior abdominal wall, with peritoneum running across its anterior surface. The SMA runs downwards ventral to the duodenum's third part. The attachment of the root of the small bowel mesentery extends from the ligament of Trietz obliquely downwards and to the right as far as the caecum (Fig. 32.3). All these events are normally complete by 13 weeks gestation [6]. It is the length and broadness of this attachment that largely prevents the small bowel from undergoing volvulus.

32.2.2 Abnormal Embryology

Incomplete rotation of the duodenum and colon interferes with the process of attachment to the posterior abdominal wall. If the caecum and ascending colon do not rotate a full 270° they cannot become anchored in the right paracolic gutter, and peritoneal condensations run anterior to the duodenum: these tend to tighten and cause obstruction of the duodenum if volvulus occurs.

Where rotation has not occurred, the width of attachment of the small bowel mesentery is much shorter, being largely confined to the region around the SMA (Fig. 32.4). This is sometimes referred to as a "universal mesentery" and is the pedicle around which the midgut can twist. Thus, the predisposition for volvulus is a combination of failure of rotation and failure of adequate fixation, leaving only a narrow attachment of the mesentery of the small bowel (Fig. 32.5). Abnormalities of midgut rotation fall into four broad categories (Table 32.2) of which non-rotation is by far the most common.

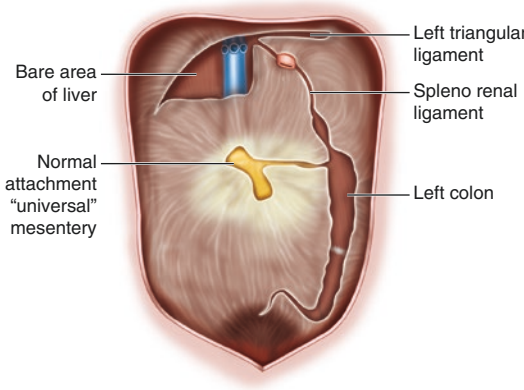

Fig. 32.4 In malrotation, the small bowel mesentery is attached only narrowly to the posterior abdominal wall, and only in the region of the superior mesenteric vessels. It is this lack of breadth of attachment that predisposes to volvulus

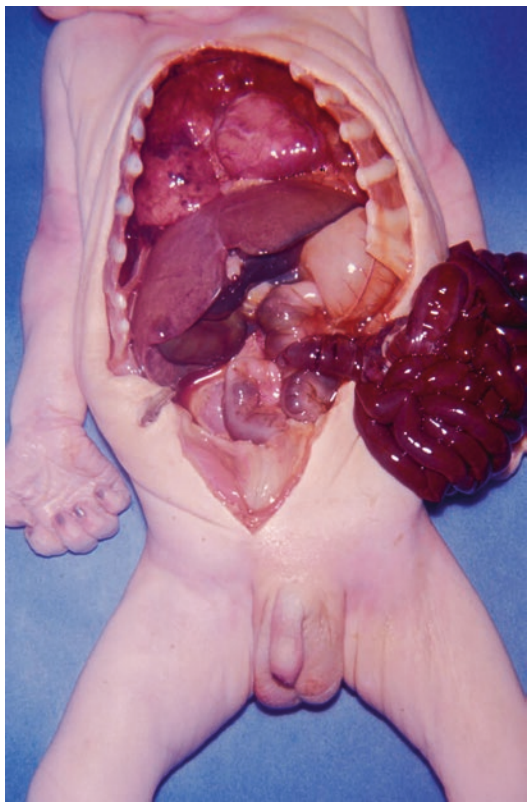

Fig. 32.5 Postmortem appearance of volvulus of the midgut complicating non-rotation where the extremely narrow base to the small bowel mesentery ("universal mesentery") has clearly contributed to the twisting of the small bowel on its mesentery

Table 32.2 Classification of rotational abnormalities of the midgut

Type	Embryology and Pathology
1. Non rotation (most common)	Failure of anticlockwise rotation of both pre and post-arterial segments of midgut Failure of fixation (especially of caecum and ascending colon) Narrow small bowel mesentery (figure)
2. Failure of rotation of pre-arterial segment	Non rotation of duodenojejunal (pre-arterial) segment Normal rotation and fixation of post-arterial segment Broad mesenteric attachment
3. Reverse rotation of midgut	Reverse rotation of pre-arterial segment causes duodenum to lie anterior to SMA May occur in isolation, leading to paraduodenal hernia (which appears as a mesenteric pouch opening to the right) May occur in conjunction with reverse rotation of post-arterial segment, leading to transverse colon lying behind SMA
4. Failure of rotation of post-arterial segment	Failure of the caecum and colon (post-arterial limb) to rotate interferes with its ability to fix to the posterior abdominal wall Leads to narrow small bowel mesentery Peritoneal bands to colon may cause duodenal obstruction Caecal volvulus may occur

32.2.3 Non Rotation

Complete failure of rotation of the midgut is the most frequent abnormality in this spectrum of conditions. Neither the pre-arterial nor post-arterial segments of midgut have rotated. As a consequence, the duodenum remains anterior, and is located mainly to the right of the midline. The ascending colon and caecum are only loosely attached, and can be variable in position, often lying anteriorly in the mid abdomen (Fig. 32.6). It is this variant that is at greatest risk of volvulus. Volvulus occurs around the superior mesenteric artery and tends to tighten the fascial condensations of peritoneum that run across the anterior part of the duodenum (so-called Ladd bands) which causes duodenal

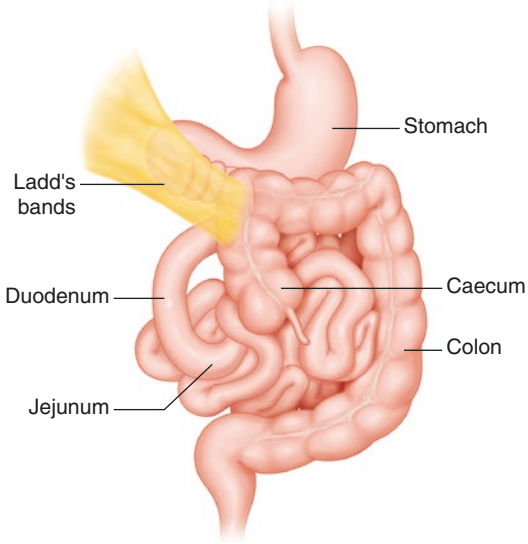

Fig. 32.6 Complete failure of rotation of the midgut (non-rotation with a "universal mesentery"). This is the most common variant, and predisposes to volvulus

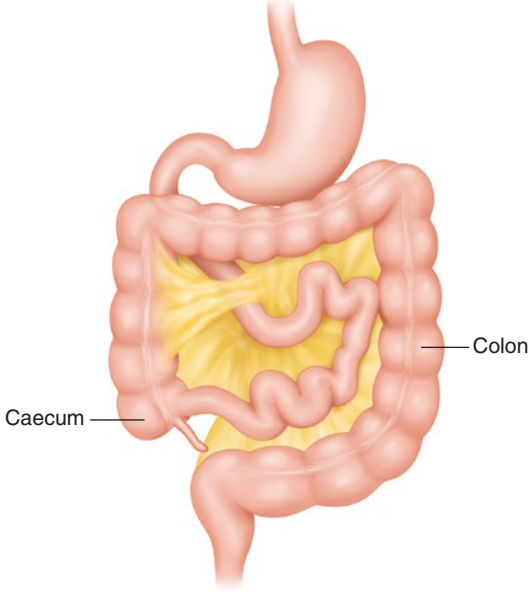

Fig. 32.7 Non-rotation of the pre-arterial (duodeno-jejunal) segment usually presents as duodenal obstruction because of tightening of the Ladd bands which run across the front of the duodenum, but because the caecum has rotated and is lying in the correct position, volvulus is uncommon

obstruction. But of much greater concern is that the twisting may cut off flow through the superior mesenteric artery (and obstruct the

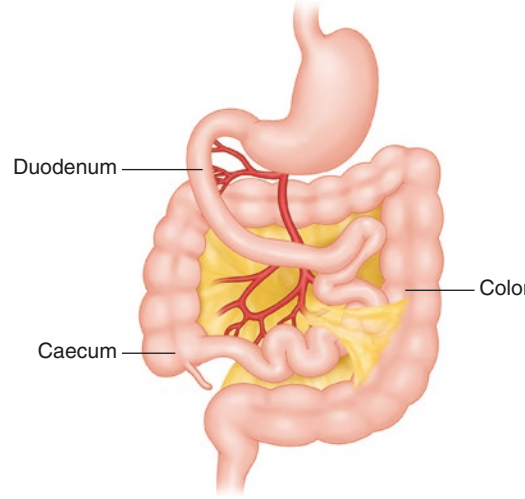

Fig. 32.8 Reverse rotation of the pre-arterial (duodeno-jejunal) segment in such a way that it passes in front of (ventral to) the vascular pedicle, with reverse rotation of the colon behind the superior mesenteric vessels, usually presents with distal bowel obstruction because the vessels compress the transverse colon

superior mesenteric vein) causing the bowel to become ischaemic.

32.2.4 Failure of Rotation of Pre-arterial Segment of Midgut

This less common abnormality results from non-rotation of the pre-arterial segment of midgut (duodenojejunal limb), in the presence of normal rotation and fixation of the post-arterial segment (caeco-colic limb) (Fig. 32.7). This abnormality may cause obstruction of the duodenum because mesenteric bands to the ascending colon and caecum still run across the front of the duodenum. However, the risk of midgut volvulus itself is relatively low because of the broad attachment of the base of the mesentery to the posterior abdominal wall.

32.2.5 Reverse Rotation

Extremely rarely, reverse rotation can occur (Fig. 32.8). This brings the duodenum anterior to the SMA (rather than posterior) and causes the

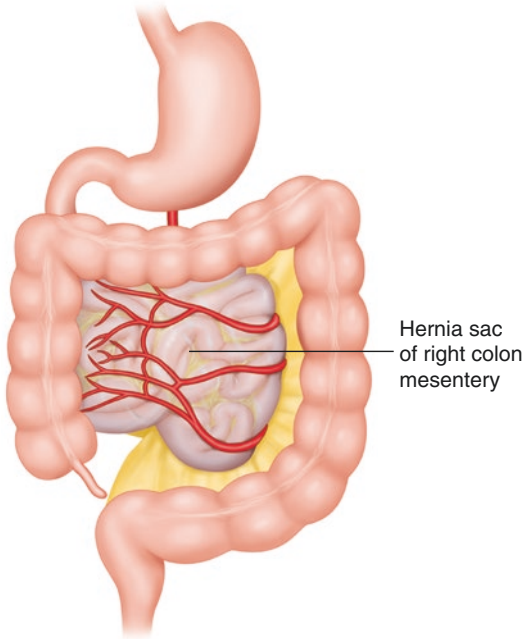

Fig. 32.9 When reverse rotation of the pre-arterial (duodeno-jejunal) segment occurs in conjunction with normal rotation of the post-arterial segment, a paraduodenal hernia is produced. The anterior part of the sac wall is actually the mesentery of the caecum and colon. This may cause some initial confusion on entering the peritoneal cavity because there appears to be a paucity of visible small bowel

transverse colon to lie behind the SMA. This may lead to colonic obstruction. Variants of this, where there are greater or lesser° of reverse rotation of the pre or post-arterial limbs may produce the appearance of paraduodenal hernias (Fig. 32.9), and these also may cause obstruction. (They may also create a challenge for the surgeon who initially may find the appearance confusing, but has to clarify exactly what has occurred in order to rectify it).

32.2.6 Failure of Rotation of the Post-arterial Segment of Midgut

This abnormality prevents adequate fixation of the colon, and produces a narrow mesentery, predisposing to volvulus [5]. It may also predispose to caecal volvulus where there is incomplete fixation of the caecum, and this may happen at any time in life.

32.3 Associated Abnormalities

A wide range of conditions have a recognised association with malrotation (see Table 32.3). Difficulty in making a distinction between true malrotation from incomplete or loose fixation of the midgut to the posterior abdominal wall (in the absence of malrotation) may be responsible for some of the apparent associations listed in Table 32.3. For example, the defects of exomphalos, gastroschisis and congenital diaphragmatic hernia all involve incorrect placement of bowel within the abdominal cavity and this may adversely affect fixation. Malrotation is reported to occur in up to a third of patients with duodenal atresia or stenosis [7]. From a clinical perspective, the co-existence of malrotation with other major congenital gastrointestinal abnormalities may create significant challenges in establishing the correct diagnosis of both conditions [8].

Lack of rotation and excessive mobility of the caecum may predispose to intussusception in some patients [9]: concurrence of intussusception and malrotation is a well-recognised phenomenon [10], accounting for 1.6% of 225 intussusceptions in one series [11]. There is some evidence the intussusceptions may precede the volvulus [12].

In recent years, geneticists have identified malrotation due to mutations in known genes. They fall into two main groups:

1. Mutations in the forkhead box transcription factor FoxF1. Other features include congenital short bowel, alveolar capillary dysplasia, misalignment of the pulmonary veins, and urinary tract malformations. Many have features in common with the heterotaxy syndromes [1].
2. Mutations in genes controlling L-R patterning. It is normal for organs of the torso to be asymmetric in their placement (e.g. heart, stomach, liver, biliary tract, spleen, and bowel) but when mutations occur in genes that specify L-R asymmetry, a number of clinical syndromes result (Table 32.3).

In addition, there are several conditions in which malrotation is likely to have a genetic cause, but for which the chromosomal locus and

Table 32.3 Abnormalities with an apparent association with malrotation

Nature of association	Example
Incorrect placement of bowel within abdominal cavity, or inadequate fixation	Congenital posterolateral (Bochdalek) diaphragmatic hernia Exomphalos Gastroschisis Intussusception
Possible early intrauterine volvulus	Duodenal atresia (including duodenal web or stenosis) Jejunal or ileal atresia
Mutation of known gene	FOXF1 at 16q24.1: alveolar capillary dysplasia, abnormal pulmonary venous drainage, micrognathia, congenital short bowel, annular pancreas, features of heterotaxy syndromes (autosomal dominant) FLNA at xq28: chronic idiopathic intestinal pseudo-obstruction, pyloric stenosis, undescended testes, hydronephrosis, thrombocytopenia (X-linked recessive) Abnormalities of L-R patterning: CFC1, ZIC3, NKX2.5, ACVR2B, LEFTY A (most have congenital heart disease, asplenia/polysplenia, and midline liver)
Non-syndromal malrotation	Familial malrotation
Syndromal malrotation	Martin-Frias syndrome (multiple bowel atresias, foregut appendage abnormalities e.g. biliary atresia, absent gallbladder) Multiple gastrointestinal atresias "apple peel" atresia of jejunum Microgastria, limb reduction defects, oesophageal atresia, ASD, VSD
Chromosomal imbalance	Duplication of long arm of chromosome 16: short bowel syndrome, anorectal malformation, gall bladder agensis Deletion long arm of chromosome 13: Hirschsprung disease, jejunal or ileal atresia
Miscellaneous (unclassified, or part of other syndromes or associations)	Meckel's diverticulum, Trisomy 13, 18, 21, Craniofacial, Prune belly syndrome, Mesenteric cyst, Marfan syndrome, Cornelia de Lange syndrome, Cat eye syndrome, Cantrell's syndrome, Pfeiffer Syndrome Type 2

gene mutations have yet to be identified. They are either non-syndromic (where malrotation occurs in isolation) or syndromic, in which other malformations also occur. The first published example of familial non-syndromic malrotation with volvulus with clear evidence for autosomal dominant inheritance involved eight individuals over three generations [13]. The syndromic conditions usually involve malrotation and other gastrointestinal malformations, and have an autosomal recessive inheritance pattern. They include Martin-Frias syndrome (multiple bowel atresias, biliary atresia and pancreatic abnormalities) [14] and multiple gastro-intestinal atresias (mostly of French-Canadian ethnicity, and include intraluminal calcification [15]. The combination of malrotation with short bowel [16], with MMIH (megacystis, microcolon and intestinal hypoperistalsis) [17], and with "apple peel" atresia [18] is also described.

Sometimes malrotation can be due to chromosomal imbalance [1]. The two situations of most relevance to paediatric surgeons are duplication of the long arm of chromosome 16 [19] (which also includes congenital short bowel, anorectal malformations and agenesis of the gall bladder), and deletions of the long arm of chromosome 13 which occurs with Hirschsprung disease or jejunal and ileal atresia [20].

The clinical geneticist has a role in providing genetic counselling and information about recurrence risk, and for that reason should be consulted whenever malrotation occurs with other abnormalities.

32.4 Incidence

The exact incidence of malrotation has been difficult to establish, mainly because it is so often asymptomatic throughout life. It has been identified in 0.5% of autopsies [21] as an incidental finding, and on upper gastrointestinal contrast studies as an asymptomatic and incidental finding in 0.2% [22], which would be consistent with an incidence of about 1/500 live births [23]. There is a male predominance of 2:1 in neonates who become symptomatic, but the gender difference disappears in

older age-groups [24]. A strong concordance between identical twins raises the possibility of genetic factors in its patho-aetiology [25].

32.5 Age At Presentation

In paediatric institutions, more than half the cases of malrotation with volvulus are seen in the first week of life, and about 80% in the first month. If all age groups are taken into account, about half are seen in the first month, 75% by one year, and the remaining 25% occur later in life [26]. In one series 25 of 45 (56%) underwent surgery in the first month of life [27]. At the Royal Children's Hospital, Melbourne, 14 of 32 patients received surgery within a month of birth [28], and a subsequent larger review revealed an age distribution at presentation as shown in Fig. 32.10.

It must be remembered that very occasionally older children, and even adults may present with volvulus or other obstructive symptoms that are secondary to malrotation (see Fig. 32.7). In older children and in adults, the variability in symptomatology and the low index of suspicion for the diagnosis means that delay in making the correct diagnosis is common, with a mean period of delay ranging from 1.7 years [27] to up to 5 years [28–30]. About 70% adults experience symptoms for more than 6 months before diagnosis [31].

The median age at surgery was 9 days in a series of 161 patients from two tertiary centres [32]. Age at presentation is not a good predictor of the likelihood of bowel infarction when volvulus occurs: infarction can be the consequence of volvulus at any age [33], although most cases of volvulus occur in the first few months of life.

32.6 Presentation (Table 32.4)

32.6.1 Antenatal Diagnosis

Malrotation is difficult to diagnose on antenatal ultrasonography in the absence of volvulus. The main clue to malrotation is a horizontally and medially positioned stomach [34], a finding that warrants an early post-natal upper GI contrast study to confirm the diagnosis. There is a higher index of suspicion when abnormalities known to be associated with malrotation (such as congenital diaphragmatic hernia, congenital heart disease and duodenal atresia) are diagnosed.

Volulus is one explanation for unexpected cessation of fetal movement and fetal distress, and may prompt ultrasonographic review of the fetus. It may also precipitate spontaneous rupture of the membranes [35]. It has been conjectured that fetal stress and fetal pain may activate both fetal-placental adrenal and hypothalamic stress hormones leading to premature uterine activity [36]. In these situations, malrotation is more likely to be deduced on antenatal ultrasonography because of features which represent the consequences of volvulus. These include a distended stomach and small bowel dilatation [35], heterogeneous echogenicity within the dilated bowel, the disappearance of peristalsis [37], fetal ascites, dilated loops of bowel [38], and features of meconium peritonitis. A convoluted mass in the mid-abdomen may be seen, and this has a whirlpool or snail configuration and has no peristaltic movement [37, 39]. While none of these alone is pathognomonic, their combination is strongly suggestive of volvulus. Later, peritoneal calcification and pseudocyst

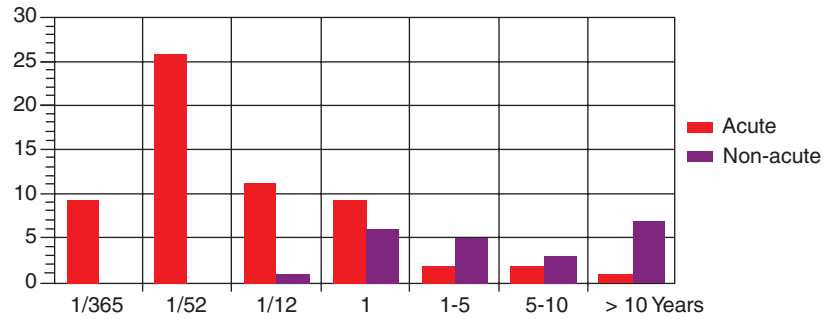

Fig. 32.10 Age at presentation of all cases of malrotation according to acuity. Volvulus can occur at any age, but is more likely in the neonate

Table 32.4 Presentation of malrotation

Antenatal diagnosis	Ultrasound evidence of consequences of volvulus
Postnatal diagnosis	
Malrotation alone	Asymptomatic[a]
	As an incidental finding on imaging (e.g. during upper GI contrast study, ultrasonography)
Malrotation with volvulus	Bile stained vomiting (especially in the neonate)
	Recurrent episodes of acute abdominal pain
	Other nonspecific symptoms (weight loss, early satiety, failure to thrive, intermittent diarrhoea, malabsorption, jaundice)

[a]Sometimes in the absence of volvulus, compression caused by peritoneal bands (Ladd's bands) may cause obstructive symptoms

formation can result from necrosis and perforation [40]. Midgut volvulus may precipitate premature delivery [36, 37].

In "secondary malrotation" [41] a large intra-abdominal cyst that develops early in gestation may prevent the midgut from undergoing normal rotation and fixation. This phenomenon has been described where there has been a large cystic mesenchymal hamartoma of the liver even where it has spontaneously involuted before birth. Teele et al. [41] conjecture that the dilated proximal duodenum seen in duodenal stenosis or atresia may also prevent normal rotation and fixation, which may account for the higher than expected incidence of malrotation in duodenal atresia [7].

Malrotation without volvulus has also been diagnosed antenatally by MRI scan at 35 weeks gestation by the observation of a midline stomach and all loops of small bowel to the right of the midline and all large bowel to the left [42]. However, both false positives and false negative results have been reported for the MRI diagnosis of malrotation [43], and at present it does not have a well defined role antenatally. Malrotation with volvulus can also be diagnosed on MRI antenatally [44].

32.6.2 Presentation in the Neonatal Period

"Volvulus neonatorum" is the term used to describe malrotation with volvulus that is evident at birth. The volvulus is likely to have occurred shortly before birth, and may even precipitate birth [36]. The newborn infant has a markedly tender and distended abdomen, consistent with established peritonitis. Surgical intervention is urgent, but often much of the small bowel is already dead. The mortality rate is high [45]

A more common presentation in the neonatal period is of an infant who appeared well at birth who then has sudden onset of bile stained vomiting. Subsequently, abdominal distension and tenderness may develop, and the infant may show evidence of respiratory distress (in part from elevation and splinting of the diaphragm) and sepsis. If not recognised early, progressive infarction of the midgut leads to signs of peritonitis, shock and eventually death.

32.6.3 Presentation in Older Children

Older children also present with bile stained vomiting, but are more likely to have other symptoms as well. The most common of these is intermittent or chronic abdominal pain which may occur with or without vomiting. Features more clearly indicative of intermittent obstruction may occur, with the addition of episodes of severe colicky pain and abdominal distension. Less usual presentations are often fairly non-specific, and include malabsorption, hypoproteinaemia, solid food intolerance, feeding difficulties, jaundice from common bile duct obstruction [27, 46], aspiration, failure to thrive, abdominal mass and diarrhoea [27]. A poor nutritional state is seen in many, with almost half on or below the third centile [47]. In advanced cases, where the blood supply to the small bowel has been acutely and severely compromised by volvulus, the presentation is of peritonitis and shock. Older children are more likely to have the rarer anatomic variants of

malrotation than neonates who become symptomatic [27].

Sometimes malrotation is noted as an incidental finding at abdominal surgery or during abdominal imaging for other conditions. For example, it is sometimes noted for the first time at appendicectomy when the appendix is difficult to locate and cannot be found in the right iliac fossa.

32.6.4 Approach to Clinical Assessment

Malrotation *per se* is asymptomatic. Symptoms develop when volvulus supervenes. In general, acute volvulus produces symptoms related to:

- proximal bowel obstruction
- midgut ischaemia

This means that these patients present with bile-stained vomiting, abdominal pain and distension, and where the blood supply to the gut is compromised, signs of peritonitis (Fig. 32.11). Therefore, the key to clinical assessment is to establish whether there is any evidence of compromised small bowel—as this represents an emergency and demands urgent surgical intervention to untwist the volvulus.

Specific signs at presentation which indicate that the bowel is ischaemic or infarcted include:

- shock
- abdominal tenderness
- guarding
- rectal bleeding

These signs confirm that extreme urgency exists: aggressive resuscitation and urgent laparotomy are indicated, even in the absence of specific imaging beforehand to confirm the diagnosis.

32.7 Investigation/Imaging

32.7.1 Plain Radiology

32.7.1.1 Diagnostic Features

There are few diagnostic features specific to malrotation on plain radiology of the abdomen in the infant in the absence of volvulus.

When volvulus has supervened the plain x-ray typically shows a relatively "gasless" abdomen with air in the stomach and duodenum, but little beyond the first part of the duodenum. Dilatation of the stomach and proximal duodenum (seen as an air bubble) with paucity of gas more distally is indicative of the duodenal obstruction caused by Ladd bands. The radiological appearance may not be dissimilar to that of duodenal atresia or duodenal stenosis with its typical "double bubble", although there is usually more gas distally in malrotation than is evident in duodenal atresia. Also, the small bowel is often distended. On other occasions, the plain radiological appearance can be fairly nonspecific, particularly if the stomach is not distended as might occur after vomiting has emptied it.

In some instances the appearances may be of a complete small bowel obstruction with multiple air fluid levels and dilated loops of small bowel. This is particularly likely to be seen when there is compromised blood flow to the midgut. There

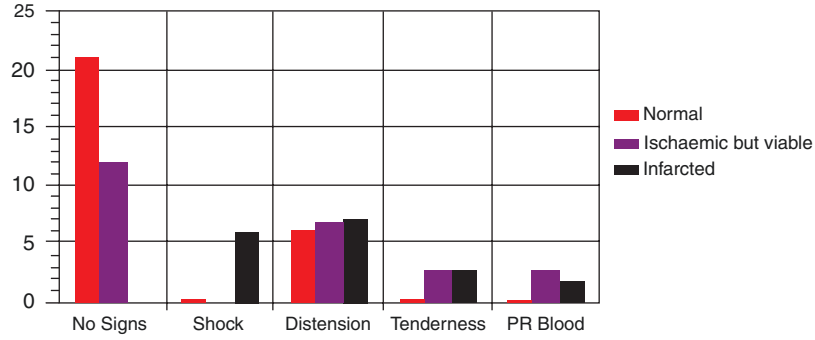

Fig. 32.11 Clinical features at presentation. The presence of shock, abdominal tenderness and rectal bleeding are all highly suggestive of vascular compromise to the bowel

may be evidence of free peritoneal fluid and thickened bowel loops. This radiological appearance will usually be associated with significant abdominal distension and tenderness, and justifies immediate surgical intervention.

32.7.1.2 Limitations

It is important to recognise that a normal abdominal radiograph in an infant with bilious emesis and suspected malrotation does not reliably exclude the diagnosis of malrotation. Even in the presence of volvulus the appearance on plain radiographs can be normal or "nonspecifically abnormal". For this reason, if malrotation and volvulus are suspected, further investigation is required.

32.7.1.3 Role

In the neonate with bile-stained vomiting or abdominal distension, plain radiology of the abdomen is mainly employed to identify or exclude other conditions such as duodenal atresia (no gas or distension distal to the duodenum) or necrotizing enterocolitis (intramural gas, portal venous gas).

32.7.2 Upper Gastrointestinal Contrast Study

32.7.2.1 Diagnostic Features

The upper gastrointestinal contrast study (which can be performed with either barium or a water soluble agent) is the most commonly performed investigation used to confirm the diagnosis of malrotation. Ideally, the examination should be performed by a paediatric radiologist under fluoroscopic control.

It is generally accepted that the key to diagnosis is establishing the exact location of the duodenojejunal junction: in the normal patient the duodenojejunal junction is anchored to the posterior abdominal wall by the ligament of Treitz, so will be to the left of the midline and at the level of the pylorus [28]. But where there is malrotation, the duodenojejunal junction tends to be located more inferiorly and to the right (Fig. 32.12). This gives an appearance of contrast running down through the duodenum in a corkscrew or spiral pattern as it connects with the jejunum, also on the right side (Fig. 32.13). Identification of the exact location of the duodenojejunal junction

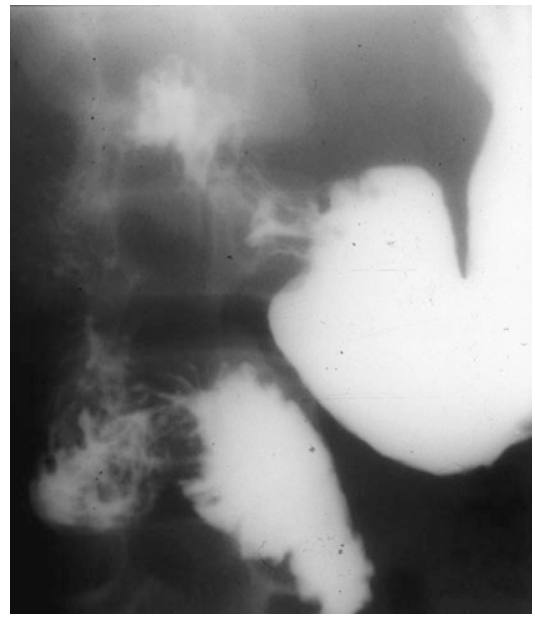

Fig. 32.12 The key to diagnosis of malrotation is demonstration of the duodeno-jejunal junction being inferior and to the right of its normal position and an upper GI contrast study

Fig. 32.13 The classical "corkscrew" or "spiral" appearance of the distal duodenum and proximal jejunum to the right of the midline

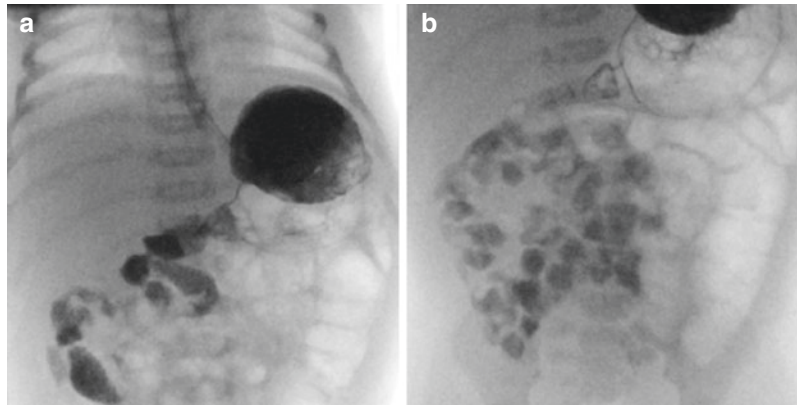

Fig. 32.14 This 4 day old infant presented with bilious vomiting. The upper GI contrast study showed (**a**) the duodenojejunal flexure displaced inferiorly and to the right, and the small bowel filling to the right of the midline; and (**b**) delayed films confirmed the small bowel opacified predominantly in the right side of the abdomen, and the colon (unopacified) to the left

necessitates continuous fluoroscopy to view carefully the flow of contrast as it exits the stomach and passes rapidly through the duodenum into the jejunum. As the contrast continues to pass through the small bowel it is noted to be predominantly on the right side of the abdomen (Fig. 32.14a,b), and later on once colonic filling occurs, the colon can be seen to the left. The caecum is abnormally positioned in 80% patients with malrotation [48].

In the presence of volvulus, obstruction of the mid duodenum is evident (Fig. 32.15)

32.7.2.2 Limitations

Its limitations are that the DJ flexure may be difficult to identify when contrast passes out of the stomach quickly (which is why continuous fluoroscopic control and a paediatric radiologist familiar with the radiological diagnostic criteria and potential pitfalls is required) (Table 32.5). Views are compromised if the stomach is too full of Barium [48]. It should be remembered that the position of the DJ flexure itself is only a consequence of malrotation—that the relationship between the third part of the duodenum and the superior mesenteric vessels is more critical [49], something that can only be inferred from the upper GI meal. Interpretation is complicated further by the normal variations that are seen in the position of the pylorus (given that it is used as the axial landmark in the lateral view for establishing the normal position of the DJ flexure).

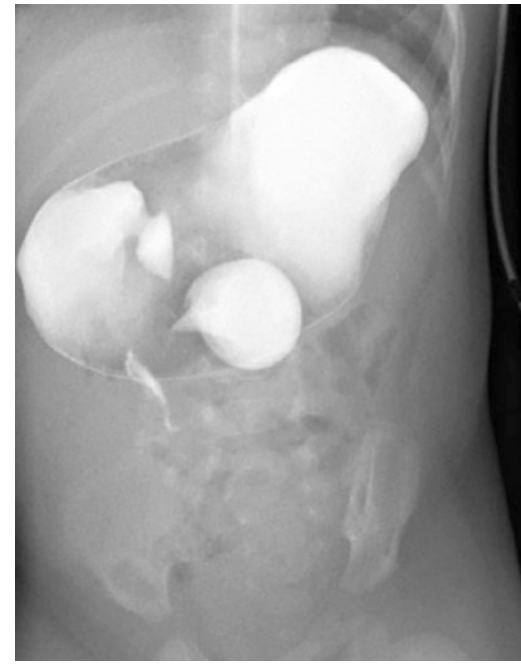

Fig. 32.15 The upper GI contrast study of a one month old infant presenting with sudden onset of bile stained vomiting showing mid-duodenal obstruction and a distended stomach. Notice the relative paucity of distal gas

Immediate follow-through of the contrast shows that the small bowel is predominantly on the right side of the abdomen, and delayed films (usually the next day) show that the colon is predominantly on the left. However, the caecal site and mobility cannot be reliably shown by a bar-

ium follow-through examination, and as such, delayed follow-through imaging has no place *per se* in the investigation of malrotation [28]. Nevertheless, the delayed films sometimes provide useful additional information on the location of the caecum and disposition of the colon. Where an upper GI study has proved equivocal in diagnosing malrotation it can be repeated a day or two later. Alternatively, ultrasonography, a distal contrast enema or diagnostic laparoscopy can be performed, depending on the facilities and expertise available, condition of the child, and the degree of uncertainty about the diagnosis.

32.7.2.3 Role

The upper GI contrast study has long been considered the "gold standard" for the diagnosis of malrotation, particularly in the absence of volvulus, although many paediatric institutions increasingly are using ultrasonography as a complementary investigation. A barium meal can also be used to confirm duodenal obstruction in volvulus. It is considered a more reliable investigation than the barium enema to diagnose malrotation, particularly in the neonate [28].

32.7.3 Distal Gastrointestinal Contrast Study

32.7.3.1 Diagnostic Features

For many years the barium enema was considered the procedure of choice, but its shortcomings mean that it is now used less commonly.

The key diagnostic feature on a contrast enema relates to identifying the position of the caecum, which should be in the right iliac fossa but in malrotation tends to be higher than normal, and even on the left side of the abdomen. Often the entire colon will be seen in the left side of the abdomen, and the ascending colon appears relatively short.

32.7.3.2 Limitations

The caecum may be difficult to identify in infants because it is less bulbous than later in life, and redundancy of the colon might obscure it (Table 32.5). The finding of a high and mobile caecum is indicative of malrotation, but this finding may also occur in about 15% of normal infants in the absence of malrotation.

Consequently, the main limitations of a barium enema relate to interpretation of the mobility of the caecum [50], which may produce a false positive result. The degree of attachment of the caecum to the posterior abdominal wall in the right iliac fossa is quite variable, and where this is loose, the caecum will also be quite variable in its position, including being situated higher and more medially than normal. This may give a false impression of post-arterial malrota-

Table 32.5 Summary of short-comings of gastrointestinal contrast studies in diagnosing malrotation

Investigation	Problems	Comment
Barium meal	Failure to correctly identify duodenojejunal (DJ) flexure Normal variation in position of neonatal DJ flexure Variability in position of pylorus	causes include: Inappropriate view Failure to see barium pass rapidly through the flexure, with sudden massive filling of proximal small bowel (that obscures further viewing) Especially if stomach full
Follow-through	site of caecum not reliably seen Mobility of caecum cannot be established	
Barium enema	Difficulty identifying position of caecum Wide normal variation in position of neonatal caecum Failure to demonstrate mobility of caecum Normally-located caecum may still be consistent with malrotation	Especially in neonate (caecum not bulbous) often high-lying

tion, where in fact, it simply represents a degree of non-fixation [28]. Moreover, duodenal obstruction may be caused by pre-arterial malrotation in the presence of a caecum in the normal position. A second limitation in the distal contrast study relates to the fact that the neonatal caecum is not particularly bulbous and may be quite difficult to identify accurately. It is most easily seen with oblique, compression, and left-side down decubitus films.

32.7.3.3 Role

The barium enema is now mainly used to provide further information when an upper GI contrast study has been equivocal, but malrotation is still suspected. In a study of the correlation in 11 patients where both studies were performed, there were no cases where both the upper and lower GI series were negative in the presence of malrotation [28].

32.7.4 Ultrasonography

32.7.4.1 Diagnostic Features

Ultrasound has the advantage that it is non-invasive but is vitally dependent on the expertise of the ultrasonographer: without a well-trained paediatric ultrasonographer it is probably of very limited value.

The key diagnostic feature is the relationship of the superior mesenteric artery to the superior mesenteric vein: if the SMV lies anterior or to the left of the SMA (rather than to its right) it indicates malrotation. Other diagnostic features include: dilatation of the proximal duodenum, a distended (obstructed) superior mesenteric vein (SMV), bowel loops fixed to the midline, the "whirlpool sign" (Fig. 32.16), and location of the third part of the duodenum [51, 52]. The "whirlpool sign" on colour Doppler ultrasonography indicates flow within the SMV as it spirals around the SMA in a clockwise direction [39, 53]. The third part of the duodenum should be retromesenteric if malrotation is to be excluded [49]. In the presence of volvulus, Doppler ultrasonography can provide further information on blood flow through the superior mesenteric vessels, as an indicator of perfusion of the midgut.

32.7.4.2 Limitations

It has a significant false negative rate, perhaps as high as 30% [54] (Table 32.6). In one study [55] identification of the SMV to the left of the SMA proved a more reliable indicator of malrotation than when the SMV was anterior to the SMA. Confirmation of the relationship of the third part of the duodenum to the mesenteric vessels may improve its reliability [49]

32.7.4.3 Role/Indications

Its main use is in the investigation of the infant with vomiting, where malrotation is one of a number of diagnostic possibilities. Particularly when it is used to diagnose pyloric stenosis, it may provide information on the rotation of the gut. Where a high level of paediatric ultrasonographic expertise is available, it is used more routinely as a primary diagnostic tool, and will often be used in conjunction with a upper GI contrast study if there is clinical suspicion of malrotation.

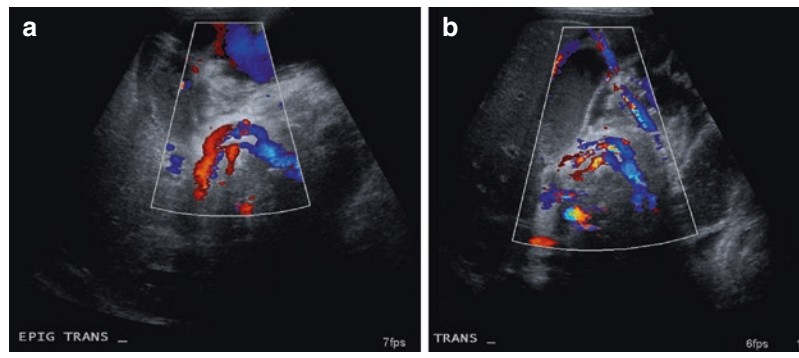

Fig. 32.16 Transverse upper abdominal transverse ultrasound images showing the "whirlpool" configuration of the superior mesenteric vessels at the root of the small bowel mesentery, with aligning dilated loops of small bowel

Table 32.6 Accuracy of imaging in diagnosing malrotation

Investigation	Accuracy	Percentage
Ba meal (Beasley “” “ “)	False negative rate	8
Follow-through study (“ “ “)	Unhelpful or misleading	67
Ba enema (Beasley and de Campo 1987)	False negative rate	17
Ultrasound (Applegate 2009) (Orzech et al. 2006) http://emedicine.medscape etc. Reid	Sensitivity	67–100
	Specificity	75–100
	False negative rate	2
	False positive rate	21
	False negative rate	30
	False positive rate	20
CT scan (Taylor 2011)	False negative rate	28.9
	False positive rate	10

32.7.5 CT Scan

32.7.5.1 Diagnostic Features

Features suggestive of malrotation include the small bowel being predominantly right-sided with the colon located on the left. It can also demonstrate an abnormal relationship between the superior mesenteric vessels (Fig. 32.17), and aplasia of the uncinate process [56]. An abnormal location of the third part of the duodenum has been identified in over 80% of patients with malrotation compared with 0% of controls [57], particularly in relation to the mesenteric vessels [49]. In adults, it is most often seen as an incidental finding at CT [58]. It has been used to correctly diagnose simultaneous volvulus and ileo-ileal intussusceptions [59].

32.7.5.2 Limitations

The radiation exposure limits its application in neonates and young children: the younger the infant, the greater the long-term risk. In addition, 10/100 control patients have an inverted SMA/SMV relationship (10% false positive rate) and 11/38 patients with malrotation had an apparently normal SMA/SMV relationship (27% false

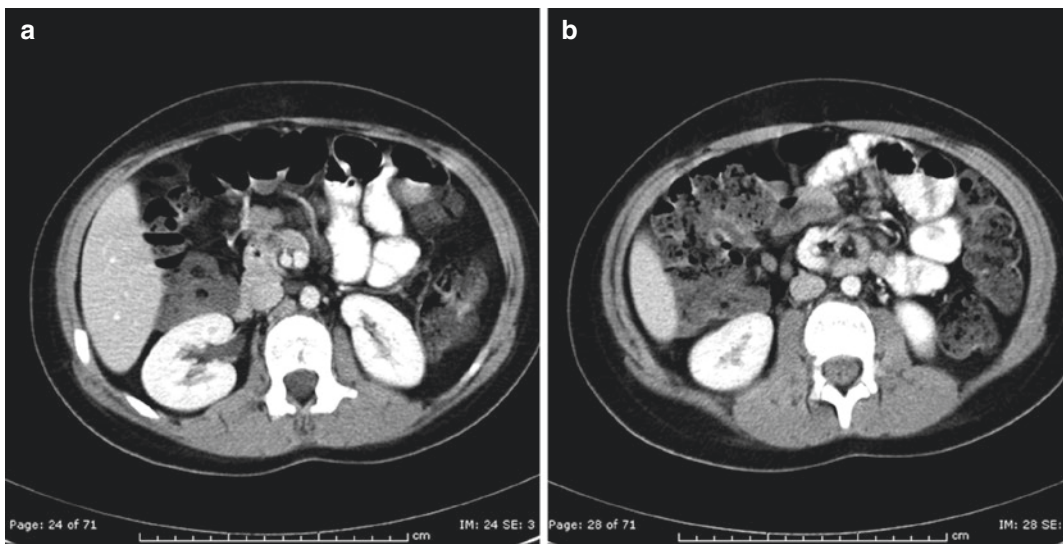

Fig. 32.17 CT study of an eight year child undergoing staging of a lymphoma, led to an incidental finding of malrotation. The axial images of the upper abdomen reveal an abnormal orientation of the superior mesenteric vessels at the root of the mesentery, with the ileocolic valve and caecum in the right upper quadrant

negative rate) [57], which suggests that this diagnostic criterion should not be used in isolation.

32.7.5.3 Role

This investigation is used rarely in neonates because of the high radiation exposure. In children and adults it occasionally reveals malrotation as an unexpected or incidental finding [58] (Fig. 32.17).

32.7.6 MRI

The role of MRI in the diagnosis of malrotation is yet to be established. A prospective non-randomised observational investigation into whether MRI could provide an alternative to contrast imaging (and thus avoid radiation) is being conducted [60].

32.8 Management

32.8.1 Initial Resuscitation (Table 32.7)

The paediatric surgical service should be notified as soon as a diagnosis of malrotation with volvulus is made: this diagnosis represents one of the few critical emergencies in paediatric surgery.

These children range from having relatively few signs initially to being profoundly shocked and unstable. Initial clinical examination determines whether there is evidence of compromised bowel perfusion: distended tender abdomen with guarding, tachycardic, or shocked and unresponsive. An intravenous line should be inserted through which fluid and electrolyte deficiencies are corrected, broad spectrum antibiotics effective against bowel organisms are administered, and vasopressor medication given to manage hypotensive shock. Oral feeds are stopped and a nasogastric tube inserted. Where the blood supply to the bowel is suspected to be compromised, an exploratory laparotomy or laparoscopy should be performed as quickly as possible, even if it means omitting imaging or other investigations beforehand.

Table 32.7 Key points for the initial management of malrotation with volvulus

• Immediate involvement of paediatric surgical service
• Insertion of intravenous line
• Take blood for haematology, blood culture, electrolyte, acid-base balance and for cross-match
• Correct fluid and electrolyte deficits
• Nil orally and nasogastric tube insertion
• Antibiotics effective against bowel organisms
• Dopamine (if required, as infusion 3 mcg/kg/min)
• Urgent surgical intervention:
– Careful discussion with family
– Consent covering all likely operative scenarios
– Do NOT delay surgery for imaging or other investigations if patient has evidence of compromised gut

32.8.2 Indications for Surgery

Emergency surgery is always indicated where volvulus causing compromised blood flow to the small bowel is suspected. The sooner the surgery, the better the outcome for the child. Even in the absence of signs of peritonitis, surgical intervention is urgent where imaging has demonstrated volvulus.

Where the history has been suggestive of malrotation with intermittent volvulus, but there is no current volvulus, surgery should still be performed reasonably promptly, before any further episode of volvulus occurs—because the next volvulus may cause irreversible vascular compromise to the bowel.

Where malrotation has been discovered incidentally in a child who is otherwise asymptomatic there has been less agreement on whether, and how urgently, surgery should be performed. Uncertainty has related to the relative risk of surgical morbidity (from a Ladd procedure) and of later volvulus if left untreated. It is the author's opinion that the consequences of volvulus are so potentially catastrophic that all children with diagnosed malrotation, even if completely asymptomatic, should undergo a Ladd procedure. This is supported by a review of a national database of 219 children older than one year undergoing a Ladd procedure which emphasized the importance of surgery in all chil-

dren with incidentally found malrotation [61]. A Markov decision analysis review of quality of life adjusted life expectancy with and without a Ladd procedure in asymptomatic patients with malrotation showed the highest advantage of surgery was in children under 1 year of age, with a declining advantage up to the age of 20 years, after which observation alone may be more appropriate [62]. However, many patients assumed to be asymptomatic have significant non-specific symptoms, or symptoms wrongly attributed to other conditions during adulthood [63]. Inability to predict who will later suffer the serious consequences of volvulus further justifies surgical intervention in all patients where a diagnosis of malrotation has been made [33].

The essential goals of surgery are to:

1. untwist any volvulus to re-establish circulation to the bowel, and assess bowel viability
2. broaden the mesenteric attachment of the small bowel to reduce the chances of subsequent volvulus

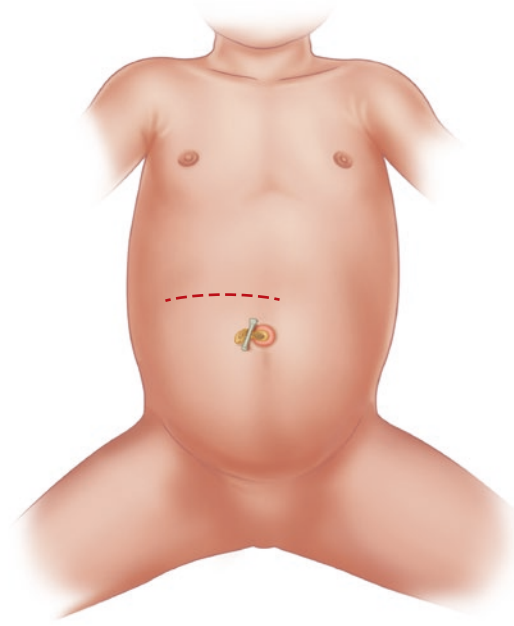

Fig. 32.18 The open approach to a Ladd procedure is performed through a supra-umbilical, predominantly right-sided transverse muscle-cutting incision

32.8.3 Surgical Approach

Traditionally, surgery for malrotation has been performed through an open approach, although recent refinements in laparoscopic techniques in infants and children now mean that the laparoscopic approach can be considered a legitimate alternative approach for selected patients. A laparoscopic approach may have a specific advantage when imaging has been inconclusive [64].

32.8.3.1 Open Approach

Currently, this is the preferred approach when there is concern about the viability of the midgut or there is marked abdominal distension. A transverse superumbilical muscle cutting incision is employed (Fig. 32.18). The peritoneum is opened, and in the neonate the falciform ligament is divided between ligatures.

32.8.3.2 Laparoscopic Approach

Laparoscopy represents an alternative surgical approach, with the choice of trocar size determined according to the size of the child. Three trocars of 3.5 mm can be used for infants [65]. Normally the scope is introduced through the umbilicus with two working ports in the mid to lower abdomen on either side (Fig. 32.19). The patient is supine near the foot of the table so the surgeon can stand between the legs. The reverse Trendelenberg position improves visualisation of the duodenum.

A laparoscopic approach may be most appropriate in the absence of volvulus, where imaging has suggested the diagnosis of malrotation in the absence of ongoing symptoms [50, 65, 66], and sometimes when imaging has not been able to exclude the diagnosis in a child with suspicious symptoms [64]. Laparoscopic derotation of volvulus in neonates and infants may be difficult and potentially dangerous where the small bowel is markedly distended or the bowel viability is marginal, and for this reason some caution its use in this situation [50]. Nevertheless, it has been performed laparoscopically with success in neonates where volvulus has not progressed to infarction [67].

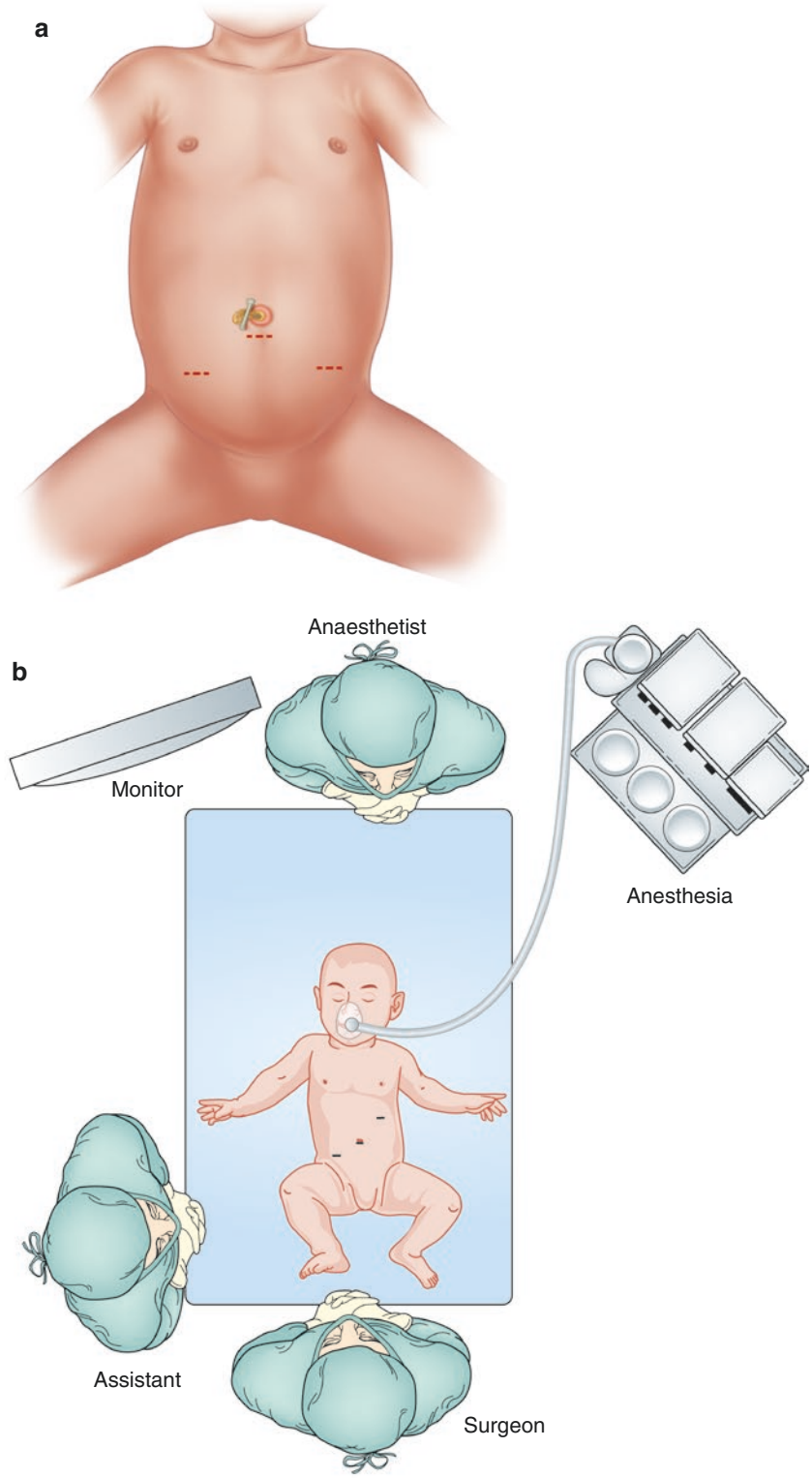

Fig. 32.19 The laparoscopic approach to a Ladd procedure is performed using an umbilical incision and usually two working ports, although sometimes a third working port (to elevate the liver edge) can be helpful

It would be reasonable to expect that in about 25–33% of cases conversion to an open procedure may be necessary [66, 68] although one report of 36 laparoscopic procedures had a conversion rate of 8.3% [69]. Rothenberg has advocated conversion to an open procedure where the dilated loops of bowel are clearly ischaemic to avoid undue delay and bowel injury [64]. Successful application of the procedure in older children with midgut volvulus has also been reported [70]. Operative times average about one hour [65], and are similar to that of the open approach [69].

32.8.4 Initial Operative Assessment

32.8.4.1 Deliver Bowel

In the open approach, once the peritoneal cavity has been opened, free fluid is aspirated, and the midgut is delivered through the wound (Fig. 32.20). The wound must be of sufficient size that this can be done without causing trauma to bowel which may already be friable. Evisceration of the small bowel is required to assess the root of the mesentery (Fig. 32.21). With the laparoscopic approach this is not possible, so the features that must be looked for to assess rotation are: the curve of the duodenum as it runs from right to left behind the superior mesenteric vessels, evidence of peritoneal condensations (Ladd bands) crossing in front of the duodenum, the location and fixation of the ligament of Treitz (which should be to the left of the superior mesenteric vessels) and the fixation of the caecum and right colon.

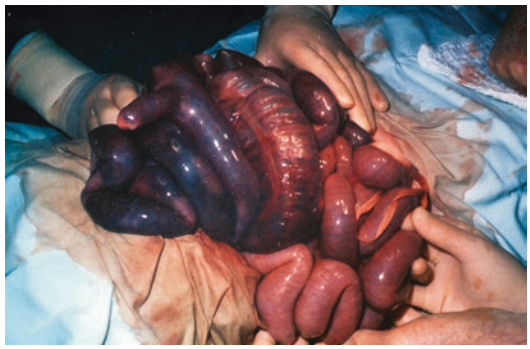

Fig. 32.20 In the open approach, the first step is to deliver the small bowel into the wound. This allows its viability to be assessed, as well as facilitates inspection of the root of the small bowel mesentery

32.8.4.2 Untwist the Small Bowel Mesentery

Where volvulus is confirmed (Fig. 32.21), the bowel is rotated in a counter clockwise direction to untwist it (Fig. 32.22). Examination of the root of the mesentery will confirm that it has been fully detorted. In the laparoscopic approach this may be easier to perform once the duodenum has been mobilised, and involves "walking" the bowel from proximal to distal.

32.8.4.3 Assess Bowel Viability

Once the volvulus has been untwisted the entire small bowel is inspected carefully (Fig. 32.23). It should be realised that assessment of the viability of ischemic neonatal bowel can be difficult, especially in the neonate. Sometimes the bowel is less

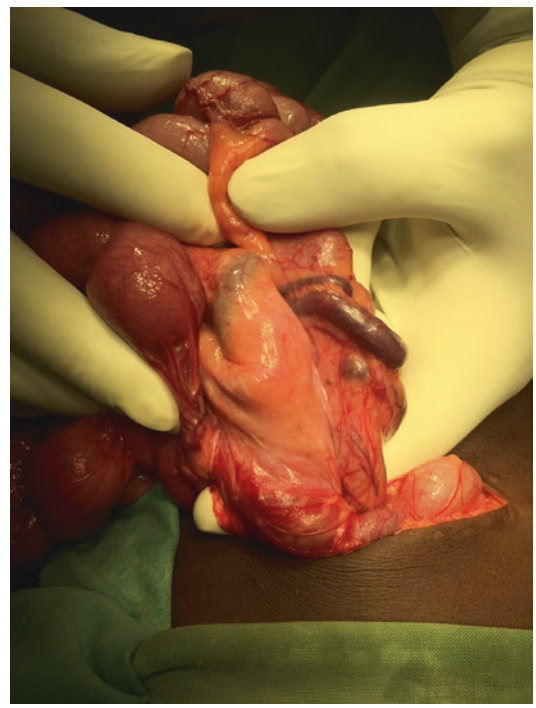

Fig. 32.21 The second step is to inspect the root of the small bowel mesentery and confirm volvulus, evident by the twisting of the bowel around the mesentery

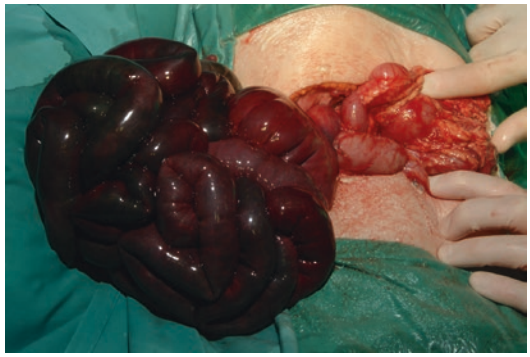

Fig. 32.22 An example of the operative appearance of ischaemic midgut due to malrotation where the blood flow through the superior mesenteric vessels has been compromised by volvulus. Only 20 cm of jejunum remained viable, but after a prolonged period of total parenteral nutrition the bowel adapted and the child survived (Courtesy P. Losty)

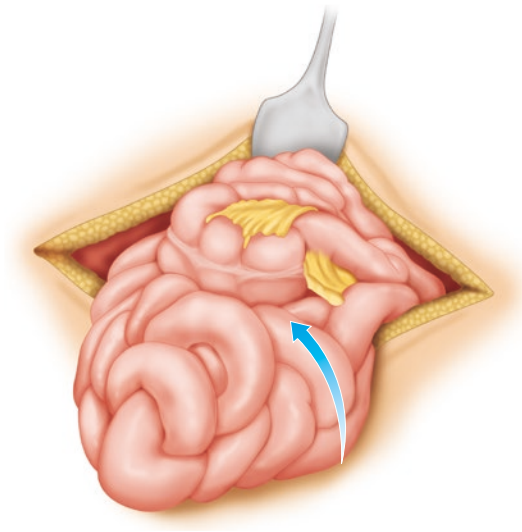

Fig. 32.23 Untwisting of midgut volvulus occurs in a counter-clockwise direction

damaged than it may appear to be on initial macroscopic inspection. A conservative approach in these patients is essential to minimise the risk of short bowel syndrome: bowel that may appear to be of marginal viability, and has not undergone full thickness necrosis is preserved and left in situ.

Where there is any ongoing doubt about the viability of bowel following detorsion of the volvulus, a second look laparotomy 1–2 days later is indicated. By then, bowel that is recoverable will have become more clearly demarcated from that in which irreversible damage has occurred. Only where there is definite full thickness bowel necrosis is resection indicated. At the edges of resection bowel viability is often precarious, for which reason primary anastomosis is not always indicated, and it may be better to fashion a temporary stoma at the lines of resection. Preferably, any stomas are placed close together at one end of the wound, to facilitate subsequent closure.

Occasionally, much of, or the entire small bowel is found to be gangrenous at the time of surgery (Figs. 32.20 and 32.23), and a decision has to be made whether it is in the infant's best interests to simply close the abdomen (leaving the bowel in situ) or whether to excise the necrotic bowel, usually with construction of stomas, with a view to long term TPN. Where the bowel is left in situ the infant usually dies from sepsis and shock within a day or two.

Operative decision-making also needs to take into account a number of other factors which include: whether there is sufficient length for potential long term bowel adaption; the availability and appropriateness of long term TPN; resources for eventual home-based TPN; whether subsequent small bowel transplantation is an option; the nature of associated abnormalities; the importance of informed parental involvement in decision making, and consideration of the likely quality of life of the patient.

It is important to involve the family fully in any discussion on management options. This should be done in conjunction with a neonatologist, social worker, and a support person(s) for the family. Preferably these discussions have started preoperatively (on the basis of the clinical features and their interpretation), which gives the surgeon an advantage should extensive necrosis be identified at surgery.

32.8.4.4 Broaden the Mesentery

In non rotation, the caecum and ascending colon are in apposition to the duodenum and proximal jejunum. There are fascial peritoneal bands between the two. These need to be divided to broaden the mesentery (Fig. 32.24).

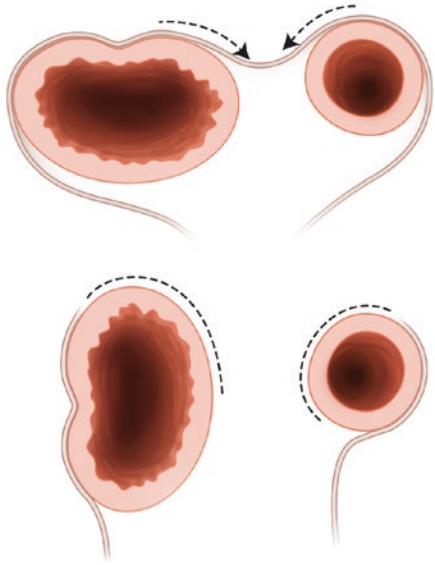

Fig. 32.24 Schematic representation of how the root of the small bowel mesentery is broadened by dissection between the duodenum and caecum, as viewed from inferiorly

Incision of the peritoneal condensations between the caecum/ascending colon on the left, and the duodenum/proximal jejunum on the right (Figs. 32.25 and 32.26), allows the small bowel mesentery to be broadened. The tight peritoneal bands extending over and to the right of the duodenum (often referred to as "Ladd bands") are divided first (Fig. 32.25) as this "straightens out the duodenum, making expansion of the mesenteric attachment between the caecum and duodenum easier (Fig. 32.26). The incision of the mesentery is extended peripherally until the mesentery is broad. Once completed, the bowel is returned to the abdominal cavity, with the small bowel predominantly to the right, and the large bowel predominantly to the left.

32.8.4.5 "en passant" Appendicectomy

Appendicectomy is usually undertaken because of the diagnostic difficulties that subsequent appendicitis produces, as the appendix is located on the left side of the abdomen with the caecum and colon. The morbidity of appendicectomy in this situation is negligible, and prophylactic antibiotics effective against bowel organisms are usually administered at the time of surgery.

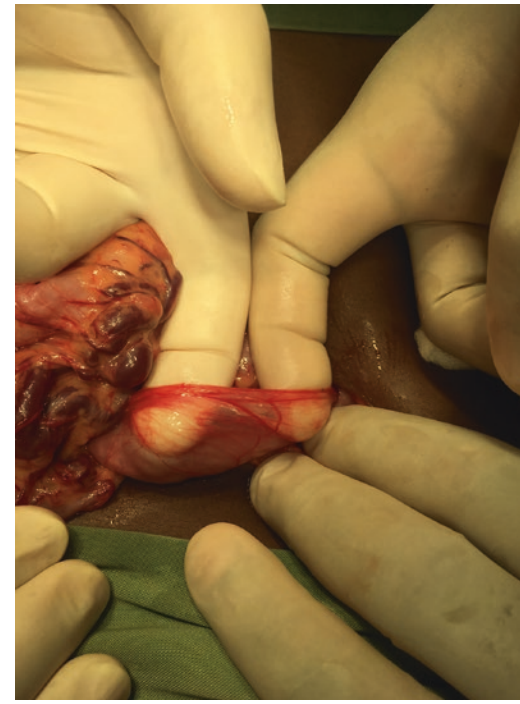

Fig. 32.25 Division of Ladd bands (which run across the duodenum and obstruct it in non-rotation with volvulus) straightens the duodenum, facilitating broadening of the root of the small bowel mesentery

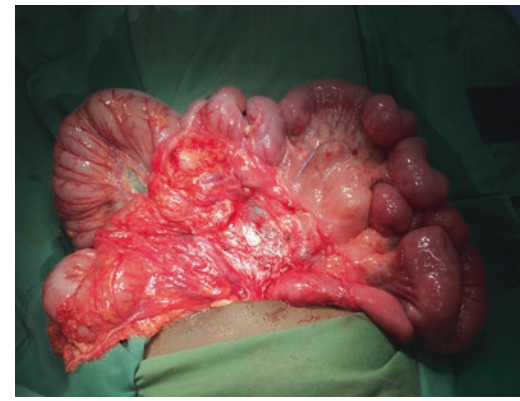

Fig. 32.26 Division of the fascial condensations between the caecum and duodenum opens up and broadens the root of the small bowel mesentery, reducing the risk of subsequent volvulus

32.9 Complications and Results (Table 32.8)

32.9.1 Early Complications

There is surprisingly little information about the complications and subsequent morbidity after surgery for malrotation and volvulus, perhaps because of the rarity of the condition and the relatively small numbers of patients any single institution treats. A number of problems can be encountered in the first days after surgery:

- Reperfusion injury effects and haemoinstability. Restoration of a blood supply to critically damaged bowel may produce a sequence of events with both metabolic and circulatory consequences. These infants must be cared for in a tertiary neonatal unit which has the capacity to provide cardio-respiratory support and prolonged mechanical ventilation. They often need inotropic support, antibiotics, and careful fluid, electrolyte and haematological monitoring.
- Prolonged ileus. This occurs because of dissection close to the root of the small bowel mesentery and duodenum, and is exacerbated if there has been any ischaemic compromise to the small bowel from volvulus. Post-operative ileus for up to a week is not uncommon. Signs that it is resolving include: decrease in the volume of nasogastric aspirates, a softer and less distended abdomen, and the passage of flatus and stools. The older child will start to feel hungry. If an ileus continues for more than a week it needs to be distinguished from ongoing obstruction due to mechanical causes such as recurrence of volvulus, adhesive obstruction and intussusception. A laparoscopic approach may be associated with shorter times to starting feeds and to attaining full feeds [69], perhaps indicating that less ileus occurs with this approach.
- Post-operative intussusception. This is rare after a Ladd procedure, but must always be considered where features of worsening obstruction occur after any retroperitoneal or complex intra-abdominal procedure [71]. Causative factors may include the appendiceal stump acting as a leadpoint, and non-fixation of the ileocaecal mesentery [72]. In one series, 5 of 159 patients undergoing the Ladd procedure suffered post-operative intussusception [73], significantly more common than post-operative intussusceptions after laparotomies for other conditions ($P < 0.001$).
- Wound infection and dehiscence. These are more likely to occur after open surgery, and contributing factors include bacteraemia/septicaemia, and a tight distended abdomen (e.g. from ileus) post-operatively. The incidence can be minimized by perioperative antibiotics and meticulous wound closure (good bites of tissue, not pulled too tightly). Improvements in antibiotics, surgical technique and suture materials mean these complications are now rare.
- Dysmotility. Dysmotility often persists after surgery for malrotation [74], but its causes are poorly understood and difficult to quantify. Some have suggested that it may be due to defective intrinsic enteric innervation [74, 75] or from damage sustained at the time of volvulus. It may be prolonged.
- Laparoscopic results. The difficult view often afforded on laparoscopy, loss of orientation, a

Table 32.8 Sequelae and complications of surgery for malrotation with volvulus

Early	• Septicaemia • Reperfusion injury effects • Haemodynamic instability • Prolonged ileus
Late	• Adhesive bowel obstruction • Recurrence of volvulus • Short gut syndrome – malabsorption – failure to thrive – complications of TPN • Motility disturbance
Death	• Secondary to extensive loss of midgut or complications of subsequent supportive management e.g. TPN, small bowel transplantation

limited working space (especially when the bowel is distended), the requirement for extensive bowel manipulation and problems with interpretation (e.g. is the mesentery narrowed to a degree that predisposes to volvulus and therefore should be broadened?) all have the potential to cause two problems: (1) injury to the bowel wall; and (2) inadequate broadening of the mesentery. Post-operative obstruction may indicate an incomplete Ladd procedure or be due to adhesions [64].

A laparoscopic approach, particularly in the absence of volvulus, produces similar results to those involving an open approach. Basically, while the surgical approach is different, the operation within the peritoneal cavity is essentially the same. Operative times in the absence of volvulus or compromised bowel are similar [69]. There is some indication that a laparoscopic approach may allow for earlier feeds and have a decreased hospital stay [69].

Laparoscopy may be difficult where volvulus has supervened, particularly if there is marked distension or dilatation of the small bowel, because of compromised operative vision.

32.9.2 Late Results and Complications

A number of problems can be encountered weeks or years after the Ladd procedure for malrotation:

- Adhesive bowel obstruction. This is the most common cause of readmission after surgery to correct malrotation [27]. In one series [76], 11 of 46 (24%) patients were readmitted within 6 months of surgery with an acute bowel obstruction, of which six required surgical division of their adhesions, and one patient died. Six patients had multiple admissions for small bowel obstruction. In the nine patients (of 161 in the series) who developed an adhesive bowel obstruction reported by El-Gohary et al. [32], five required operative adhesiolysis following failure of conservative management
- Recurrence of volvulus. This is a well recognised phenomenon, and in some cases may result from inadequate expansion of the root of the small bowel mesentery at the time of the original surgery, or in other cases there is a more localised volvulus in the presence of adhesions. It is reasonably rare: occurring once in 161 cases reported by El-Gohary [32]
- Persistent gastro-intestinal symptoms. This affects about 25% of patients. Symptoms include: vomiting, anorexia, constipation or diarrhoea and chronic abdominal pain. Often their exact cause is difficult to establish with certainty.
- Short gut syndrome. The intrinsic capacity for further adaption and lengthening of the small bowel as the infant grows is substantial, and continues to occur over many months and years. However, despite this, some children simply have insufficient bowel for adequate absorption of nutrients. All the therapeutic options are less than satisfactory and have significant morbidity in their own right. Most commonly, long-term home TPN is employed, but there are various other options available, including serial transverse enteroplasty (STEP) procedure [77], and small bowel transplantation. Not all are readily available treatment options and they all carry with them significant morbidity.
- Complications of total parenteral nutrition. Many of these patients require a central venous line for extended periods of time, and are subject to all their complications: line sepsis, dislodgement of lines, fracturing of lines, displaced tips, and the consequences of catheter tip perforation of vessels. In one series of 27 patients, 2 died of sepsis related to parenteral nutrition [63]. These patients are also subject to all the metabolic complications of long-term parenteral nutrition.

32.9.3 Mortality

Overall, the mortality rate for malrotation undergoing surgery is less than 10% [78, 79], and declining, reflecting improvements in neonatology and paediatric anaesthesia, as well as in the management of short bowel syndrome. Mortality is primarily due to extensive midgut infarction secondary to volvulus (Table 32.9). Prematurity and associated abnormalities also influence mortality [79, 80]. The survival of

Table 32.9 Factors influencing mortality in malrotation with volvulus

Key determinant	Volvulus causing extensive small bowel necrosis
Other factors	Prematurity Associated abnormalities e.g. congenital heart disease

those who are left with short bowel syndrome after extensive resection has improved in recent years as a result of refinements in intensive neonatal care, parenteral nutrition, and perhaps small bowel transplantation.

Where volvulus is producing ischemic damage to the small bowel, mortality is reduced by early diagnosis and immediate surgical intervention. In short, the main determinants of outcome are: (1) high index of suspicion of malrotation with volvulus; (2) early diagnosis; and (3) prompt treatment.

Despite this, the greatest delay in instituting treatment is between first presentation to a medical practitioner and diagnosis. This highlights the importance of educating medical practitioners to have a high index of suspicion of the possibility of malrotation with volvulus in any infant who presents with bile stained vomiting or unexplained abdominal tenderness.

32.10 The Future

32.10.1 Genetics of Malrotation

As more is learnt about the genetics of malrotation and the molecular events surrounding development of the dorsal mesentery and rotation of the bowel, it may be possible to test at risk families. New technologies are becoming available, such as high resolution chromosome analysis by DNA microarrays which are much more sensitive in detecting chromosomal imbalances than earlier techniques. Similarly, improvements in sequencing technology may facilitate the detection of previously unrecognised mutations [1]. Increasingly, the clinical geneticist is likely to become involved in the management of all patients with malrotation who have coexisting abnormalities or features suggestive of a syndrome.

32.10.2 Antenatal Intervention

If malrotation predisposing to volvulus could be identified with greater accuracy on antenatal ultrasonography, or if volvulus can be identified as soon as it occurs, the potential exists for antenatal surgical intervention (and in the former situation, deliberate early induction of labour before volvulus occurs). However, this is unlikely to be achieved in the foreseeable future because of the lack of sensitivity and specificity of diagnosis on antenatal imaging and the inability to predict accurately the true risk of volvulus prior to birth for each case. Where volvulus has been identified antenatally, additional issues relate to the delay between ischaemia occurring and its recognition on imaging, and the risk to both fetus and mother of any intervention.

32.10.3 Management of Short Gut Syndrome

Therapeutic options are limited where midgut volvulus has caused extensive necrosis of the small bowel, and none is entirely satisfactory. The amount of adaption of small bowel that occurs with time in young children is extraordinary, but there remain a difficult group of patients who, even with adaption, are simply left with insufficient bowel for adequate enteral nutrition. For these patients, the options range from long-term total parenteral nutrition [81] to intestinal transplantation. A long sequence of surgical techniques to increase the length or absorptive capacity of the small bowel have been described, tried, and mostly abandoned. Where the proximal bowel is markedly dilated, longitudinal infolding plication may be beneficial (as is used in jejunal atresia) and has the advantage that no bowel is incised or resected, with virtually no complications: peristalsis is improved and there is no loss of absorptive area. The Bianchi and STEP procedures [77] are much more invasive: although popular in a few hands, they are of arguable benefit. Survival after intestinal transplantation is now about 78% at one year, and 65% at three years, although some high-volume centres are reporting even better survival rates, up to 74% at three years [82]. Nevertheless, significant ongo-

ing problems after small bowel transplantation include: the need for immunosuppression; graft rejection; cost; and the limited availability of donor organs [83], such that in most parts of the world this is not considered a realistic alternative. Despite this, it is likely that there will be ongoing improvements in surgical interventions designed to improve gut motility and absorptive area, with a consequent reduction in morbidity.

There is another option on the horizon which has the potential also of improving the plight of children with short gut syndrome; this is tissue engineering of the small bowel to enable regeneration and restoration of small bowel function using the patient's own cells [84]. The process begins with generation of induced pluripotent stem cells (iPSCs) from somatic cells using a combination of four retrovirally transduced transcription factors: Oct3/4, Sox2, Klf4, and c-Myc [85]. The iPSCs resemble embryonic stem cells in many respects, such as their capacity for self-renewal and because they can differentiate into a variety of other cells. These characteristics make them useful for customized rejection-free cell transplant therapy by controlling their differentiation into smooth muscle sheets with peristalsis-like contraction and into intestinal epithelial cells [86, 87]. In addition, iPSCs overcome the ethical issues surrounding the use of fertilized eggs. Further refinements to improve the techniques of iPSC tissue engineering gut following volvulus are a prerequisite for its clinical application in short bowel syndrome.

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Jejuno-Ileal Atresia and Stenosis

33

Alastair J.W. Millar and Alp Numanoglu

Abstract

Successful outcome after surgery for atresia of the small intestine is still sometimes accompanied by significant complications. An understanding of the aetiology and the realization that the proximal blind ending dilated bulbous atretic bowel was the cause of most of these complications and resection of this segment with primary anastomosis of proximal to distal bowel led to a dramatic improvement in outcomes from a mortality of 90—100% to a survival of over 80% in the 1950's. Subsequent improvement in some technical aspects of bowel anastomosis and neonatal perioperative care along with advances in nutrition both parenteral and enteral have made current treatment one of the many success stories of neonatal surgery.

Keywords

Intestinal atresia • Aetiology • Pathogenesis • Classification • Surgery Outcomes

33.1 Introduction

Successful outcome after surgery for atresia of the small intestine is still sometimes accompanied by significant complications [1, 2]. An understanding of the aetiology and the realization that the proximal blind ending dilated bulbous atretic bowel was the cause of most of these complications and resection of this segment with primary anastomosis of proximal to distal bowel led to a dramatic improvement in outcomes from a mortality of 90–100% to a survival of over 80% in the 1950s [3–8]. Subsequent improvement in some technical aspects of bowel anastomosis and neonatal perioperative care along with advances

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_33

in nutrition both parenteral and enteral have made current treatment one of the many success stories of neonatal surgery [9–16].

33.2 History

Intestinal atresia has long been recognized as a cause of neonatal bowel obstruction and is well described in the literature [3, 17, 18]. The first description of ileal atresia was credited to Goeller in 1684. In 1911, Fockens of Rotterdam reported the first successfully treated case of small intestinal atresia [19]. Up until 1952, however, the mortality rate of atresia of the small intestine remained very high, even at the best pediatric surgical centers [3, 20]. Late presentation, dysmotility of the dilated bowel proximal to the atresia after end to end anastomosis, the blind loop syndrome, malnutrition, infections, prematurity, and associated congenital abnormalities contributed to this high mortality. In a comprehensive review of the world literature up to 1950, Evans could find reports of only 39 successfully treated cases of jejunoileal atresia [3]. In 1952, Louw published results of an investigation of 79 patients treated at Great Ormond Street Hospital, London from 1925 recording a mortality of up to 100% in the more distal ileal atresias [20]. Due to delayed presentation his overriding impression was that of ischaemia of the proximal bulbous blind end which resulted from prolonged raised intraluminal pressure. He supported the proposal by Spriggs that jejuno-ileal atresia was probably due to a vascular accident rather than being the result of inadequate recanalization, as had previously been commonly accepted [3, 21, 22]. The findings of bile pigment, lanugo hairs and squames distal to the atresia seemed to confirm this hypothesis.

At his instigation, Barnard perfected an experimental model in pregnant mongrel bitches and reproduced all types of atresia found in humans [23]. This not only confirmed Louw's hypothesis, but also provided the opportunity to improve the technical aspects of corrective surgery, which involved resection of the dilated proximal blind ending bowel and primary end-to-end anastomosis. These factors, along with advances in neonatal care, have achieved survival rates greater than 90% in the current era [4–6]. Interestingly, Nixon had come to the same conclusion i.e. that resection of the bulbous blind end was necessary as he had observed marked dysmotility with ineffective peristalsis of this dilated segment if primary end to end anastomosis without resection had been done. He suggested that this was the prime reason for poor results. He also proved this hypothesis experimentally [7, 8]. He also advocated resection of the most dilated bowel with end to end anastomosis. Thus occurred a great leap forward in the outcomes of treatment for intestinal atresia.

33.3 Classification

The accepted classification is Grosfeld's modification of that described by Bland Sutton. The most proximal atresia or stenosis determines whether it is classified as jejunal or ileal [10, 17] (Fig. 33.1).

Stenosis [10%]: The proximal dilated and distal collapsed segments of intestine are in continuity with an intact mesentery but at the junction there is a short, narrow, somewhat rigid segment with a minute lumen which may mimic atresia type I. The small intestine is of normal length.

Atresia Type 1 [24%]: (Fig. 33.2) The dilated proximal and collapsed distal segments of intestine are in continuity and the mesentery is intact. The obstruction is caused by a membrane with intestinal mucosa on both proximal and distal sides. The pressure in the proximal intestine may expand the membrane into the distal intestinal lumen, so that the transition from distended to collapsed intestine is conical in appearance; the 'windsock' effect. The distal intestine is completely collapsed but the bowel immediately distal to a 'windsock' may be dilated by the windsock. The small intestine is of normal length.

Atresia Type II [9%]: Blind ends joined by a short fibrous cord. The proximal intestine terminates in a bulbous blind end that is grossly distended and hypertrophied for several centimeters but more proximally assumes a normal appearance. This dilated blind end often has poor prograde peristalsis. The distal completely collapsed intestine commences as a blind end that is occasionally bulbous, owing to the remains of a fetal intussusception. The

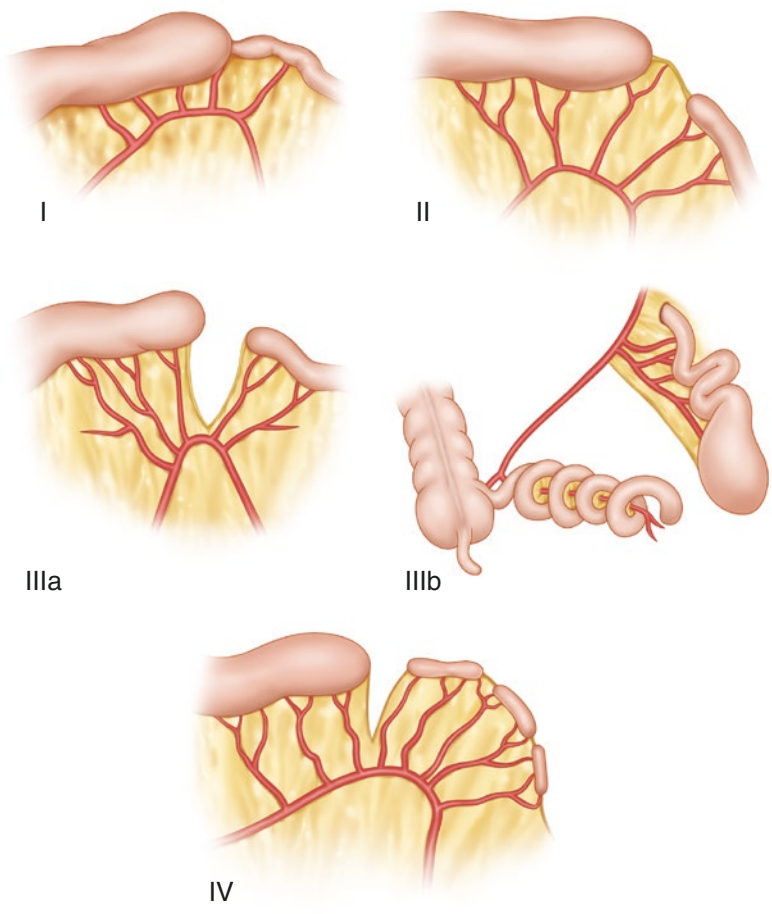

Fig. 33.1 Classification of Intestinal Atresia. From Grosfeld JL et al., Operative Management of Intestinal Atresia and Stenosis based on pathological findings. J Pediatric Surg 1979; 14: 368; used with permission

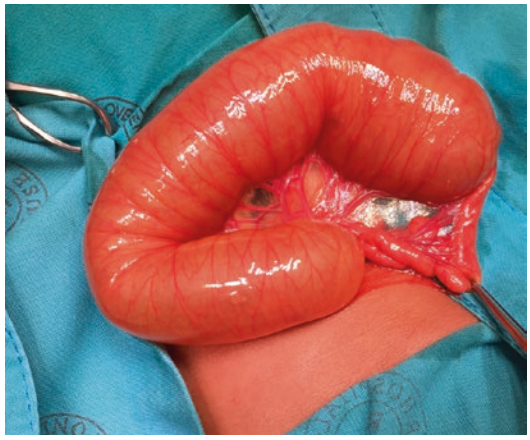

Fig. 33.2 Type I jejunal atresia. Abdominal radiograph had shown a triple bubble of dilated gas filled bowel proximal to the atresia (see Fig. 33.10) which was confirmed at laparotomy showing the typical dilated proximal jejunum and adjacent distal collapsed worm-like bowel

two blind ends are joined by a thin fibrous band, with the corresponding intestinal mesentery intact. The small intestinal length is usually normal.

Atresia Type IIIa [15%]: The appearance is similar to that in type II, but the blind ends are completely separate. There is always a mesenteric defect of varying size and the proximal intestine may, as a secondary event, undergo torsion or become over-distended with resultant increase in intraluminal pressure leading to necrosis and perforation. The total length of intestine is reduced to a varying extent.

Type IIIb [19%] ['Apple Peel' or 'Christmas Tree' deformity]: (Figs. 33.3, 33.4, and 33.5) As in type IIIa, the blind ends are unconnected and the mesenteric defect is large. The atresia is usually localized in the proximal jejunum near the ligament of Treitz, with absence of the superior mesenteric artery beyond the origin of the middle

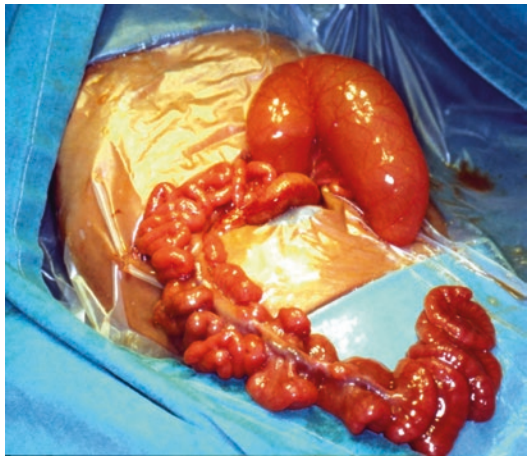

Fig. 33.3 Typical type IIIb 'apple peel' atresia with a dilated blind ending jejunum and loss of proximal mesentery. The single vascular arcade to the distal ileum arising from the right and middle colic arteries is evident. Malrotation is present with a central lying caecum

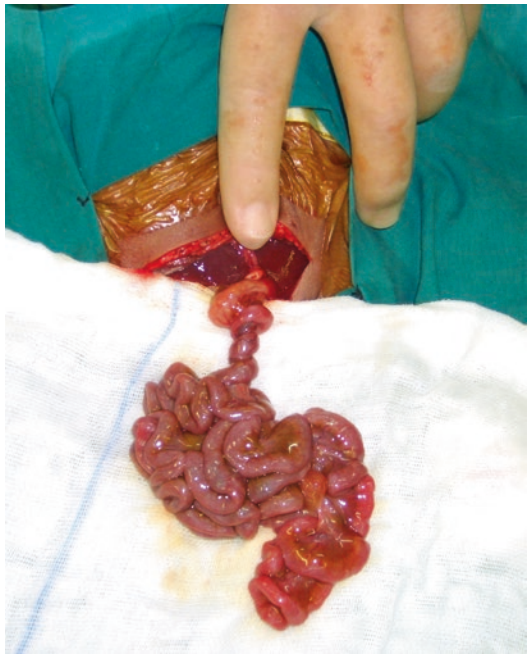

Fig. 33.4 Type IIIb jejunal atresia with tenuous blood supply and 720° anti-clockwise volvulus [unusual]

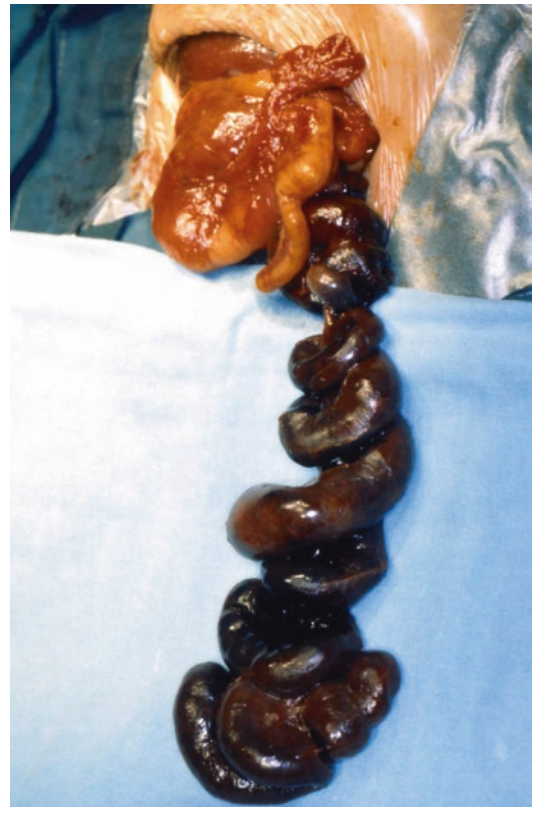

Fig. 33.5 An established type IIIb atresia where the remaining bowel has undergone ischaemic infarction from torsion shortly before birth

colic branch and absence of the dorsal mesentery. The distal intestine assumes a helical configuration around an attenuated single artery of blood supply arising from the ileocolic or right colic arcade. Occasionally further atresias of type I or II are found in the distal intestine, usually close to the blind end. There is always a significant reduction in intestinal length. Vascularity of the distal intestine may be impaired and secondary volvulus of the 'apple peel' may occur resulting in very short lengths of surviving bowel.

Type IV [23%] [multiple atresias]: (Figs. 33.6, 33.7 and 33.8) Multiple atresias can be combinations of types I–III and often present morphologically as a string of sausages. Multiple atresias are often localized to a short segment of intestine. The site of the most proximal atresia determines whether it is classified as jejunal or ileal.

33.3.1 Prognosis

The prognosis for all types of intestinal atresia is currently excellent with most recent series reporting long term survival of greater than 90% [12, 24]. A small number may succumb from

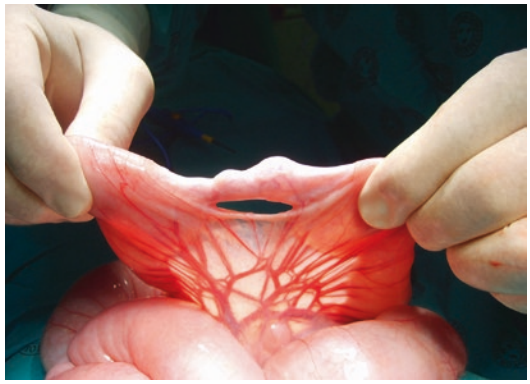

Fig. 33.6 Segment of stenotic jejunum but showing deficient mesentery in a type IV atresia

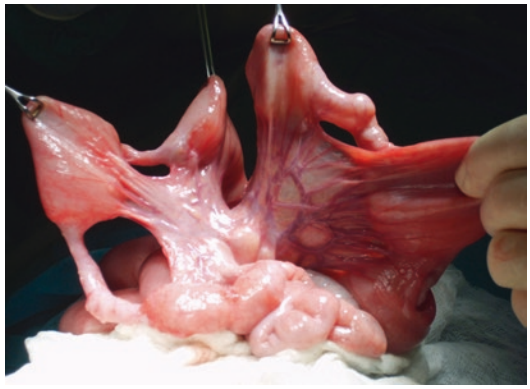

Fig. 33.7 Type IV atresia with evidence of multiple mesenteric defects

prematurity, associated abnormalities, which are rare outside the gastrointestinal tract, ultra-short gut syndrome and complications of either parenteral nutrition (liver disease or central line related) or occasionally as a consequence of complications from bowel transplant in those few in whom enteral autonomy cannot be established [2, 12, 25–28].

33.4 Epidemiology

The prevalence of jejunoileal atresia widely varies among different countries and geographical areas. In France, the prevalence is 2.25 cases per 10,000 live births [29, 30]. The overall prevalence of small intestinal atresia in Spain and Latin America is 1.3 cases per 10,000 live births and in Africa 1 per 3000 live births [31]. There

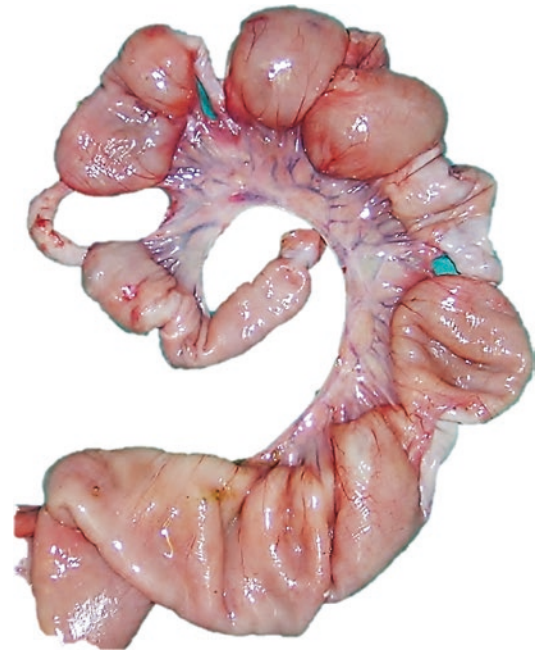

Fig. 33.8 Resected specimen of Type IV atresia (Fig. 33.7) with multiple sacular segments of bowel with types I, II and II atresias

also appears to be an increased incidence in twin pregnancies at 7.3 per 10,000 live births [32].

Intestinal atresia accounts for about one third of all cases of neonatal intestinal obstruction. In West Africa, intestinal atresia is the fourth most common cause of neonatal intestinal obstruction after anorectal malformations, Hirschsprung disease, and strangulated inguinal hernias [31, 33]. In an 11-year retrospective review of 500 children in India, intestinal atresias were found to be the most common cause of intestinal obstruction in newborns and the second most common cause (11.8%) after intussusception (20.8%) in all age groups [33]. Boys and girls are equally affected [34].

33.5 Aetiology and Genetics

Our present understanding of the etiology of intestinal atresias is based upon the classic experimental work of Louw and Barnard reported in 1955 [23]. These investigators observed that ligating mesenteric vessels and causing strangulated obstruction in fetal dogs resulted in atretic lesions of the small intestine that were similar to those

observed clinically in human neonates. Thus, atresias and stenoses of the small intestine are believed to be due to an ischemic insult. This etiologic mechanism explains the frequent association of atresias with mesenteric defects and with other conditions that may cause strangulated obstruction of the intestinal tract (e.g. volvulus, intussusception, internal hernias and gastroschisis) [35–39]. Ischaemic experimental animal models in lambs, rabbits, rodents and chick embryos have replicated the work of Louw and Barnard confirming the ischaemic aetiology of most cases [40–43]. This etiology may also explain why intestinal atresia is associated with maternal smoking and vasoconstrictor drug exposure during pregnancy and thrombophilic diatheses [44]. Inherited thrombophilia has been shown to be present with increased frequency in infants with congenital atresia suggesting that in-utero thrombotic events may play a role in the aetiology [40, 44–47]. There have also been several case series reported of familial small bowel atresia most frequently type IV lesions [48]. More recently some of the established concepts have been questioned [49]. However the localized nature of the vascular accident occurring late in fetal life would explain the low incidence (less than 10%) of coexisting abnormalities of extra-abdominal organs. It is proposed that the ischaemic segment is absorbed with proximal and distal healing. Ongoing proximal peristaltic activity results in the typical bulbous dilatation of the bowel immediately adjacent to the atresia. The proximal bowel may perforate in utero leading to meconium peritonitis. If the insult has occurred later in gestation, evidence of the cause eg. intussusception, volvulus may be observed. The anomaly is usually not genetically determined although affected monozygotic twins and siblings have been described. A genetic basis however has been established for type III b and IV multiple atresias [48, 50–55]. However, most cases are sporadic with no familial history [56].

33.6 Associated Anomalies

Associated anomalies outside the gastrointestinal tract are rare, however there is a < 1% incidence of association of proximal jejunal atresia with duodenal atresia and several reported cases of an association with biliary atresia [46]. Also there are specific immunodeficiency syndromes decribed with multiple atresias in addition to epidermolysis bullosa [57–59]. There is a well-known association with cystic fibrosis and less frequently ileal atresia may be seen with total colonic aganglionosis [31, 60, 61].

33.7 Antenatal Presentation

Fetal diagnosis is now possible in many cases of jejuno-ileal atresia which may show polyhydramnios, dilated echogenic and thickened bowel on ultrasound scanning [62] (Fig. 33.9). This may be clearly advantageous, as delivery can be planned at or near a specialist centre with full neonatal surgical capability. Counseling is essential by a multidisciplinary team (obstetrician, paediatric surgeon, neonatologist) and a careful search for associated anomalies is important. However prenatal detection rates vary widely in fetal medicine centres (9–24%), and there appears to be a high rate of false positive scans with the more distal atresias being less likely to be diagnosed [43, 62, 63].

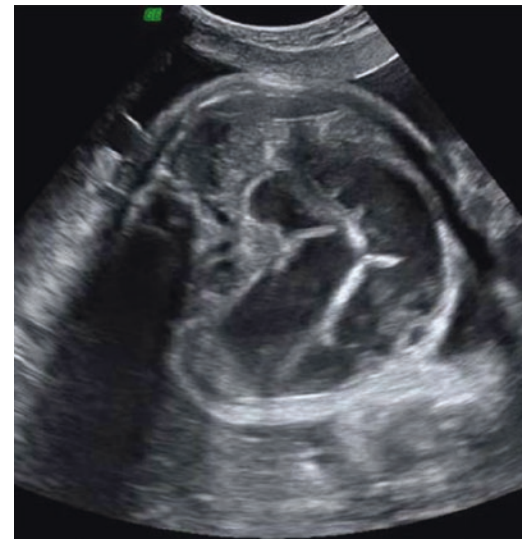

Fig. 33.9 Antenatal ultrasound scan showing dilated hyperechoic loops of fluid filled bowel

33.8 Clinical Presentation and Diagnosis

Intestinal atresia should be suspected in any newborn showing evidence of bowel obstruction (bilious vomiting, abdominal distension and failure to pass meconium) [1, 13, 64]. Many are born prematurely or small for gestational age presumably due to failure to absorb nutrient from ingested amniotic fluid or when in association with the abdominal wall abnormalities of gastroschisis and exomphalos [65]. Aspiration via a naso-gastric tube of more than 25 ml of fluid from the stomach in a newborn is very suggestive of obstruction. Antenatal ultrasound scanning as noted may show dilated loops of bowel with vigorous peristalsis, which is diagnostic of obstruction. Polyhydramnios may develop but is more commonly seen in duodenal and oesophageal obstructions [62, 63, 66]. The more distal the atresia the more generalized the abdominal distension and the lower the incidence of polyhydramnios. After aspiration of gastric contents the abdomen will be less distended and visible peristalsis may be observed. There is a failure to pass meconium and typically small volume grey mucoid stools are passed. Abdominal tenderness or peritonitis only develops with complications of ischaemia or perforation. This commonly occurs with delay in diagnosis and is due to either increased intraluminal pressure from swallowed air or secondary volvulus of the bulbous blind ending bowel above the level of the first obstruction [6, 24]. In most patients a simple abdominal x-ray with antero-posterior and either cross-table or left lateral decubitus projection are adequate to make the diagnosis based upon the presence of dilated air-filled intestinal loops and air-fluid levels [67] (Figs. 33.2 and 33.10). In addition, plain abdominal x-rays will suggest the level of obstruction based upon the number of dilated bowel loops. The presence of multiple dilated bowel loops of varying calibre without air-fluid levels suggests the possibility of meconium ileus, particularly if the intestinal content has a 'ground glass' appearance. A single very dilated loop with a large fluid level is often indicative of a distal atresia in ileum or colon [61, 68, 69].

The differential diagnosis includes other causes of intestinal obstruction in the neonate [24]. In patients with evidence of a proximal complete obstruction, the differential diagnosis is limited and no additional diagnostic studies are required. In patients with multiple dilated bowel loops suggesting a distal obstruction, the differential diagnosis includes several conditions for which surgical intervention may not be required. Therefore, in these patients a contrast enema may

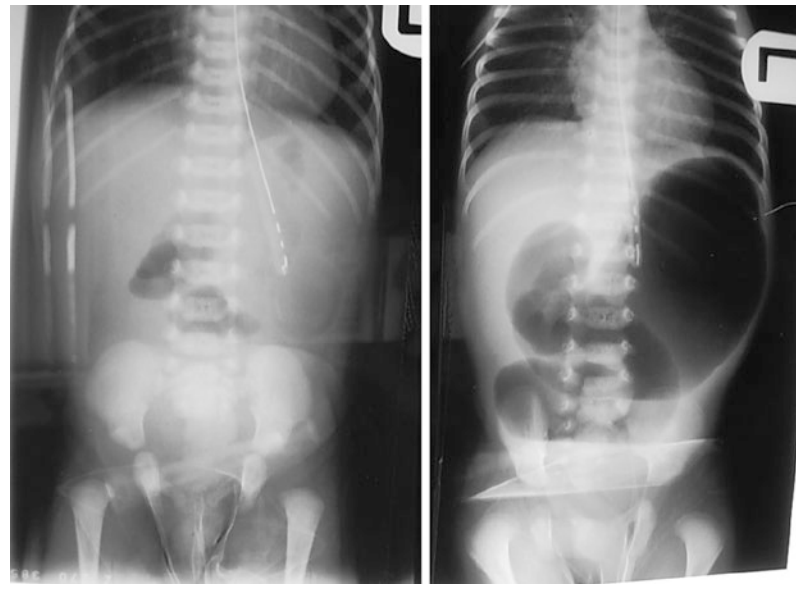

Fig. 33.10 Abdominal radiographs of an infant with jejunal atresia before aspiration via the nasogastric tube and after injection of air as contrast

be helpful to look for evidence of meconium plug or meconium ileus which may respond to non-operative managements. In addition, a contrast enema may demonstrate findings suggestive of Hirschsprung's disease which would direct initial management toward obtaining confirmatory tests for this disease. A contrast enema showing a patent colon is also helpful in that demonstration of colonic patency by injection of saline at operation, a sometimes tedious procedure, is not required (Fig. 33.11).

In patients with intestinal stenosis diagnosis is frequently delayed as the obstruction is incomplete. Plain abdominal x-rays may demonstrate proximal bowel dilation, however in most patients a gastrointestinal contrast meal or enema is required to confirm and locate the site of partial obstruction. The classical appearance of the colon distal to jejuno-ileal atresia is an unused or microcolon. Malrotation may also be observed in 10–30% of babies with jejuno-ileal atresia [24] (Fig. 33.12). Occasionally dystrophic intraperitoneal calcification of meconium peritonitis may be seen on plain radiograph, signifying intrauterine bowel perforation. If the atresia has formed late in intrauterine life, the bowel distal to the atresia may assume the calibre of a used colon.

33.9 Surgical Management

All patients should receive judicious fluid hydration prior to operative intervention. In addition, a nasogastric or orogastric tube should be passed to

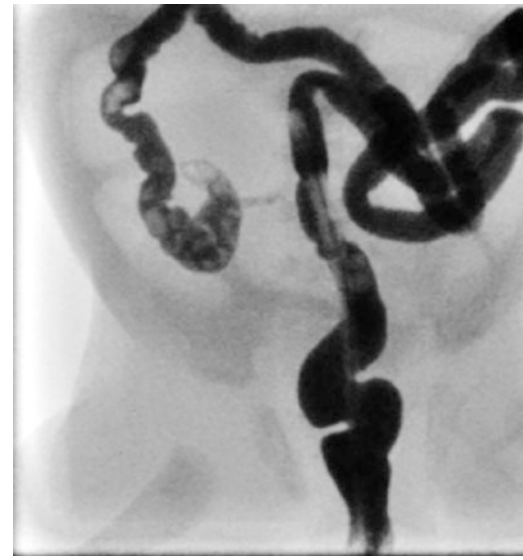

Fig. 33.12 Contrast enema in infant with Type IIIb atresia. Note large air filled loops indicating a proximal atresia with a patent 'unused' colon ending in the right upper quadrant suggesting malrotation or possible right sided colonic atresia

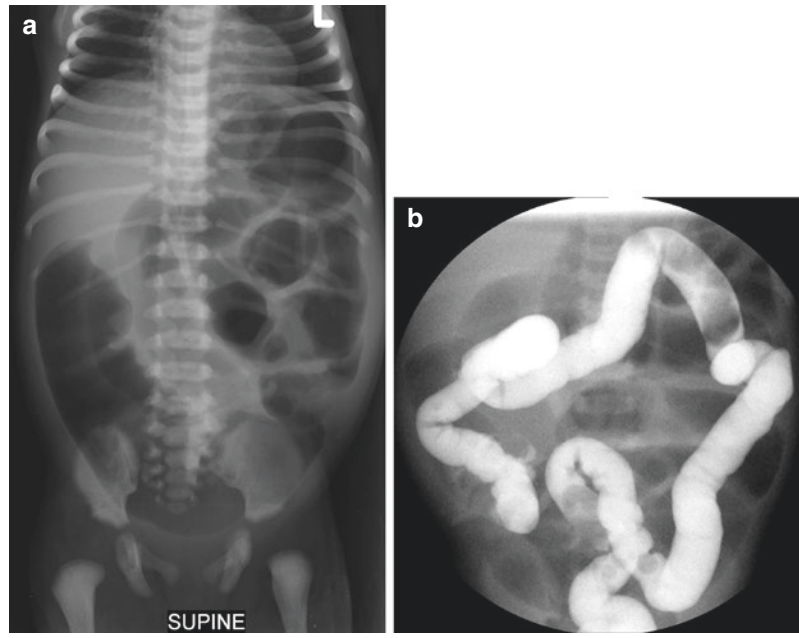

Fig. 33.11 (**a**) Abdominal radiograph of infant with ileal atresia. Note multiple dilated gas-filled loops of bowel and one large loop in the right lower abdomen. (**b**) Contrast enema in the same patient shows a patent normal colon of good size indicating a possible late in-utero event causing the atresia

empty the stomach and decrease the risk of vomiting and aspiration. In general, patients with intestinal atresias have a low risk of associated cardiac anomalies, so that preoperative special investigation is not required unless the patient has clinical evidence of a serious cardiac defect. Adequate operative exposure is obtained through a supra-umbilical, transverse incision transecting the rectus muscles 1–2 cm. above the umbilicus. However, increasingly minimally invasive techniques are used with small circum-umbilical incisions or even laparoscopic techniques and extra-corporial anastomosis [70–73]. At exploration, the site of the most proximal atresia is readily identified by the marked change in intestinal caliber. The outer wall of the intestine at the site of obstruction may appear intact, ischaemic and congested or there may be an associated defect in continuity of the intestine and the mesentery (type III). The intestine proximal to the obstruction which is dilated and hypertrophied frequently has a cyanosed appearance and may have some necrotic areas either from sustained intraluminal pressure or secondary volvulus, especially if there has been a delay in presentation. Perforation may have developed antenatally, leading to meconium peritonitis or may occur as a postnatal event, especially if diagnosis is delayed. The peristaltic movements in this segment are subnormal and ineffective, and histologic and histochemical abnormalities can be observed up to 20 cm cephalad to the atretic segment [8, 74–76]. In contrast, the distal bowel is unused and worm-like in appearance, but potentially normal in length and function. Generally, surgical treatment requires excision of the ends of the intestine involved in the atresia. It is also essential to look for distal sites of obstruction, which can occur in up to 20% of patients and may not be immediately obvious due to lack of calibre change beyond the proximal atresia [24]. These distal points of obstruction can be identified by flushing the distal intestinal lumen with saline to confirm intestinal continuity to the level of the ileocaecal valve or rectum if a preoperative enema showing colon patency has not been performed. After resection of the atretic segment, the surgeon is faced with the task of re-establishing continuity between intestinal segments often with marked lumen size discrepancies. This is best achieved by end-to-end extra-mucosal single layer anastomosis with larger gaps between interrupted sutures on the dilated segment. Discrepancies in size of bowel lumen of up to 8:1 have been accommodated using this technique. Another consideration is the potential dysmotility of the proximal markedly dilated segment which may result in delayed intestinal function and problems with bacterial overgrowth [4, 77]. Therefore, in patients with a relatively short segment of severely dilated proximal intestine, resection of the dilated segment with reestablishment of continuity by end-to-end anastomosis is the best option. However, in patients with long segments of proximal intestine that are significantly dilated, or loss of intestinal length eg. Type III a and b, resection of the whole involved segment may result in inadequate remaining intestinal length to allow absorption of enteric nutrients (i.e. short-bowel syndrome). Therefore, these patients frequently are treated by either imbrication or tapering enteroplasty of the proximal dilated segment [78]. To date, no randomized studies have compared the outcomes in patients with intestinal atresias with or without the addition of an enteroplasty or plication however some benefit appears evident [77, 79–82].

In patients with jejunal atresia just distal to the ligament of Treitz duodenal derotation and tapering duodeno-jejunoplasty is advocated [82]. It is important to be careful to avoid cutting back too far such that the pancreas and ampulla of Vater are protected [83]. Passage of a trans-anastomotic feeding tube for early commencement of enteral feeding is a useful adjunct to post-operative nutrient support particularly if delay in restoration of foregut function is expected due to gross dilatation of the proximal bowel and if parenteral nutrition is not available, a situation still common in many parts of the world. The trans-anastomotic tube can either be passed via the nasogastric route or via a Stamm gastrostomy performed on the anterior aspect of the stomach. The total residual length of bowel should be measured with a tape and recorded as this gives some guidance as to prognosis.

Patients who have multiple atresias (type IV) or an apple-peel deformity (type IIIb) are particularly challenging management problems [77, 78, 84–87]. These patients may require multiple anastomoses and frequently will experience long-term delays in return of intestinal function [86]. In addition, many of these patients will have short-bowel syndrome due to inadequate residual intestinal length. In type IIIb atresias the blood supply to the remaining small bowel (closer to the distal blind end) may have a particularly precarious blood supply (see Figs. 33.3, 33.4 and 33.5). The bowel should be displayed in a position of non-rotation keeping the free mesenteric border in sight and restrictive fibrotic bands along this free edge should be divided prior to primary anastomosis to enhance blood supply and venous drainage. The mesentery from any resected bowel is retained and may assist in closure of mesenteric defects [24]. This technique is very helpful and prevents kinking or distortion of the anastomosis. Furthermore, the potential for kinking the single marginal artery and vein requires careful placement of the bowel into the peritoneal cavity at the completion of the anastomosis. Multiple atresias are often localized to a short segment of intestine, and resection with one anastomosis is preferred if sufficient intestinal length remains. If the bowel length is critical, multiple anastomoses should be performed [25, 85]. In type IV atresias with multiple segments of bowel it is useful to pass a nasogastric tube through these segments consecutively like a string of beads. This facilitates performing the multiple anastomoses and may even act as a stent during the post-operative period [56, 85, 88].

In general the formation of stomas is unnecessary and should be avoided as dilated bowel does not reduce in calibre and fluid and electrolyte losses may be severe (vide infra). In infants with congenital short bowel, lengthening procedures such as the serial transverse enteroplasty procedure (STEP) and lengthening and tailoring procedures (LILT, Bianchi) have no defined place at the initial operation although sporadic reports have appeared in the literature [89–92]. It would seem wiser to perform a primary end-to-end anastomosis and allow for adaptation to progress before intervening surgically when a plateau of enteral tolerance has been achieved and the infant is well grown and outside the neonatal period. The fashioning of stomas, e.g. Bishop–Koop, Santulli, Rehbein or double barrel, as practiced by some, is not routinely advocated unless there is gross intraperitoneal contamination, making a primary anastomosis unsafe [34, 38, 93, 94]. The Bishop-Koop stoma seems to be particularly associated with an increased incidence of complications [12]. Jejuno-ileal atresia associated with a gastroschisis is treated by resection and primary anastomosis if there is limited oedema and matting from amniotic peritonitis. If there is marked oedema and matting initial reduction of the eviscerated bowel with the atresia intact and primary closure of the abdominal wall defect, if possible, is preferred [95]. After allowing for disappearance of the oedema (10–14 days), a second laparotomy is performed with resection of the atretic segment and primary anastomosis. In the long term there is up to 20% incidence of prolonged dysmotility which may benefit from surgical interventions of tapering or imbrication [74, 81, 96–98]. So-called ‘closing gastroschisis’ may be associated with the both exit and entry level atresias with loss of intestinal length. Serial antenatal ultrasound scanning may show increasing bowel dilatation which should prompt early preterm delivery [99].

Postoperative care requires nasogastric decompression for several days after the operation (longer for high jejunal atresias). Therapeutic antibiotics are usually continued for 5–7 days or longer directed by culture of gastric aspirate and enteric content, and an oral antifungal agent is given prophylactically. Gavage feeding can begin as soon as there is evidence of bowel peristalsis. If a trans-anastomotic tube has been placed, hourly feedings can commence in small volumes from the day following surgery. Oral intake is commenced when the neonate is alert, sucks well, and there is evidence of prograde gastrointestinal function, i.e., clear gastric effluent of low volume, a soft abdomen and stools have been passed. Surveillance should continue until the infant has established normal gastrointestinal function. If at any time there is suspicion of a leak at the anastomosis

(suggested by ileus, abdominal distension, vomiting and peritonitis), a plain radiograph of the abdomen should be taken. If this reveals free air in the abdomen more than 24 h after operation, laparotomy should be performed immediately and the leaking site sutured or the anastomosis redone. Parenteral nutrition is given initially and weaned slowly as enteral feeding is increased as per protocols. There is increasing evidence that keeping the daily fat load to 1 g/kg body weight and the use of fish oil containing lipid will reduce the incidence and severity of parenteral nutrition associated liver disease [100, 101].

33.10 Complications and Special Considerations

Although a survival rate of more than 90% can be expected, complications are not infrequent [24, 36, 56, 102]. These include anastomotic leaks and stricture formation, ischemia of the bowel due to the delicate blood supply, especially in type IIIb, adhesive bowel obstruction, the short bowel syndrome, infections related to the wound, intravenous access, chest, septicemia and bacterial overgrowth with blind loop syndrome or episodes of gram negative central line infections from bacterial translocation. In predicting the ultimate functional outcome, the following factors must be taken into consideration: the ileum adapts to a greater degree than the jejunum, the neonatal small intestine still has a period of maturation and growth ahead of it, and the actual residual small intestinal length is difficult to determine accurately at the time of the initial surgery. The proximal obstructed bowel segment is dilated and its functional potential may be overestimated, while that of the distal unused collapsed bowel may be underestimated. Of some importance is an intact ileocecal valve, which allows for accelerated intestinal adaptation with shorter residual jejunoileal length. The absence of the ileocecal valve may also lead to an increased transit-time, malabsorption, diarrhea and increased bacterial contamination of the small bowel. The full management of the short bowel syndrome is beyond the scope of this chapter [103].

33.10.1 Outcome

Before 1952 the mortality rate for congenital atresias of the small intestine even in the best centres was around 90% [3, 20]. Between 1952 and 1955, there was moderate improvement in outcome due to improved neonatal care [16]. At that stage most were treated by primary anastomosis without resection. With liberal resection of the blind ends and end-to-end anastomosis, the survival rate increased to 78% during 1955–1958 in one centre [4–6].

During the 25 year period from 1990 to 2015, 160 patients with jejuno-ileal atresias and stenoses were admitted to the pediatric surgical service at the Red Cross War Memorial Children's Hospital. There were 13 deaths (92% survival). Factors contributing to the mortality rate were: type of atresia (type III), proximal bowel infarction with peritonitis (delayed presentation), anastomotic leaks, missed distal atresia, the short bowel syndrome with PN associated liver disease, sepsis and more recently HIV infections [104]. The morbidity of patients with intestinal atresia is directly related to the length of the bowel if there is gross insufficiency (short bowel syndrome) as well as any degree of dysmotility which is particularly prevalent in babies with gastroschisis.

Infants with Ultra-short bowel [less than 10% of expected length] are usually infants with type III or IV atresia [24, 105].

33.11 Quality of Life and Long-Term Outcome

The quality of life in the long-term is dependent on the length of residual bowel, associated disease, [2, 12, 102, 106, 107] (Table 33.1) e.g., Cystic fibrosis, dysmotility especially with gastroschisis and the medical management of the short bowel syndrome. Increasingly, with appropriate medical and surgical management, most of these children can achieve enteral autonomy. A few may require life-long parenteral nutritional supplementation or may develop irreversible intestinal failure associated liver disease requiring

Table 33.1 Jejunal atresia and stenosis: Red Cross Children's Hospital—Experience 1959–2015

Type	Jejunum	Ileum	Total	(%)
Stenosis	22	14	36	10
Type I	68	18	86	24
Type II	22	14	36	10
Type IIIa	28	27	55	15
Type IIIb	68	1	69	19
Type IV	67	14	81	22
Total	275	88	363	100
Mortality related to type of atresia[a]				
Type	Patients	Mortality	%	
Stenosis	36	0	0	
Type I	86	4	6	
Type II	36	4	11	
Type IIIa	53	8	15	
Type IIIb	68	10	16	
Type IV	81	12	15	
Total	363	36	10	

[a]Last 25 year survival (1990–2015) 147/160 (92%)

either bowel or bowel and liver transplant. There are some who may require parenteral nutritional support from time to time in childhood during periods of enteric stress as they have little or no reserve. All children with short bowel are at risk of subclinical vitamin and micro-nutrient deficiency and can be divided into four main clinical categories: (a) those with normal alimentary function; (b) those with adequate function for growth and development but little or no reserve; (c) those with adequate function for survival after a prolonged period of adaptation and parenteral nutrition support and (d) those with uncorrectable intestinal insufficiency.

In those patients in group c) it is remarkable how far one can go with very little bowel using all the surgical and medical techniques available. In our own series, there are two infants with presenting lengths of 11 and 14 cm (ileocaecal valve intact 1 cm and 2 cm ileum respectively). Both have achieved full enteral autonomy at 13 months and 20 months of age after Bianchi procedures were done at around 6 months of age when a plateau of 80% enteral tolerance was reached without surgical intervention apart from the initial end to end anastomosis without resection. Neither of these have any evidence of liver disease using SMOF [a soya, medium chain triglyceride, olive oil and fish oil balanced fat emulsion lipid] as the preferred parenteral nutritional formula along with all other modalities of short bowel syndrome care [108].

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Duplications of the Alimentary Tract

34

Antti I. Koivusalo and Risto J. Rintala

Abstract

Duplications of the alimentary tract are cystic or tubular structures most often in close proximity with a section of the alimentary tract. The most common location is abdomen and the most common location is small intestine. Duplications possess a surrounding muscular layer, an inside mucosal layer, intrinsic nerves and peristalsis. Approximately 10% of duplications are multiple and there is a high prevalence of coexisting malformations of vertebral column, intestines and urinary tract and genitals. A diagnosed duplication should always warrant for search of others and the coexisting malformations. Duplications may contain heterotropic gastric or other kind of mucosa.

Duplications are increasingly often diagnosed antenatally. One third of foregut and midgut duplications present during infancy whereas hindgut duplications without an external sign of duplicated anus or genitalia may remain undiagnosed longer. In an infant the most common symptom is vomiting from gastric outlet obstruction by a large cystic duplication, alternatively duplication may cause intestinal volvulus or intussusception. Duplications in the mouth, oropharynx, neck and thorax may cause airway obstruction. Heterotropic gastric mucosa in duplication may ulcerate and cause haemorrhage or perforation. Because of the risk of significant complications and the risk of eventual malignant transformation surgical removal of duplication is practically always indicated.

Keywords

Alimentary tract duplications • Embryology • Surgery • Outcomes

34.1 Introduction

Duplications of the alimentary tract can occur anywhere from oropharynx to anus. Depending on their embryonic origin duplications can be

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_34

divided to foregut, midgut and hindgut duplications, all of which have a characteristic presentation and a pattern of associated malformations.

Approximately two thirds of all intestinal duplications are discovered within the first two years of life, with one third identified in the newborn period. Although duplications may have a protean modes of presentation the most common symptoms are associated with the tendency of the duplications to occupy space and compress hollow viscus and the tendency to haemorrhage from the heterotrophic gastric mucosa. Duplications can be diagnosed antenatally and in some cases intrauterine or immediate postnatal interventions are indicated. Neonatal emergencies associated with duplications are high airway obstruction, respiratory distress, haemorrhage and intestinal obstruction. Alimentary tract duplications are associated with potentially fatal complications and when diagnosed surgical treatment is always indicated. With time malignant transformation of the duplications can occur.

34.2 Definition, Etiology, Epidemiology and Anatomical Characteristics

Early criteria by Ladd required the alimentary tract duplications to possess (I) a well-defined coat of smooth muscle, (II) an epithelial lining representing some portion of the intestinal tract (III) intimate anatomic association with some portion of the gastrointestinal tract [1]. More recently it has been found that duplications may contain several kinds of heterotropic mucosa, respiratory epithelium, bronchogenic cartilage [2–4] and duplications may be located far apart from the section of the alimentary tract from which their mucosal lining is derived. The muscular wall of duplications possesses intrinsic innervation and exerts peristalsis [5, 6].

The embryologic origin of alimentary tract duplications has remained somewhat obscure. The theories of the etiology of alimentary tract duplications include those of abortive or partial twinning, split notochord and anomalous adhesions [7], diverticula and canalization defect [8] and environmental factors [9]. Although these theories may explain long doubled segments of intestine and anal opening, dorsal location with tethering to the vertebral column and occurrence of associated anomalies, no single theory explains the anatomical and histological variations found in alimentary tract duplications. It is assumed that duplications occur early in fetal life and develop after the formation of the notochord after the third gestation week. There is some evidence that expression of the sonic hedgehog gene by the notochord affects the Shh-GLi signalling pathway and may contribute to a spectrum of bronchopulmonary, alimentary tract and associated anomalies [10]. Foregut duplications and lesions in foregut derived respiratory tract such as bronchogenic cyst and congenital pulmonary airway malformations (CPAM) and other foregut malformations such as oesophageal atresia may actually share a common etiology [11–14]. Thoracoabdominal duplications may interfere with the development of diaphragm, vena cava and the portal vein [15–18]. Despite the obscure genetic and embryological origin it has become practical to refer to foregut, midgut and hindgut derived duplications. Thus duplications from the pharynx to the papilla of Vater are considered foregut derived, duplications of the third and fourth part of duodenum, jejunum, ileum and little over the middle portion of the transverse colon midgut derived and duplications of rest of the colon, rectum and anus hindgut derived.

Alimentary tract duplications have a reported incidence of 1 in 4500 fetal and neonatal autopsies [19]. There is a slight overall male preponderance [6].

Approximately 20% of duplications are located in the mediastinum, 1–2% are cervical or oral and 2% are thoracoabdominal, whereas rest of the locations are abdominal including gastric (2%), duodenal (6%), jejunal and ileal (53%), colonic (13%) and rectal (4%) [20].

Rectal duplications may have a fistulous vaginal or cutaneous opening [6, 21]. Duplications of

pancreas, gallbladder and the extrahepatic biliary tract [22–24] and even gastrointestinal triplications [25, 26] have been reported. Of alimentary tract duplications 75–85% are cystic which predominantly lack communication with their adjacent intestine, whereas the remaining duplications are tubular that may or may not have one or more direct communications across the common septum [27, 28]. Duplications are typically located in the dorsal aspect of the adjacent intestine. According to Li and colleagues 75% lie parallel to the mesentery receiving a main artery from one leaf of mesentery whereas 25% are intramesenteric and receive arteries from both mesenteric leaves, [29], but occasionally separate duplications with vascular pedicle occur [30]. Some duplications are located retroperitoneally completely isolated without contact from their organ of derivation [31].

Enteric duplications are multiple in 10–20% of patients, and detection of one duplication indicates search for other noncontiquous duplications [6] and also CPAM lesions [11]. Of all alimentary tract duplications 35–70% contain heterotropic gastric mucosa, the occurrence being highest in foregut and small bowel and lowest in hindgut duplications [6, 27]. Ulceration with subsequent haemorrhaging of the heterotopic gastric mucosa within duplication is a typical manifestation in 10–20% of patients [6, 32–34]. Other types of heterotropic tissue in duplications include those derived of pancreas, thyroid, lung, bronchi and adrenal cortex [6, 32, 35]. Children with enteric duplications have a relatively high incidence of associated anomalies. Vertebral anomalies including malformed vertebraes, spina bifida occulta, anterior meningocele, scoliosis and tethetring connections to the spinal canal can occur in 50% of thoracic and thoracoabdominal lesions whereas midgut duplications are associated with intestinal atresias, intestinal malrotation, and hindgut duplications with genital and urinary tract anomalies [6, 32, 35]. The presence of multiple noncontiguous duplications increase the probability of associated malformations to 100% [6]. Duplication cysts which extend into the spinal cord are referred as neurenteric cysts.

34.3 Clinical Presentation

Clinical presentation of alimentary tract duplications depend on their anatomic level, mass effect and space occupying capacity and specific complications related especially with the heterotopic mucosa. Often duplications are found incidentally in routine imaging or in prenatal ultrasound. Duplications can cause symptoms in a fetus. An intrathoracal duplication with mediastinal shift and hydrops in a fetus [36] and bleeding fetal oesophageal duplication [37] have been reported. Approximately two thirds of all intestinal duplications are discovered within the first two years of life, with at least one third identified in the newborn period [6, 20, 27, 33, 38]. As much as 30% of abdominal duplications are detected prenatally [28].

Duplications of mouth, mandible, oral cavity and tongue are often evident immediately after birth and large duplication cysts in the oropharyngeal region can cause congenital high airway obstruction syndrome (CHAOS) [39, 40]. Cervical and thoracic enlarged foregut duplications, primarily oesophageal duplications and bronchogenic cysts, may begin to compress oesophagus and bronchi and cause cough, wheezing, dyspnoea, and respiratory infection [10, 30, 33, 41]. Ulceration of gastric mucosa in the duplication can cause haemoptysis [10].

The most common symptoms in a neonate with an abdominal duplication is vomiting and abdominal distention [28, 38, 41]. Gastric, pyloric, duodenal or pancreatic duplications can cause gastric outlet or duodenal obstruction with the resulting copious vomiting and compression of the common bile tract by a duplication cyst may cause jaundice and recurrent pancreatitis [6, 10, 32, 35].

Duplications of the small and large bowel present as intestinal obstruction caused either by mechanical obstruction of the enlarged duplication, or, a duplication may cause intussusception or volvulus [28, 32] Ulcerated haemorrhaging gastric mucosa in small bowel duplication can cause an enlarged mass in the intestinal wall with the resulting perforation, peritonitis or melena [6, 32]. Hindgut duplications may present as a second opening in the perineum or in females

into the back wall of vagina [6]. In addition, the mass effect of hindgut duplications may cause abdominal distention, constipation and obstruction of the urinary tract [6].

34.4 Diagnosis

Fetal ultrasound screening [28, 42, 43] and fetal MRI [39, 44] have improved significantly the detection and diagnosis of the alimentary tract duplications. In antenatally detected abdominal duplications as high as 24% incidence of volvulus has been reported [28], arguing for early surgical intervention or close postnatal observation in neonates with antenatally diagnosed duplication in the abdomen. Fetal ultrasound and MRI imaging of duplications at risk of causing airway obstruction are crucial in determining whether an intervention for CHAOS is indicated [39].

In neonatal diagnostics ultrasound scan is the most common imaging modality. Ultrasound scan has, however, limitations in the evaluation of thoracic duplications. In MRI most duplications have low signal intensity in T1 images and very high intensity in T2 images, whereas in CT duplication is sharply marginated and has homogenous a near water attenuation. In CT scan the image of a duplication may be confused with that of an abscess with a similar the enchanging rim and cystic appearance, but the lack of septic symptoms in an infant should suggest duplication. Lack of gas in the duplication indicates non-communication with the neighboring part of the alimentary tract [45].

In neonates half of the abdominal cystic duplications present as a palpable mass. In ultrasound examination at least 50% of duplications can be detected as a fluid—filled structure with the characteristic echogenic signal of the mucosal layer surrounded by a dense layer representing the surrounding smooth muscle. This double-layered appearance is usually not circumferential as the layers are not uniform in thickness [45] (Fig. 34.1). This characteristic wall structure is not present in lymphatic malformations, cystic hamartomas, ovarian cysts, and mesenteric or omental cysts, but these structures as well as Meckel's diverticulum can cause false positive findings [46]. Other radiologic studies including

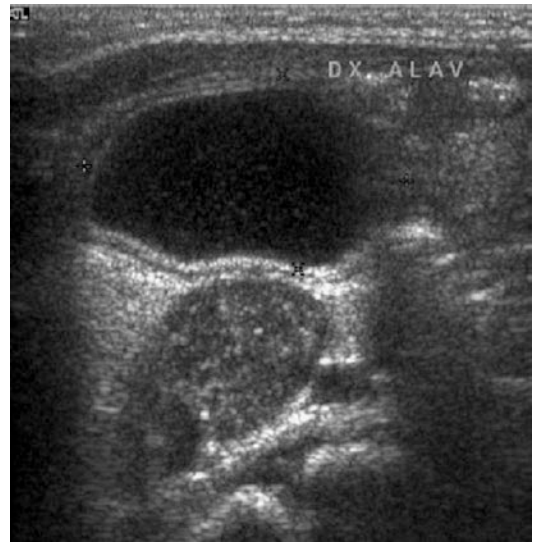

Fig. 34.1 A typical ultrasound scan of a cystic duplication of the terminal ileum, markings indicate the characteristic multi-layered wall

plain radiographs, gastrointestinal contrast studies and MRI will further assist the diagnosis, and associated malformations and simultaneously occurring other duplications may be detected simultaneously. In an evaluation of a child with abdominal pains and anaemia a technetium 99 pertechnate scan for Meckel's diverticulum may detect heterotropic gastric mucosa in a duplication [47, 48]. Duplications are sometimes difficult to diagnose radiologically and it is not rare that a duplication is diagnosed at the operation.

34.4.1 Duplications of Oropharynx

Duplications of oropharynx may be of similar etiology than those of the more distal gastrointestinal tract. Theories of etiology include duplications of the prosenccephalon, olfactory placodes, stomatoideal plate and branchial archs and split notochord. Duplications of mouth, floor of the mouth, lips, and mandible may require complex surgery. Lingual duplications and duplications at the floor of the oral cavity may cause feeding problems, but sometimes even cause high airway obstruction and may require immediate intubation or extrauterine intrapartum (EXIT) intervention [39, 49].

34.4.2 Cervical Oesophageal Duplications

Cervical oesophageal duplications are exceedingly rare and approximately 20 cases have been reported [50–52]. The most common presentation is respiratory distress, which can be life threatening. Rapid intubation, imaging with CT or MRI and surgical excision are indicated. If the lesion cannot be completely excised, stripping of the mucosa will result in obliteration of the cyst cavity. Differential diagnosis includes lymphatic malformations, bronchogenic cysts, laryngeal and tracheobronchial retention cysts and branchial and thyroglossal cysts [50].

34.4.3 Thoracic and Thoracoabdominal Duplications

Thoracic and thoracoabdominal duplications represent 20% of all alimentary tract duplications. Most common location is in the lower half of the posterior mediastinum with the predominance of the right side, but the lesions may protrude into either hemithorax. Thoracic duplications are predominatly cystic and often located within the oesophageal wall without communication into the oesophageal lumen. Thoracal duplications are often associated with vertebral anomalies and may possess a tethering adhesion with the vertebral column [10, 12, 27, 35, 38]. Thoracic and thoracoabdominal cysts may present as neurenteric cysts which are duplications which extend into spinal canal. Neurenteric cyst presents often with neurological symptoms and if radiological imaging suggests a neurenteric cyst, a neurosurgeon is included in the team which perform the evaluation and the ultimate treatment [27, 53]. Bronchogenic cyst is a variant of alimentary tract duplication with cartilagenous wall and ciliated respiratory epithelium. Bronchogenic cyst is noncommunicating and often located near the tracheal bifurcation but can occur anywhere along the alimentary canal [10, 12].

Appropriate imaging of the duplication and spinal column with ultrasound, CT or MRI (Fig. 34.2) is mandatory. Differential diagnostics include neurogenic tumors, anterior mediastinal masses such as lymphoma, teratoma and pericardial cyst, CPAM and cystic structures of the diaphragm. Treatment consists of excision of the lesion either via thoracotomy or thoracoscopically. A duplication cyst of the oesophagus may be resected without entering the mucosal lumen of the oesophagus. After excision it is recommendable to instil air or fluid into oesophagus to ascertain that no inadvertent perforation of the oesophageal wall remain unregocnized.

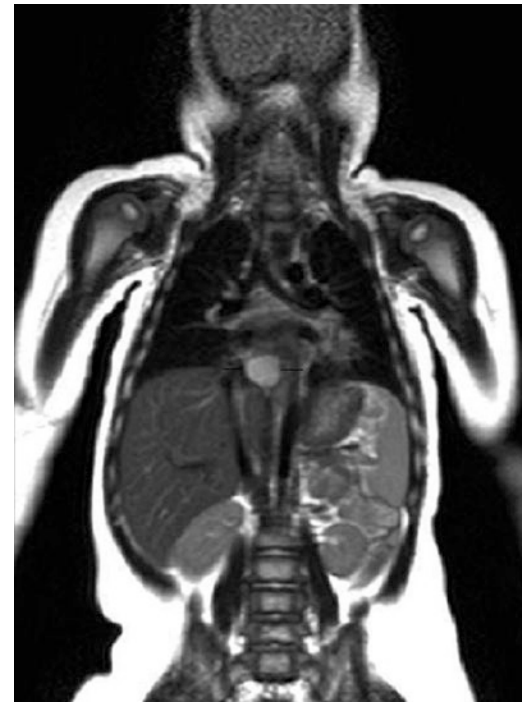

Fig. 34.2 Oesophageal duplication (between *black line*) in mediastinal MRI scan

34.4.4 Thoracoabdominal Duplications

Foregut duplications can expand from thorax to abdomen through the diaphragm or hiatus. It is not unusual that they adhere to several of adjacent organs such as oesophagus, stomach, duodenum and pancreas and may contain tissue from mixed sources [35, 53, 54]. Associated anomalies of vertebral column occur frequently. Thorough preoperative imaging of the lesion and the surrounding

structures is of paramount importance. Large duplications may distort the anatomy of the mesenteric vasculature unexpectedly. Surgical approach requires combination of thoracotomy and abdominal incision but sometimes combined thoracoscopic and laparoscopic resection can be made. Sometimes all extensions of thoracoabdominal duplications may be difficult to detect and incomplete extension with missed neurenteric or abdominal components have led to fatal meningeal and abdominal infections [54, 55].

34.4.5 Gastric Duplications

Gastric duplications occur most often on the greater curvature. They are predominantly cystic and may grow relatively large, and are often seen in antenatal ultrasound. Symptoms begin often at the first months of life. Mass effect of the duplication cause gastric outlet obstruction and abdominal distension and symptoms include vomiting, gastrooesophageal reflux and abdominal pain. A palpable mass can often be felt. Differential diagnostics include duodenal duplication, choledochal cyst, mesenteric cyst, cystic lesions of the liver, and cystic neurogenic tumours and in older children pancreatic pceudocyst In rare occasions the duplication is located at the pylorus [56]. Communication to pancreatic or biliary ductal systems is usually seen in duodenal duplications but may occur also in gastric duplications [57, 58]. The treatment of gastric duplication is resection whenever possible. In some cases segmental resection of the stomach or a partial resection of the duplication with mucosal stripping are required. Small duplications may be resected laparoscopically.

34.4.6 Duplications of the Duodenum and the Pancreas

Duodenal duplications are predominantly cystic, usually located in the second and third part of the duodenum on the posteromedial aspect and often in close proximity with the papilla of Vater and biliary and pancreatic ducts. Approximately 30% communicate with the pancreaticobiliary system and aberrant ducts to pancreatic head may occur. In some cases the main pancreatic and biliary ducts drain into the duplication. The symptoms include those of gastric outlet obstruction, abdominal pain, recurrent pancreatitis jaundice and haemorrhage. Approximately 10% of cases present before the age of one year, most often the presentation is during the first decade of life [59, 60]. In a neonate differential diagnostics include choledochal cyst, cystic variant of biliary atresia and cystic lesions of the liver.

The most common treatment for symptomatic duodenal duplications in children is open surgical resection. The proximity to pancreaticobiliary ducts and common wall between duplication cyst and duodenum adds difficulties to complete resection. Appropriate imaging of the relationship and anatomy of the duplication and the pancreaticobiliary system with MR cholangiogram or ERCP or with operative cholangiogram is highly recommendable [10]. Complete resection or partial resection with mucosectomy of the duplication is possible in most of the cases. In some cases the best option is drainage of the cyst into duodenum with mucosal stripping or if complete mucosal stripping may injure pancreaticobiliary tract the absence of gastric mucosa may be ascertained with intraoperative frozen sections [54]. In intraluminal duodenal duplications which do not contain gastric heterotropic tissues internal endoscopic drainage may be another treatment option [60]. In duodenal duplications involving the pancreatic head and biliary tract pancreaticoduodenectomy is the treatment of choice [61].

Duplications of the pancreatic head pose similar diagnostic and therapeutic challenges as duodenal duplications and before surgical excision is attempted a thorough imaging is mandatory. Surgical treatment may include complete excision or local excision with stripping of the mucosa with or without drainage to Roux-Y jejunal loop, or pancreaticoduodenectomy [10, 22, 62]. Duplications of the tail of the pancreas may be treated with spleen saving distal open or lapa-

roscopic pancreatectomy [10, 62]. Because the high risk of complications and the possibility of malignant transformation incidentally diagnosed or asymptomatic gastric duodenal and duplications should be evaluated for prophylactic surgical treatment. Gastric mucosa in gastric, duodenal and pancreatic duplications have been reported to cause hypergastrinemia with the presentation of recalcitrant gastrooesophageal reflux and gastric ulcers [22, 23].

34.4.7 Duplicated Liver, Common Bile Duct and Gallbladder

These lesions are rare and often present as properly developed functioning structures rather than attached non-communicating cysts. A boy with central diaphragmatic defect has been reported to possess a fully duplicated liver [23]. Also a case of intrahepatic location of an ileal duplication cyst has been reported [63]. There are many reported anatomic variations in the human biliary tree and they include a few cases of the duplications of the common bile duct [64, 65] Gallbladder duplications may present as a bilobed or bifid gallbladder or two gallbladders may have separate cystic ducts or share a Y or H shaped cystic duct [66].

34.4.8 Duplications of the Small Bowel

Duplications of the small intestine are the most common duplications of the alimentary tract. Small bowel duplications occur most often in the ileum and 50% are found near the ileocolic junction. Their shape may be tubular or cystic and typical location is in the mesenteric side of the intestine. Duplications of the small bowel are increasingly diagnosed with antenatal ultrasound.

The duplication shares often a common wall with the neighbouring intestine. Communication with the neighbouring intestine is not common but has implications into the clinical presentation. A proximal communication into a tubular duplication may allow accumulation of intestinal contents and subsequent dilatation of the duplication, whereas a distal communication allows drainage into the neighbouring intestine. Small cystic duplications may function as a leading point for volvulus or intussusception. Of small bowel duplications 20–50% contain gastric mucosa [27, 67] that can cause ulceration, bleeding and perforation and be diagnosed with technetium scan. Ten percent of patients with small bowel duplications have concomitant intestinal atresias, and approximately 10–20% may have a coexisting abdominal or thoracic duplication [6].

Symptoms from small bowel include intestinal obstruction caused by dilatation of a cyst obstructing the neighbouring intestine or intestinal volvulus or intussusception, or melaena and anaemia from a bleeding duplication [32, 67]. Antenatal complications are rare [43].

Optimal treatment is excision of the duplication. In duplications of convenient size laparoscopy or a small umbilical laparotomy may be used. A cystic duplication may be removed by excising the duplication with a small section of the neighbouring intestine. If there is a risk of resecting the ileocaecal valve a local resection of the cystic duplication with stripping of the mucosa is often adequate. In the case of long tubular duplications excision together with the neighbouring intestine may lead to excess loss of functional small bowel and intestinal failure. In some cases it is possible to open the muscular wall of the duplication and remove the mucosa. Some duplications may be amenable for resection by using the split mesentery technique by Bianchi [68]. Creating communications from the duplication to the neighbouring intestine retains the risk of bleeding from heterotropic gastric tissue, but may function as a temporary drainage if for example it is estimated that in a growing infant the lengthening of small bowel will allow resection of the lesion at a later date without a risk of intestinal failure. Infants with asymptomatic small bowel duplications need not to be operated in the neonatal period but should undergo evaluation for prophylactic resection within a few months [67].

34.4.9 Duplications of the Colon and Rectum

Duplications of the colon and rectum are much less common than duplications of the small bowel [28]. They constitute 17% of all gastrointestinal tract duplications. However, they are more commonly complex and the spectrum ranges from simple duplication cyst to partial or complete hindgut duplications that may be associated with complex anorectal and cloacal anomalies. Hindgut duplications are also not uncommon in patients with cloacal exstrophy. Most common type of duplication in the colon and rectum is a cystic duplication, these constitute more than half of the cases [28, 69]. Although cystic duplications can be found throughout colon and rectum, the most common site is cecum. Rectal cystic duplications are usually situated low in the rectum but unlike midgut duplications they almost always rise from the posterior rectal wall. Some of these low rectal duplications cysts may prolapse through the anus. Tubular duplications are more common in the colon and rectum than in other parts of the gastrointestinal tract. In the colon the tubular duplication usually resides, as midgut duplications, in the mesentery. However, rectal tubular duplications usually lie between rectum and sacrum; this suggests a different pathogenetic mechanism. Anterior duplications are extremely rare [70]. The extreme form of tubular duplication is the duplication of most or whole length of colon and rectum. These are commonly associated with genitourinary, vertebral and spinal anomalies. These duplications are usually side-to-side with the colon and rectum. The duplicated colon and rectum may end as a rectourethral or rectovaginal fistula, may end blindly or as a double anus. There is usually a communication between both colons. These long colorectal duplications are sometimes associated with duplicated genitalia and rarely with duplicated urinary bladder.

The duplications of colon and rectum may not be symptomatic in the newborn unless there is an obstruction. Some of the duplications present as a cystic mass that may have been detected already antenatally. The long tubular duplications that are associated with anorectal or urogenital malformations usually present in the newborn. In case one of communication to the urogenital tract the presenting symptom is meconium or stool passing from the urethra in males or vagina in females. Rectal cystic duplications commonly present in early infancy, a typical finding is a mass prolapsing partially or completely through the anus. If there is no obstruction of the bowel continuity the diagnosis of simple colonic and rectal duplications is usually delayed. Later symptoms may include constipation, vague abdominal pain, failure to thrive and bleeding [70, 71]. The bleeding source may be ectopic gastric mucosa that may be present in colon and rectum duplications, too [28].

The diagnosis of duplications of the colon and rectum may be difficult. Intra-abdominal duplications are commonly visualised by echography. Echography, however, does not necessarily provide exact anatomical localization of the lesion. MRI studies, especially MRI enterography, exactly delineate the anatomy of duplications. MRI is especially useful in rectal duplications that may not be detected by echography. MRI shows the extent of the lesion and its relationship to sacrum, rectum and urinary tract. Long tubular duplications that have an ectopic opening in the urogenital tract or perineum may be studied by retrograde contrast injections.

The optimal treatment of duplications of colon and rectum is surgical removal. Cystic lesions and short tubular colonic lesions are easily treated by limited resection of colon with the duplication. In long duplications innovative surgical techniques may need to be applied. If the length of the duplication is not too long, the mucosa may be stripped from the entire length of the duplication. Another option is to create a wide window between the duplication and the native bowel in both ends of duplication. Short rectal tubular duplications and cystic duplication well above the anal canal may be removed by a posterior sagittal approach. The duplications share a common muscular wall with the rectum, usually the intergrity of the native rectal mucosa can be preserved thus avoiding bowel diversion. If the duplication has been infected and drained before, the definitive surgery should be performed under colostomy cover because scar formation around

the duplication may preclude removal without resection of the full-thickness posterior rectal wall. Longer rectal duplications may be managed by creating a long side-to-side anastomosis with staplers applied both through rectum and transabdominally, openly or laparoscopically. If a colorectal duplication is associated with an anorectal malformation, the best policy is to retain the anus that is in its normal position and resect the distal part of the bowel that ends as a rectourogenital fistula. The drainage of the duplicated colon and rectum to normal bowel has to be ascertained. If both bowel terminations end as fistulae to perineum or urogenital tract, innovative surgical solutions have to be used that may need to include pull-through of the distal bowel and reconstruction of sphincter complex.

34.4.10 Duplication of the Anal Canal

Duplication of the anal canal is a specific entity that comprises of a duplicated anus and anal canal that lie posteriorly to the normal anus. Over 40 cases have been reported in the literature [72]. The anus is small in size (Fig. 34.3) but has a separate voluntary sphincter system. The proximal extension is variable but usually not more than a couple of centimetres (Fig. 34.4). This anomaly occurs almost extensively in females. Communication with the native anal canal is very uncommon. Anal canal duplication is sometimes

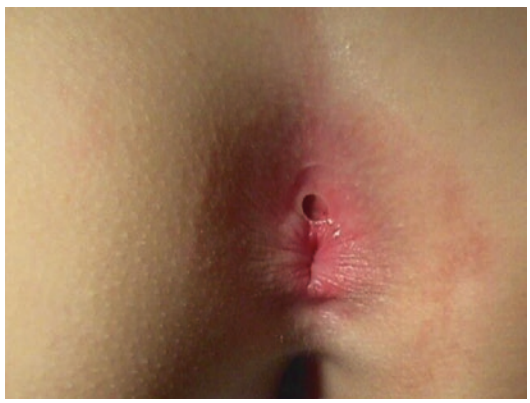

Fig. 34.3 Posterior anal canal duplication

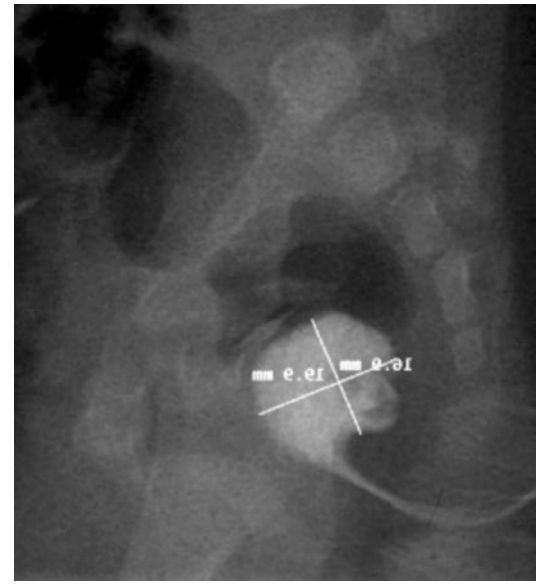

Fig. 34.4 Lateral contrast X-ray of the anal canal duplication

associated with presacral mass or teratoma, and sacral deformities consistent with Currarino syndrome [72–74].

Diagnosis can be made by clinical inspection only, further useful studies are contrast fistulography through the duplicated anus and MRI that detects the possibly associated presacral and sacral abnormalities. The treatment of anal canal duplication is straightforward; the lesion may be excised through a posterior perineal approach in most cases. Care must be taken as the proximal part of the duplicated anal canal share a common muscular wall with the normal anal canal. Longer proximal extension or associated presacral mass may require the use of a formal posterior sagittal approach. The functional prognosis following removal is excellent as the sphincter system of the native anus is normal.

34.5 Complications and Long-Term Results

Recurrence and complications may occur because of incomplete resection, missed transdiaphragmatic duplication tract, missed neurenteric component, loss of small bowel due to missed volvulus

or excessive resection of small bowel and or haemorrhage from inadvertently retained heterotropic gastric mucosa. Following surgery for duplications mortality rate may be as high as 8%. Highest mortality is associated with thoracoabdominal duplications. After appropriate surgical resection the long-term outcomes are, however, excellent.

Untreated duplications may bleed, perforate [75] and become colonized by bacteria [76, 77]. In addition several cases of malignancy in duplications has been reported [78–80]. These have occurred especially in rectal duplications [80]. Surgical resection of a diagnosed duplications is therefore always warranted.

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Meconium Ileus

35

Andrea Conforti and Pietro Bagolan

"Woe is the child who tastes salty from a kiss on the brow,
for he is cursed, and soon must die,"

17th Century German Children's Song

Abstract

Baron Carl von Rokitansky in late nineteenth century observed "a case of foetal death due to meconium peritonitis", while Landstainer firstly described meconium ileus (MI) in 1905, when thickened meconium was noted in a newborn with pathologic changes of the pancreas (Landsteiner, Zentralbl Allg Pathol 16:903–907, 1905). An unknown enzyme deficiency was supposed to cause both fibrotic changes of the pancreas and meconium inspissation. In 1936, the term cystic fibrosis of the pancreas (CF) was coined by Fanconi to describe the association between chronic pulmonary disease and pancreatic insufficiency (Zigler, Curr Probl Surg 31:441–444, 1994). Nonetheless, it was only two years later that Anderson described the connection between MI and CF reporting similar pattern of hystologic pancreatic abnormalities in both CF and MI newborns, suggesting a causative link between CF, abnormal intestinal mucus secretion and the abnormally viscid nature of meconium in MI infants (Anderson, Am J Dis Child 56:344–399, 1938). However, it was only in 1996 when Rozmahel et al. firstly reported a modifier locus for MI on chromosome 7 in a murine CF model (cfm1) (Rozmahel et al., Nat Genet. 12:280–287, 1996).

Keywords

Meconium ileus • Newborn intestinal obstruction • Gastrografin enema
Cystic fibrosis • Surgery • Stoma

35.1 History

Baron Carl von Rokitansky in late nineteenth century observed "a case of foetal death due to meconium peritonitis", while Landstainer firstly described meconium ileus (MI) in 1905, when thickened meconium was noted in a newborn with pathologic changes of the pancreas

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_35

[1]. An unknown enzyme deficiency was supposed to cause both fibrotic changes of the pancreas and meconium inspissation. In 1936, the term cystic fibrosis of the pancreas (CF) was coined by Fanconi to describe the association between chronic pulmonary disease and pancreatic insufficiency [2]. Nonetheless, it was only two years later that Anderson described the connection between MI and CF reporting similar pattern of hystologic pancreatic abnormalities in both CF and MI newborns, suggesting a causative link between CF, abnormal intestinal mucus secretion and the abnormally viscid nature of meconium in MI infants [3] (Fig. 35.1). However, it was only in 1996 when Rozmahel et al. firstly reported a modifier locus for MI on chromosome 7 in a murine CF model (cfm1) [4]

In 1941, Rasor and Stevenson first described mechanical intestinal obstruction due to inspissated stool in patients beyond neonatal period [5]. This condition, known as meconium ileus equivalent, as well as MI was invariably lethal up to late '40s, when Hyatt and Wilson reported the first series of five consecutive patients survived, treated with enemas though enterotomies [6].

Fig. 35.1 (**a**) Baron Carl von Rokitansky; (**b**) Karl Landstainer; (**c**) Guido Fanconi; (**d**) Dorothy Hansine Anderson

About 20 years later, in 1969 Noblett introduces a novel therapy applying hyperosmolar diatrizoate enema (Gastrografin ®) in uncomplicated patients [7]. Since the introduction of non-operative management of MI, the first-line approach was progressively shifted from surgery to intervention radiology. During mid 70', neonatal screening for CF was gradually introduced and became common practice [8].

Actually survival rate of MI newborns is approaching 100% in developed countries, depending mostly on management of CF complications.

35.2 Definition and Classification

Meconium ileus (MI) is defined as a foetal/neonatal intestinal obstruction caused by ispissated meconium at the level of the terminal ileum. It can be classified into two categories: *uncomplicated* (or simple) and *complicated (or complex)* [9]. Later in life presentation is usually referred as meconium ileus equivalent or distal ileal obstruction syndrome (DIOS).

Uncomplicated meconium ileus should be diagnosed prenatally (hyperechoic bowel, bowel loop dilatation), however it is usually recognized after birth in term newborn admitted for distal small bowel obstruction causing abdominal distension. Classically, vomiting (bilious) and failure to stool highlights abdominal obstruction. Characteristic inspissated meconium is found at surgery. Prenatal suspicious should arise in case of confirmatory genetic findings or suggestive intestinal dilatation associated with echogenic bowel. Nonetheless latter sign have poor prognostic value due to its a-specificity [10].

Conversely, *complicated meconium ileus* has high prenatal detection rate due to the evidence of complications (intestinal perforation and/or necrosis, ascites, volvulus) discovered during in utero evaluations. Calcifications are frequently presented and may be found either prenatally (as hyper-echogenic spots or loop dilatation or foetal ascites) or postnatally at abdominal plain x-rays. Signs of peritonitis (including erythematous and edematous abdominal skin) should be present.

35.3 Epidemiology

The meconium syndromes occur primarily in Caucasians and in the past they were considered closely linked to cystic fibrosis (CF), one of the most common serious genetic diseases in whites, given that 80–90% of new-borns with meconium ileus (MI) were believed to have CF [11]. This opinion has changed since it was observed that more than 20% up to 40% of the population with MI are not affected by CF [12, 13]. The pathogenesis of MI in the absence of CF is not yet clear, even though it is assumed that both the immaturity of the myenteric plexus and the interstitial cells of Cajal may predispose to MI as it has been recently reported [14, 15]. However MI and CF remain closely linked in most of the patients.

Cystic fibrosis is transmitted as autosomal recessive disease, thus both parents must be heterozygotes for the gene and each offspring has one in four chance of developing the disease. The highest heterozygote frequency is reported in whites (1/29 births) while it is much less common in non-Caucasian population (1/17.000 births in blacks and 1/90.000 births in Asians). As a consequence the incidence of homozygous condition (just CF) in whites is 1/1150 to 2500 live birth [16, 17].

MI is the first clinical manifestation of CF in 10–20% of affected infants. In families with a first child affected by CF with MI the risk rate of a subsequent child with the identical clinical presentation of CF and MI is 30% compared with 6% in families in which the first child with CF did not have MI [18]. The number of males and females affected is similar. It has been estimated that number of cases with CF is constantly rising, from 3500 at the end of 1980s to more than 7000 by the millennium [19].

35.4 Etiology and Pathophysiology

Two pathogenetic events appear to begin in utero and result in an intraluminal accumulation of highly viscid and tenacious meconium: (1) the pancreatic exocrine enzyme deficiency; (2) the

secretion of hyperviscous mucus by pathologically abnormal intestinal glands.

Other common manifestations of cystic fibrosis (CF) include azospermia in nearly all patients, pancreatic insufficiency in 90%, diabetes mellitus in 20%, obstructive biliary disease in 15–20%, and meconium ileus in 10–20%. Abnormally thick and viscous mucus secretions are responsible for bowel, pancreatic duct and airways in the lung obstructions. Exocrine glands throughout the body are affected by an abnormal function of chloride transport. Pathologic data suggest that the intestinal glandular disease plays a primary role in the pathogenesis of MI associated with CF while pancreatic disease plays a secondary one [16]. Two main explanations of secretion changes have been proposed: A) the hyper-permeability to water loss of an already viscid secreted mucus, thus further concentrating secretions; B) the impairment of fluid movement to and from the extravascular space, preventing the normal dilution of material of the cellular lumen that becomes toxic to those cells laden with the product [20]. The analysis of meconium in infants affected by CF shows a low water, minerals (sodium potassium and magnesium are almost the half in concentration when compared with meconium of controls), protein-bound carbohydrate and trypsin content. On the other hand samples of meconium from patients with CF show a greater amount of albumin, mucoproteins and calcium. The meconium hyperviscosity is probably due to the increased concentration of proteins (neonates with MI and CF have a protein content of 80–90%, compared with 7% in normal infants) [21] and to the simultaneous decreased concentration of carbohydrates [22].

The mutated gene of CF that encodes for the cell membrane protein, termed the Cystic Fibrosis Transmembrane Regulator (CFTR) was identified in 1989 by F. Collins [23] and more than 1000 different CF mutations have been identified until now. The locus was located on the long arm of chromosome 7, band q31 [24]. The most common mutation (ΔF508) is responsible for approximately 70% of clinical cases. It acts through the CFTR protein degradation in the endoplasmic reticulum prior to folding and trafficking. Functionally the gene encodes a protein that is primarily responsible for regulating the opening and closing of chloride channels. The defect affects all epithelial-lined structures. The mutation of the CFTR leads to an abnormal chloride transport in the apical membrane of epithelial cells (preventing excretion) and sodium (up-regulating the absorption). The biological normal function of CFTR differs according to its tissue location: in its location on the apical membrane of epithelial cells of sweat glands it is responsible for reabsorption of chloride and sodium, thus its deficient function lead to an abnormally high content of both electrolytes in the sweat of affected infants (Fig. 35.2). Similarly, there are

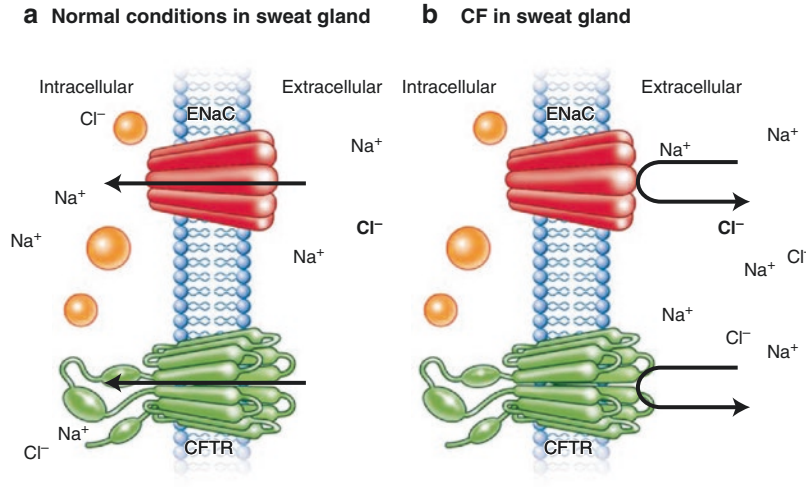

Fig. 35.2 (**a**) Normal CFTR channels in the sweat gland: CFTR channels transport chloride in epithelial tissue to maintain salt and fluid balance. (**b**) CFTR dysfunction leads to pronounced abnormalities in the sodium chloride homeostasis (loss of chloride ion reabsorption). the result is a higher concentration of chloride in the sweat test

also alterations of the water and electrolyte component of the mucociliary clearance mechanism in the respiratory tract resulting in an increasingly viscous mucous [19]. The precise manner in which the deficient chloride (and sodium) transport leads to the manifestations of CF is not well known. All tubular structures lined by the affected epithelia (respiratory, gastrointestinal, biliary, pancreatic and reproductive system) will be characterized by desiccation and reduced clearance of their secretion. Patients who are homozygotes for this mutation typically develop pancreatic insufficiency but may have variable pulmonary disease.

The occurrence of MI in patients with CF is clearly influenced by genetic factors as it was reported in a large twin study that showed a greater concordance for MI in monozygous twins compared with dizygous ones [25]. The variation might be explained by the CFTR genotype. In fact the homozygosity for most common CFTR mutation (ΔF508) in infants with CF is strongly associated with MI [19]. Nevertheless also non-CFTR genes (so called "modifier genes") may influence the risk for developing MI. In 1996 Rozmahel et al. [4] firstly reported a modifier locus for MI on chromosome 7 in a murine CF model (cfm1). Subsequently several markers on human chromosome 19 (the region syntenic to the mouse locus) showed significant linkage with the presence of MI in 185 sibling pairs [26]. Recently Van der Doef et al. reported an association between a variant in the CLCA1 gene and meconium ileus in European CF patients [27]. The causal role between human modifier genes CFM1, CLCA1 and others recently provided as new candidates, such as ADIPOR2 and SLC4A4 [28], and MI has yet to be discovered.

Because the small intestinal mucus glands produce thick secretion even in utero, the meconium is abnormally viscid, sticky and adherent. Typically in new-born babies affected by MI, the proximal ileum is greatly dilated and contains this abnormal meconium, the distal ileum is obstructed by thickly packed, round, mucus plug that resemble a rosary crown. Colon is collapsed and small because not used ("ex non usu"). Infants born with this clinical form have the so-called "simple" MI. However it may progress, even in utero, toward a "complicated" MI. In these cases the massively dilated proximal bowel may volvulize and/or perforate. When this happens early in gestation, one or more intestinal atresia may be produced while infants may present either free or encysted meconium peritonitis when perforation arrives late in gestation. Each of these presentations has different clinical and radiological manifestations and needs specific therapeutic considerations.

No much is known neither about the differences of MI in newborns with and without CF, nor about the specific genetic basis of MI in patients affected by CF [13]. Patients with MI and CF generally have mild pancreatic involvement and more severe intestinal glandular disease. In contrast those with CF without MI have a pattern of progressive pancreatic involvement with age. At birth, the lungs are normal in CF patients. However progressive and diffuse pulmonary disease develops as a result of mucus plugging of the small airways and secondary infections. The sweat sodium and chloride levels are elevated from birth in patients with CF but unrelated to the severity or distribution of organ involvement [29]. Different clinical characteristics have been recently reported in patients affected by MI without and with CF. Complex meconium ileus (including meconium peritonitis), prematurity and low birth weight are more frequently associated with MI without CF and this also implies that in preterm infants, especially presenting with complex MI, counselling of the parents in the first days of life should take into account the relatively low risk that their child is affected by CF [13].

35.5 Diagnosis

35.5.1 Prenatal Detection

Complicated MI is usually detected during pregnancy: ultrasonographic evaluations may reveal dilated hyperechoic bowel loops, abdominal calcifications possibly associated with ascites [30]. In some cases signs of meconium periorchi-

tis (rare disorder caused by foetal meconium peritonitis with subsequent spillage of meconium into the scrotal sac) may be detected [31]. Nonetheless, complicated MI represents a minority of cases.

More frequently during routinely performed second trimester ultrasonographic examination, the presence of hyperechogenic foetal bowel loops associated or not with bowel dilatation and/or polyhydramnios, and or giant pseudocysts may raise suspicion of MI (Fig. 35.3). Hyperechogenic bowel is a relatively common event (detected in 0.04—1.80% of fetuses) and it is not pathologic in itself, however it may be an indicator of different disorders (hypothyroidism, chromosome abnormalities, infections, gastrointestinal disorders, foetal growth restriction, intra-amniotic bleeding, etc.) [32, 33]. Familial history of CF (reported in up to 33% of patients with MI), coupled with in utero amniocentesis with restriction fragment length polymorphism analysis and prenatal sonographic findings, allow accurate prediction of intestinal obstruction due to MI and CF [34]. Different algorithm have been reported as the one showed in Fig. 35.4. It is well established that all types of intestinal obstructions, included all types of intestinal atresia, should be associated to CF with various frequencies [35]. In all cases of supposed intestinal obstruction (especially if MI is suspected) during foetal life, parental genetic screenings as well as amniocentesis are warranted [35].

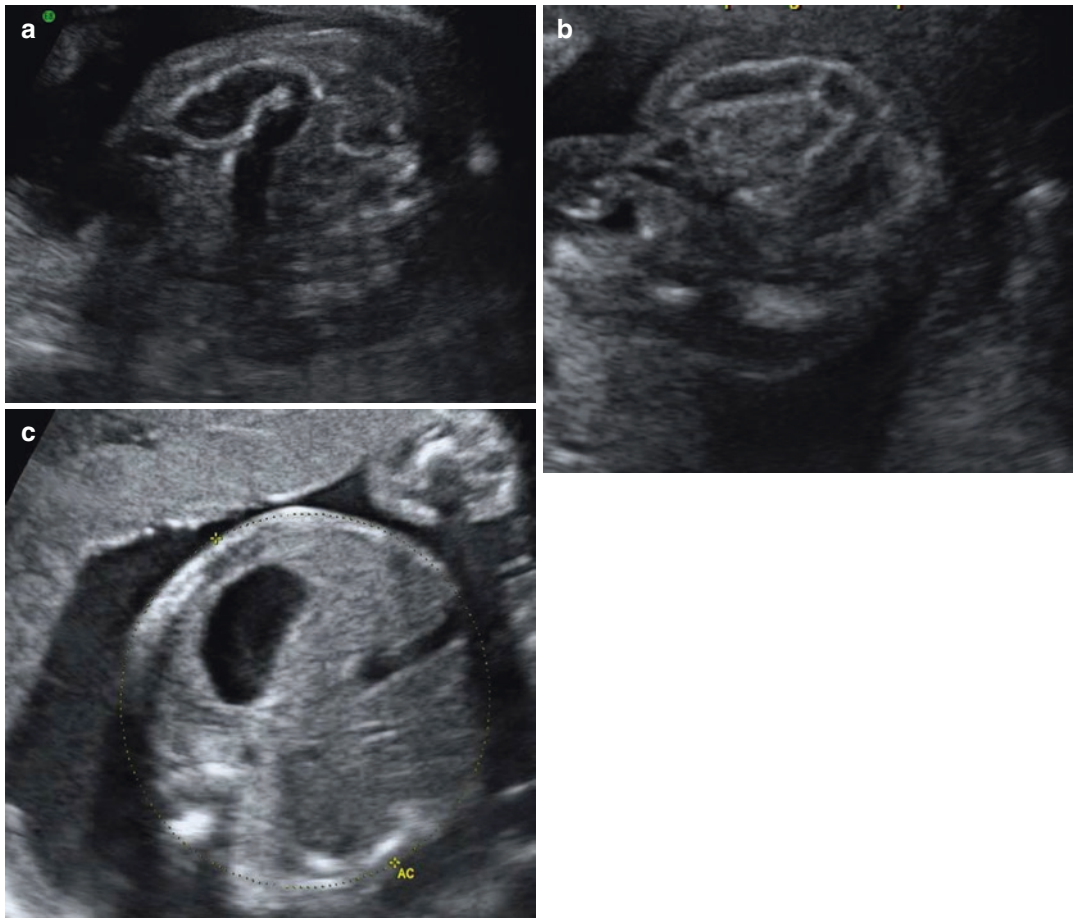

Fig. 35.3 (**a**) Intestinal hyperechogenicity; (**b**) Diffuse hyperechogenicity; (**c**) Prenatal pseudocyst

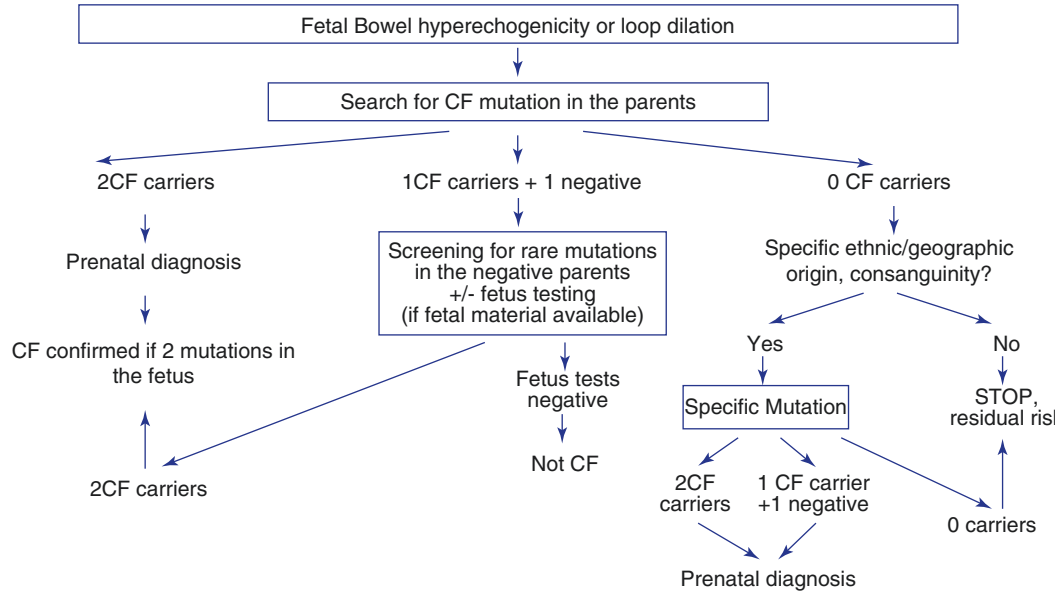

Fig. 35.4 Diagnostic testing in fetal bowel hyperechogenicity or loop dilatation. Modified from: Dequeker E, Stuhrmann M, Morris MA et al.: Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders – updated European recommendations. Eur J Hum Gen 2009; 17: 51–65.

35.5.2 Postnatal Presentation

Newborn affected by MI frequently present abdominal distension at birth before air swallows. Failure to pass meconium usually leads to progressive small bowel over-distension and bilious vomiting. Visible peristaltic waves are often present as well as palpable, thick, malleable bowel loops. Classical clinical sign report on the "putty sign" when finger pressure over a firm loop of bowel conduct to intestine indentation. No signs of peritoneal irritation are present at birth in case of uncomplicated MI. Rectal examination is usually unremarkable and classically no meconium is expelled on withdrawal of the examining finger/rectal tube.

In case of complicated MI, prenatal bowel perforation lead to abdominal pseudocyst arrangement. Classically, intestinal occlusion develops due to the pseudocyst creation, with bile stained gastric fluid, bile or faecal vomiting, abdominal distension, and impossibility of meconium passage. A palpable abdominal swelling is usually present on clinical examination at birth, as well as signs of peritoneal irritation (not mandatory) and skin discoloration. Hypovolemic shock and sepsis may rapidly rise, and clinical and radiological signs (free abdominal air, air-fluid levels within the pseudocyst or in the bowel loops) of intestinal perforation can be detected.

Less frequently, when prenatal intestinal perforation spontaneously heals, intestinal continuity could be re-established and no intestinal occlusion is detected at birth. In those cases the only findings is the presence of calcification on abdominal X-rays or US.

35.5.3 Imaging

Radiological findings in case of uncomplicated MI demonstrate typical abdominal obstruction, with air-fluid levels. Singleton's (granular "soap bubble") and/or Neuhauser's (ground-glass appearance) signs should be frequently detected in the right lower abdominal quadrant. Nonetheless, those features are not exclusively diagnostic for MI, even if collectively they strongly suggest it [35, 36] (Fig. 35.5a). A confirmative study is the contrast enema with water-soluble contrast agent

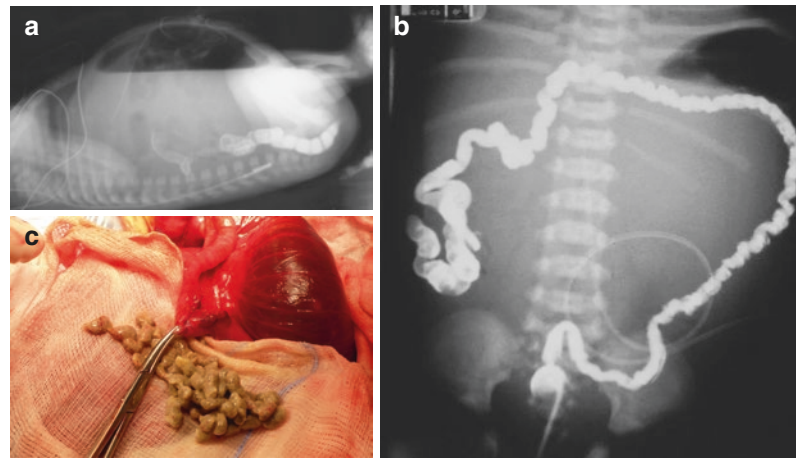

Fig. 35.5 (**a**) Plain abdominal X-ray: note the appearance of abdominal obstruction, with diffuse air-fluid levels; (**b**) Contrast enema with water-soluble contrast agent: normally positioned colon characterized by small calibre (microcolon); (**c**) Meconium pellets

whether hyper or iso-osmolar (to prevent mucosal damage). Contrast enema (Fig. 35.5b) will reveal a normally positioned colon characterized by small calibre, the so-called "microcolon" or "unused" colon. It may be empty or it may contain pellets of thickened meconium. If contrast enema refluxes through ileo-cecal valve, meconium pellets should be observed in the terminal ileum. Furthermore, refluxes of contrast enema in the more proximal ileum may reveal a transition zone to dilated proximal loops. The passage of contrast into the terminal ileum may results in pellets evacuation (Fig. 35.5c), with complete or partial resolution of intestinal obstruction. Contrast studies have to be followed under fluoroscopy to prevent possible unexpected colonic perforation [34, 37].

Frequently, contrast fails to reflux to terminal ileum neither confirming the diagnosis of MI nor excluding the level of the occlusion. Therefore, surgical intervention is required for therapeutic and diagnostic purposes.

35.5.4 Laboratory Test

Even when strong suspicion of MI may raise from clinical history, physical examination as well as imaging, definitive diagnosis of CF should be obtained only with the sweat test. Sweat is collected from infant's skin and pilocarpine ionophoresis is applied to quantify chloride and sodium. The accuracy of sweat test is strictly linked to the minimum amount of sweat to be collected (100 mg) and therefore it is commonly believed that it is really significant in newborn-infants weighted 3.0, 3.5 Kg or more A measured concentration of sweat chloride more than 60 mEq/L is diagnostic for CF. The discovery of CFTR confirmed the role of electrolyte transport in the etiology of CF and gave a molecular rationale to the sweat test for diagnosing CF. Although the ability to test for CFTR gene mutations gives a new dimension to diagnosing CF, the sweat chloride test remains the standard procedure to confirm a CF diagnosis [38, 39]. Despite the potential usefulness of the information, acquiring a CF genotype can be difficult. Although currently available mutation screening panels can identify 90% of CFTR mutations, 9.7% of genotyped individuals in the Cystic Fibrosis Foundation Patient Registry have at least 1 un-identified mutation. Furthermore, the consequences of the vast majority of CFTR mutations remain unknown, even if the genotype is identified [39].

Historically, a number of tests have been developed to support the diagnosis of MI in CF patients: an increase albumin level (>20 mg/g) in faecal specimen as well as a decrease in trypsin concentration (<80 mg/g) were reported to be a good indicator for MI [34]. Nonetheless, due to the low specificity and sensitivity of those tests, all current protocols rely on immunoreactive trypsin (IRT) test as the primary screening test and on sweat test for confirming or excluding the diagnosis of CF. [39] The elevation of immunoreactive trypsin (IRT) in the blood of neonates with CF and its measurement in dried blood spots was first described in 1979, [40, 41]. Since then it gradually became the gold standard first-line screening for diagnosis of CF.

35.6 Differential Diagnosis

MI should be the earliest manifestation of CF, with a frequency reported as high as 10–20% of neonatal cases affected by CF. MI is reported to account for 10–25% of all cases of neonatal intestinal obstruction [34, 35]. As a result, major causes of differential diagnosis reside within the multiplicity of conditions resulting in neonatal intestinal obstruction. The foremost conditions to be investigated and excluded are: intestinal atresia, midgut volvulus, Hirschsprung disease, meconium plug syndrome, neonatal small left colon, hypothyroidism and prematurity.

35.6.1 Intestinal Atresia

Intestinal atresia is usually associated with upper abdominal distension. Characteristically, newborns affected by upper jejunal atresia present bilious vomiting, increasing abdominal distension, failure to pass meconium. A plain abdominal x-ray may reveal thumb-sized intestinal loops ("rule of thumb") and air-fluid levels. The site of the atresia frequently appears as a larger loop with significant air-fluid level, with no air beyond that point.

Proximal jejunal atresia may be associated with upper abdominal distension, while a more generalized distension usually denotes a distal bowel obstruction. Severe enlargement of intestinal loops may lead to respiratory distress as a result of diaphragmatic elevation. At physical examination visible veins and intestinal patterning, characterized by visible bowel loops can be present.

Definitive diagnosis may require laparotomy.

35.6.2 Midgut Volvulus

Acute midgut volvulus represents the classical neonatal surgical emergency, with sudden onset of bilious vomiting in a previously healthy infant. Infants with complete obstruction rapidly develop intestinal ischemia with a firm distended abdomen, hypovolemia and shock.

Prenatal volvulus may lead to intestinal atresia, associated with MI, presenting as complicated MI. Prenatal US reveal intestinal distension associated with calcification secondary to complicated MI, while postnatal radiological findings include sign of intestinal occlusion associated or not with signs of meconium peritonitis [42, 43].

35.6.3 Hirschsprung Disease

HD should be considered in any child who has a history of constipation. Classically, patients affected by HD have a history of delayed passage of meconium within the first 48 h of life. Physical examination often demonstrates abdominal distension that was absent at birth. Rectal examination of newborn infant with HD reveals a tight anus that may be incorrectly diagnosed as anal stenosis. Rectal examination usually leads to emission of gas and faecal matter under pressure. Contrast enema should be useful to detect the classical transition zone (passage from a narrow, spastic intestinal segment to a dilated proximal segment), while rectal biopsies allow definitive diagnosis [42, 43]. Exclusion of ano-rectal malformations (mainly low-lying imperforate anus) is a cornerstone of differential diagnosis of constipation.

35.6.4 Meconium Plug Syndrome and Neonatal Small Left Colon

Meconium plug syndrome (MPS) and neonatal small left colon syndrome (SLCS) are diagnoses to be excluded. MPS was firstly described in 1956 as a distinct condition characterized by transient large bowel obstruction relieved by the passage of meconium plugs. Conversely, SLCS was firstly described in 1974 as a neonatal obstructive condition reported in infants of diabetic mothers in whom contrast enema showed a narrow left colon. Recent reports are less prone to consider those as specific diagnoses, due to the high incidence of overlapping between MPS and SLCS and others well-defined diseases (e.g. Hirschsprung's disease and Cystic Fibrosis) that impose discrimination [44, 45].

35.6.5 Hypothyroidism

Hypothyroidism is not a surgical challenge, however it may became evident during neonatal period as a delayed passage of meconium beyond 24–48 h of life, with subsequent sub-occlusive characteristics. Dosage of thyroid hormones allows a correct diagnosis and substitutive therapy.

35.6.6 Prematurity

Functional gastrointestinal dysmotility is a common condition that affects premature infants. Delay in achievement of full enteral nutrition results in dependence on prolonged parenteral nutrition, predisposing to adverse outcomes. Intestinal immaturity is believed to be responsible for this condition, which may require surgical intervention to treat possible complications such as necrotising enterocolitis and spontaneous perforations. Even if no definitive data are available, intestinal dismotility in preterm babies should be related to some degree of depletion of interstitial cells of Cajal [46].

35.7 Treatment

Even though there are many operative considerations in CF such as jejunoileal atresia, intussusceptions, fibrosing colonopathy, inguinal hernias, bronchiectasis, pneumothorax, hepatobiliary and pancreatic disease and rectal prolapse, none are associated so intimately with CF as MI [47]. MI was considered pathognomonic for CF of which is the first clinical manifestation and it is also now recognised that patients with MI (and with CF) probably represent a different phenotype with earlier presentation and worse pulmonary function [48, 49]. However MI has been described also in association with rare conditions such as pancreatic aplasia and total colonic aganglionosis [50]. As previously said, in neonates with MI meconium is extremely viscid and sticky causing multiple intraluminal plugs leading to a complete obstruction of the terminal ileum. Approximately half of these newborn babies are affected by a simple uncomplicated obstruction while the remaining present typical complications of MI including volvulus, gangrene, atresia, perforation which may result in giant cystic meconium peritonitis. Therefore management of MI is greatly different depending on the presence of a simple (uncomplicated) or a complex (complicated) clinical presentation.

35.7.1 Nonoperative Management (Simple MI)

Hypertonic enema washout has become the initial non-surgical procedure for diagnosis and treatment of infants with uncomplicated MI and it is nowadays considered the procedure of choice for solubilising and washing out obstructing plugs of meconium in those selected cases [51]. As a consequence the surgeon has to examine always the patient to define the real indications and rule out possible contraindications to enema. In her original paper Noblett reported the main rules for the successful use of non operative management of MI: (1) rule out other types of neonatal intestinal obstruction (by a preliminary enema); (2) exclude cases with complicated MI; (3) attend as a neonatal surgeon to the procedure; (4) always perform the technique under fluoroscopic control; (5) give fluids to the baby (one to three times maintenance) and administer prophylactic antibiotic therapy; (6) be, the patient and surgeon, prepared for possible emergent operation should complications arrive [7].

The contrast material used must be water soluble to loosen the inspissated pellets of meconium and to be safer than barium in case a perforation occurs during the study. These enemas break up the plug by two mechanisms: (1) on the contact, the enema acts as a direct solvent; (2) the greater osmolality of the agent results in the shift of fluid into the bowel lumen, which hydrates and softens the inspissated meconium. Preliminary management includes naso-gastric decompressive tube and intravenous fluids to replace pre-existing deficits or ongoing losses (because of the hyperosmotic nature of the enema). Broad spectrum antibiotics should be administered and blood cul-

ture obtained to rule out sepsis. The most frequently used agent is Gastrografin®. Thanks to its hyperosmolar (meglumine diatrizoate 1900 mOsm per L), and emulsifying (0.1% polysorbate 80) properties, Gastrografin® is able to draw liquid into the intestinal lumen inducing an osmotic diarrhoea (and a putative osmotic dieresis) until the contrast is passed. Many radiologists today are used to dilute the gastrografin to 25–50% or to increasingly use new dilute contrast agents to reduce serious fluid derangements and potential complications (hypovolemic shock, colonic mucosal and submucosal inflammation, intestinal perforation and ischemic enterocolitis). Perforations secondary to contrast enema has been reported to occur from 2.7% more recently to 23% of patients in the past [52]. Nonetheless in recent experimental studies, Gastrografin® resulted the most efficacious agent for the in vivo relief of obstruction and for reducing viscosity without intestinal mucosal damage [53]. A comparative study also found a significantly increased rate of success when using Gastrografin® compared to other agents [38]. Risks can be minimized if care is taken to avoid overdistension of the bowel, such as with the use of fluoroscopy for administration.

Thus the solution (50% Gastrografin®) is gently infused under fluoroscopic observation through an enema-tip non-balloon catheter (the buttocks taped together around the catheter) into the rectum, the microcolon, till the terminal ileum. The injudicious non use of both fluoroscopic control or non-balloon catheter have been reported as potentially responsible for bowel injury leading to intestinal perforation [20]. When the contrast medium reaches the dilated meconium-impacted ileum, the study is terminated. An abdominal radiograph should be repeated in 8–12 h to rule out perforations and determine whether the obstruction has been relieved. When the evacuation is obtained but obstructions persists, more than one contrast hyperosmolar enemas may be performed with the same method [7] provided that the patient does not show any signs of deterioration or complications [29]. N-acetylcysteine has also a role in non-operative management of MI even though, because of its delay in effectiveness, it is not recommended as a first line therapy [53]. Warm saline enemas containing 1% N-acetylcysteine can be administered to facilitate complete evacuation upon returning to the neonatal unit. Moreover N-acetylcysteine (5–10 mL of 5%–10%) can be administered per nasogastric tube every 6 h to clearing meconium from above [54]. Heart rate, systemic blood pressure and urine output have to be carefully observed before, during and after the procedure. Usually, passage of meconium pellets followed by semiliquid meconium occurs within the first 12 h. About 30% up to 50% of patients with simple MI may be managed this way, but the success varies widely in reported series. Recent report [52] show that early studies treating MI with Gastrografin reported higher success rate (63–83%) [55] when compared with more recent studies [56] despite the same enema agent has been used. The explanations for the discrepancies may be possibly two: the more cautious approach of radiologists to these patients resulting in a low complication rate that is inversely related to a high failure rate and the use of different and less osmotically active than Gastrografin contrast agents. When either non evacuation occurs after a successfully refluxing enema or the contrast agent cannot be refluxed in the dilated ileum, the non operative technique should be abandoned and operative intervention planned [20].

35.7.2 Operative Management 1 (Unresponsive to Medical Treatment)

Infants that can't be successfully managed by hyperosmolar contrast enema require operative management. Nearly one half to two thirds of infants need operative management of their MI intestinal occlusion due either to a failed non-operative management with MI or to the presence of complications (intestinal atresia, volvulus with or without gangrene, perforation, giant meconium cysts formation, or a combination of these) (Fig. 35.6) [57]. The aims of operation are: (1) the complete relief of the meconium impaction (unsuccessful non-operative manage-

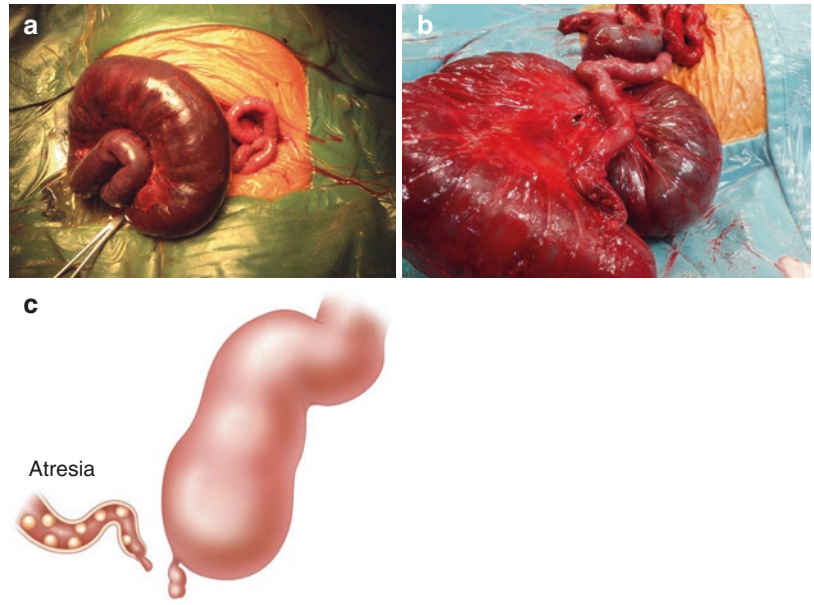

Fig. 35.6 Intestinal Atresia: intraoperative findings (**a**, **b**) and explicative diagram (**c**). Ileal atesia is usually suggested by a distal bowel obstruction pattern on plain radiograph with associated presence of air-fluid levels. Meconium ileus can be associated with ileal atresia, and at operation, the findings of sticky meconium should raise suspicions

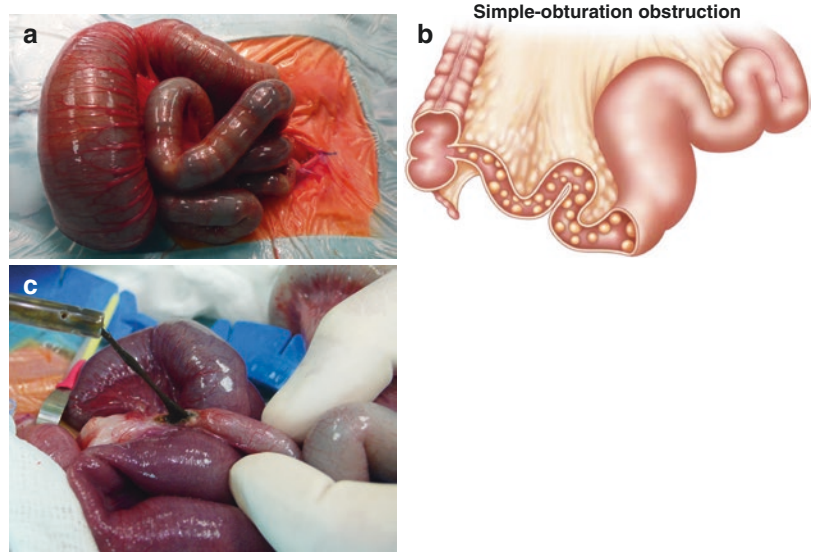

Fig. 35.7 Uncomplicated Meconium Ileus. (**a**) Characteristic meconium pearls at surgery; (**b**) Explicative drawing: distended terminal ileus, inspissated meconium forming meconium pearls and the typical unused microcolon; (**c**) Sticky meconium at surgery

ment); (2) The removal of the specific surgical complication (patients with complicated MI); (3) The complete restoration of bowel continuity when possible.

Several operative procedure have been proposed to surgically remove impacted meconium: enterotomy and irrigation, limited resection with irrigation, different types of obstruction-relieving stoma with or without partial resection; tube enterostomy; tube decompressive stoma plus irrigating tube, primary resection and anastomosis. Intraoperative irrigation of impacted meconium is always required, so enterotomy and intraoperative irrigation for mechanical separation of the pellets from the bowel wall and evacuation of the meconium is the recommended technique currently (Fig. 35.7). Several irrigating solution can be used such as warmed saline, 50% (or more) diatrizoate solution, 2–4% N-acetylcysteine (the most commonly used) [58]. The irrigating agent

is introduced through a minimal enterotomy and the meconium, once solubilised, is gently milked distally (into the colon) or evacuated proximally (through the enterostomy).

A tube (simple or "T" shaped) enterostomy can be created soon after terminal ileum has been disimpacted. Leaving this tube in place, generally located at the junction of the proximal dilated ileum with distal collapsed one (were surgeon has just removed intraluminal meconium pearls) ensures a route for the continuous local instillation of solubilising agent beginning on the first postoperative days. The aforementioned tube enterostomy also avoids the need for reoperation and stoma closure once the obstruction will be definitively relieved on 10th–15th postoperative day. A pursestring suture is placed on the antimesenteric border of the dilated ileum near the transition from large to small caliber ileum. A small (8 French), soft pluri-windowed catheter is inserted through the enterotomy and gently advanced in the distal ileum (Fig. 35.8). It is then used to irrigate by manual mixing of the solubilising agent with the thick meconium and meconium pearls. The meconium is removed through the enterotomy and pellets are either manually removed or flushed into the colon. By the 14th–15th days the catheter can be removed stated that any irrigant (milk included) pass freely into the colon and the obstruction is definitely relieved. Appendectomy, irrigation with gastrografin through the appendix stump followed by gentle expression of the meconium has been proposed as an alternative technique to evacuate meconium avoiding enterotomy, enterostomy or bowel resection [59]. Nowadays enterotomy with irrigation is the treatment of choice for patients with uncomplicated MI that couldn't be successfully managed with non-operative management.

A temporary obstruction-relieving stoma (with or without resection) may be an alternative surgical strategy. The stoma can be fashioned in different ways as shown in the Fig. 35.9.

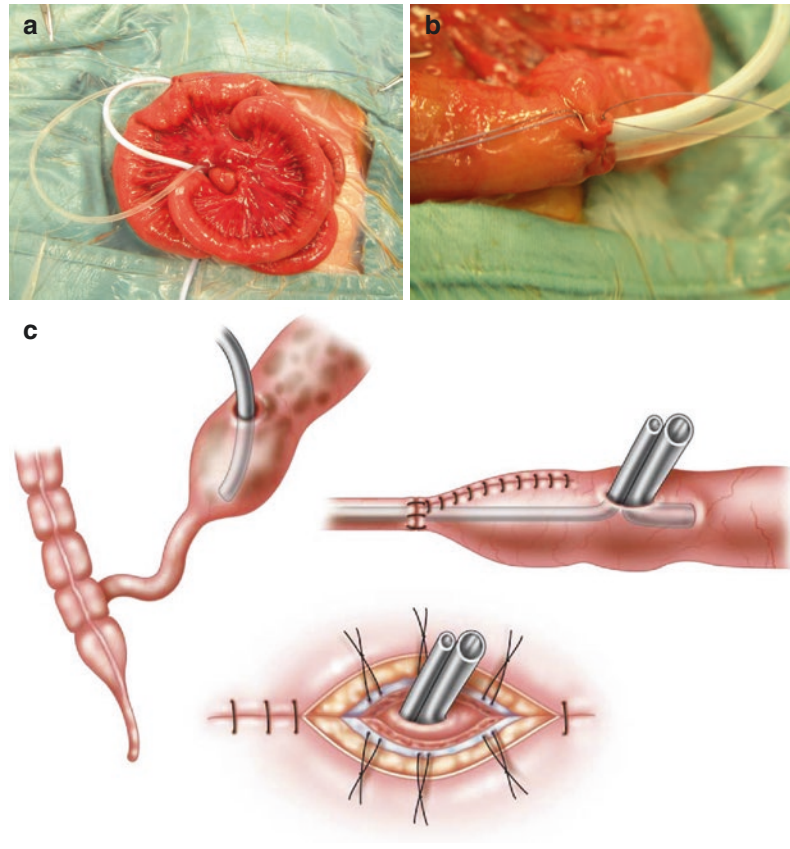

Fig. 35.8 (**a**) Tube ileostomy in the proximal ileus (usually a 10 Ch tube is inserted through the enterotomy); a second 5–7 Ch tube is inserted into the distal narrow ileus and/or microcolon for constant irrigation with increasing amount of fluids, promoting enlargement of the distal intestine. (**b**) Intraoperative picture and (**c**) explicative diagrams

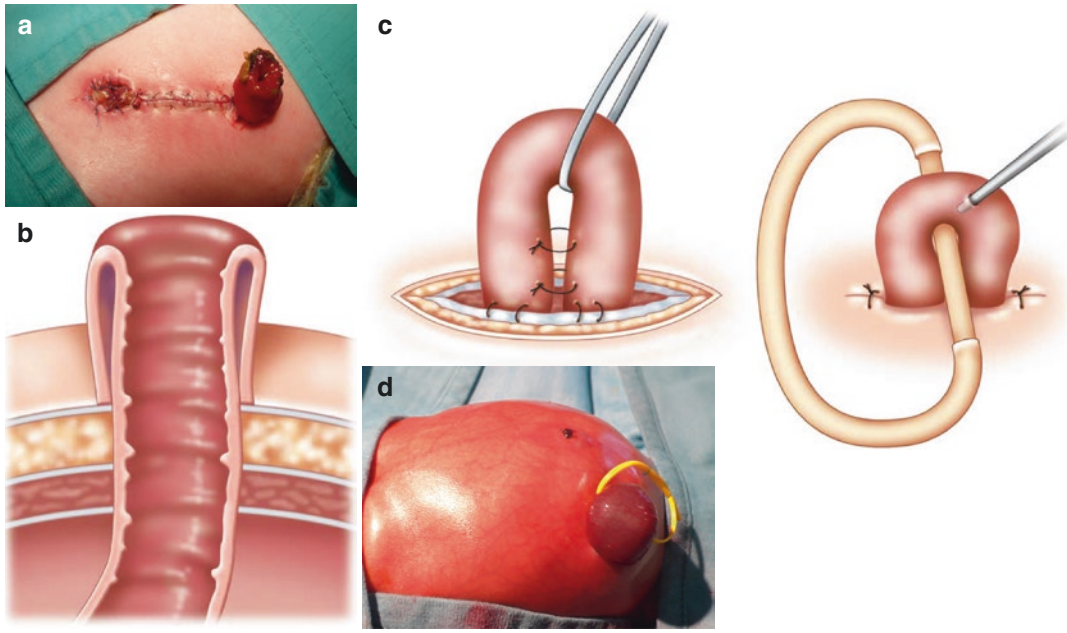

Fig. 35.9 (**a**) Ileostomy: note the discrepancy between the proximal and distal ileus; (**b**) Ileostomy diagram; (**c**) Loop ileostomy diagram; (**d**) Intraoperative view

Classic Mikulitz side-by-syde enterostomy quick to perform and without the necessity of intraoperative meconium evacuation, thereby minimizing intraperitoneal contamination;

Bishop-Koop end (proximal)-to-side (distal) anastomosis and distal loop ostomy: the dilated intestinal loop with inspissated meconium is resected, an appropriately sized end (proximal ileum) to side (distal ileum) anastomosis peformed, approximately 4–5 cm. From distal open and close to the anterior abdominal wall. The distal ileum is exited to assume the function of decompressive stoma of proximal ileum while the distal one is persistently obstructed. In the immediate post-operative period (12–24 h), the stoma should be used as a catheter access to instil solubilising agents to remove meconium pearls in the distal ileum, relieving obstruction. The initial large enterostomy output will diminish once the distal obstruction is relieved due to the passage of stool through the end-to-side anastomosis, into the terminal ileum and microcolon. This technique enhances irrigation of distal ileum while the more enlarged loop of the proximal one (filled with inspissated meconium) is resected to create an appropriately sized end to be anastomosed to the distal one. A second surgical procedure is always required to close the ostomy.

Santulli side (proximal)-to-end (distal) anastomosis and proximal loop ostomy, the reverse of Bishop-Koop technique. The distal ileum is end-to-side anastomosed to the proximal one that is also exited without resection as an end enterostomy. The proximal ileal loop is easily decompressed without a mandatory resection and its irrigation enhanced. The catheter for the postoperative distal intestinal loop instillation of solubilising agents has to be passed through the stoma intraoperatively.

Because of the high output of ileal temporary stoma, it is always necessary to close such a stoma as soon as possible to avoid excessive liquid and electrolytes losses. Thus a second surgical procedure is always required.

35.7.3 Operative Management 2 (Complicated MI)

By definition, complicated MI includes infants with intestinal atresia, bowel gangrene and volvulus (Fig. 35.10) or perforation with varying degrees of meconium peritonitis. Complicated MI

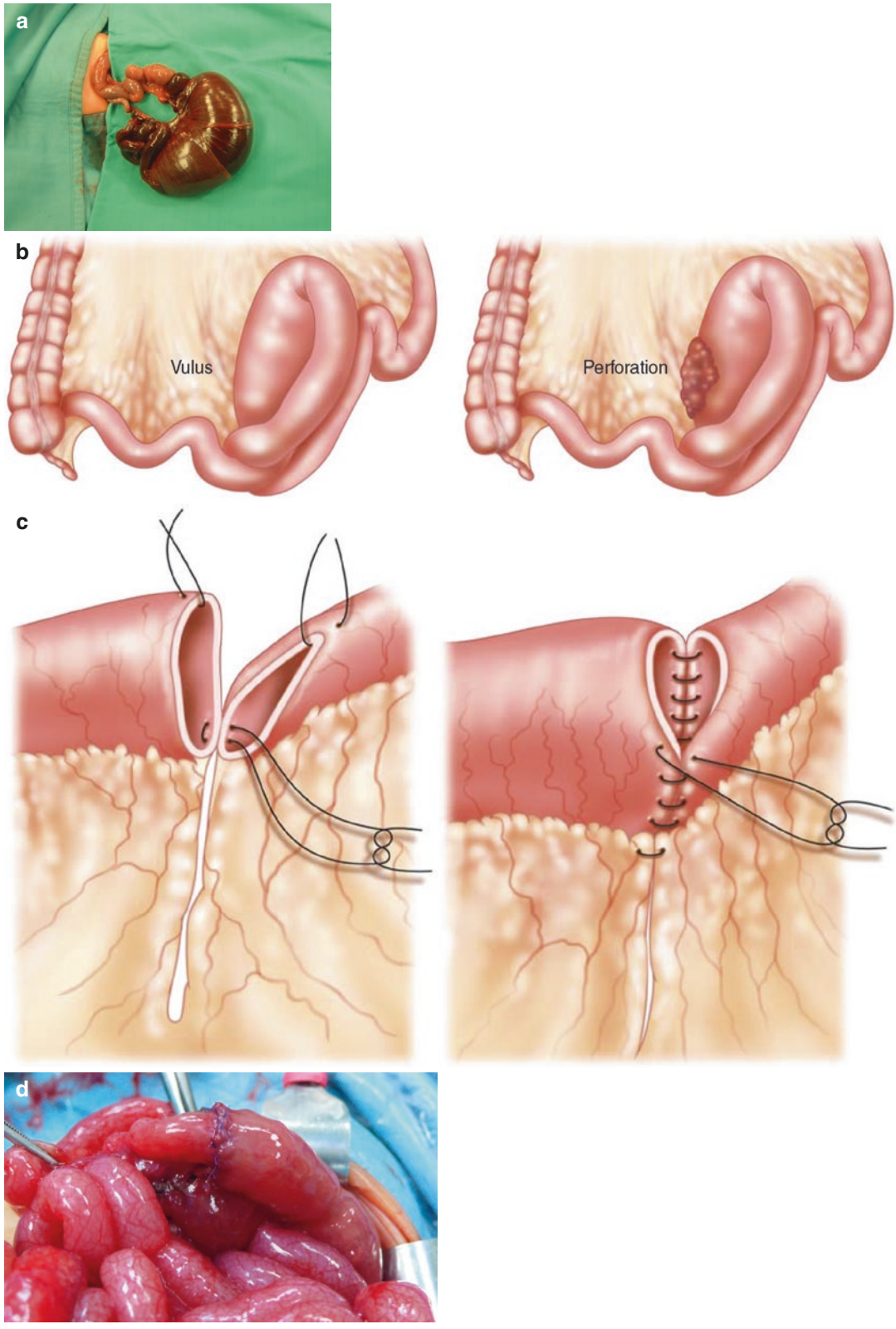

Fig. 35.10 (**a**) Complicated Meconium Ileus: intraoperative view of volvulus; (**b**) Explicative drawings; (**c**) End-to-end ileal anastomosis: diagrams and intraoperative view (**d**)

with prenatal volvulus of ileum may lead to ischemic necrosis, intestinal perforation and foetal peritonitis, intestinal atresia, or combination of these events. CF has been observed in 6–12% of neonates with jejunoileal atresia [35, 60]. The treatment of complicated MI requires operation in most patients. An exception to this rule is the rare baby where a prenatal perforation has left extraluminal intraperitoneal calcified meconium after a spontaneously self-sealed perforation without interruption of intestinal continuity. Sterile meconium extruded after foetal perforation may be partially reabsorbed (and trace amounts becoming calcified) or lead to several surgical appearances: meconium pseudocyst (a membrane into which the perforated bowel empties), adhesive meconium peritonitis (perforation for weeks before delivery), meconium ascites and absence of calcifications (perforation only few days before delivery), bacterially infected ascites (colonization by intestinal organisms from the neonatal perforated intestine). In cases with complicated meconium ileus, surgical procedure has to be adapted to the specific operative findings. The dissection may be bloody and difficult because of dense vascular adhesions. Resection of atretic or necrotic intestinal loop, bowel irrigation, and primary end-to-end anastomosis are sufficient in most neonates with jejuno-ileal atresia without compromised bowel and volvulus. In cases with atresia the blind proximal dilated pouch is frequently atonic if left in place, so it should be sacrificed when it still an adequate bowel length can be ensured. Short gut prevention is always a guiding principle. In patients with inadequate bowel length and significant bowel dilatation, consideration should be given to preserve sufficient intestinal length by tapering enteroplasty or leaving the dilated bowel in place for subsequent bowel elongation. Most neonates require peritoneal drainage and temporary diversion that can then be closed three to 6 weeks after the first laparotomy [61].

35.8 Outcomes

A number of authors reported a decrease in morbidity and mortality for MI patients in recent years [56, 62, 63]. This is consistent with the observed improvement of overall survival in patients affected by CF [64, 65] Even if, newborn screening for CF offers the opportunity for early medical and nutritional intervention that can lead to improved outcomes, there is a paucity of evidence on the care of infants diagnosed with CF. To fulfil this gap, in 2009 Borowitz and colleagues, on behalf of the Cystic Fibrosis Foundation developed recommendations based on a systematic review of the evidence and expert opinion. These guidelines encompass "monitoring and treatment recommendations for infants diagnosed with CF". Guidelines were intended to help guide families, primary care providers, and specialty care centres in the care of infants with CF [66]. To this purpose a routine monitoring and care recommendations for the infant diagnosed with CF was developed.

A CF care team at a dedicated centre should see patients at least once every 3 months [66, 67]. At each visit, patients should have a history and physical examination performed by a specialised CF physician. Furthermore, a nutritionist or registered dietician should also evaluate patients with speciality care in CF, and if possible, patients should perform spirometry to monitor lung function. On a yearly basis or when clinical symptoms dictate, a chest X-ray, blood work, and full pulmonary function testing (including measurement of lung volumes and diffusing capacity) should be performed.

Intravenous aminoglycosides are commonly used to treat lung infections. Aminoglycoside levels should be monitored while the patient is on therapy. Hearing screens should be performed at least annually on all CF patients receiving aminoglycosides. Levels of nephrotoxic antibiotics should be monitored while the patient is on therapy. Serum creatinine levels should be checked weekly in these patients and antibiotic doses should be adjusted accordingly. Immunisation for influenza should be carried out in all children who are eligible [66].

Different authors have also studied the impact of neonatal meconium obstruction in patients affected by CF at late follow-up. MI in patients with CF was not associated to higher risk for late clinical deterioration or decreased survival. Some investigators suggest that adequate initial

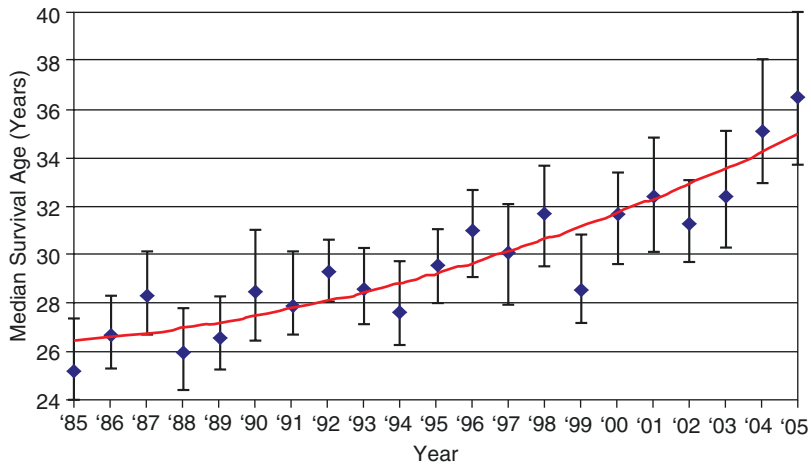

Fig. 35.11 This represents the age by which half of the current CF registry population would be expected to be dead, given the ages of the patients in the registry and the mortality distribution of the deaths in 2005. The whiskers represent the 95% confidence intervals for the survival estimates, so the 2005 median predicted survival is between 33.7 and 40.0 years. From: Strausbough SD and Davis PB Cystic fibrosis: a review of epidemiology and pathobiology. Clin Chest Med 2007; 28: 279–288

nutritional and medical management of MI allows further similar nutritional status and pulmonary function tests compared to other early-diagnosed CF patients [57, 68]. However, Escobar and colleagues found in their 32-year evaluation of outcomes of surgically treated CF patients, an increased risk for late complications including meconium ileus equivalent and fibrosing colonopathy (actually cumulatively addressed as DIOS) [47]. Nevertheless, epidemiological studies have demonstrated striking improvement in outcomes for patients affected by CF in the last 30 years, with an actual median survival now approaching the fifth decade of life [69] (Fig. 35.11).

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Ascites in the Newborn

36

Stavros P. Loukogeorgakis and Paolo De Coppi

Abstract

Ascites (Greek: ascos; "baglike") is a gastroenterological term that describes the accumulation of fluid, which may consist of transudates (low protein count) or exudates (high protein count). The incidence of ascites in paediatric patients is unknown, but the condition is rare. Ascites may be present in the fetus, and there are significant differences in its aetiology between neonates and older children.

Keywords

Newborn ascites • Aetiology • Pathogenesis • Surgery • Peritoneo-venous shunts

36.1 Overview

36.1.1 Background

Ascites (Greek: *ascos*; "baglike") is a gastroenterological term that describes the accumulation of fluid, which may consist of transudates (low protein count) or exudates (high protein count). The incidence of ascites in paediatric patients is unknown, but the condition is rare. Ascites may be present in the fetus, and there are significant differences in its aetiology between neonates and older children.

Fetal ascites has been associated with a wide variety of conditions and may occur in isolation or in conjunction with hydrops both immunological (secondary to alloimmune haemolytic disease or Rhesus isoimmunisation) and non-immunological (intra-uterine infections, chromosomal abnormalities, fetal tumours including sacro-coccygeal teratoma, cardiac anomalies, twin-to-twin transfusion) [1]. Neonatal ascites can be classified broadly in chylous, biliary and urinary. Ascites may be present at birth (associated with fetal ascites) or develop in the early post-natal period. In older paediatric patients, ascites can be secondary to trauma, infection, cancer, as well as gastrointestinal, hepatobiliary or pancreatic disease. Geographic and socio-economic factors have a significant impact on the aetiology of ascites. Trauma and infection (e.g. tuberculosis) are more common causes of paediatric ascites in developing counties, whereas neoplasms, and conditions

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_36

affecting the gastrointestinal and hepatobiliary systems are more frequent in developed countries [2]. Ascites after major surgery is also a well-recognised entity in paediatric patients of all ages, and usually appears as a consequence of major retroperitoneal dissection. The latter is typically associated to neuroblastoma resection and requires early intervention [3, 4].

36.1.2 Clinical Presentation

Neonates and infants with ascites usually present with abdominal distension; clinical examination reveals a fluid "thrill" (sensitivity 20–80%; specificity 82–100%) [2], shifting dullness on percussion (sensitivity 60–88%; specificity 56–90%) [2], and hepatosplenomegaly. Jaundice may be present but this is dependent on the underlying cause. Moreover, patients with gross ascites may present with increased work of breathing (intercostal recession, raised respiratory rate) and hypoxia/hypercapnia due to diaphragmatic "splinting". There may be evidence of sepsis including temperature instability, hypo−/hyperglycaemia, and raised inflammatory markers. Peritoneal irritation (pain and guarding on palpation) is uncommon in neonates with ascites, but is often observed in older infants and children. Its presence is determined by the primary aetiology.

36.1.3 Investigations

An abdominal X-ray is often performed as part of the initial patient assessment. Characteristic features include diffusely increased density of the abdomen, poor definition of soft tissue shadows, medial displacement of bowel and solid viscera, and increased separation of bowel loops (Fig. 36.1a). Definitive radiological diagnosis of ascites is made with trans-abdominal ultrasound (first line radiological investigation) (Fig. 36.1b), and/or computerised tomography (CT; more sensitive for small amounts of intra-peritoneal fluid) (Fig. 36.1c). With the advent of attempts to reduce ionising radiation exposure, magnetic resonance imaging could play a more important role in the detection of free fluid in the peritoneal cavity [2].

Abdominal paracentesis and laboratory analysis of the intra-peritoneal fluid may be required for specific diagnosis when the cause of ascites is not apparent. Paracentesis can usually be performed quickly, inexpensively, and safely [2, 5]. Traditional classification of the causes of ascites has been based on measurement of protein content and specific gravity of intra-peritoneal fluid [Transudate (low protein content, specific gravity <1.0): due to portal hypertension of any cause; e.g. cirrhosis, fulminant liver failure, Budd-Chiari syndrome, portal vein thrombosis; Exudate (high protein content, specific gravity >1.0): non-portal hypertensive aetiology; e.g. infection, neoplasia, biliary leak, nephrotic syndrome]. However, this has now been superseded by measurement of the serum-ascites albumin gradient (SAAG), which has been shown to be a better discriminant compared to older measures (SAAG >1.1 g/dL: equivalent to transudate; SAAG <1.1 g/dL: equivalent to exudates) [6]. Depending on the differential diagnosis, ascitic fluid collected from paracentesis should also be submitted for white blood cell count (and differential), as well as bilirubin, amylase, triglyceride, urea and creatinine measurements. Moreover, bedside inoculation of blood culture bottles with ascitic fluid should be performed if indicated.

36.2 Fetal Ascites

Isolated fetal ascites is defined as fluid accumulation in the abdominal cavity without accumulation in other body cavities or sub-cutaneous tissue (hydrops fetalis). The natural history of isolated ascites remains unclear, but several investigators have reported that it is often caused by in-utero infection (e.g. cytomegalovirus; CMV) [7], cardiac (e.g. arrhythmia, heart failure) [8, 9], renal (e.g. polycystic kidney disease) [10], gastrointestinal (e.g. intestinal atresia, meconium peritonitis) [11, 12], hepatobiliary (e.g. biliary atresia, portal venous malformations) [13], and metabolic disorders (e.g. Niemann-Pick disease) [14] (see Table 36.1 for summary of causes). Isolated fetal

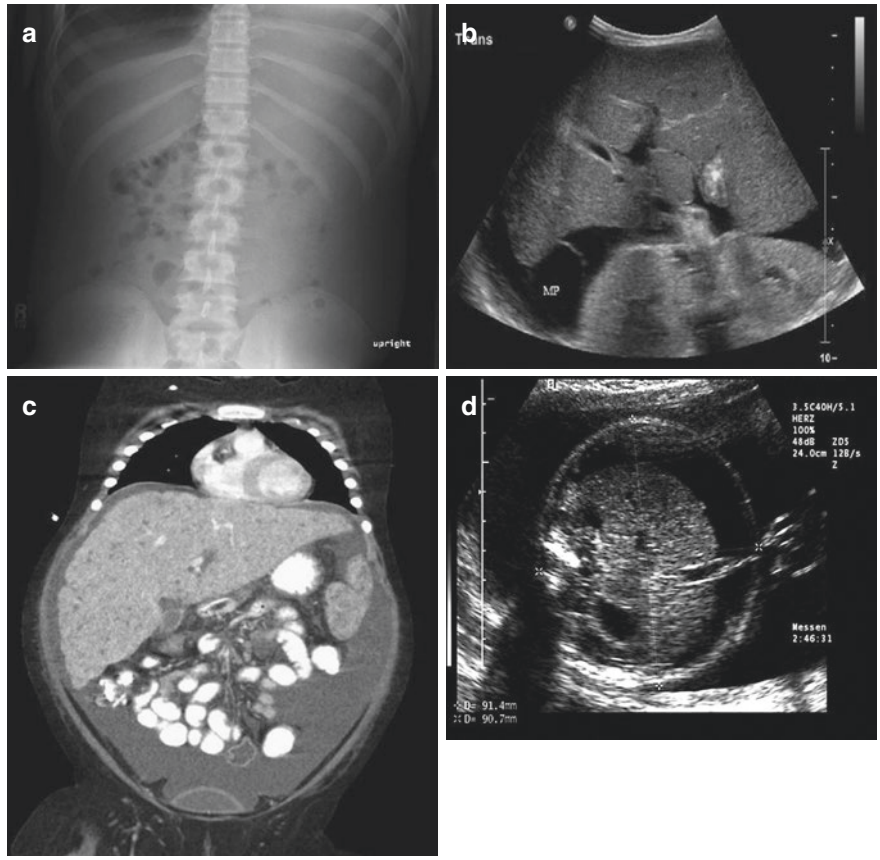

Fig. 36.1 Radiological investigations of fetal and neonatal ascites. (**a**) Abdominal X-ray of patient with ascites. (**b**) Ultrasound image of ascites visible in the hepato-renal fossa. (**c**) Ascites on computerised tomography (CT) with contrast. (**d**) Isolated fetal ascites on prenatal ultrasound at 29 weeks gestation. Adapted from Giefer et al. JPGN 2011; 52 [5] 503–513 and Schmider et al. Fetal Diagn Ther 2003; 18,230–236; used with permission

ascites occasionally occurs primarily without an identifiable cause (idiopathic fetal ascites). Although the mechanisms of idiopathic fetal ascites are not fully understood, in many of these fetuses there is chylous ascites after birth secondary to congenital lymphatic abnormalities [15].

Fetal ascites is usually a radiological diagnosis detected prenatally during imaging of the fetus with ultrasound (Fig. 36.1d), typically performed at gestational age between 21 and 30 weeks [2], and it is often associated with poly- or oligohydramnios [16, 17].

The prognosis for fetuses with isolated ascites is mostly favourable, and survival rates as high as 94% have been reported [18]. Gestational age at onset of ascites has been shown to be the most significant prognostic factor (onset during early gestation associated with worse outcomes) [19]. A large patient series focusing on fetal ascites has shown that ascites accompanied by hydrops fetalis had less favourable prognosis compared to isolated fetal ascites [20]. However, close monitoring after identification of fetal ascites is recommended since isolated ascites can also be the first sign of hydrops fetalis and thus these conditions are not mutually exclusive. The presence of isolated fetal ascites is a rare diagnosis and work-up should be followed to ensure identification of an underlying cause, as most of the cases are associated with other abnormalities [1, 18, 19].

Fetal abdominal paracentesis (FAP) has been advocated by some authors as a potential prenatal intervention for gross fetal ascites to reduce abdominal circumference [21]. Recent studies

Table 36.1 Causes of fetal and neonatal ascites

Type of disorder	Fetus	Neonate
Hepatobiliary	Biliary atresia Portal venous malformations	Cirrhosis Alpha-1-antitrypsin deficiency Budd-Chiari syndrome Biliary atresia Biliary perforation Portal venous malformations
Gastrointestinal	Meconium peritonitis Malrotation (+/− Volvulus) Intestinal atresia Intussusception Cystic Fibrosis	Intestinal perforation Malrotation (+/− Volvulus) Intestinal atresia Necrotising enterocolitis Pancreatitis
Genitourinary	Hydronephrosis Polycystic kidney disease Urinary obstruction Cloaca	Obstructive uropathy: Posterior urethral valves Ureterocele Ureteral stenosis/atresia Bladder perforation (iatrogenic) Nephrotic syndrome
Lymphatic	Congenital lymphatic abnormality (unspecified)	Congenital lymphatic abnormality (unspecified)
Cardiac	Arrhythmia Heart failure	Arrhythmia Heart failure
Metabolic	Niemann-Pick (Type C) Glycosylation disorders Lysosomal storage disorders	Niemann-Pick (Type C) Glycosylation disorders Lysosomal storage disorders
Haematological	Haemolytic anaemia Haemochromatosis	Haemochromatosis
Infection	Cytomegalovirus Parvovirus Syphillis Toxoplasmosis	Appendicitis Acute hepatitis
Chromosomal	Turner syndrome Trisomy 21	
Other	Maternal/fetal abuse Idiopathic	Abdominal trauma Idiopathic

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however have shown that FAP has no long-term effect on preventing an enlarged abdomen because of rapid fluid re-accumulation [22] while it may still have a therapeutic role according to others since FAP may reduce the rate of caesarean section and ensure the safe delivery of the baby due to a short-term reduction in fetal abdominal size [21]. Abdominal-amniotic shunting (AAS) has also been proposed [23–25] for the management of fetal ascites, though its efficacy has been debated. Indeed, the benefits of AAS have been limited by high complication rates; some authors have reported shunt displacement and/or malfunction in up to 30% of cases.

36.3 Neonatal Ascites

The aetiology of neonatal ascites is similar to that of ascites in the fetus (see Table 36.1 for summary of the causes), although many congenital diseases do not typically manifest with ascites until after birth [2]. The three main types of neonatal ascites that come to the attention of paediatric surgical teams (chylous, bili-

ary, and urinary) are described below. In addition, there are multiple iatrogenic causes of ascites in the newborn, including extravasation of parenteral nutrition from femoral or umbilical venous catheters [26], and gastric perforation from gastric catheters and/or feeding tubes. Treatment of the latter usually requires exploratory laparoscopy and/or laparotomy, drainage of the leaked content, and (when possible) repair of the injury. Ascites may also be a postoperative complication of procedures involving major retroperitoneal dissection (e.g. resection of neuroblastoma) [27].

36.3.1 Chylous Ascites

36.3.1.1 Aetiology

Chylous ascites occurs in neonates with a slight male predominance and is generally rare [28, 29]. Neonatal chylous ascites is almost always idiopathic, and congenital lymphatic abnormalities are thought to be the usual underlying cause [30]. Moreover, conditions causing external compression of lymphatics (e.g. malrotation, hernia, intussusception, and tumours) can also result in chylous ascites in neonates [31]. Trauma with disruption of lymphatic ducts is another cause, but it is more common in infants and older children. Anecdotally, chylous ascites has been found in patients undergoing laparoscopic procedures (e.g. hernia repair), subsequently diagnosed with malrotation and volvulus [32, 33].

36.3.1.2 Diagnosis

Neonates with chylous ascites present with increased abdominal girth and non-specific symptoms such as irritability and poor feeding. Recent weight gain despite reduced oral intake may also be present. Following detailed history and clinical examination, ultrasonography and/or CT scanning may confirm the chylous fluid (unique biphasic fat-fluid level in the supine patient) [34], and may help rule out underlying causes. The gold standard for diagnosis of chylous ascites is abdominal paracentesis. Laboratory analysis reveals lymphocytosis (>75% of cells seen in microscopy), and markedly elevated triglyceride content (>1500 mg/dL).

36.3.1.3 Management

Conservative and symptomatic management is usually the treatment of choice once surgical causes (e.g. malrotation, neoplasia) have been excluded. Surgery is considered only when conservative therapy fails. Medical therapy aims to decrease the rate of chyle formation, promoting damaged lymphatics to seal as well as the development of alternate lymphatic pathways [35]. Standard treatment comprises dietary modification combined with diuretics (spironolactone) and paracentesis [36]. In particular high protein and low fat combined with medium-chain triglycerides are usually effective in transient conditions such as inflammation or leaky lymphatics [37]. However, stopping of enteral feeding and parenteral nutrition it is usually a more effective treatment and allows maintenance of calorie intake [38]. The somatostatin analogue octreotide has also been successfully used to reduce ascites in less-responsive cases [39]. These non-operative techniques however may take weeks to work and have limited success [27, 36, 37]. Treatment of the ascites using a permanent drain may initially be effective but it is not recommended; the fluid discarded not only rapidly re-accumulates in most cases but also is rich in electrolytes, protein, and white cells [35].

When all the conservative options have failed, surgical intervention may have a role. Various methods have been used to identify the site of leakage intra-operatively including the use of dyes (e.g. Sudan dye), a high-fat pre-operative meal, pre-operative lymphangiography and lymphoid scintigraphy [40]. The first reported surgical cure by direct ligation of a leaking lacteal was in 1977 by Pearl and colleagues [41]. More recently laparoscopic ligation of the lymphatic trunk has been successfully adopted and while it may difficult to locate the exact point of leakage, direct suturing of the leaking area is usually successful [40].

If direct repair fails, a peritoneovenous shunt (PVS) may be needed [4, 35]. Use of early shunts was limited by high failure rates secondary to blockage [42]. Introduction of the LeVeen and Denver

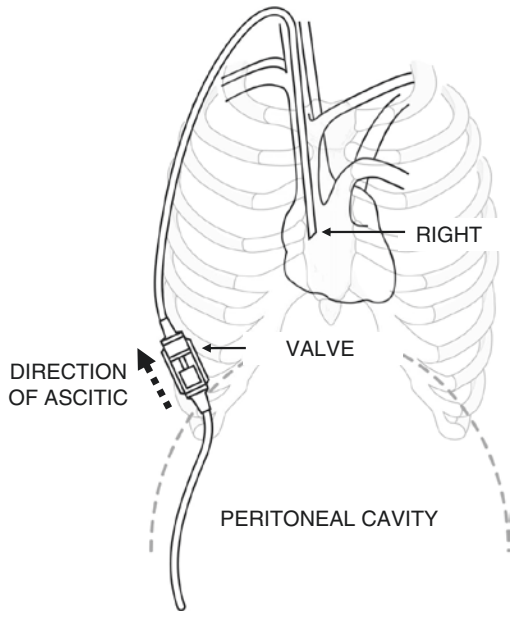

Fig. 36.2 The Denver shunt. Adapted from Rahman et al. JPS 2011; 46: 315–319; used with permission

shunts renewed interest in this form of management [35, 43]. These shunts allow ascitic fluid to flow down a pressure gradient from the peritoneal cavity to the venous circulation, and have a valve mechanism that prevents backflow of blood if the venous pressure rises above the intra-abdominal pressure. The advantage of the Denver shunt (Fig. 36.2) is that the valve chamber lies in the subcutaneous tissue and therefore can be manually compressed to relieve blockage and promote flow [35].

Use of PVS in our institution has resulted in resolution of persistent chylous ascites in the overwhelming majority of patients (>90% response to treatment) [4, 35]. The use of the Denver shunt has reduced the number of shunt failures owing to shunt blockage, as the shunt chamber can be pumped to relieve blockage, and flushed percutaneously if necessary. Blockage should be suspected if there is re-accumulation of ascitic fluid. Shunt infections may respond to intravenous antibiotics, but removal may be necessary [4, 35]. Other complications that have been reported include cardiac congestion, disseminated intravascular coagulation, sepsis, nephritis, dissemination of malignant cells, and perforation of the coronary sinus [44].

36.3.2 Biliary Ascites

36.3.2.1 Aetiology

Biliary ascites in neonates is typically an isolated finding probably related to congenital bile duct malformations [45]. The almost universal site of perforation is at the junction of the cystic duct with the common bile duct, but spontaneous rupture of the intrahepatic duct has been also reported (especially the left intrahepatic bile duct) [46, 47]. The pathophysiology of these "spontaneous" bile duct perforations is currently unclear, but congenital weakness and/or vascular insufficiency of the bile duct wall, elevated intra-ductal pressure from a long common channel and pancreatic reflux have been implicated. Biliary atresia and perforation of a choledochal cyst can also be causative [48, 49]. Biliary ascites is occasionally observed in association with sepsis and ABO blood group incompatibility.

36.3.2.2 Diagnosis

Neonates with biliary ascites present with abdominal distension and jaundice (conjugated hyperbilirubinaemia) [50]. Usually, there are no symptoms and signs of peritonitis. Ultrasonography is used to confirm the presence of ascites and may detect biliary congenital anomalies or obstructing lesions. Cholescintigraphy (Hepatobiliary Imino-Diacetic Acid scan; HIDA scan) may also be useful in demonstrating a biliary leak; following intravenous injection of ^{99}Tc-IDA, radio-nuclide is detected outside the biliary tree and within the peritoneal cavity [46, 51]. Diagnostic paracentesis reveals elevated bilirubin levels in the intra-peritoneal fluid [51].

36.3.2.3 Management

The mainstay of treatment for biliary ascites in the newborn is surgical drainage [45, 47]. This can be achieved with open (laparotomy) or laparoscopic procedures. At operation, sterile bile ascites and bile staining of the peritoneal cavity are found. An intra-operative cholangiogram should be performed through the gallbladder and a drain should be placed at the site of perforation [45, 47, 49]. Lesions are usually self-limiting, and the perforation seals with drainage [45, 47, 49].

Aggressive surgical intervention is not indicated because the congenitally weakened bile duct may be further damaged during attempts at anastomosis.

36.3.3 Urinary Ascites

36.3.3.1 Aetiology

Neonatal urinary ascites is most commonly due to bladder or ureteric perforation secondary to distal obstruction of the urinary system. Posterior urethral valves (PUV) are the most common cause [52–54], and as a result the incidence of urinary ascites in greater male newborns. Moreover, some newborns with PUV present with upper tract perforation (forniceal rupture or parenchymal "blow-out"); the resulting urinary extravasation may lead to peri-renal urinoma formation and in some cases urinary ascites [55, 56]. Other factors predisposing to urinary ascites include the presence of a ureterocele, congenital bladder diverticuli or intra-peritoneal bladder [57, 58]. Iatrogenic urinary ascites is frequently observed, due to trauma to the dome of the bladder or a patent urachus during umbilical arterial catheterisation [59, 60]. Complex urinary anomalies (e.g. cloaca) may allow reflux of urine through the genital tract into the peritoneal cavity, without the presence of a perforation [61].

36.3.3.2 Diagnosis

Neonates with urinary ascites present with gross abdominal distension and associated respiratory embarrassment due to diaphragmatic elevation. In advanced cases the Potter sequence may also be present (oligohydramnios associated with congenital abnormalities in the urinary system resulting in physical deformities including characteristic facies, and lower extremity anomalies). Patients may also present with a history of failure to thrive, lethargy and recurrent urinary tract infections (with or without sepsis). Baseline biochemical tests may reveal deranged renal function, electrolyte abnormalities (due to urinary re-absorption), and acidosis [62]. Evaluation of urinary ascites begins with ultrasonography, and micturating cysto-urethrography (MCUG) should also be performed. The latter will aid in the diagnosis of PUV, but may not always demonstrate the site of perforation [58, 63]. Renal scintigraphy (^{99}Tc-MAG3 scan) may be useful in the diagnosis of upper tract perforations [64]. Biochemical analysis of ascitic fluid reveals concentrations of urea and creatinine higher than in the serum [58, 63].

36.3.3.3 Management

Initial treatment is usually directed at decompressing the bladder and upper urinary tract by trans-urethral insertion of a 5- or 8-Fr feeding tube into the bladder. This may be sufficient to stop leakage of urine in the peritoneal cavity. Rehydration, correction of electrolyte abnormalities, and administration of antibiotics should also be performed. In the case of PUV, cystoscopic ablation should be performed as soon as possible to ensure permanent relief of distal urinary tract obstruction [53]. Therapeutic paracentesis may be indicated in cases of gross urinary ascites with respiratory compromise, worsening renal function and electrolyte imbalance, infection and/or hypertension. If MCUG demonstrates bladder rupture, a cutaneous vesicostomy may be necessary [54, 65]. If leak from a hydronephrotic kidney occurs, insertion of a percutaneous nephrostomy often solves the problem. Unfortunately, with forniceal rupture the kidney is typically decompressed. In these cases, the involved kidney should be explored through a small flank incision, and a temporary cutaneous pyelostomy or ureterostomy may be formed. However, in most cases, mobilizing the kidney, separating it from the adjacent peritoneum, and leaving a drain in the retroperitoneal space will allow the leak to resolve, provided that the distal urinary tract has been decompressed.

Table 36.2 summarises the aetiology, clinical characteristics and management of the major types of neonatal ascites.

Table 36.2 Major types of neonatal ascites

	Chylous	Biliary	Urinary
Cause	Idiopathic Congenital lymphatic anomalies External lymphatic compression Trauma	Bile duct perforation Choledochal cyst perforation Biliary atresia	Obstructive uropathy: PUV Ureterocele Ureteral stenosis/atresia Bladder perforation (iatrogenic) Cloaca
Clinical Presentation	Abdominal distension Irritability/Lethargy Poor feeding	Abdominal distension Jaundice (conjugated) Irritability/Lethargy Poor feeding	Gross abdominal distension Respiratory compromise UTI/Urosepsis Electrolyte derangement Renal failure Irritability/Lethargy Poor feeding
Diagnosis	USS (CT/MRI) Raised lymphocytes in AF Raised triglycerides in AF	USS (CT/MRI) HIDA Intra-op. cholangiogram Raised bilirubin in AF	USS (CT/MRI) MCUG ^{99}Tc-MAG3 Raised urea and creatinine in AF
Management	Medium chain triglycerides (diet) Diuretics (spironolactone) Therapeutic paracentesis Octreotide Direct surgical repair Peritoneovenous shunt	Surgical drainage (open/lap.)	Urinary catheterisation Therapeutic paracentesis PUV ablation Vesicostomy Ureterostomy Pyelostomy

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USS ultrasound, *CT* computerised tomography, *MRI* magnetic resonance imaging, *AF* ascitic fluid, *HIDA* hepatobiliary imino-diacetic acid scan, *PUV* posterior urethral valves, *MCUG* micturating cysto-urethrography

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Neonatal Bowel Obstruction

37

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Abstract

The purpose of this chapter is to introduce the concepts of neonatal bowel obstruction to the reader and outline its presentation, effects upon the child, investigation, and general principles of treatment. Common causes are described in detail elsewhere in the book, but rare causes and miscellany are discussed here in more detail.

Keywords

Newborn intestinal obstruction • Classification • Diagnosis and management

37.1 Introduction

The purpose of this chapter is to introduce the concepts of neonatal bowel obstruction to the reader and outline its presentation, effects upon the child, investigation, and general principles of treatment. Common causes are described in detail elsewhere in the book, but rare causes and miscellany are discussed here in more detail.

Neonatal bowel obstruction occurs when the normal passage of meconium or milk from mouth to anus is interrupted by physical forces or by bowel dysfunction. Its presentation may be acute or chronic, affect proximal or distal gut and have variable effects on the neonate, which will determine overall outcome. The classical surgical sieve to define the causes of bowel obstruction apply; extrinsic, intra-mural (intrinsic) or luminal. Obstruction may also be partial, intermittent or complete. Use of the term "sub-clinical obstruction" should be avoided, as any level of obstruction will have consequences to the gut and become clinically apparent, otherwise there is no obstruction. Functional bowel obstruction describes the scenario where bowel dysfunction contributes to the development of meconium or milk bolus stasis, which then leads on to physical luminal obstruction. However, it is perhaps better to approach classification of obstruction as to how it relates to presentation, because this is how the diagnosis is made.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_37

37.2 Key Features

A normal, term neonate can begin feeding immediately after birth. This has advantages not only in terms of nutrition, but also for the development of normal feeding and bowel reflexes, immunological defence and psychological benefits for mother and child alike. Premature infants should also be fed, but with caution in the context of gestational age and weight, also in terms of co-existing morbidities. Specific problems that can arise in feeding the preterm infant are discussed later.

The suspicion for bowel obstruction can be raised either antenatally, where polyhydramnios or intrauterine growth retardation may have been a feature, with or intrauterine without other findings associated with obstruction, such as increased nuchal thickness to suggestive of trisomy 21 and thus duodenal atresia. Alternatively, and more commonly, it is the symptoms and signs the neonate displays after birth which prompt investigation. The key features of bowel obstruction are progressive vomiting, abdominal signs such as tenderness or distension, constipation and, later, radiological evidence. Further signs may include irritability, or abnormal physiological parameters, such as tachy/bradycardia or tachy/bradypnoea, which represent responses to the primary insult. For a neonate, these require interpretation.

37.2.1 Vomiting

Quite distinct from the complex, centrally mediated action of vomiting, regurgitation of feed should be recognised as a separate entity in the neonate, although its presence instead of vomiting should not reassure the clinician into a false sense of security. Generally, neonatal regurgitation of recently ingested feed, provided it does not represent the entire feed after every feed, usually does not represent serious or surgical pathology. However, if the initial feed results in regurgitation with distress especially if accompanied by coughing or choking, apnoea or bradycardia, then investigation should commence towards exploring the diagnosis of oesophageal atresia. This is normally confirmed on plain chest X-ray where the nasogastric tube (NGT) is seen coiling in the upper oesophagus, with the presence of distal abdominal gas identifying the presence of a tracheo-oesophageal fistula. Congenital oesophageal stenosis, an extremely rare condition is caused by either intramural ectopic tracheobronchial elements or fibromuscular hypertrophy or a luminal membrane typically affecting the distal oesophagus [1]. Endoscopic dilatation or surgical options such as resection of the affected segment with primary anastamosis or myotomy have been described. Affecting as few as 1 in 50,000 live births, presentation may only occur when solid food is commenced [1].

Vomit produced by a neonate should be classified carefully into one of three groups:

(a) Non-bilious vomit: Colourless or luminous yellow, contains enteric juice from the stomach and may be clear in the absence of feed, or milky if a feed has been taken.
(b) Bilious vomit: Dark green, akin to mint sauce. Freshly produced bile of golden colour has been acted upon by stomach acid to produce the green colour.
(c) Non-bilious vomit developing into bilious vomit: Often after prolonged vomiting, the colour may change from milky to lime green to dark green. Conversely, an improving obstruction for example may produce vomit or aspirate that lightens in colour from dark green to clear, again via a lime green stage.

In relation to bowel obstruction, interruption of flow proximal to the ampulla of Vater will produce non-bilious vomit. Depending upon the distance of the obstruction distal to the ampulla, vomit may be immediately bilious, or become bilious after non-bilious vomiting.

Persistent non-bilious, milky vomiting of the entire feed, permanent hunger and stomach distension raises the possibility of an early presentation of pyloric stenosis, which is not a congenital abnormality and usually presents between 2 and 6 weeks of life, or pyloric atresia, a rare cause of gastric outlet obstruction. The latter occurs in 1 in 100,000 live births and can exist, in descending order of frequency, as a membrane (Type I), a

solid core of tissue (Type II) or complete atresia where there is a gap between the stomach and duodenum [2]. Its most frequent association is epidermolysis bullosa, but may also co-exist with other intestinal atresias. Treatment is surgical, with either excision of the web, pyloroplasty or gastroduodenostomy [2] where, as an isolated problem, prognosis is good.

Neonatal bilious vomiting should be considered to be a surgical emergency until proved otherwise. Physical obstruction to the gut requires rapid assessment and occasionally immediate surgery after resuscitation. The type and site of obstruction cannot be hypothesised without consideration of other presenting features.

37.2.2 Abdominal Tenderness and Distension

A neonate who handles poorly, with labile physiological responses to abdominal palpation, or who appears to be in pain, often intermittently (colicky), should be considered to have an intra-abdominal pathology, especially in the presence of bilious vomiting. The presence or absence of abdominal distension is moot in such cases, except to allow the clinician to consider what type of insult is evolving. Proximal small bowel obstruction may largely result in stomach distension whereas distal large bowel obstruction may result in massive pan-gut distension. The level of distension can only reflect the most proximal obstruction, so one cannot exclude multiple obstructions or duel pathology on this basis.

37.2.3 Constipation

A term neonate should pass meconium within 24 h of life. As feed is introduced, the stool changes to a lighter colour, often yellow and seedy, and this confirms continuity of the bowel. Clearly, when confronted with a neonate who is vomiting bile and has abdominal signs, the relevance of constipation can only be assessed in hindsight, and it is common for babies to pass meconium despite bowel obstruction. The presence of meconium throughout the gut implies that continuity has at one stage existed, and so the bowel obstruction has been a late event. The consistency of the meconium may indicate the length of time gut stasis has occurred or may reflect an inherent increased viscosity of the bowel mucus as seen in cystic fibrosis. The absence of meconium distal to the obstruction implies an insult early in gestation such as duodenal atresia, and the lack of conditioning of this segment by the flow of amniotic fluid of can lead to secondary problems such as small calibre gut, which may be dysmotile.

37.2.4 Abdominal Radiology

Whilst resuscitating the child, arrangements should be made to image the abdomen. The simplest and most informative radiological procedure is the plain chest and abdominal X-ray. From this one investigation, confirmation of the hypothesis of bowel obstruction can be achieved, with some information about the level of the obstruction.

The X-ray should be interrogated for signs in the chest, such as position of the endotracheal tube (if any), adequacy and clarity of the lung fields in cases of grossly distended abdomen and respiratory embarrassment, and to predict the need for ventilation. The presence of gut in the chest should also be sought. The course of the NG tube should be studied and interpreted with the clinical findings.

In the abdomen, the information to be gleaned should be the extent and position of bowel gas, whether there is gas present in the rectum and if there are distended loops, to what degree and at what level. Air fluid levels may be seen. Widely spaced bowel loops, thickened bowel wall or mucosal inflammation are signs of pathology. Necrotising enterocolitis can be implied from gut demonstrating wall pneumatosis, with or without evidence of portal venous gas. Evidence of free gas would confirm perforation. On a supine antero-posterior film this may be identified with the so-called “football sign”, an incongruous gas shadow overlying the liver and epigastrium that

could not be contained in a bowel loop. The outline of the falciform ligament may also be seen. Rigler's sign, where both the inner and outer lines of end-on bowel are seen clearly is also suggestive, but composite shadowing of overlying bowel loops should not confuse the issue. If there is doubt, a lateral decubitus film with the right side uppermost should be used to see air above the liver. Calcification of meconium implies long-standing stasis and may be identifiable outside of the bowel loops, which would suggest previous perforation.

Just as important is analysis of areas of paucity of gas, suggestive that the gut either contains no gas or there is a significant quantity of ascites or space occupying lesion causing the loops to "float" centrally or be pushed to one side respectively. Finally, the bony structures should be examined, particularly an assessment of the sacral spine.

In the case of a neonate with bilious vomiting (where Hirschsprung's disease, anorectal malformation or other lower GI anomalies are unlikely), it is essential to perform upper gastrointestinal contrast studies, to establish primarily whether the gut is normally rotated. Subtle abnormality in the position of the fourth part of duodenum relative to the pylorus is just as valid a sign for malrotation as the characteristic corkscrew appearance in midgut volvulus. Once diagnosed laparotomy should occur as a matter of urgency. If the diagnosis of volvulus is suspected but not confirmed by these modalities, ultrasonography may help with assessment of the superior mesenteric arterial and venous axis. In normal individuals the artery should lie to the left of the vein, but in volvulus it may be anterior or even to the right. Ultrasound showing a normal mesenteric axis does not exclude volvulus. As such, where in doubt despite investigations, a diagnostic laparotomy remains the safest option.

In other types of intestinal obstruction, the contrast study is also important in identifying the level and type of obstruction, in terms of partial or complete obstruction, but in the latter, only the most proximal obstruction will be identified. In cases of inspissated meconium, the contrast study, by virtue of its high osmolarity, can act both as diagnostic and therapeutic tool, but there should be awareness of the hypovolaemic effect of significant fluid shifts from the neonatal circulation into the gut and remedies should be in place before treatment.

37.3 Management

Principles of management of the neonate with bowel obstruction begin as with any other clinical case, with assessment of the airway, breathing and circulation. Consideration of co-morbidities should be made, especially when considering surgical options. The overall state of the child will depend upon the aetiology, but the following principles should be observed. The child should receive no enteral input. Adequate intravenous access should be secured and blood taken for assessment of renal function (bearing in mind time after birth), haematological parameters, clotting and for potential transfusion. Blood gas analysis should take place to assess the overall condition of the child and the extent of any metabolic acidosis. Although non-specific, if the bowel is thought to be at risk of ischaemia, elevated blood gas lactate levels may add to this concern [3]. However, it should be noted that a normal lactate does not exclude bowel necrosis/ischaemia. As the child is not feeding, regular blood sugar levels should be taken. Crystalloid intravenous fluid should be given according to local guidelines. If the child is shocked or is suspected to have large third space losses of fluid into the gut, deficit fluid boluses should be administered. A NG tube should be passed and its position checked with aspiration of fluid onto Litmus paper or by X-ray. All fluid aspirated this way should be replaced volume for volume. Extra potassium may need to be given to account for these losses.

Should a child need assisted ventilation, full intubation is preferable, as external positive-pressure ventilation will cause the gut to inflate, exacerbating the obstructive symptoms and risking respiratory embarrassment.

During this time, some progress should have been made towards confirming the diagnosis. Depending upon the type of obstruction and the condition of the child, a plan for surgical inter-

Table 37.1 Causes of physical intestinal obstruction in the neonatal period

Gastric	Early pyloric stenosis Pyloric web or atresia Epidermolysis bullosa pyloric atresia syndrome
Duodenum	Stenosis Atresia Malrotation Annular pancreas
Jejunum	Stenosis Atresia
Ileum	Stenosis Atresia Malrotation Meconium ileus Vitello-intestinal duct remnant Intussusception Milk curd obstruction
Colonic	Stenosis Atresia Imperforate anus Poorly developed colon e.g. megacystis microcolon intestinal hypoperistalsis syndrome
Global	Duplication anomalies Internal hernia or inguinal hernia Volvulus with or without (e.g. about a Meckel's band) malrotation Neoplasm

vention can be made. Neonatal bowel obstruction may be *physical* or *functional* in nature. Physical obstructions are caused by intrinsic, extrinsic or luminal compromise of the gut, usually occurring at a specific level which can be determined in advance radiologically, or at surgery. The common types are discussed elsewhere. Table 37.1 shows the causes of physical neonatal intestinal obstruction related to intestinal level. Where the symptoms and signs of bowel obstruction are present without physical obstruction, be it from within the gut or without, it is said to be functional obstruction. This occurs when peristalsis fails to propel bowel content toward the anus and may in turn lead to physical obstruction by excessive absorption of water and desiccation of meconium.

Mature intestinal motility depends upon the coordinated contraction and relaxation of the gut resulting in segmentation and peristalsis of bowel content from mouth to anus. The development of an intact neuronal pathway to control and effect these motor actions is essential. Development of the enteric nervous system occurs in a cephalocaudal direction, as does maturation of the ganglion cells. Incomplete population by ganglion cells renders the distal gut aganglionic and so a term neonate who has not passed meconium within 24 h of birth should be observed closely for signs of obstruction and be considered for rectal biopsy to determine the presence or absence of ganglion cells. Hirschprung's disease will be discussed in detail in a later chapter.

In a premature infant of very or extremely low birth weight (VLBW <1.5 kg; ELBW <1 kg), meconium may not be passed for a number of days but does not immediately warrant such investigation because of immaturity of the enteric nervous system. The motor patterns associated with mature gut cannot be assumed to occur in these infants. Abnormal consistency of meconium can also exacerbate the effect of immature gut in pre-term bowl obstruction [4]. It has been suggested that the consistency of the bowel content may determine the extent of propulsion the gut utilises at a given level (reviewed by [5]). For example, liquid matter may only require peristalsis just proximal to the bolus, whereas more solid material may also require distal relaxation. In E/VLBW infants, where the gut would expect to propel liquid meconium, any increased viscosity in the bowel such as that resulting from milk ingestion or a pathological processes such as cystic fibrosis [6], may render the gut unable to prevent obstruction. This is particularly pertinent to the use of formula milk and milk fortifiers, designed to enhance the nutritional status of feed given to premature or small for gestation infants. It is recognised that human milk is not enough for adequate growth in these infants and so formula +/− fortifier is used. Both are often rich in calcium and fat, and also contain proteins, carbohydrate, minerals and other electrolytes. Growth is enhanced, more so in small for gestation compared to appropriate for gestation VLBW neonates [7]. For the reasons stated above, the immature gut may not be able to propel liquids of high viscosity, stasis occurs and obstruction develops. Milk curd obstruction usually occurs at

the terminal ileum and analysis of material removed at laparotomy has revealed a precipitate of calcium and fatty acid [8, 9]. Once suspected, feeds should be stopped and gastrograffin enema can be performed as a diagnostic and therapeutic measure; established obstruction with inspissated milk may require laparotomy. In the absence of an obvious cause of obstruction in E/VLBW infants, it should not be assumed that insufficient peristaltic activity is purely attributable to immaturity; those undergoing laparotomy for intestinal obstruction or perforation should also have full-thickness biopsies sent for histological analysis to exclude rarer causes such as muscular dysplasia or aplasia, possibly occurring as a result of ischaemic insult [10, 11].

If gut immaturity can be responsible for functional obstruction in VLBW infants, then it follows that delayed maturation of ganglion cells in a term infant may lead to failure to pass meconium and intestinal obstruction. This condition should be considered where ganglion cells are present on rectal biopsy but they appear small and nuclear morphology and cytoplasmic immunohistochemistry is abnormal [12]. Another group of patients with signs and symptoms of Hirschprung's disease but with normal rectal biopsy have been identified [13]. Labelled as benign transient non-organic ileus, neonates displayed abdominal gaseous distension with X-ray features similar to Hirschprung's disease but with a normal ano-rectal reflex. Both these groups (which may have significant overlap) by their nature are self-limiting problems, which may respond to anal stimulation, rectal washout or enema, and so they are important to recognise prior to what may be unnecessary surgical intervention.

A rare cause of functional bowel obstruction in combination with a non-obstructed, distended urinary bladder is the megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS). This severe, often fatal congenital condition is characterised by reduced or absent peristaltic bowel activity, microcolon and malrotation. The huge, lax bladder fails to empty and without drainage by catheterisation or vesicostomy, upper tract damage persists. A number of aetiological theories have been postulated, which centre upon the role of the mesenchyme in terms of muscular, neurological and endocrine function (reviewed by [14]). Observations of degeneration in smooth muscle with vacuolation, coupled with the presence of excessive connective tissue were fortified with the finding that expression of collagen type I was markedly increased and smooth muscle actin, desmin and dystrophin muscle proteins were decreased in MMIHS detrusor compared to normal controls [15]. Furthermore, the finding that MMIHS small bowel lacked nicotinic acetylcholine receptor subunit 3 may suggest a neurogenic background to the disorder [16]. Affecting females predominantly, outcomes are poor; a systematic review of 227 cases between 1976 and 2011 revealed 80% mortality, the majority of the survivors being entirely reliant upon total parenteral nutrition (TPN) [17], although multivisceral transplantations have occurred with some success [18].

The development of functional bowel obstruction can be anticipated in certain cases, with knowledge of maternal medical history. Already susceptible by virtue of being a neonate, further immunosuppression as a result of haematological disease or human immunodeficiency virus (HIV) for example increases the risk of neonatal infection, especially when carried by the mother. Cytomegalovirus (CMV), the most common congenital viral infection [19], is responsible for most developmental disabilities attributable to infection [20] and may be transmitted during pregnancy or by breast milk. Although the spectrum of damage caused by CMV does not classically include the gut, the effects of gastrointestinal infection are well described (reviewed by [21]). Although the infection itself may cause inflammation, diarrhoea, or haemorrhage, its link as a primary causative agent in surgical pathology of the gut is not as clear. The presence of typical nuclear inclusion bodies in resected gut and mesentery may only prove co-existence of CMV with a primary pathology, but nevertheless it has been suggested that both functional and physical bowel obstruction may be caused by the infection. The mechanism by which CMV may be involved in cases of necrotizing enterocolitis, Hirschprung's disease, intestinal perforation or

even atresia has not been established. It follows, however, that inflammation and vasculitis in the developing mesentery and gut could lead to ischaemic damage and thus the spectrum of atresias and their complications; intrauterine parvovirus B19 has been implicated in the same way [22]. CMV is an aetiological factor in enteric ganglioneuronitis in children with HIV infection [23] and so it follows that an insult to the developing enteric nervous system by the infection could result in a disease clinically similar to Hirschprung's. Interestingly, the use of antiretroviral therapy in neonates of mothers with HIV has itself been implicated in the development of functional distal bowel obstruction; this resolved once the drug was stopped and no surgical intervention was necessary [24].

The scenario of a neonate with the signs and symptoms of bowel obstruction and a mother with diabetes mellitus (DM), should raise the suspicion of the rare small left colon syndrome [25]. Characteristic contrast enema appearances of a narrow descending colon and sharp transitional zone at the splenic flexure is seen in these patients, up to 50% of whom have mothers with DM. Clearly, with such appearances Hirschprung's disease must be excluded, but when positively identified, bowel washouts and the contrast enema is sufficient to relive the obstruction with no further problems being encountered [25]. The pathogenesis of this condition is unclear, although it may relate to the balance of autonomic stimulation upon the developing bowel in the presence of fluctuating levels of glycaemia.

37.4 Summary

Early recognition of neonatal bowel obstruction is essential for the rapid resuscitation and homeostasis. Delay in treatment may result in dehydration, shock, profound electrolyte imbalance, sepsis, loss of gut or death. The three key signs of bilious vomiting, delayed or absent stooling and abdominal distension or tenderness should be heeded and transfer to a specialist centre arranged immediately for further investigation. Radiological assessment of the abdomen with and without contrast agents is a critical tool in determining the level and type of obstruction. Treatment is almost universally surgical, with the aim to restore continuity of the gut, either with a primary procedure or staged approach with the use of stomas.

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Necrotising Enterocolitis

38

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Abstract

Necrotising enterocolitis (NEC) is a devastating disease of infants and the commonest gastrointestinal emergency in the newborn period. It is a condition characterised by intestinal necrosis affecting the ileum and/or colon. There is a wide spectrum of clinical manifestations. In the least severe cases there may be mild inflammation of the intestinal wall in a baby with mild abdominal distension and minimal systemic upset. The most severely affected cases, however, may show evidence of full thickness intestinal necrosis with perforation, respiratory and cardiovascular collapse, multisystem organ failure and in some cases death

Keywords

Necrotising enterocolitis (NEC) • Bell's classification • Staging • Peritoneal drainage • Surgery • Stomas • RCTs

38.1 Introduction

Necrotising enterocolitis (NEC) is a devastating disease of infants and the commonest gastrointestinal emergency in the newborn period. It is a condition characterised by intestinal necrosis affecting the ileum and/or colon. There is a wide spectrum of clinical manifestations. In the least severe cases there may be mild inflammation of the intestinal wall in a baby with mild abdominal distension and minimal systemic upset. The most severely affected cases, however, may show evidence of full thickness intestinal necrosis with perforation, respiratory and cardiovascular collapse, multi-system organ failure and in some cases death.

The term 'necrotizing enterocolitis' first appeared in the European literature in the 1950s when Schmid and Quaiser described infants dying from necrotic lesions of the gastrointestinal tract [1]. However, it was not until the 1960s, when Santulli

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_38

et al. reported a series of 64 infants with NEC that it became recognized as a distinct clinical entity [2]. Since then, the condition has been increasingly recognised, at least partly due to the advances made in neonatal care in the past 40 years and the increasing survival of infants at the extremes of prematurity creating a larger population at risk of developing NEC.

Currently, the reported incidence of NEC varies from 0.5 to 5 per 1000 live births [3] but NEC is predominantly a disease of preterm infants and those of low birth weight. The incidence is as high as 10–14% in infants less than 1000 g [4, 5] and more than 90% of affected infants are born prematurely [6]. Despite several decades of active research in the field of NEC, the mortality rate remains unchanged [7] and is over 30% in infants weighing less than 1000 g [8]. New treatments are desperately needed to improve outcome from this devastating condition.

38.2 Pathogenesis and Risk Factors

Several theories and mechanisms of injury have been proposed to explain the aetiology of NEC. However, despite over 30 years of research the aetiology remains unclear and no single mechanism at present can account for the pathogenesis in all cases. The interaction of multiple factors is likely to be responsible in the majority of cases. Several risk factors have been shown to be associated with NEC, and others implicated by strong association. Intestinal immaturity of premature infants, particularly those of extremely low birth weight, is thought to be central to the pathogenesis, although the precise nature of this immaturity and the mechanisms by which disease ensues are unclear. Proposed risk factors are summarised in Table 38.1.

Table 38.1 Proposed risk factors for NEC

Peripartum events
Absent or reversed end diastolic umbilical artery blood flow
Maternal eclampsia
Fetal distress
Premature rupture of membranes
Delivery by caesarean section
Perinatal asphyxia
Perinatal hypothermia
Neonatal period
Respiratory distress syndrome
Apnoeic episodes
Congenital heart disease
Persistent fetal circulation
Persistent ductus arteriosus (PDA)
Sepsis
Umbilical catheterisation
Exchange transfusion
Nsaid treatment of PDA
Feeding regimen
Formula feed (as opposed to breast milk)
High density milk formulae
Early enteral feeding
Rapid advancement of enteral feeding
Bacterial involvement
Precise role unclear (intraluminal bacteria probably essential for the development of NEC)

38.2.1 Peripartum Events

There are several risk factors related to pre- and peri- natal events which are associated with NEC. Absent or reversed end diastolic blood flow in the umbilical artery has been reported as a predisposing factor [9] most likely due to creating a degree of chronic relative intestinal ischaemia. In addition there is an association with maternal eclampsia, fetal distress and premature rupture of membranes. In the immediate postnatal period, risk factors include asphyxia, hypothermia, respiratory distress syndrome, apnoeic episodes, cyanotic congenital heart disease, persistent fetal circulation, persistent ductus arteriosus and sepsis. In addition, there is some evidence that NEC may be associated with red blood cell transfusion [10]. It is likely that all result at least in part in a degree of relative intestinal ischaemia or hypoxia perhaps predisposing the infant to developing NEC in the presence of subsequent risk factors.

38.2.2 Feeding Regimen

The majority of infants who develop NEC have been fed enterally. There is often pressure to provide feeds of increased calorific density in order to meet the growth requirements of the premature neonate. Such feeds are often hyperosmolar and may result in mucosal damage in the pre-existing immature intestine and thereby contributing to the development of NEC. Breast milk appears to offer some protection against NEC, probably as a result of its immunologically active components including immunoglobulins, cytokines and complement proteins [11, 12]. An association between the development of NEC and the administration of milk containing bovine derived proteins has also been proposed.

38.2.3 Altered Blood Supply

NEC has been associated with a number of predisposing factors which are believed to result in intestinal vascular insufficiency and subsequent selective mesenteric ischaemia. The causes of this vascular insufficiency include pre- and perinatal stress (e.g. reversed umbilical arterial blood flow, maternal pre-eclampsia), umbilical catheterization, exchange transfusion, congenital cardiac disease and indomethacin treatment. This results in the loss of the protective mucosal barrier, autodigestion and presents an opportunity for bacterial invasion. In addition to these associations, evidence for a vascular component in the aetiology of NEC comes from an experimental animal model in which a disease like NEC is observed following an intestinal ischaemia reperfusion injury [13].

38.2.4 Bacterial Involvement

While the precise role of bacterial agents in the development of NEC is unclear, several factors suggest their involvement. Occasionally NEC is seen to occur in clusters, in which a higher than expected number of cases are observed in one centre [14]. Identical organisms are grown from babies within these clusters and the initiation of infection control measures has been shown to control such outbreaks [15]. However, different organisms are grown from separate outbreaks so it cannot be claimed that a single organism is involved in development of NEC. Bacterial involvement in the pathogenesis of NEC is also implicated by association; endotoxaemia [16, 17] and positive blood cultures are common in infants with NEC and the gastrointestinal pneumatosis found in NEC contains 30% hydrogen, a gas produced solely by bacterial metabolism [18]. Furthermore, in experimental animals, an NEC-like illness can be inuced by ingestion of *Clostridium* species [19] and administration of bacterial endotoxin [20, 21]. Recent advances in pyrosequencing techniques to identify the intestinal microbiome have led to a surge in interest in examining the development of NEC in relation to the intestinal microflora. Although a precise bacterial signature has not been identified, it seems that development of NEC is immediately preceded by a loss in bacterial diversity [22]. Microbial triggering of the hyper-inflammatory cascade of NEC involves the toll-like receptor family, and other recent work is dissecting the molecular events involved in the initiation of mucosal damage [23].

38.3 Prevention

A variety of interventions have been proposed to prevent NEC. This is the most logical approach to combating a disease for which there are no specific therapies. Given the multifactorial aetiology of the disease any intervention decreasing the incidence of one of the recognized risk factors may be decrease the incidence of NEC. Although interventions such as immunoglobulin administration [24] or prophylactic enteral antibiotics have been shown to reduce incidence of NEC in individual studies, subsequent reviews and concerns over adverse effects have precluded their widespread usage [25, 26].

Other novel agents have been suggested for the prevention of NEC including lactoferrin [27], recombinant erythropoietin [28], glutamine [29] and arginine [30]. Whilst there is some evidence to support a reduction in incidence of NEC with these compounds, the mechanisms of action are unclear and may be attributable to other secondary effects. None is in current widespread use, although further studies of these and other agents are warranted.

The most robust evidence for interventions to prevent development of NEC exists for the administration of probiotics (reviewed [31]) and modulation of feeding regimes in infants at highest risk of NEC. The role of bacteria in the pathogenesis of NEC has led investigators to determine the effect of probiotics on the incidence on NEC. Several randomised controlled trials have demonstrated a significant reduction in incidence of NEC following routine probiotic administration [32, 33] and meta-analysis of these studies appears to confirm this [34]. However, the population at highest risk, i.e. those born at <30 weeks gestation and/or <1000 g birthweight, have been notably underrepresented in randomised controlled trials and therefore the meta-analyses, and a recent large randomised controlled trial in the UK showed no benefit of probiotic administration [35]. Furthermore, there remain unanswered questions as to which probiotic should be used and at what dose [36].

There is little doubt that one of the most important preventative measures is that of feeding infants at risk of NEC with breast milk as opposed to formula milk. This effect has been known for more than 20 years [11], but despite changes in infant formula, breast milk still appears to offer significant protection [12, 37]. Quigley et al., in a Cochrane review, demonstrated a significantly lower incidence of NEC in human milk-fed infants [38]. If fortification of breast milk is necessary to achieve adequate growth then a fortifier based on human milk appears to lower the incidence of NEC (and NEC requiring surgery) compared to a cow's milk based fortifier [37]. However, availability of either human milk and/or human milk based products is problematic.

In addition to this it has been a long held belief that the time at which enteral feeds are first introduced and the rate at which they are increased may affect the incidence of NEC. In an attempt to demonstrate this definitively, several groups have recently published results of well-designed randomised controlled trials investigating the effect of early versus delayed enteral feeding in infants at risk of NEC [39, 40]. Whilst both demonstrated a trend towards reduction in incidence of NEC with delayed enteral feeding, neither study in isolation demonstrated a statistically significant effect, and current meta-analyses do not support the use of a delayed introduction or slower rate of enteral feeds to prevent NEC.

Clusters of cases of NEC have been described, and anecdotally there is marked geographic variation in prevalence between countries and/or centres. How much of this is due to differences in feeding practise or other aspects of neonatal care, and how much of it may be due to genetic or environmental factors is unknown. Although there is some evidence that certain genotypes may predispose infants to NEC [41–43], the effects of these genotypes are not strong and most of the studies have been relatively small-scale.

38.4 Clinical Features and Diagnosis

Infants with NEC usually display both specific and non-specific gastrointestinal signs. In the early stages of the disease, abdominal distension with or without tenderness, feeding intolerance with increased gastric residuals, vomiting and occult blood in the stools may all be present. These findings may become more severe as the disease progresses to include abdominal wall oedema, erythema and ascites. A small proportion of infants with NEC present with a palpable abdominal mass (usually due to matted loops of bowel around an area of gangrene or perforation) and/or persistent intestinal obstruction.

In addition to these gastrointestinal signs, generalized non-specific signs indicative of systemic deterioration or sepsis are often present. In their mildest form, these include temperature instabil-

ity, hypovolaemia, tachycardia, and mild respiratory distress. In more advanced disease, clinical features of a systemic inflammatory response frequently develop including hypotension requiring inotropes, respiratory failure requiring ventilatory support, coagulopathy and renal failure.

Whilst there are no defining laboratory parameters of use in the diagnosis of NEC, a number of haematological and biochemical abnormalities may be observed including raised or depressed white cell count, thrombocytopenia, metabolic acidosis, glucose instability and elevated C-reactive protein levels [17, 44–46], although none of these are universally present in all cases. There also potentially some other more specific markers of intestinal damage, such as intestinal fatty-acid binding protein [47, 48], but these are not yet suitable for routine clinical use. Urinary and plasma proteomics has identified other potential markers, but again translation to the clinical scenario may take some years [49, 50].

Radiographic imaging is essential in the diagnosis of NEC. The pathognomonic radiological finding is that of pneumatosis intestinalis (Fig. 38.1) representing gas within the wall of the bowel, which is believed to originate from pathogenic bacteria. If this gas becomes absorbed into the mesenteric circulation it may result in the presence of portal venous gas seen as a narrow, linear air-dense area in the hepatic region on X-ray. The most significant radiological finding is that of pneumoperitoneum (Fig. 38.2) resulting from intestinal perforation, as this is a clear indication that surgery is required. Free air may be seen in a number of ways including:

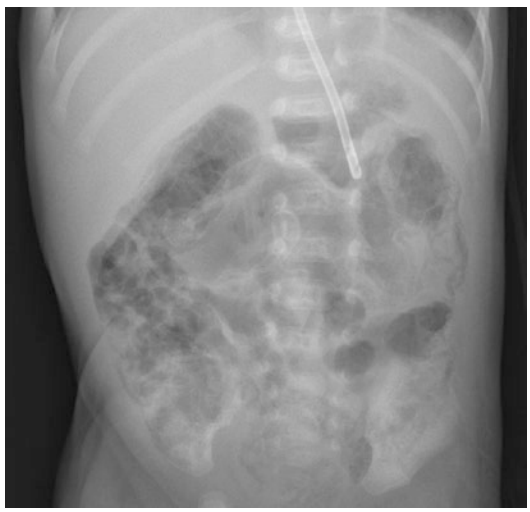

Fig. 38.1 Plain AXR demonstrating pneumatosis intestinalis in an infant with suspected NEC

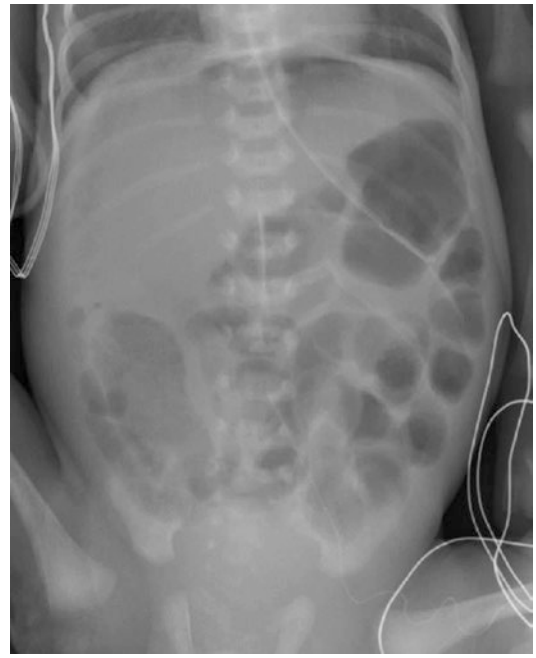

Fig. 38.2 Plain AXR demonstrating pneumoperitoneum in an infant with NEC

- The football sign (free gas outlining the falciform ligament and umbilical arteries)
- As a triangular gas shadow clearly not within the intestinal lumen often bordered by the subhepatic space and hepatorenal fossa
- As Rigler's sign, in which there is clear visualization of the outer as well as the inner wall of a loop of bowel

In many cases the identification of perforation is challenging and a lateral decubitus or lateral shoot through radiograph may be useful (Fig. 38.3). There are cases in which intestinal perforation may be represented by a completely gasless abdomen and it is not unusual to find a sealed perforation at laparotomy in the absence of free air on the abdominal radio-

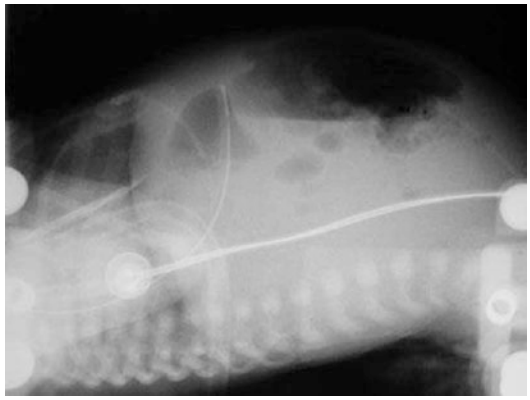

Fig. 38.3 Lateral shoot-through AXR in an infant with NEC demonstrating pneumoperitoneum

graph. An abdominal ultrasound scan may be helpful for diagnosis in these cases. Colour doppler ultrasound has been advocated in some centres, but this requires specific training [51–53] and has the disadvantage of being very operator dependent.

38.5 Staging

This combination of clinical features, laboratory indices and radiological findings have been grouped together to form a staging system (Table 38.2) for NEC known as Bell's staging [54]. The use of such a staging system has been used by some surgeons to select the most appropriate treatment but its value is probably greatest in defining severity of disease in determining the effectiveness of therapy on survival and outcome. Some authors have attempted to define staging on the basis of only radiographic findings [55], but this has not found widespread usage.

38.6 Clinical Management

38.6.1 Medical Management

Most infants with suspected (Bell's Stage I) or less advanced (Stage IIA or B) NEC are managed non-surgically although they may require intensive medical care. This may be described as predominantly supportive as there are no specific treatments for NEC. This supportive treatment includes appropriate ventilatory support, adequate fluid resuscitation, inotropic support as required and correction of acid–base imbalance, coagulopathy, and thrombocytopenia. The intestine is rested and decompressed with a nasogastric tube and broad spectrum antibiotics are given usually for 7–10 days. Antibiotics may be modified appropriately in light of microbiological culture results.

Although there are no specific therapies for NEC, various therapeutic agents or manoeuvres have been tested in experimental models of NEC. These include captopril [56], platelet activating factor antagonists [57], moderate controlled hypothermia [58], and stem cells [59, 60]. However, because of the experimental models studied, it is not clear whether some of these agents are effective at prevention or as therapy. Of note, moderate therapeutic hypothermia was found to be feasible and safe in infants with NEC [61] and a randomised controlled trial to test effectiveness is currently in progress (CoolNEC).

Serial clinical and radiological examination is of extreme importance to monitor progression of disease and detect any evidence of intestinal perforation or other indication for surgical intervention. In the absence of such indication, medical management should continue for 7–10 days depending on severity of illness. Following this, feeds may be slowly reintroduced paying particular attention to feed intolerance suggestive of a repeat episode of NEC or intestinal stricture. From the time of diagnosis to re-establishment of full enteral feeds it is essential to maintain nutritional input with parenteral nutrition (PN) adequate for tissue healing and repair, and body growth.

38.6.2 Surgical Management

Despite aggressive medical treatment, a proportion of infants with NEC require acute surgical intervention. Surgeons differ over indications for surgery since there is the potential to cause serious harm by operating on a fragile, critically unwell preterm infant [62]. Indications for surgery are listed in Table 38.3.

Table 38.2 Modified Bell staging criteria for NEC

Stage	I	IIA	IIB	IIIA	IIIB
Description	Suspected NEC	Mild NEC	Moderate NEC	Severe NEC	Severe NEC
Systemic signs	Temperature instability, apnoea, bradycardia	Similar to stage I	Mild acidosis, thrombocytopenia	Respiratory and metabolic acidosis, mechanical ventilation, hypotension, oliguria, DIC	Further deterioration and shock
Intestinal signs	Increased gastric residuals, mild abdominal distension, occult blood in the stool	Marked abdominal distension ± tenderness, absent bowel sounds, grossly bloody stools	Abdominal wall oedema and tenderness ± palpable mass	Worsening wall oedema with erythema and induration	Evidence of perforation
Radiographic signs	Normal or mild ileus	Ileus, dilated bowel loops, focal pneumatosis	Extensive pneumatosis, early ascites ± PVG	Prominent ascites, fixed bowel loop, no free air	Pneumoperitoneum

Modified from Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33:179–201; used with permission
DIC disseminated intravascular coagulopathy, *PVG* portal venous gas

Table 38.3 Indications for surgery in acute NEC

Absolute indications
Pneumoperitoneum
Clinical deterioration despite maximal medical treatment
Abdominal mass with persistent intestinal obstruction
Relative indications
Increased abdominal tenderness, distension and/or discolouration
Portal vein gas

The principles of surgical treatment for acute NEC are to remove necrotic intestine and control intra-abdominal sepsis whilst preserving as much intestinal length as possible. Within these principles, a number of surgical options exist and the procedure of choice is somewhat contentious. The traditional surgical approach to NEC has been to perform a laparotomy, resect all areas of necrotic intestine and exteriorize the bowel to allow adequate time for healing and growth before restoring intestinal continuity at a later stage. However, stomas, and in particular ileostomies are poorly tolerated by preterm infants as they may predispose to nutritional and metabolic disturbances and poor growth as a consequence of fluid and electrolyte depletion. Some surgeons therefore advocate primary anastomosis following intestinal resection for NEC wherever possible and this is feasible even in small, critically unwell infants [63]. However, there is no good evidence to support one approach over the other. In children who are unstable during surgery or have intra-operative complications such as haemorrhage the quickest approach is usually preferable; this is usually to fashion a stoma.

Some children have more than one section of bowel affected by NEC, so-called multifocal disease. For this a number of operations have been proposed including multiple resections and multiple primary anastomoses. A ‘clip and drop’ approach may also be useful in multifocal disease followed 24–48 h later by a ‘second-look’ laparotomy [64].

Unfortunately a number of infants present at laparotomy with extensive or panintestinal NEC. Surgical options in this scenario are limited and many surgeons would consider withdrawing care faced with an infant with panintestinal gangrene (NEC totalis). However, some infants with very extensive disease may benefit from a high diverting jejunostomy [65].

A final surgical manoeuvre used in infants with perforated NEC is placement of a peritoneal drain. Primary peritoneal drainage (PPD) was initially proposed as a method of stabilizing infants with intestinal perforation prior to definitive surgical treatment [66]. Subsequently, it was reported as definitive treatment for intestinal perforation as some infants required no further surgical treatment [67, 68]. There have been two recent prospective randomised controlled trials investigating the use of PPD in infants with perforated NEC compared to laparotomy [69, 70]. Neither definitely demonstrated an advantage of either PPD or laparotomy over the other, and this was also true when a meta-analysis of the two trials was performed ([69]; Fig. 38.4). However, one study concluded that PPD was not an effective definitive procedure for perforated NEC as its use was followed by a rescue laparotomy in approximately ¾ of the infants [69]. Whether there remains a role for PPD in the stabilisation of a critically unwell child with perforated NEC and respiratory compromise prior to transfer to another centre for a laparotomy remains unclear [71].

The authors' proposed surgical management of NEC is illustrated in Fig. 38.5.

38.7 Outcome

Despite intensive medical and surgical treatment a number of infants do not survive the acute episode of NEC. These fall broadly into two groups: those who have panintestinal disease whose intestine cannot be salvaged and those who have surgically and medically and treatable disease but who develop a significant inflammatory response syndrome resulting in multi-organ dysfunction syndrome. Whilst overall mortality from NEC is may be as high as 35%, birth weight is a significant determinant predictor of mortality such that the mortality from NEC is as high as 42% in infants

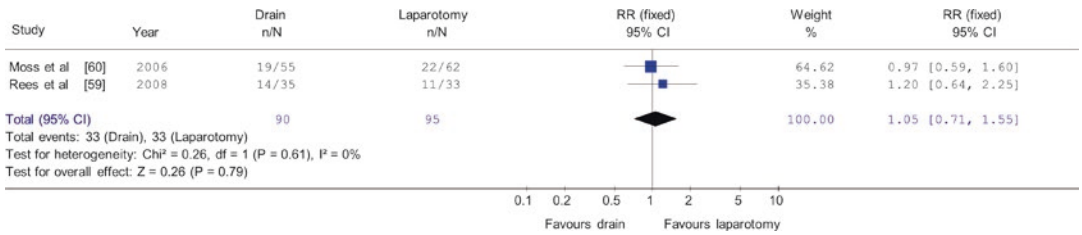

Fig. 38.4 Meta-analysis of primary peritoneal drainage vs. primary laparotomy for NEC. Outcome is mortality. [59, 60]

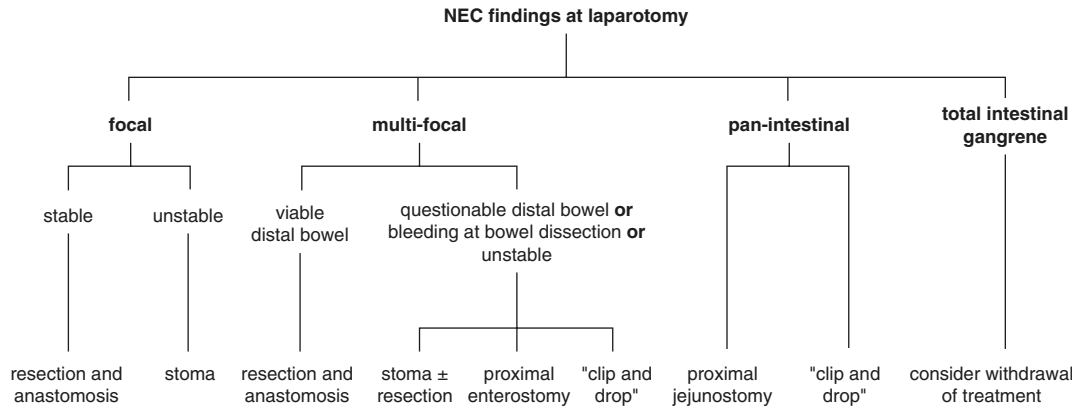

Fig. 38.5 Proposed surgical strategy for NEC. Modified from Pierro A, Hall N. Surgical treatment of infants with necrotizing enterocolitis. Semin Neonatol 2003;8:223–32

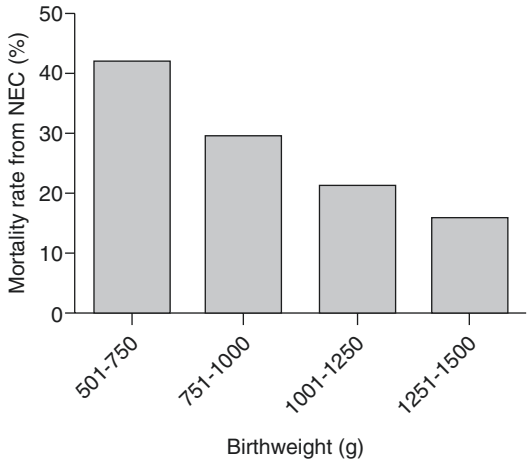

Fig. 38.6 Mortality of NEC by birthweight category [8]

born <750 g [8]. With increasing birth weight, mortality from NEC decreases (Fig. 38.6). However, the mortality of those infants requiring surgery does not seem to be birth weight dependent [7].

In those who survive the acute episode of NEC, a proportion will develop an intestinal stricture either related to medically treated NEC or at the site of a previous anastomosis. Surgical resection of such strictures is usually necessary. Longer term outcome is related to remaining intestinal length and its capacity for adequate nutrient absorption. Malabsorption may result from a variety of factors including gut dysmotility, enzyme deficiency, abnormal intestinal mucosa, bacterial overgrowth, decreased bowel length and vitamin B12 deficiency secondary to ileal resection. Short bowel syndrome is the most serious gastrointestinal complication associated with NEC and great efforts are taken to avoid resection of more bowel length than is absolutely necessary. Supporters of resection and primary anastomosis cite this as one of the advantages over stoma formation.

PN-related complications are commonly encountered in infants with NEC and include sepsis, suppression of the immune response and impairment of liver function. Standard strategies to minimise the risk of these complications are used aggressively as some of these infants may have a long term PN dependency.

In addition to the intestinal sequelae of NEC, it is being increasingly recognised that NEC has a deleterious neurodevelopmental effect, the mechanisms of which are not understood [72, 73]. Whilst it is recognised that many preterm infants suffer from neurodevelopmental impairment, neurodevelopmental outcome appears worse in infants who have had NEC. In addition to the intestinal function following NEC it is essential that this important outcome measure is monitored as we strive towards novel therapeutic strategies that are desperately needed.

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Neonatal Intestinal Failure and Transplantation

39

Mikko P. Pakarinen and Antonino Morabito

Abstract

Neonatal intestinal failure is a devastating condition which carries a significant morbidity and mortality. The most important causes of intestinal failure include short bowel syndrome, motility disorders and rare mucosal enteropathies. The management of these complex patients is challenging and requires a multidisciplinary approach for optimal outcomes. Multidisciplinary coordinated efforts are aimed to optimize nutritional, surgical and medical therapy. The main goals of the treatment include assuring adequate growth and development, optimal utilization of the adaptation potential of the remaining bowel in order to achieve intestinal autonomy and effective prevention and treatment of complications. Survival and successful adaptation depends on an early institution of intestinal rehabilitation which consist of liver-sparing parenteral nutrition, careful central venous feeding line management to avoid and control infections and to maintain venous access sites, individualized enteral nutrition, optimal medical management and carefully planned surgical procedures as well as social integration. Recent refinements in surgical, nutritional and medical treatment have been associated with significant reductions in morbidity and improvements in survival. Autologous gastrointestinal reconstruction is a valuable option in selected patients from the very beginning in the planned management of these patients. The resultant reduction in parenteral nutrition requirement limits the extent of the side effects improving both patients' prognosis and quality of life. The great majority of neonates with short bowel syndrome can be weaned from par-

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_39

enteral nutrition while liver-intestinal transplantation serves as a salvage therapy for those who develop life-threatening complications such as liver failure, central vein thrombosis or recurrent catheter-associated bloodstream infections.

Keywords

Autologous intestinal reconstruction • Intestinal failure • Intestinal transplantation • Neonates • Longitudinal intestinal lengthening and tailoring • Parenteral nutrition • Short bowel syndrome • STEP

39.1 Introduction

Neonatal intestinal failure (IF) refers to any intrinsic intestinal disease leading to an inability to sustaining growth by adequate enteric absorption of fluids, electrolytes and energy. IF carries a significant morbidity and mortality as well as economical burden. The most important causes of IF include short bowel syndrome (SBS), motility disorders and rare mucosal enteropathies. The management of these complex patients is challenging and requires a multidisciplinary approach for optimal outcomes. Recent refinements in surgical management, medical treatment and delivery of parenteral nutrition (PN) have been associated with significant reductions in morbidity and improvements in survival. The great majority of neonates with IF can be weaned from PN while intestinal transplantation serves as a salvage therapy for those who develop life-threatening complications such as liver failure or recurrent catheter-associated bloodstream infections.

39.2 Epidemiology and Mortality

The exact incidence and prevalence figures are difficult to define due to variable definitions of IF but number of patients appears to be increasing. A recent nationwide Italian study reported 0.1% occurrence rate of IF out of 30,353 newborns [1]. Incidence of neonatal IF was 0.05% in a prospective nationwide study covering all of Finland with 60,430 newborns corresponding 46 per 100,000 live births [2]. IF was defined as the need for PN for longer than 4 weeks in both above-mentioned studies [1, 2]. A population-based survey from Canada estimated the incidence of surgically treated SBS to be 25 per 100,000 live births [3]. The occurrence of SBS increases along with decreased birth weight and prematurity being 0.7% among low birth weight preterm infants and 1.1% among very low birth weight infants [4].

Before the advent of PN in 1968 IF was a fatal condition [5]. Since then mortality rates have markedly declined and survival rates may currently reach 90% [1, 2, 6–10]. Establishment of special multidisciplinary care teams for neonates with IF appears to be the major contributor for the improved survival rates [11, 12]. During the first 2 years of life the overall and the disease-specific mortality of neonatal SBS is three and five times higher in relation to control cohort with comparable underlying disease characteristics [3]. IF associated mortality has a bimodal distribution [12]. Most of the deaths occur during the first years of life due to underlying disease or surgery associated complications [11, 13]. Recently, a multicenter follow-up of 272 infants reported 73% 5-year survival rate [85]. Delayed complications of IF such as intestinal failure associated liver disease (IFALD) and sepsis due to catheter-associated bloodstream infections and bacterial translocation from the intestine continue to cause mortality among long-term survivors requiring PN [84]. A 5 years survival rate of

95% has been reported for IF patients weaned from PN by the age of 2.5 years as opposed to 52% for those not weaned [14]. In addition to weaning off PN, occurrence of cholestasis (conjugated bilirubin > 2.5 mg/dL) and short age-adjusted small bowel length (< 10% of normal) is the major predictors of mortality in pediatric SBS [11, 15]. The overall mortality is higher in neonates with severe motility disorders and mucosal enteropathies as the underlying cause for IF in relation to those with SBS [16].

39.3 Definition

Neonatal IF is defined as any intrinsic intestinal disease leading to an inability to sustain hydration, electrolyte, nutrient and energy balance, growth and development by adequate enteric absorption. The definition may also be based on the absolute or age-adjusted length and anatomy of the remaining bowel, the extent and duration of PN requirement, factual intestinal absorptive capacity or fecal energy loss [12, 15, 17]. In the literature, the duration of PN requirement signifying IF usually ranges from 28 to 42 days and from two to 6 months [1, 2, 8, 10, 11, 13]. The percentage of normal age-adjusted bowel length may be a stronger predictor of weaning from PN than absolute length of the remaining intestine, which depends on gestational age of a neonate [15, 18]. Age-specific norms for intestinal length in children are available [18]. A commonly used limit for neonatal SBS is a residual small intestinal length less than 25% of predicted for gestational age [3, 10, 13]. Citrulline is a nonessential amino acid that is principally synthesized by small bowel enterocytes. Serum citrulline concentration reflects small intestinal mucosal mass and enteral feeding tolerance and may be used as a biomarker to define the degree of IF [19–21]. Among pediatric IF patients a serum citrulline positively correlates with the length of the remaining small intestine and a level below 12 μmol/L is strongly predictive of permanent dependence of PN [19–21].

By definition, IF results in prolonged dependence of PN regardless of the underlying intestinal disease which greatly modulates the natural history on IF. PN may be partial or total and temporary or permanent. Most neonates with IF can be weaned from PN whereas others require partial or total PN for several years or even permanently. Some patients develop complications especially during long-term PN including liver failure and catheter-related sepsis. These patients may be considered as candidates for intestinal transplantation.

39.4 Causes of Intestinal Failure

The causes of IF and their relative frequencies are outlined in Table 39.1. The frequency distribution of the underlying intestinal diseases varies by different centers while SBS, severe motility disorders and mucosal enteropathies account for the majority of cases [1, 2, 14, 17, 22]. Different etiologies may coexist in one patient. Clearly, the most common cause for neonatal IF is SBS characterized by reduction of functional gut mass (or length) below the minimal amount necessary for

Table 39.1 Etiology of neonatal intestinal failure

Short bowel syndrome (70–90%)
Necrotizing enterocolitis
Malrotation midgut volvulus
Adhesive volvulus
Small intestinal atresia
Gastroschisis
Operative complications
Severe intestinal motility disorders (5–20%)
Chronic intestinal pseudo-obstruction
Extensive aganglionosis (Hirschsprung)
Intestinal neuronal dysplasia
Autoimmune
Mitochondrial cytopathies
Epithelial diseases of the small intestine (5–10%)
Epithelial dysplasia
Mikrovillus atrophy
Autoimmune enteropathy

adequate digestive and absorptive capacity associated with rapid intestinal transit. SBS may result from resection, disease related intestinal loss or congenital short bowel. The primary etiologies of neonatal SBS include necrotizing enterocolitis, intestinal atresia, gastroschisis and malrotation with mid-gut volvulus [1–3, 12].

Severe intestinal motility disorders result in recurrent or chronic intestinal obstruction in the absence of mechanical occlusion due to impaired motor activity and peristalsis. Of these total colonic aganglionosis (Hirschsprung disease) with extended jejuno-ileal involvement and chronic intestinal pseudo-obstruction are relatively common causes of IF [1, 2, 10, 14, 22]. Chronic intestinal pseudo-obstruction is very heterogenous condition including neuropathic and myopathic forms with or without urinary tract involvement [23, 24]. Megacystis microcolon intestinal hypoperistalsis syndrome represents a rare and severe form of dysmotile intestinal obstruction in the newborn resulting in IF in the vast majority of cases [24].

Mucosal enteropathies, which often result in IF include congenital diseases of enterocyte development such as microvillus atrophy and intestinal epithelial dysplasia [17]. Autoimmune enteropathy is characterized by a defect in regulatory T-cells and immune dysregulation and may respond to immunosuppressive therapy [17].

39.5 Pathophysiology

39.5.1 Adaptation

With time the majority of neonates with SBS can be weaned from PN which is the mainstay of treatment. Weaning from parenteral to full enteral nutrition is possible due to intestinal adaptation which refers to structural and functional changes following resection resulting in a gradual increase in absorptive capacity of the remaining bowel. The adaptation process is well characterized in experimental animals [25]. Enlargement of diameter and length of the remaining bowel as well as increase in villus height and crypt depth result in enlargement of intestinal absorptive surface both at macroscopic and microscopic level [25]. These adaptation mechanisms appear to occur also in human neonates [26], although systematic studies are missing. Clinically, postresectional adaptation-related bowel dilatation often occurs to an extent which impairs intestinal peristaltic function predisposing to bacterial overgrowth, malabsorption and unprogressive weaning from PN.

The amount, anatomy and functional state of the remaining intestine as well as the etiology of IF essentially influences the possibility of achieving intestinal autonomy. Predictors of prolonged PN dependence are shown in Table 39.2. The chances for weaning off PN are markedly worse in children with severe intestinal dysmotility disorders or congenital enteropathies when compared to those with SBS as an underlying cause for IF [10, 16, 22–24, 86]. While the majority neonates with SBS achieve intestinal autonomy, most of those with intestinal dysmotility or microvillus atrophy and intestinal epithelial dysplasia remain dependent on PN [16, 22, 86]. In SBS the remaining bowel is most often functionally intact enabling adaptation, whereas primarily and permanently diseased intestine in motility disorders and enteropathies rarely improves with time and is highly resistant to various modes of medical and surgical treatment.

Among neonates with SBS, the length of the remaining small intestine is strongly correlated with PN dependence being the most important single predictor of PN dependence [6, 16, 27–29]. In general, the presence of ileocecal valve (ICV) and residual colon or ileum are associated with shorter duration of PN and improved chances of weaning off PN [6, 15,

Table 39.2 Predictors of prolonged PN duration in neonatal intestinal failure

Remaining small intestinal length <40 cm <10% of age adjusted
Resected ileocecal valve
No remaining ileum
No or short remaining colon
End ostomy
Dysmotility or epithelial disorder as etiology

27–29]. The vast majority of neonates with more than 35–40 cm of small bowel remaining eventually achieve intestinal autonomy [6, 27, 28]. In a material of 135 neonates with SBS, 40% of those with less than 40 cm residual small bowel and without ICV remained dependent on PN after 8 years, whereas 80% of those with 40–80 cm residual small bowel and an intact ICV were weaned off PN within 1 year [30]. Among 272 infants with a mean residual small intestinal length of 41 cm 47% weaned off PN by 5 years [85]. However, a wide variance exists and some neonates wean off PN with as little as 10 cm of small intestine below the ligament of Treitz [31]. Some of this variance may be explained by rapid in utero growth of small intestinal length, doubling during the last trimester of gestation [18]. Accordingly, instead of the absolute length, the percentage of normal age-adjusted bowel length may be a more accurate determinant of weaning from PN [15, 18]. Functional destruction of the remaining intestine may prolong PN despite favorable anatomy. For example, motility of the remaining bowel may be impaired due to ischemic injury and scarring in necrotizing enterocolitis.

Retained ICV restrains colonization of the small intestinal lumen by colonic bacteria and subsequent development of bacterial overgrowth and is beneficial by slowing transit. Because the presence of ICV in the clinical setting is almost invariably associated with partly retained ileum, some of the beneficial functional effects of ICV may be, in fact, mediated by the residual ileum. Even a short segment of preserved ileum is advantageous in several ways. Active absorption of conjugated bile acids and vitamin B_{12} is confined to the distal ileum. Interruption of the enterohepatic circulation of bile acids results in impaired micelle formation and malabsorption of fat and fat-soluble vitamins. In children with SBS significant malabsorption of bile acids continues after weaning off PN being markedly more severe among those without any remaining ileum [32]. The ileum is capable of acquiring absorption functions that occur in the proximal small intestine under physiological conditions, such as absorption of cholesterol [33]. In addition to its ability to absorb water and electrolytes, residual colon has been shown to significantly increase energy absorption in adults with SBS by metabolizing carbohydrates to short chain fatty acids which are effectively absorbed from the colon [34].

39.5.2 Bacterial Overgrowth

In children with SBS, PN dependence is prolonged by development of bacterial overgrowth [12, 17, 35]. Bacterial overgrowth exacerbates intestinal malabsorption by causing mucosal injury, by metabolizing intraluminal nutrients and by deconjugating bile acids [36]. Deconjugation interferes absorption of bile acids, which leads to disruption of digestion and absorption of lipids (see above). Moreover, bacterial overgrowth predisposes to bacterial translocation through inflamed and damaged intestinal epithelium with increased permeability and may thereby contribute to development of IFALD [36, 37, 87]. D-Lactic acidosis is relatively common consequence of bacterial overgrowth as a result of the production of D-lactic acid by gram-positive anaerobes [12, 16, 36]. Signs of D-lactic acidosis in neonates include an anion gap acidosis with low L-lactate combined with neurological symptoms such as ataxia and altered level of consciousness.

Bacterial overgrowth is a frequent complication occurring in up to 60% of children with SBS [35]. It is associated with abdominal distension, vomiting, increased intestinal excretions, diarrhea and poor progression of enteral feedings. Bacterial overgrowth may involve a single episode, but often become a recurrent chronic problem. The first diagnosis is most often made by the second year of life [35]. Ideally, the diagnosis should be based on direct cultures of small intestinal aspirates or hydrogen breath test. However, interpretation of these methods has significant limitations in SBS [36] and may be impossible to perform among neonates.

A dilated small intestinal segment with impaired motility, resection of ICV and an intestinal stricture causing partial occlusion predis-

pose to bacterial overgrowth. Symptomatic dilatation of the small bowel or stricture should undergo prompt surgical treatment after radiological confirmation. If this is not possible, intermittent enteral antimicrobial therapy including metronidazole, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole or fluconazole is usually effective [10, 35, 36]. Instead of bacterial eradication, the goal of antibiotic treatment is to modify bacterial flora enough to improve symptoms. The use of broad-spectrum antibiotic should be as limited as possible in order to avoid development of multiresistant strains. Restriction of dietary carbohydrates is advisable to decrease fermentative diarrhea and to prevent D-lactic acidosis [38]. Currently, the use of probiotics is controversial because they are capable of translocating into blood stream and causing sepsis [12].

39.5.3 Intestinal Failure Associated Liver Disease

Depending on definition, IFALD occurs in up to 60–80% of neonates with IF, who require prolonged PN [1, 2, 13, 39]. Biochemical signs include conjugated hyperbilirubinemia associated with increased gamma glutamyl transferase and aminotransferases. Histology of IFALD in neonates involves cholestasis, periportal inflammation, and steatosis, and may progress to bile duct proliferation, fibrosis and biliary cirrhosis leading to liver failure [40]. Biochemical cholestasis is not well correlated with the presence or degree of histologically observed liver fibrosis, which a common finding after long-term PN despite well preserved biochemical liver function [41, 42, 88]. Despite resolution of cholestasi and portal inflammation, liver fibrosis and steatosis persists in about half of the patients after weaning off PN [88, 89]. Although laboratory markers of liver function usually normalize after weaning off PN liver histology remains abnormal for years in the majority of patients. At present, the clinical significance of persistent histological changes of the liver remains unclear, but clearly point to ongoing need to follow up these children also after weaning off PN.

Jaundice is the hallmark and usually the first clinical sign of IFALD. Cholelithiasis may occur in form of biliary sludge especially among neonates. Portal hypertension and associated esophageal varices with splenomegaly and hyperpslenism as well as decrease in liver-derived coagulation factors as a sign of impaired hepatic synthetic capacity are usually observed late in the disease course. Neonates who develop jaundice or signs of IFAL require full biochemical work up with hepatobiliary ultrasound examination and liver biopsy if any diagnostic uncertainty remains.

The cause of IFALD is multifactorial and still incompletely understood [40]. Etiological factors are displayed in Table 39.3. Bacterial overgrowth and increased intestinal permeability may provide mechanisms causing and maintaining IFALD [88]. In mice, PN-induced increase in permeability promotes Toll-like receptor dependent Kupffer cell activation and liver injury, presumably due to bacterial translocation [87]. In children with SBS, infections, loss of the ileocecal valve, bowel dilatation and impaired motility are know risk factors of bacterial overgrowth and histological liver injury [88]. A plant sterol, stigmasterol, a component of soy and olive oil PN lipid emulsions, promotes cholestasis, hepatic macrophage activation and liver injury in mice [90]. In neonates, serum stigmasterol content parallels the amount and duration of PN and correlates positively with direct bilirubin concentration [2]. Immaturity of liver function in neonates may explain their susceptibility to IFALD over

Table 39.3 Risk factors of intestinal failure associated liver disease

Short intestinal remnant
Duration of parenteral nutrition
Lack of enteral feeding
Interrupted enterohepatic circulation
Prematurity and low-birth weight
Recurrent sepsis
Bacterial overgrowth
Excess parenteral glucose
Excess parenteral fat
Excess parenteral plant sterols
Soy bean based parenteral fat emulsion
Lack of parenteral ω[omega]-3 fatty acids

older children. Preventive measures consist of avoiding excessive parenteral energy especially as intravenous fat infusions, cyclic PN infusions, enteral feeding, avoidance and prompt treatment of infectious complications and management of bacterial overgrowth. Delivery of parenteral fat may be restricted to every other day or discontinued especially during episodes of sepsis. Neonates tolerate well interruption of PN infusion for up to several hours without hypoglycemia as long as enteral feedings are continued during the break. Routine assessment of liver function is mandatory in neonatal IF. Ursodeoxycholic acid 10–30 mg/kg/day may improve biochemical signs of cholestasis and jaundice [43]. Optimal dosing, duration of therapy and effect on outcomes concerning IFALD remain unclear.

With progression of enteral feedings or modification of PN, biochemical cholestasis resolves in majority of patients. This is first reflected by a normalization of bilirubin followed by a delayed resolution of aminotransferases. On the other hand, persistent elevation of bilirubin has an adverse prognosis and it is an independent predictor of liver failure in neonatal SBS [40, 44]. The probability of liver failure is at least 36% for a total bilirubin level of 6 mg (102 μmol/L) between 3 and 6 months age [44].

39.6 Management of Intestinal Failure

Neonatal IF is currently managed by multidisciplinary coordinated efforts aimed to optimize nutritional, surgical and medical therapy. The main goals of the treatment include assuring adequate growth and development, optimal utilization of the adaptation potential of the remaining bowel in order to achieve intestinal autonomy and effective prevention and treatment of complications. Survival depends on an early (at diagnosis) institution of intestinal rehabilitation which consist of liver-sparing PN, careful central venous feeding line management to avoid and control infections and to maintain venous access sites, individualized enteral nutrition, optimal medical management and carefully planned non-transplant surgery as well as social integration. Expertise on liver and intestinal transplantation should be readily available for a small proportion of children who develop potentially fatal complications during their management.

39.6.1 Parenteral Nutrition

PN is used to compensate for intestinal fluid loses and to provide adequate nutritional intake of energy, vitamins and micronutrients for normal growth while minimizing adverse effects [12, 17, 30]. It should ensure positive energy balance, sufficient protein synthesis and adaptation of the remaining bowel while preventing nutritional deficiencies [30]. PN is tailored for individual requirements while amount and composition of parenteral energy is adjusted based on weight gain, head circumference, growth and liver function. Excessive parenteral energy either as fat (>1 g/kg/day) or glucose (>12–14 g/kg/day) should be avoided. Stable neonates with IF seldom require parenteral energy over 80–90 kcal/kg/day for adequate growth. Fat and water soluble vitamins and trace elements are routinely supplemented as a part of PN.

Soy oil-based lipid emulsion has been identified as a risk factor of cholestatic liver disease, putatively due to its high omega-6 fatty acid and plant sterol, especially stigmasterol, content [40]. As omega-3 fatty acids are associated with reversal of cholestasis, use of fish oil, which is devoid of plant sterols and high in omega-3 fatty acids may be beneficial. A number of studies have reported beneficial properties of fish oil either alone or in combination with other lipids [45]. These studies indicate that use of fish oil emulsion as PN lipid source among neonates with IF is associated with decreased occurrence of cholestasis as well as faster and higher rate of recovery from IFALD [45–48]. It is plausible that benefits of fish oil are mediated by reduced lipid and plant sterol administration rather than omega-3 fatty acids [90, 91]. Although exact dosing and optimal combination with other lipid sources are currently unclear, fish oil emulsions

appear to be beneficial in the treatment of IF and should be considered at least for patients with anticipated prolonged duration of PN and for those who develop PN associated cholestasis [46]. Fish oil is not an universal solution for IFALD and an optimally balanced lipid product remains to be established. Both olive oil based lipid preparations and SMOF have less omega-6 fatty acids and plant sterols in relation to soy oil. In relation to soy base emulsions, olive oil is rich in omega-9 fattyacids and an antioxidant α-tocopherol and poor in omega-6 fattyacids and plant sterols. Combination of fish oil with olive oil based lipid emulsion may be especially beneficial in neonates with SBS by providing sufficiently energy, omega-3 fatty acids and α-tocopherol and lesser amounts of plant sterols and omega-6 fatty acids [2, 49].

39.6.2 Catheter-Related Sepsis and Thrombosis

Patients with IF and dependent on PN require a reliable central venous (CV) access to survive. Four main routes are available for CV catheter insertion: subclavian, external jugular, internal jugular and femoral vein. The superior vena cava is the preferred location which should always be confirmed by radiologic evaluation. Regardless of the method of insertion, every effort avoiding contamination and preserving the vessel used for insertion should be made. Despite careful care, complications are common including infections, mechanical complications and trombosis.

Central line-associated bloodstream infection is a too common complication of central line use and strict protocols to maintain CV catheter should be implemented. With any suspicion of infection a blood culture at least through the central line should be taken. The single most common organism isolated is coagulase-negative Staphylococci followed by Enterococci, Staphylococcus aureus and Candida sp. The catheter should be replaced if the patients' condition does not improve after 24–48 h therapy with broad-spectrum antibiotics or if signs of cardiovascular instability develop. Antimicrobial therapy is narrowed according to antibiotic sensitivity. Effective prevention central line infections is possible with antibiotic, taurolidine or ethanol locks [50]. Ethanol and taurolidine avoids the problem of antibiotic resistance and over four-fold reduction of central line infection rate has been reported by ethanol lock therapy administered 3 days per week [51].

Fibrin deposition, which is also a source for microbial colonization, is the most common cause of central line occlusion [52]. Ultrasonography is combined with venography if diagnostic uncertainty remains. Catheters occluded by a fibrin sheet or intraluminal blood clot usually reopens by fibrinolytic agents such as alteplase. Venous thrombosis related to CV catheter requires anticoagulation with subcutaneous low molecular weight heparin or intravenous unfractioned heparin [52]. After initial therapy both K-vitamin antagonists and low molecular weight heparin can be used to prevent recurrent venous thrombosis and loss of central venous access sites. A blockage secondary to drug precipitate or PN components often responds to 70% ethanol solution left in the catheter's lumen for 1 h. This procedure can be repeated on a daily basis.

39.6.3 Enteral Nutrition and Medical Treatment

Enteral nutrition is essential in the management of neonatal SBS. As much nutrition as possible should be provided via the intestine while overfeeding should be avoided [92]. In addition to promoting intestinal adaptation, enteral nutrition prevents IFALD by stimulating hepatobiliary axis and by preventing translocation of enteric bacteria by supporting mucosal integrity. An optimal formula for enteral nutrition in pediatric IF has not been established. Most of those who achieve intestinal autonomy continue to require a significant surplus of dietary energy up to 50% above normal requirement combined with supplementations of fat-soluble vitamins (A,D,E,K) and vitamin B_{12} trace elements such as zinc, selenium and magnesium according to their serum

concentrations. Close and long-term follow-up of these children is mandatory.

Enteral feedings are started as soon as possible and advanced gradually as tolerated. PN is tapered proportionally to increased enteral intake. Advancement of enteral feeds may be based on a predetermined limit of intestinal excretions such as 50 mL/kg/day. Other prerequisites include positive fluid balance, adequate growth and an absence of perineal rash due to excessive diarrhea. To assure optimal water absorption and to control high-volume intestinal excretions, enteral sodium supplementation may be used with a starting dose of 4 mmol/kg/day to an extent to keep urinary sodium above 30 mmol/L. Oral feeding is important in order to establish prerequisite for development of eating skills and to avoid food aversion. It may also promote intestinal adaptation by stimulating secretion of salivary epidermal growth factor and pancreaticobiliary secretion. At leas a part of enteral feeds should be given orally whenever possible. If progression of enteral bolus feeds fails, continuous enteral feeding is an effective way to increase mucosal contact time and intestinal absorption [30, 53]. Initially a significant portion of enteral nutrition is often delivered via nasogastric tube or, preferentially, via percutaneous endoscopic feeding gastrostomy. Excessive tube feeding may aggravate bowel dilatation and bacterial overgrowth especially in patients with dysmotile intestine [84, 92]. Transgastric or open feeding jejunostomies are reserved for those with impaired gastric emptying. To improve intestinal adaptation in newborns with SBS, breast milk is incorporated to enteral formulas that mainly consist of preparations containing hydrolyzed protein and medium chain triglycerides. Breast milk contains beneficial immunomodulatory factors as well as growth hormone and epidermal growth factor, which may promote intestinal adaptation [54]. Solid foods are started at the age of 4–6 months to improve eating skills while enteral formula may be changed to a more energy-dense low osmolar whole protein preparation.

Composition of enteral feeds is modified individually according to tolerance and anatomy of the remaining intestine. For example, in patients with colon in continuity soluble fibers such as pectin may be beneficial [30]. Soluble fibers are fermented into short chain fatty acids which are absorbed in the colon providing energy [34]. Because short chain fatty acids stimulate electrolyte and water absorption soluble fibers can be expected to increase stool consistency in patients with remaining colon [10, 30]. Gastric hypersecretion of acid and fluid following massive small intestinal resection is a result of decreased intestinal gastrin catabolism and hypergastrinemia. Increased gastric fluid secretion contributes to increased intestinal water and electrolyte loses while increased acid secretion decreases luminal pH leading to bile acid precipitation and subsequently impaired micelle formation as well as inactivation of pancreatic enzymes impairing lipid absorption. Gastric acid hypersecretion responds to proton pump inhibitors and adequate lipid digestion can be ascertained with enteral pancreatic enzyme substitution. Rapid intestinal transit associated with SBS may be treated empirically with antimotility agents such as loperamide and clonidine. However, their use may exacerbate abdominal distension and symptoms of bacterial overgrowth.

Proadaptive medication aims to pharmacologically enhance intestinal adaptation beyond physiological level by improving absorptive function and growth of the intestinal remnant. Glucagon-like-peptide 2 have been show to decrease PN requirement and increase villus height among adults with SBS [55]. Beneficial proadaptive effects have been described for recombinant human growth hormone and epidermal growth factor in small pilot studies of children with SBS [56, 57]. Unfortunately, sustained treatment effect requires continuing therapy and clinical value of currently available pharmacological proadative regimens in pediatric SBS remains unclear.

39.6.4 Surgical Principles and Initial Operative Management

The main principles in surgical treatment of SBS include bowel preservation, recruitment of all available absorptive surface into intestinal continuity, bowel lengthening surgery and intestinal

transplantation. Possible intestinal strictures and fistulas are treated according to standard surgical principles.

At the initial operation every effort is made in order the conserve as much viable bowel as possible. In cases of uncertain bowel viability only frankly necrotic bowel is removed and a second look operation is performed after 24–48 h following resuscitation. During this time the margins of intestinal necrosis delineate more clearly facilitating the decision making for additional resections. The anatomy and length of the remaining bowel should be recorded in detail to guide later treatment. Continuity of the entire intestinal tract is established without any unnecessary delay after stabilization of general status and confirmation of adequate pulmonary function. Re-establishment of intestinal continuity brings all remaining bowel to contact with luminal chyme, which is the most important single factor promoting intestinal adaptation.

The inherent predisposition for dilatation can be exploited by generating controlled expansion of the remaining bowel as part of the initial management of short bowel among neonates with less than 45 cm of the remaining small bowel with the poorest changes of spontaneous adaptation [58, 59, 94]. A large tube is passed into the end of proximal and distal bowel and brought out onto the abdominal wall (Fig. 39.1). The proximal tube is clamped for an increasing period of time for achieving controlled bowel obstruction driven dilatation. Proximal stoma effluent is recycled via tube into the distal intestine. In 20–24 weeks time the remaining bowel dilates enough to perform a lengthening procedure.

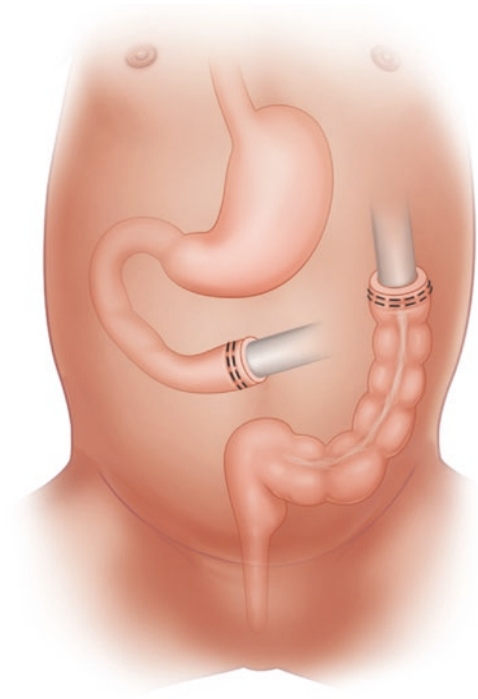


Fig. 39.1 The inherent predisposition for dilatation can be exploited by generating controlled expansion of the remaining bowel as part of the initial management of short bowel among neonates with less than 45 cm of the remaining small bowel. A large tube is passed into the end of proximal and distal bowel and brought out onto the abdominal wall. The proximal tube is clamped for an increasing period of time for achieving controlled bowel obstruction driven dilatation. Clamping is performed at each oral feed aiming to have the tube closed between feeds e.g. for 3–4 h. Proximal stoma effluent is recycled via tube into the distal intestine. In 20–24 weeks the remaining bowel dilates enough to perform a lengthening procedure

Neonates with a rare form of Hirschsprung disease where aganlionosis extends to or beyond the duodenojejunal flexure are very difficult to manage. Removal of the entire aganglionic bowel would result in intractable short bowel without changes for adaptation. These patients can be salvaged by myectomy-myotomy of the retained proximal jejenum as initially described by Ziegler [60]. After histological confirmation of the transitional zone by multilevel biopsies, the entire aganglionic bowel is resected excluding 40 cm of the proximal jejunum which is brought to the abdominal as a jejunostomy. Few weeks later antimesenteric myectomy-myotomy of the aganglionic segment is performed. In addition to providing perquisite for stable PN without massive stomal fluid losses, the operation facilitates significant enteral tolerance preventing development of liver disease [60, 86]. Maintenance of abdominal domain by distending small bowel also aids in preparation for intestinal transplantation [86].

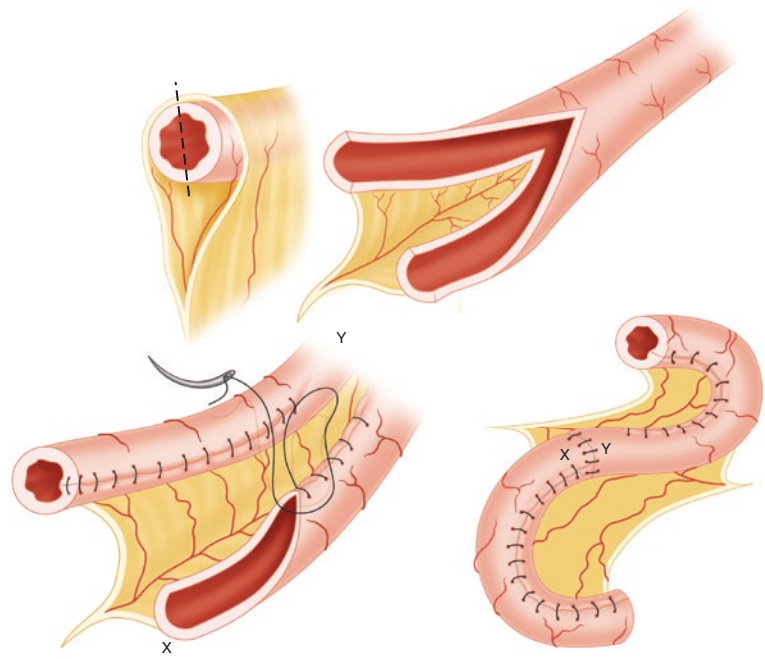


Fig. 39.2 In the LILT procedure the mesentery supplying the dilated small bowel segment is bluntly dissected into two leaves. The bowel is then divided longitudinally between the two leaves, preserving with each half the associated mesentery and blood supply. Each half is remodeled into a tube either by performing longitudinal division of the bowel with a surgical stapler or by suturing. These two hemi-loops of bowel, each with half of the original diameter, are then anastomosed end to end in an isoperistaltic fashion, doubling the length of the dilated segment

39.6.5 Autologous Intestinal Reconstruction

Non-transplant surgery or bowel lengthening may be regarded as a process, potentially involving more than one procedure, aiming to achieve enteral autonomy [58, 61]. This process is better known as autologous gastrointestinal reconstruction (AGIR), which is used as adjunct to medical management for a selected group of children with SBS who reach a plateau in advancement of their enteral nutrition, develop bowel dilatation and bacterial overgrowth [58, 61, 93]. The goal of AGIR is to improve intestinal absorption and facilitate enteral autonomy by manipulation of existing dilated bowel remnant [58, 61]. The resultant reduction in PN requirement limits the extent of the side effects improving both patients' prognosis and quality of life. The principle of AGIR relies on postresectional adaptation-induced bowel dilatation, which often occurs beyond physiological level impairing intestinal function by causing impaired motility, obstruction, stasis and bacterial overgrowth. The most widely used AGIR procedures in children today include longitudinal intestinal lengthening and tailoring (LILT) and serial transverse enteroplasty (STEP). Operations such as colonic interposition, intestinal segment reversal, recirculating loops, artificial valves and the Iowa procedure are associated with less predictable outcomes and are more rarely used.

The modern era of AGIR started after Bianchi published his LILT procedure in 1980 [62]. The mesentery supplying the dilated bowel segment is bluntly dissected into two leaves (Fig. 39.2). The bowel is then divided longitudinally between the two leaves, preserving with each half the associated mesentery and blood supply. Each half is remodeled into a tube either by performing longitudinal division of the bowel with a surgical stapler or by suturing. These two hemi-loops of bowel, each with half of the original diameter, are then anastomosed end to end in an isoperistaltic fashion, doubling the length of the dilated segment.

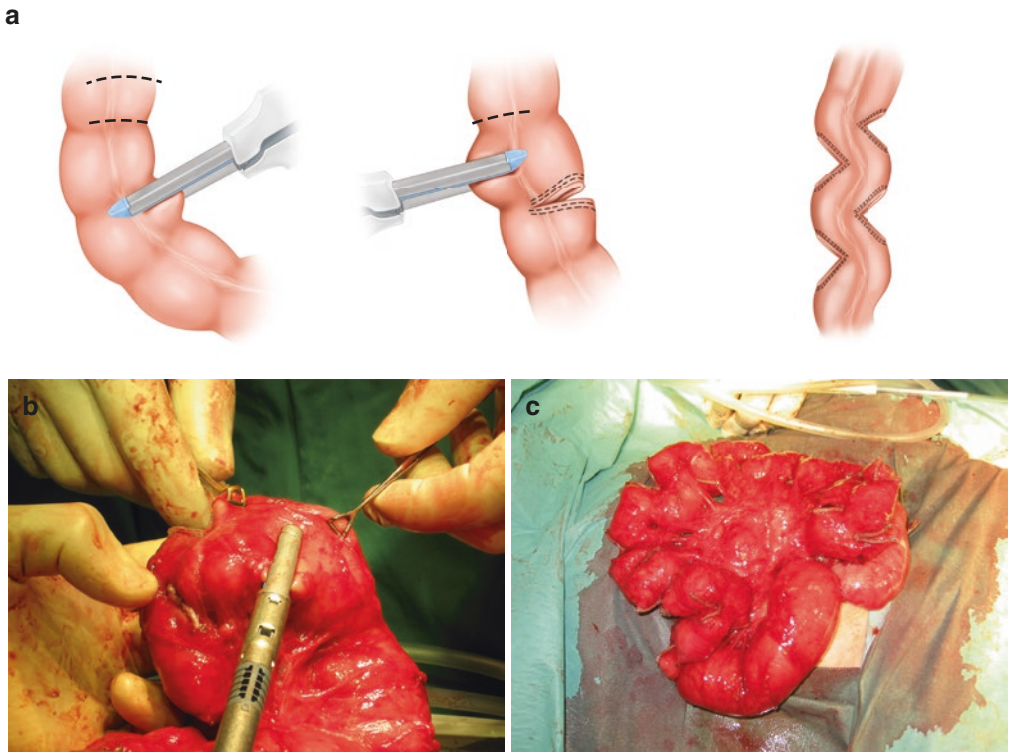


Fig. 39.3 (**a**) The STEP procedure is performed by firing linear staplers alternatively from the mesenteric and anti-mesenteric edge perpendicular to the long axis of the dilated small bowel. (**b**) Small openings in the mesentery are created at each point of stapler application. The distance between subsequent firings of the stapler is guided by the normal diameter of the small bowel being approximately 2 cm. (**c**) The length of the dilated bowel segment increases depending on the degree of dilatation. In this case of combined small bowel atresia and gastroschisis the length doubled after STEP performed at the age of 8 months. The initial length of the remaining proximal small bowel was 30 cm with an absent ileocecal valve. The patient weaned off parenteral nutrition at the age of 3 years 5 months after repeat STEP procedure

Kim et al. initially described the STEP procedure in 2003 [63]. The operation is performed by firing linear staplers alternatively from the mesenteric and anti-mesenteric edge perpendicular to the long axis of the dilated small bowel (Fig. 39.3). Small openings in the mesentery are created at each point of stapler application. The distance between subsequent firings of the stapler is guided by the normal diameter of the small bowel being approximately 2 cm. The length of the dilated bowel segment increases depending on the degree of dilatation even more than 100% [64]. The STEP can be performed on both symmetrical and asymmetrical bowel for example after previous LILT surgery.

Patient selection for AGIR surgery has clarified during the recent years. Autologous gastrointestinal reconstruction is not the last resort in the treatment of short bowel, but valuable option from the very beginning in the planned management of these patients. The main indication is persistent dependency of PN without evidence of further adaptation (progression of enteral nutrition) despite optimized medical therapy with the presence of dilated remaining small intestine. In addition to a radiological gastrointestinal contrast

study, magnetic resonance imaging enterography provides useful information in preoperative assessment of the remaining bowel. The STEP is an effective surgical treatment for recalcitrant bacterial overgrowth with or without d-lactic acidosis in the setting of SBS and in neonatal bowel obstruction associated with marginal small bowel length that would be further compromised by simple tapering such as intestinal atresia [61, 65]. Patient assessment for AGIR should be performed before development of liver disease. End-stage liver failure is a clear contraindication for bowel lengthening procedures [66, 67], although the presence of jaundice and mild hepatic fibrosis without concurrent portal hypertension or decreased hepatic synthetic function may not decrease overall survival [64]. Reversal of liver disease occurs in the great majority of patients who are weaned off PN after intestinal lengthening [64, 67]. In patients with complicated cirrhosis including coagulopathy, ascites or portal hypertension the preferred initial treatment is intestinal transplantation.

The current follow-up times extend to decades after LILT, but are still limited to few years after STEP [58, 61, 64–72]. In these reports survival rates after LILT range between 30% and 100% [58, 64, 66, 68–70] being 77% in the largest single center report of 53 children [64], and around 90% in two recent series [66, 70]. Comparable survival between 79 and 100% has been reported after STEP [64, 65, 71, 72, 95]. The main causes of mortality after both procedures are liver failure and septic complications [64–66, 70, 72]. Variance in patient selection strongly modifies outcomes after AGIR surgery both in terms of survival and rate of weaning PN. Combining the available data on bowel lengthening, PN requirement decreases almost invariably while 40–70% of children including non-survivors achieve enteral autonomy mostly during the first postoperative year without significant differences between LILT and STEP. The final length of the remaining small intestine is the main predictor of achieving enteral autonomy after AGIR surgery [64, 66]. The great majority of patients are operated on between the age of 6 months and 2 years.

The main surgical complications of AGIR procedures include anastomotic leakage, adhesive bowel obstruction, inter-loop fistulae, bacterial sepsis, stricture, gastrointestinal bleeding from the stapler or suture line and bowel redilation. Bowel redilation after intestinal lengthening prevents achievement of intestinal autonomy in a significant proportion of patients [73, 74]. Excluding case reports two series have addressed the efficiency of repeat bowel lengthening with the STEP procedure among children with bowel redilation [73, 74]. An average time to redilation was about 12–24 months and 13–43% weaned off PN after repeat STEP regardless of type of initial bowel lengthening. Despite inferior results in relation to primary bowel lengthening, repeat STEP is a valuable treatment among patients, who remain dependent on PN with stable liver function not precluding the possibility of intestinal transplantation [73].

39.7 Transplantation

39.7.1 Indications and Timing

Intestinal transplantation (ITx) is well established and the only remedial treatment for patients with irreversible IF who develop life-threatening complications during long-term PN [75]. Failure of PN may result from liver failure, recurrent catheter related sepsis, thrombosis of major central venous accesses or intractable water and electrolyte losses associated with recurrent severe dehydration [17]. Dependence on PN alone is not indication to ITx, because most children with IF including those with the shortest remaining bowel can be managed successfully by other means [96–98]. Scarcity of appropriate size donor organs increases waiting list mortality among very young pediatric patients [76]. Progression of above mentioned complications

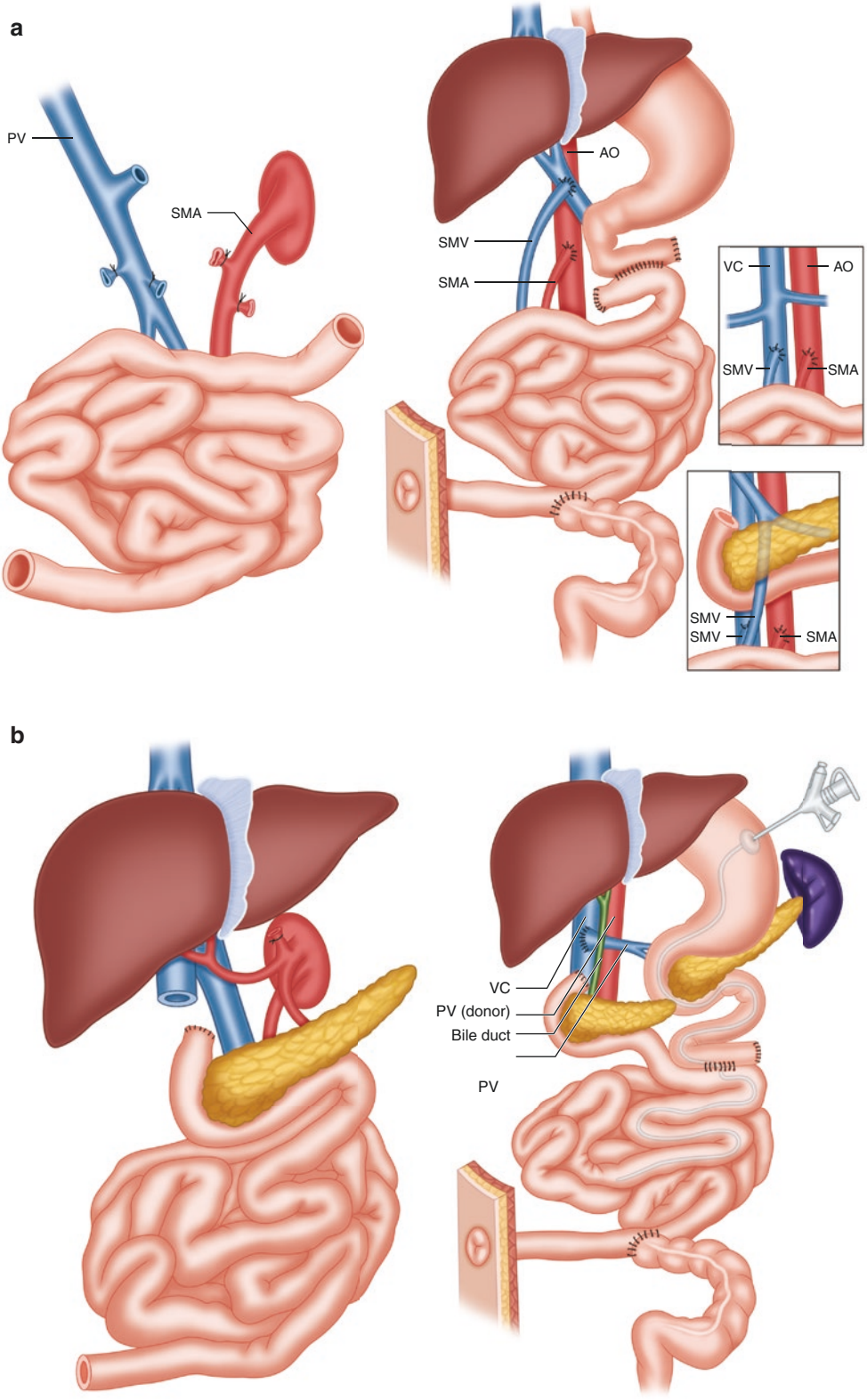
of PN during long waiting times may hamper performance and recovery from transplantation thereby decreasing the changes of survival. To ascertain the best possible changes of success specific guidelines regarding assessment for ITx have been published [17, 75, 77]. These include bilirubin level over 3 mg/dL or complications of portal hypertension, thrombosis of two or more central veins, two or more episodes of central line related sepsis per year or one episode of line fungemia and frequent episodes of intractable dehydration. Essentially, all intestinal failure programs should have active collaborative connections to centers performing liver and intestinal transplantation [77]. Optimization of medical treatment and nutrition as well as confirmation of unfeasibility of autologous intestinal lengthening procedures before transplantation is mandatory. The decision to proceed with ITx must be discussed extensively among multidisciplinary team including pediatric transplant surgeons and gastroenterologists and the changes of survival carefully balanced with the risks of transplantation. The parents must be fully informed about these issues.

39.7.2 Type of Transplant and Technical Considerations

The type of transplant is planned individually for each recipient based on liver function, the underlying disease for IF, for example SBS versus dysmotility, and physical condition and anatomy of the remaining intestine and vasculature. Broad categories of ITx include isolated intestinal, liver-intestinal and multivisceral transplantation (Fig. 39.4). The right colon is often included in the intestinal allograft in patients without native colon in order to improve absorption of water and electrolytes. Careful assessment of liver function before transplantation is essential. Although significant hepatic fibrosis and liver disease may regress following isolated ITx [64, 78], patients with complicated portal hypertension and deranged synthetic function require additional liver replacement. In practice, very young pediatric patients have most often concomitant irreversible hepatic and intestinal failure being potential candidates for combined liver-intestinal transplantation. In some children liver cirrhosis and advanced portal hypertension may hinder intestinal adaptation and prevent potentially achievable weaning off PN. In these patients enteral autonomy is achievable following isolated liver transplantation with or without additional autologous intestinal reconstructive surgery [79].

In intestinal or liver-intestinal transplantation nonfunctional recipient intestine is removed all the way to the very proximal jejunum. In isolated ITx the donor portal vein extending to the superior mesenteric vein or the inferior vena may be utilized for graft venous outflow (Fig. 39.4). In children with SBS the superior mesenteric vein may be inaccessible due to multiple previous laparotomies leaving the inferior vena cava the most feasible option. The arterial inflow is obtained either from the superior mesenteric artery or

Fig. 39.4 (**a**) In isolated ITx the donor portal vein extending to the superior mesenteric vein or the inferior vena may be utilized for graft venous outflow. The arterial inflow is obtained either from the superior mesenteric artery or infrarenal aorta. In order to avoid tension and twisting of the vascular anastomoses, interposition grafts are sutured to the chosen vessels before the graft is brought to the field. (**b**) Liver-intestinal transplantation in most commonly performed using en bloc allograft with preserved duodenum, biliary tract and portal vein. The recipient portal vein is anostomosed to the inferior vena cava in order to drain retained native splanchnic circulation. The suprahepatic vena vaca of the allograft is connected to the common ostium of the hepatic veins and a Carrel patch including the hepatic and the superior mesenteric artery is anastomosed to the aorta. The intestinal continuity is restored and a direct access to the proximal graft for postoperative nutrition and medication is ascertained by a feeding jejunostomy. A temporary ileostomy for endoscopic monitoring is performed


a
PV
SMA
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PV (donor)
Bile duct
PV

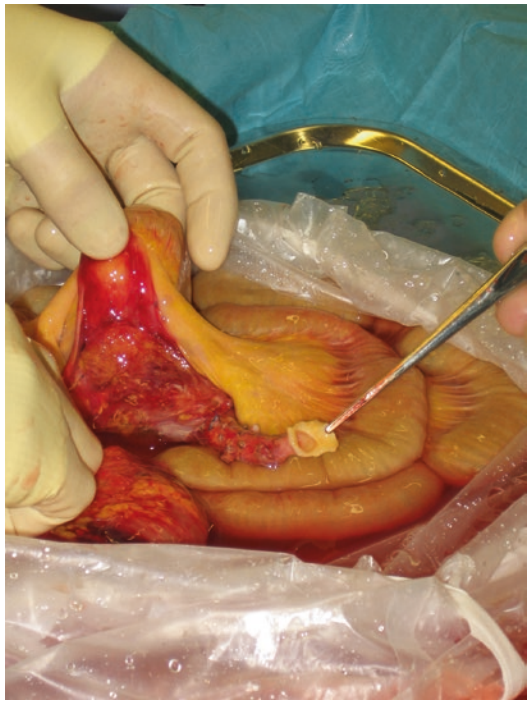

Fig. 39.5 Perfused intestinal graft including the ascending colon ready for implantation. The superior mesenteric artery (in forceps) was anastomosed to the infrarenal aorta

infrarenal aorta (Fig. 39.5). In order to avoid tension and twisting of the vascular anastomoses, interposition grafts are sutured to the chosen vessels before the graft is brought to the field. Liver-intestinal transplantation in most commonly performed using en bloc allograft with preserved duodenum biliary tract and portal vein. After removal of the liver, the recipient portal vein is anostomosed to the inferior vena cava in order to drain retained native splanchnic circulation. The suprahepatic vena caca of the allograft is connected to the common ostium of the hepatic veins and a Carrel patch including the hepatic and the superior mesenteric artery is anastomosed to the aorta. The intestinal continuity is restored and a direct access to the proximal graft for postoperative nutrition and medication is ascertained by a feeding jejunostomy. A temporary ileostomy for endoscopic monitoring is performed.

39.7.3 Outcomes

Most patients regain full enteral autonomy in few months after ITx. Although intestinal transplant contains significant amounts of donor lymphocytes, graft versus host disease is uncommon. Despite different tacrolimus-based immunosuppression protocols and frequent graft monitoring with endoscopically guided biopsies, acute rejection occur in 60% of children [80, 81]. Other common complications include bacterial and viral infections. Cytomegalovirus prophylaxis is continued for several months together with routine surveillance of Cytomegalo- and Epstein-Barr viral load. Infection or reactivation of Epstein-Barr virus predisposes to post transplantation lymphoproliferation disease, which may proceed to monoclonal B-cell lymphoma without treatment (Fig. 39.6). Overall, post transplantation lymphoproliferation occurs in 10% of cases [80, 81]. Renal insufficiency due to calcineurin inhibitor toxicity and other complications of high-dose immunosuppression are major concerns while chronic graft rejection necessitating retransplantation especially following isolated ITx continues to cause delayed graft losses [80].

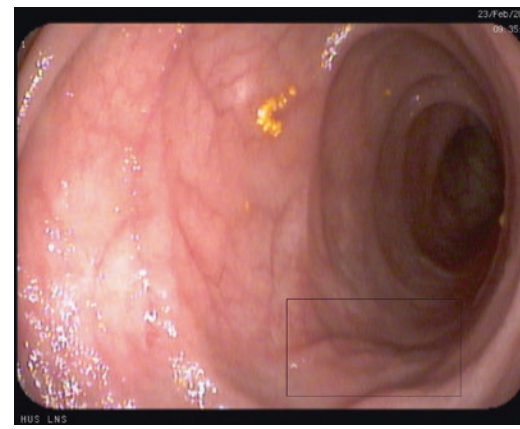

Fig. 39.6 An endoscopic view of the ileum 3 months after transplantation. The *black rectangle* high lights a mucosal nodule with a central depression, which demonstrated Epstein-Barr virus-positive polyclonal lymphoproliferation. Complete resolution occurred after reduction of immunosuppression and anti-CD20 antibody treatment

Currently, 1 and 5 year graft survival after combined liver-intestinal transplantation reaches 90% and 80% in large centers [80]. Although patient survival is higher after isolated ITx due to feasibility of graft enterectomy and re-transplantation, five-year graft survival remains around 60% as a result of more frequent chronic rejection in relation to combined liver-intestinal transplantation [80, 81]. In a large registry-based report of 852 children from US 50% were alive 10 years after isolated ITx [82]. Importantly, normal growth and good quality of life are achievable following ITx and long-term intestinal autonomy is possible in the majority of patients [80, 83]. During the recent years the rate of intestinal and especially combined intestinal liver transplantation among children has decreased. This most likely reflects advancements in surgical and medical therapy of SBS as well as increased awareness of liver protecting strategies in neonatal IF.

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Hirschsprung's Disease

40

Prem Puri and Florian Friedmacher

Abstract

Hirschsprung's disease (HD) is a relatively common cause of intestinal obstruction in newborn infants. It is characterized by the absence of ganglion cells in the distal bowel, which begins at the level of the internal anal sphincter and extends proximally for varying distances. The absence of ganglion cells has been attributed to the failure of migration of neural crest cells.

Keywords

Hirschsprung disease • Aetiology and pathogenesis • Surgery • Outcomes

40.1 Introduction

Hirschsprung's disease (HD) is a relatively common cause of intestinal obstruction in newborn infants. It is characterized by the absence of ganglion cells in the distal bowel, which begins at the level of the internal anal sphincter and extends proximally for varying distances. The absence of ganglion cells has been attributed to the failure of migration of neural crest cells.

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40.1.1 Historical Background

In 1691, the Dutch anatomist Ruysch [1] described a 5-year old girl with abdominal pain who finally died from an intestinal bowel obstruction. More than 200 years later, Jacobi [2] described two newborns with intestinal bowel obstruction that may have been attributable to congenital megacolon. The Danish pediatrician Hirschsprung described in 1887 two cases of infant boys who had died from constipation due to dilatation and hypertrophy of the colon [3]—a condition that later bore his name. In 1901, Tittel [4] noted the absence of ganglion cells in the distal colon of a child with HD. The Swedish pediatric surgeon Ehrenpreis [5] recognized in 1946 the aganglionosis as the cause of congenital megacolon in newborns. Whitehouse and Kernohan [6] presented in

P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_40

1948 a series of 11 cases, which demonstrated that the aganglionosis within the distal colon is the cause of functional obstruction in infants with HD. In 1948, Swenson and Bill [7] recommended recto-sigmoidectomy with preservation of the sphincters as the optimal treatment for HD. Since then, neonatal diagnosis of HD and improvements in surgical techniques have resulted in an evolution towards one-stage pull-through operations with minimal invasive access. All these advances have resulted in a significantly improved morbidity and mortality in newborns with HD [8].

40.1.2 Classification

While the internal anal sphincter is the constant inferior limit [9], HD can be classified as classical recto-sigmoid HD when the aganglionic segment does not extend beyond the upper sigmoid colon, long-segment HD when aganglionosis extends to the splenic flexure or transverse colon, and total colonic aganglionosis when the aganglionic segment involves the entire colon with a short segment of terminal ileum (total colonic aganglionosis [TCA]) [10–12]. Table 40.1 shows the relative frequency of different forms of HD. Total intestinal aganglionosis with absence of ganglion cells from the duodenum to the rectum is the rarest form of HD and associated with high morbidity and mortality rates [13, 14]. Ultrashort-segment HD is a rare condition, characterized by an aganglionic segment of 1–3 cm length [15–17]. "Zonal aganglionosis" is a phenomenon involving a zone of aganglionosis occurring within a normally inverted intestine [18–20]. Skip segment HD (SSHD) involves a "skip area" of normally ganglionated intestine, surrounded proximally and distally by aganglionosis [21–23]. The occurrence of SSHD has no clear embryological explanation. To date, 24 cases of SSHD have been reported in the literature [24].

Table 40.1 Forms of Hirschsprung's disease (HD) and frequency

Form of HD	Level of aganglionosis	Frequency (%)
Recto-sigmoid	Sigmoid colon	72–88
Long-segment	Splenic flexure or transverse colon	9–24
Total colonic aganglionosis	Terminal ileum	3–13

40.1.3 Epidemiology

Several demographic studies have shown a remarkably constant incidence of HD, which is approximately 1:5000 live births [25–27]. However, significant interracial differences in the incidence of HD have been reported: 1:10,000 in Hispanic subjects, 1:6000 in white subjects, 1:4761 in black subjects, and 1:3571 Asian subjects [28]. Different levels of consanguinity may explain some of these differences, but recent genetic studies point to different frequencies of HD-associated mutations within different ethnic populations [29]. With a male-to-female ratio of 4:1, HD is far more common in boys [11, 30]. Interestingly, the male preponderance is less evident in long-segment HD, where the male-to-female ratio is 1.5–2:1 [25–27]. In TCA, the gender distribution even seems to be reversed with a reported male-to-female ratio of 0.8:1 [31].

40.2 Etiology

40.2.1 Failure of Neural Crest Cell Migration

The enteric nervous system (ENS) is the largest and most complex division of the peripheral nervous system, containing about 100 million neurons [32]. Embedded within the walls of the gastrointestinal tract, it represents a unique network of innervations, which functions largely independently of the central nervous system. Most of the neurons are located either in myenteric or submucosal ganglia and only a few are scattered within the mucosa. One of the main functions of the ENS is to coordinate the normal bowel motility and secretory activities.

It is generally accepted that the enteric ganglion cells primarily originate from the vagal neural crest cells (NCCs) [33–35]. The embryonic neural crest arises in the neural tube, originating within the central nervous system, but NCCs detach from this tissue via reduction of cell-cell and cell-matrix adhesion. The epithelio-mesenchymal transformation allows NCCs to migrate along pathways. Pathway selection is most likely achieved by balanced combinations of molecules that promote and reduce adhesion [36, 37]. Several investigators have suggested that the enteric neurons follow a dual gradient of development from each end of the gut toward the midline, with vagal NCCs providing the main source of enteric neurons [38]. Furthermore, animal studies have shown that sacral NCCs also contribute to the hindgut ENS [39, 40]. However, to which extent the sacral NCCs contribute to the ENS in humans is less clear. Failure of the vagal-derived NCCs to colonize the hindgut results in failure of ENS development in this region, suggesting an interaction between sacral and vagal enteric NCCs may be necessary for sacral NCC contribution to the ENS [38].

In the human fetus, neural crest-derived neuroblasts first appear in the developing esophagus at 5 weeks, and then migrate down to the anal canal in a cranio-caudal direction during the 5th–12th week of gestation [41]. The NCCs first form the myenteric plexus just outside the circular muscle layer. The mesenchymally derived longitudinal muscle layer then forms, sandwiching the myenteric plexus after it has been formed in the 12th week of gestation. In addition, after the cranio-caudal migration has ended, the submucous plexus is formed by the neuroblasts, which migrate from the myenteric plexus across the circular muscle layer and into the submucosa; this progresses in a cranio-caudal direction during the 12th–16th weeks of gestation [35]. The submucosal plexus can be divided into an outer plexus (Schabadasch's plexus), which is located in the submucosal layer adjacent to the circular muscle layer, and an inner submucous plexus (Meissner's plexus), located close to the muscularis mucosae [42]. The absence of ganglion cells in HD has been attributed to a failure of migration of NCCs. The earlier the arrest of migration, the longer the aganglionic segment is.

40.2.2 Genetic Factors

Evidence for a role of genetic factors in the etiology of HD is indicated by an increased risk of recurrence for siblings of affected individuals compared with the general population: an unbalanced sex-ratio, the association of HD with other genetic diseases (including chromosomal anomalies and congenital malformation syndromes), and the existence of several animal models of colonic aganglionosis showing specific Mendelian modes of inheritance [43]. HD is known to occur in families. The reported incidence of familial cases in recto-sigmoid HD varies between 3.6 and 7.8%. In TCA, a familial incidence of 15–21% has been observed and in the rare total intestinal aganglionosis an incidence of 50% [44, 45].

The recurrence risk in siblings is dependent upon the sex of the affected person and the extent of aganglionosis. Badner et al. [30] calculated the risk of HD transmission to relatives and found that the recurrence risk to siblings increases as the aganglionosis becomes more extensive. The brothers of patients with recto-sigmoid HD have a higher risk (4%) than sisters (1%). Much higher risks are observed in cases of long-segment HD. The brothers and sons of affected female individuals have a 24 and 29% risk of being affected, respectively [8]. Besides that, a different reproductive rate between male and female carriers could contribute to the parental transmission asymmetry seen in HD [46].

Although HD occurs as an isolated phenotype in at least 70% of cases, associations with various chromosomal anomalies, hereditary syndromes and congenital malformations have been frequently reported. Trisomy 21 (Down syndrome) is by far the most frequent chromosomal anomaly, occurring in 2–15% of all HD cases [47–50]. As individuals with Down syndrome display a 40-fold greater risk of HD than the general population, chromosome 21 is clearly involved in the etiology of HD [51, 52].

Other chromosomal anomalies that have been described in association with HD include interstitial deletion of distal 13q, partial deletion of 2p, reciprocal translocation, and trisomy 18 mosaic [8]. Numerous syndromes and coexisting anomalies (including multiple endocrine neoplasia type 2 and familial medullary thyreoid carcinoma, neuroblastoma, congenital central hypoventilation syndrome, Waardenburg syndrome and related pigmentary anomalies) are associated with HD. Other syndromes and malformations with HD as a frequent feature are: Mowat-Wilson syndrome, Goldberg-Shprintzen syndrome, Bardet-Biedl syndrome, McKusick-Kauffman syndrome, Smith-Lemli-Opitz syndrome, Cartilage-hair hypoplasia syndrome, and distal limb anomalies [53, 54].

During the past 15 years, several genes have been identified that control the morphogenesis and differentiation of the ENS. It has been demonstrated that mutations or deletions of these genes interfere with the development of the ENS. So far, at least 18 susceptibility genes are known to be involved in the development of HD [55–88] (Table 40.2). Of these genes, the RET gene (encoding a tyrosine-kinase receptor) is the major gene causing HD [89, 90]. Mutations in the coding region of RET are responsible for 50% of familial HD cases and 15% of sporadic ones [69, 91]. Thus, both rare and common mutations contribute to the multifactorial HD liability [92]. As all known genes that have been implicated in the development of HD together only account for 20% of all HD cases [72, 84, 93, 94], further genes may also be involved in the development of HD.

Table 40.2 Genes involved in the development of Hirschsprung's disease

Gene	Locus	Reference
RET	11q11.2	[6, 48, 109]
GDNF	5p13.1-p12	[4, 53]
NRTN	19p13.3	[23]
GFRA1	10q26.11	[97]
EDNRB	13q22	[2, 68, 116]
EDN3	20q13.2-q13.3	[10, 141]
ECE1	1p36.1	[47]
SOX10	22q13.1	[44, 113, 136, 139]
PHOX2B	4p12	[18, 32]
HOXB5	17q21.3	[18, 34, 74, 164]
NKX2.1	14q13	[33]
ZFHX1B	2q22.3	[31, 57, 155]
TCF4	18q21.1	[127]
KIAA1279	10q22.1	[12]
NRG1	8p12	[35, 146, 147]
NRG3	10q23.1	[145]
L1cam	Xq28	[153, 157]

40.3 Pathophysiology

The underlying pathophysiologic feature in HD is the functional intestinal obstruction caused by a narrowed distal aganglionoic colon that prevents the propagation of peristaltic waves. However, the pathophysiology of HD is still poorly understood. It has long been recognized that the obstructive symptoms in HD are secondary to the abnormal motility of the distal narrow segment, but there is still no clear explanation for the occurrence of the spastic or tonically contracted aganglionic segment of the bowel [95]. Several abnormalities have been described to explain the basis for the motility dysfunction in the contracted bowel.

40.3.1 Cholinergic Hyperinnervation

There is a marked increase in cholinergic nerve fibers in the intermuscular zone and submucosa of the aganglionic segment in HD. These fibers appear as thick nerve trunks and correspond to extrinsic preganglionic parasympathetic nerves [96–100]. The continuous acetylcholine release from the axons of these parasympathetic nerves results in an excessive accumulation of the enzyme acetylcholinesterase (AChE) that is typically found in the lamina propria mucosae, muscularis mucosae, and circular muscle with histochemical staining techniques. Both, the thick nerve trunks and the increased AChE activity are most pronounced in the most distal aganglionic rectum and progressively diminish proximally as nor-

mal bowel is approached [101]. The proximal extent of increased cholinergic activity does not necessarily correspond to the extent of the aganglionosis, which usually extends more proximally to a variable degree. Pharmacologic investigations of the colon in HD have demonstrated a higher acetylcholine release in the aganglionic segment at rest and after stimulation compared with the proximal ganglionic bowel [102, 103]. AChE concentration has also found to be higher in the serum and erythrocytes of children suffering from HD [104]. Since acetylcholine is the main excitatory neurotransmitter, cholinergic nerve hyperplasia has been proposed as the cause of spasticity of the aganglionic segment. However, the aganglionic bowel still appears narrow after the application of benzalkonium chloride or corrosive sublimate in experimental animal models of aganglionosis and animals exhibit typical obstructive symptoms [105, 106]. Therefore, the cholinergic hyperinnervation does not seem to be a prerequisite to the appearance of a narrow spastic segment.

40.3.2 Adrenergic Innervation

Fluorescent-histochemical studies for localization of adrenergic nerves have demonstrated a numerically increase and chaotic distribution in the aganglionic segement of HD. They are also present in the circular and longitudinal muscle layers as well as in the mucosa, whereas they are almost never found in normal ganglionic bowel [107–109]. However, despite the elevated number of adrenergic fibers in the aganglionic colon, the sensitivity to epinephrine is apparently not increased [110, 111]. The tissue concentration of norepinephrine is 2–3 times higher in the aganglionoc bowel than in the normal colon. Furthermore, there is also a corresponding increase in tyrosine hydroxylase, an enzyme that regulates the norepinephrine biosynthesis [109]. Because adrenergic nerves normally act to relax the bowel, it is unlikely that the adrenergic hyperactivity is responsible for the increased tone in the aganglionic segment [8].

40.3.3 Nitrergic Innervation

Nitric oxide (NO) is considered to be one of the most important neurotransmitters involved in relaxation of the smooth muscle of the gut [112]. It is synthesized in a reaction catalyzed by nitric oxide synthase (NOS) using L-arginine and molecular oxygen as co-substrates to form L-citrulline and NO. When NO binds to cytosolic guanylate cyclase, it increases the production of 3′5'-cyclic guanosine monophosphate (GMP) with subsequent relaxation of smooth muscle [37]. NOS has been shown to colocalize with reduced nicotine adenine dinucleotide phosphate (NADPH) diaphorase, which has been demonstrated to have identical functions [113, 114]. Several investigators have studied NOS distribution in the ganglionic and aganglionic bowel in patients with HD using NOS immunohistochemistry or NADPH diaphorase histochemistry [115–119]. In normal and ganglionic colon from patients with HD, there is a strong NADPH diaphorase staining of the submucous and myenteric plexuses and a large number of positive nerve fibers in the circular and longitudinal muscle as well as in the muscularis mucosae [37]. However, in the aganglionic segment are no ganglia present and there is an absence or marked reduction of NADPH diaphorase positive nerve fibers in both muscle layers and in the muscularis mucosae. The typical hypertrophied nerve trunks appear weakly stained [37]. Kusafuka and Puri [120] examined the expression of neural NOS mRNA in the aganglionic segment from seven patients with HD and demonstrated that NOS mRNA expression was decreased at least 1/50–1/100 of the level of expressed in ganglionic bowel. These findings indicate that there is an impaired NO synthesis in the aganglionic segment and this deficiency could prevent smooth muscle relaxation, thereby causing the lack of peristalsis in HD. In an interesting experiment, Bealer et al. [121] compared the effect of an exogenous source of NO, S-nitroso-*N*-acetylpenicillamine (SNAP) on the isometric tension of smooth muscle strips from aganglionic bowel and demonstrated a 70% reduction of resting tension. These results suggest that the defec-

tive distribution of nerves containing NOS may be involved in the pathogenesis of HD.

40.3.4 Interstitial Cells of Cajal

Interstitial cells of Cajal (ICC) form a network of mesenchymal cells that are widely distributed within the submucosal, intra- and intermuscular layers of the gastrointestinal tract. ICCs act as the pacemaker cells of the gut, which are electrically coupled to the smooth muscle cells by generating slow waves [122]. Abnormalities of ICCs have been described in several disorders of human intestinal motility including HD. Vanderwinden et al. [119] using a c-kit immunohistochemistry first described that ICCs were scarce and its network appeared disrupted in aganglionic segments of HD whereas the distribution of ICCs in the ganglionic bowel of HD was similar to that observed in controls. Yamataka et al. [123, 124] found few c-kit positive cells in the muscle layers in HD and a moderate number around the thick nerve bundles in the space between the two muscle layers in the aganglionic bowel. Horisawa et al. [125] reported no differences in c-kit immunopositive cells in aganglionic segments compared with corresponding area of ganglionic bowel. Using a whole-mount and frozen sections stained with c-kit immunohistochemistry preparations, Rolle et al. [126] showed an altered distribution of ICCs in the entire resected bowel of HD patients and not only in the aganglionic segment. Moreover, gap junctions connecting ICCs were immunolocalized by anti-Connexin 43 antibody and found to be absent in the aganglionic part and highly reduced in the transition zone [127]. Rolle et al. [126] furthermore proposed that persistent dismotility problems after pull-through operation in HD may be due to altered distribution and impaired function in ICCs. Investigating the tissue distribution of Ca^{2+}-activated K^+ channels 2 and 3 (SK2 and SK3) in ICCs, Piotrowska et al. [128] found a strong expression in normal human colon with a markedly decreased expression of SK3 channels in aganglionic bowel, which may also contribute to the motility dysfunction in HD.

40.3.5 Enteroendocrine Cells

Using the generic enteroendocrine cell immunohistochemical markers chromogranin A and synaptophysin, Soeda et al. [129] demonstrated that the number of enteroendoccrine cells in the aganglionic colon in patients with HD were significantly increased compared with the number in the normal ganglionic segment. The increase of enteroendocrine cells in the mucosa of aganglionic colon may well influence sustained contraction of the bowel wall mainly mediated by the release of 5-hydroxytryptamine [8].

40.3.6 Smooth Muscle Cells

Since smooth muscle cells (SMCs) are the final effector for bowel motility, it is likely that they could also be abnormal in HD. The cytoskeleton of SMCs consists of proteins whose primary function is to serve as a structural framework that surround and support the contractile apparatus of actin and myosin filaments in the body of these cells. Nemeth et al. [130] studied the distribution of cytoskeleton in SMCs of HD bowel by means of immunohistochemistry and found that dystrophin, vinculin, and desmin immunoreactivity was either absent or weak in aganglionic bowel, whereas it was moderate to strong in the normal ganglionic bowel from patients with HD. Neural cell adhesion molecule (NCAM) is a cell surface glycoprotein involved in cell-cell adhesion during development that has been suggested to play an important role in development and maintenance of the neuromuscular system [131–133]. NCAM is present in the innervation of normal infant bowel and, less densely, in some components of the enteric smooth muscle. Contradictory results have been published regarding the NCAM expression in the smooth muscle of aganglionic bowel. Kobayashi et al. [117] described a lack of expression of NCAM in the muscularis propria of the aganglionic bowel compared with the ganglionic segment, whereas Romanska et al. [134] have found an increased NCAM expression in muscle, particularly in the muscularis mucosae. In any case, both authors agree that there is a

strong expression of NCAM in the hypertrophic nerve trunks from the aganglionic segment.

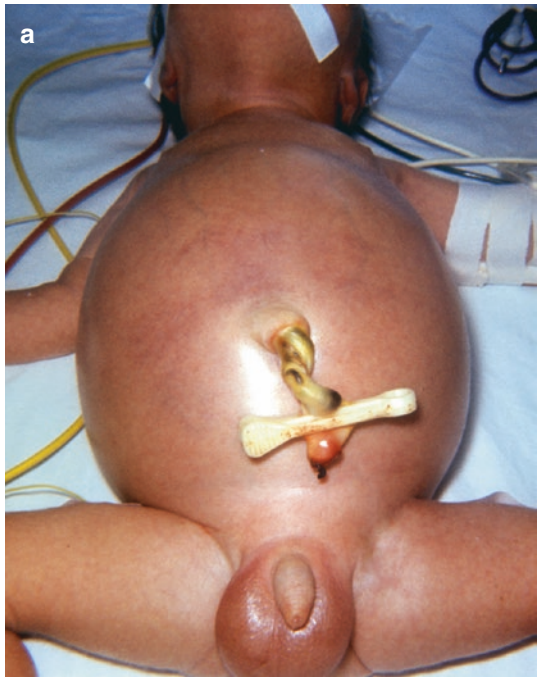
40.3.7 Extracellular Matrix

Although extracellular matrix (EM) abnormalities have been described mainly related to the pathogenesis of HD, they could also have an influence on its pathophysiology. The lethal spotted mouse, an animal model which develops aganglionosis in its distal bowel, displays an abnormal distribution of EM components including laminin, collagen type IV, glycosaminoglycans and proteoglycans in the smooth muscle layer [135, 136]. Parikh et al. [137] demonstrated that the laminin concentration in aganglionic bowel was twice as high as in the ganglionic bowel of HD and three times higher than in age-matched controls. Moreover, by means of immunohistochemistry, they found an uneven distribution of laminin and collagen type IV in the muscularis propria of aganglionic bowel, being more intensely expressed in the circular layer than in the longitudinal layer [138]. The same authors have described that EM components tenascin and fibronectin are more intensely expressed in aganglionic bowel from patients with HD [139].

40.4 Pathology

The characteristic gross pathological feature in HD is the dilatation and hypertrophy of the proximal colon with an abrupt or gradual transition to narrowed distal bowel (Fig. 40.1b). Although the degree of dilatation and hypertrophy increases with age, the cone-shape transition zone from dilated to narrow bowel is usually evident in the newborn.

Histologically, HD is characterized by the absence of ganglionic cells in the myenteric and submucous plexuses and the presence of hypertrophied non-myelinated nerve trunks in the space normally occupied by the ganglionic cells



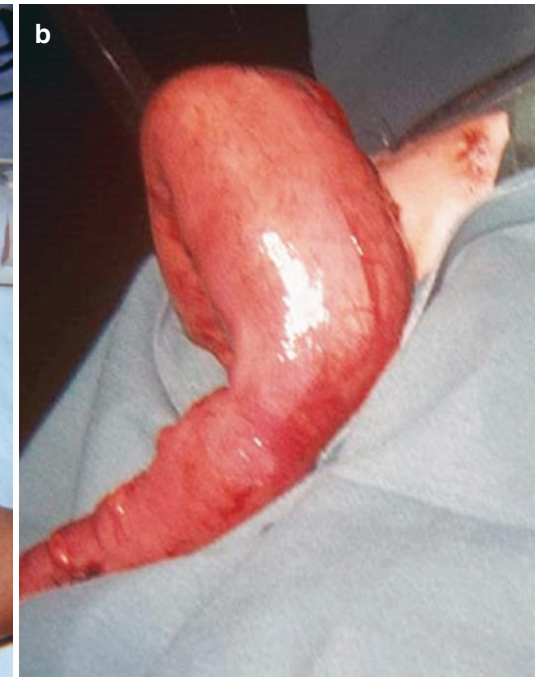


Fig. 40.1 Two-day-old newborn with Hirschsprung's disease presenting with marked abdominal distension and failure to pass meconium (**a**). Typical gross pathology in Hirschsprung's disease showing dilatation and hypertrophy of the proximal colon with transitional zone at recto-sigmoid level (**b**)

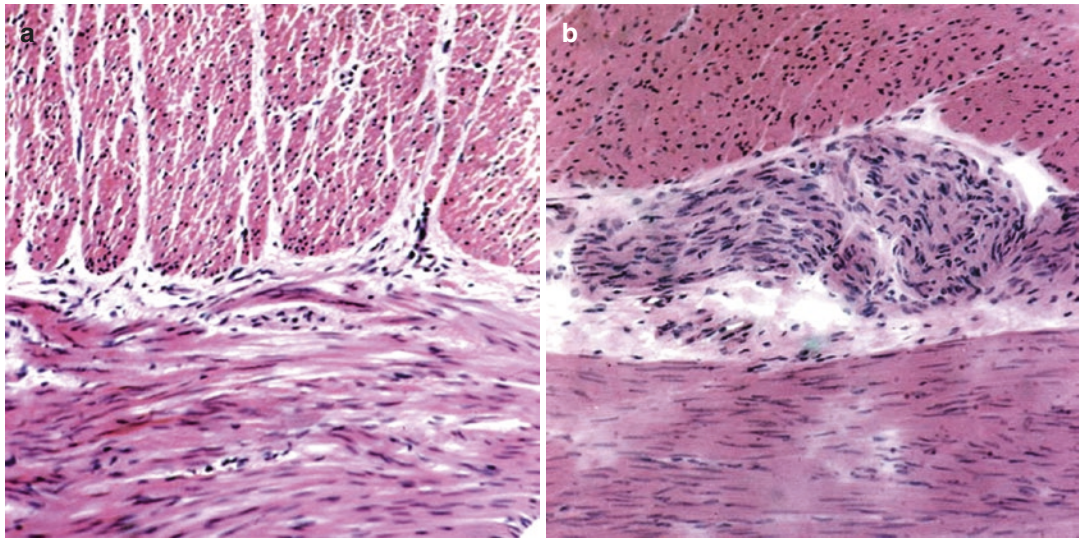


Fig. 40.2 Rectal biopsies showing presence of ganglionic cells in the myenteric and submucous plexuses of normal bowel (**a**), and absence with replacement by hypertrophied nerve trunks in a patient with Hirschsprung's disease (**b**)

(Fig. 40.2b). The aganglionic segment of bowel is followed proximally by a hypoganglionic segment of varying length. This hypoganglionic zone is characterized by a reduced number of ganglion cells and nerve fibers in myenteric and submucous plexuses.

40.5 Diagnosis

The diagnosis of HD is usually based on clinical history, radiological studies, anorectal manometry, and in particular on histological examination of the rectal wall biopsy specimens.

40.5.1 Clinical Features

80–90% of all patients with HD have clinical symptoms and are diagnosed during the neonatal period. Delayed passage of meconium is the cardinal symptom in neonates with HD. Over 90% of affected patients fail to pass meconium in the first 24 h of life. The usual presentation of HD in the neonatal period is with constipation, abdominal distension, and vomiting during the first few days of life (Fig. 40.1a). About 20% of the babies with HD present with diarrhea. Diarrhea in HD is always a symptom of Hirschsprung's associated enterocolitis (HAEC), which represents the most common cause of death in patients with HD. HAEC usually resolves under adequate therapy or may result in life-threatening toxic megacolon, which is characterized by a sudden onset of marked abdominal distension, bile stained vomiting, fever, signs of dehydration, sepsis, and shock. Rectal examination or introduction of a rectal tube results in the explosive evacuation of gas and foul-smelling stools. In older children, the main symptom is persistent constipation and chronic abdominal distension.

40.5.2 Radiological Evaluation

In newborns with HD, a plain abdominal X-ray film will show dilated loops of bowel with fluid levels and airless pelvis. Occasionally, one may be able to see a small amount of air in the undistended rectum and dilated colon above it raising the suspicion of HD (Fig. 40.3a). Plain abdominal X-ray films obtained in patients with TCA may show characteristic signs of ileal obstruction with air-fluid levels or simple gaseous distension of small intestinal loops. In patients with HAEC,

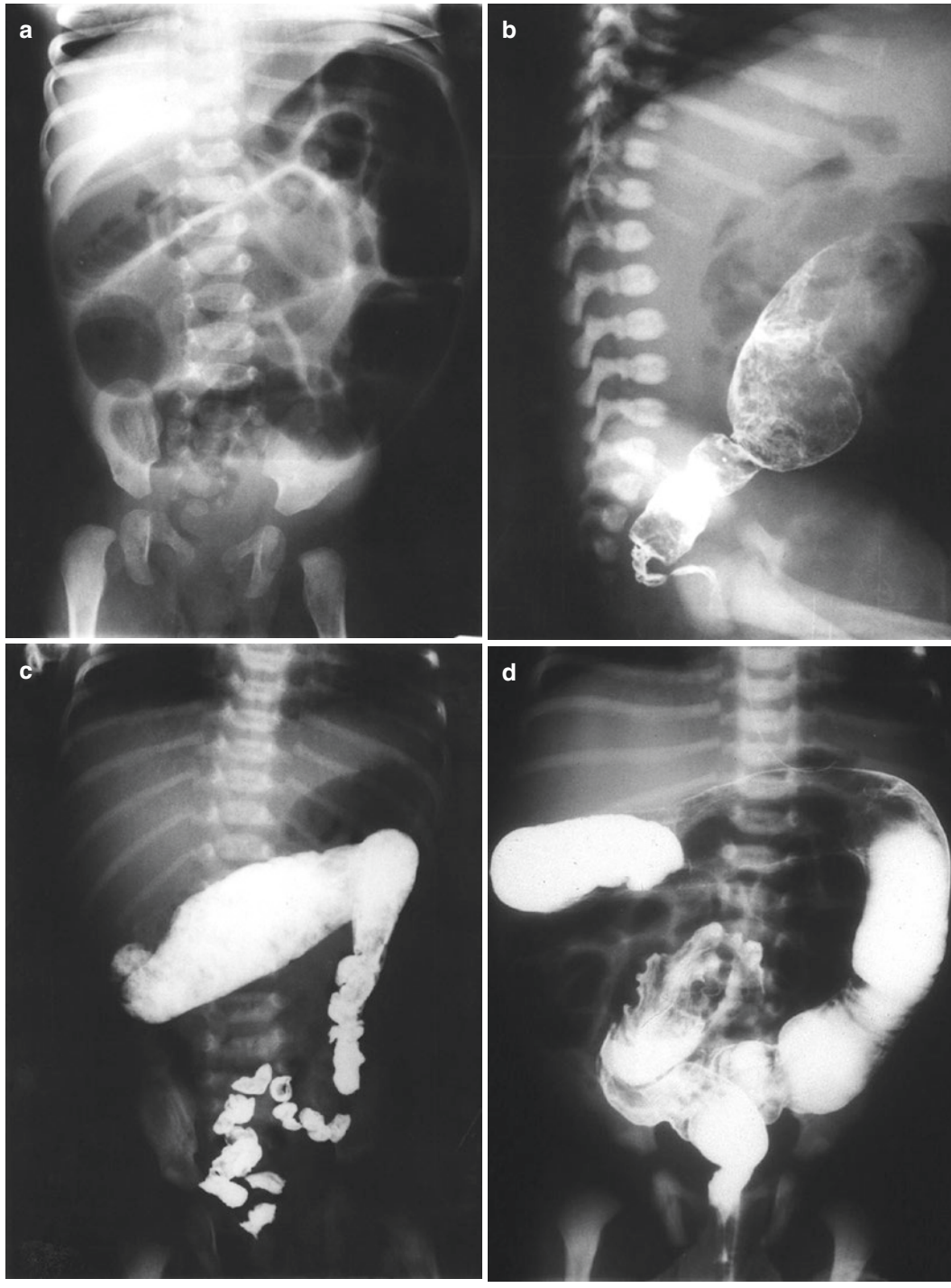


Fig. 40.3 Radiological evaluations for Hirschsprung's disease: Plain abdominal X-ray film in a 4-day-old newborn showing marked dilatation of large and small bowel loops with gas in the undilated rectum (**a**). A barium enema in this patient revealed the transition zone at the recto-sigmoid level (**b**). Delayed 24-h film in lateral position showing barium retention with accentuated transition at splenic fixture in a 10-day-old newborn (**c**). Enterocolitis complicating Hirschsprung's disease: Spasm at recto-sigmoid level with fine mucosal ulceration and mucosal edema giving cobblestone appearance (**d**)

plain abdominal X-ray films may show thickening of the bowel wall with mucosal irregularity or a grossly dilated colon loop, indicating toxic megacolon. A pneumoperitoneum may be found in those with perforation. Spontaneous perforation of the intestinal tract has been reported in 3% of patients with HD [140]. Using a careful technique, a barium enema performed by an experienced radiologist, should achieve a high degree of reliability in diagnosing HD in newborns. It is important that the infant should not have rectal washouts or even digital examinations prior to barium enema, as such interference may distort the transition zone appearance and give a false-negative diagnosis. A soft rubber catheter is inserted into the lower rectum and held in position with firm strapping across the buttocks. Due to the risk of perforation and the possibility of distorting a transition zone by distension, a balloon catheter should not be used. The barium should be injected slowly in small amounts under fluoroscopic control with the baby in the lateral position. A typical case of HD will demonstrate flow of barium from the undilated rectum through a cone-shaped transition zone into dilated colon (Fig. 40.3b). Some cases may show an abrupt transition between the dilated proximal colon and the distal aganglionic segment, leaving the diagnosis in little doubt. In some cases, findings on the barium enema are uncertain and a delayed abdominal X-ray film at 24 h may confirm the diagnosis by demonstrating the retained barium and often accentuating the appearance of the transition zone (Fig. 40.3c). In the presence of)HAEC, a barium enema can demonstrate spasm, mucosal edema, and ulceration (Fig. 40.3d). In TCA, the contrast enema is not pathognomonic and may not provide a definitive diagnosis. The colon in TCA is of normal caliber in 25–77% of cases [141].

40.5.3 Anorectal Manometry

In normally innervated bowel, distension of the rectum produces relaxation of the recto-sphincteric reflex. In normal individuals, upon distending the rectal balloon with air, the rectum immediately responds with a transient rise in pressure lasting 15–20 s. At the same time, the rhythmic activity of the internal anal sphincter (IAS) is depressed or abolished and its pressure falls by 15–20 cm. The duration of relaxation coincides with the rectal wave (Fig. 40.4a). In patients with HD, the rectum often shows spontaneous waves of varying amplitude and frequency in the resting phase. The rhythmic activity of the IAS is more pronounced. However, there is a complete absence of IAS relaxation upon rectal distension. (Fig. 40.4b). Failure to detect the recto-sphincteric reflex in premature and term infants is believed to be due to technical difficulties and not to immaturity of ganglion cells. Light sedation, particularly in infants and small children, may overcome technical difficulties encountered in this age group.

40.5.4 Rectal Biopsy

The diagnosis of HD is usually confirmed by examination of rectal biopsy specimens. The introduction of histochemical staining techniques for the detection of AChE activity in rectal suction biopsies (RSBs) has resulted in a reliable and simple method for the diagnosis of HD [142–144]. A rapid technique for performing AChE histochemistry in only 6 min has also been developed [145]. A full-thickness RSB is rarely indicated for the diagnosis of HD except in TCA. In normal individuals, barely detectable AChE activity is observed within the lamina propria and muscularis mucosa. On the other hand, the submucosal ganglion cells show strong staining for AChE (Fig. 40.5a). In HD, there is a marked increase in AChE activity in the lamina propria mucosae and muscularis mucosae, which is associated with the hypertrophied extrinsic nerve fibers of the aganglionic segment [145–149] (Fig. 40.5b). In TCA, AChE activity in RSB presents an atypical pattern, different from the classical one. Positive AChE fibers can be found in the lamina propria as well as the muscularis mucosae. However, cholinergic fibers present a lower density than in classical HD. Furthermore, it has been shown that NADPH diaphorase histochemi-

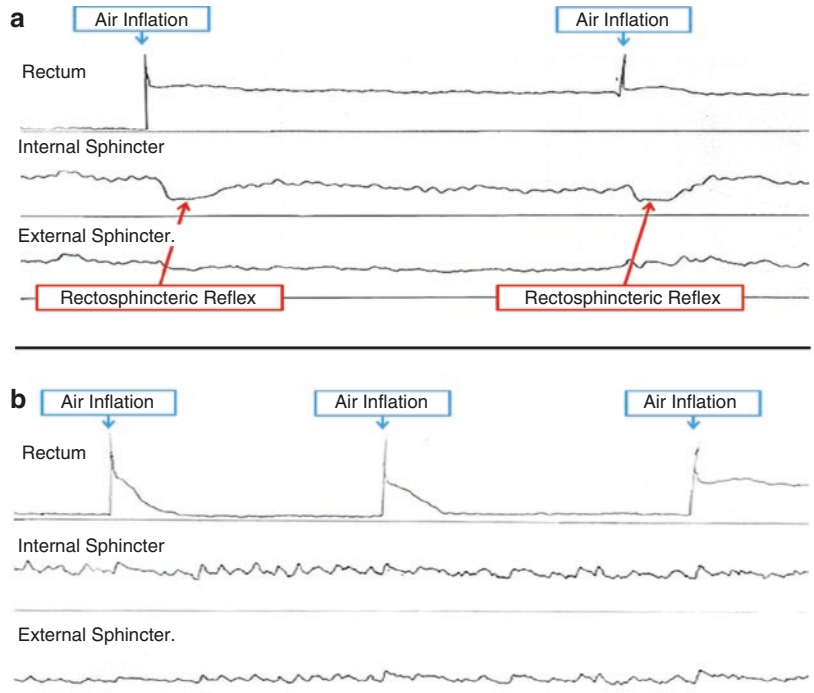


Fig. 40.4 Anorectal manometry showing evidence of the normal internal anal sphincter (IAS) recto-sphincteric reflex on rectal balloon inflation (**a**), and absence of IAS relaxation and presence of marked rhythmic activity of the IAS in a patient with Hirschsprung's disease (**b**)

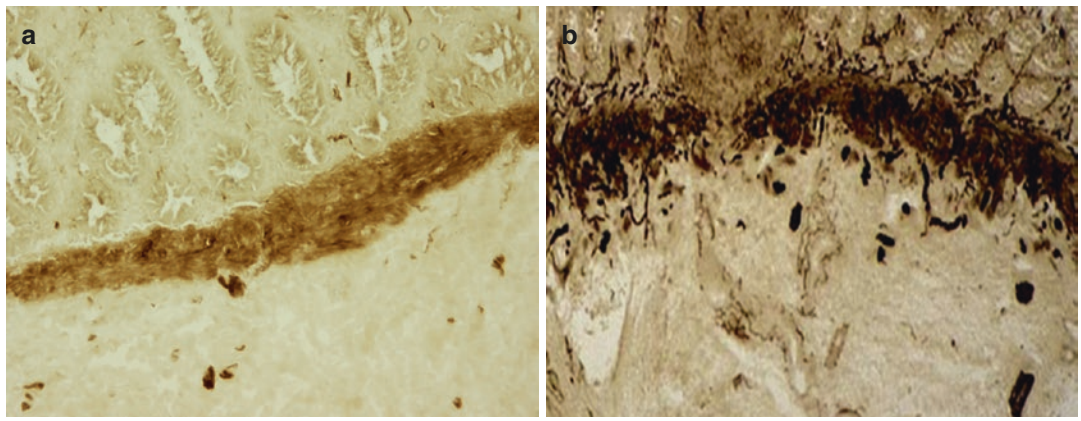


Fig. 40.5 Normal rectum showing minimal acetylcholinesterase (AChE) staining in mucosa, lamina propria, and muscularis mucosae (**a**). Hirschsprung's disease is characterized by a marked increase in AChE-positive nerve fibers in the lamina propria and muscularis mucosae (**b**)

cal staining may be an important additional technique for diagnosing HD [150].

40.5.5 Differential Diagnosis

Several conditions must be considered when an infant is being evaluated for HD. Table 40.3 provides a list of common differential diagnosis. Colonic atresia gives similar plain abdominal X-ray film findings as in HD, but is readily excluded with barium enema showing complete mechanical obstruction. Distal small bowel atresia shows gross distension of the bowel loop immediately proximal to the obstruction with the widest fluid level in it. In meconium ileus the

Table 40.3 Differential diagnosis of Hirschsprung's disease

Location	Differential diagnosis
Small intestine	Small bowel obstruction
	Malrotation, volvulus
	Intestinal atresia
	Meconium ileus
Colon	Colonic atresia
	Meconium plug syndrome
	Small left colon syndrome
	Anorectal malformation
Other causes	Intestinal motility disorders
	Pseudo-obstruction
	Necrotizing enterocolitis
	Sepsis
	Electrolyte abnormalities
	Hypothyroidism
	Drugs

typical mottled thick meconium may be seen. Also, clear, sharp fluid levels are not a feature in erect or lateral decubitus views. However, HD can sometimes simulate meconium ileus in plain abdominal X-ray films and may give equivocal findings on Gastrografin or barium enema. Meconium plugs obstructing the colon can present as HD with strongly suggestive history and plain abdominal X-ray films. Small left colon syndrome with marked distension proximal to narrowed descending colon also simulates HD at the left colonic flexure. These two conditions usually resolve with Gastrografin enema, but a minority of these cases will actually have HD which should be excluded clinically.

40.6 Surgical Management

A number of different surgical techniques have been described for the treatment of HD. The four most commonly used procedures are the recto-sigmoidectomy developed by Swenson and Bill, the retrorectal approach developed by Duhamel, the endorectal procedure developed by Soave, and deep anterior colorectal anastomosis developed by Rehbein [8, 151]. The basic principle in all these procedures is to bring the ganglionic bowel down to the anus. The long-term results of any of these operations are satisfactory if they are performed correctly.

In recent years, the vast majority of cases of HD are diagnosed in the neonatal period. Many centers are now performing one-stage pull-through operations in the newborn with minimal morbidity rates and encouraging results. The advantages of operating on the newborn are that the colonic dilation can be quickly controlled by washouts and at operation the caliber of the pull-through bowel is near normal, allowing for an accurate anastomosis that minimizes leakage and cuff infection. A number of investigators have described and advocated a variety of one-stage pull-through procedures for newborn with HD using minimal invasive laparoscopic techniques. More recently, a transanal endorectal pull-through (TERP) operation performed without opening the abdomen has been used with excellent results in recto-sigmoid HD.

40.6.1 Preoperative Management

Preoperatively, a good barium enema study is essential for this technique. A typical case of recto-sigmoid HD usually demonstrates flow of barium from undilated rectum through a cone-shaped transition zone into dilated sigmoid colon. Once the diagnosis of HD has been confirmed by RSB, the newborn should be prepared for surgery. Rectal irrigations are carried out twice a day for 2–3 days prior surgery. Intravenous gentamicin and metronidazole are started on the morning of operation. If the newborn has HAEC, correction of dehydration and electrolyte imbalance by infusion of appropriate fluids will be required. It is essential to decompress the bowel as early as possible in these babies. Deflation of the intestine may be carried out by rectal irrigations, but some babies may require colostomy.

40.6.2 Transanal One-Stage Endorectal Pull-through Operation

A one-stage pull-through operation can be successfully performed in these patients using a

transanal endorectal approach without opening the abdomen. This procedure is associated with excellent clinical results and permits early postoperative feeding, early hospital discharge, no visible scars, and low incidence of enterocolitis [152, 153]. Most pediatric surgeons prefer the TERP operation for managing patients with classical segment recto-sigmoid HD.

40.6.2.1 Operative Technique

The patient is positioned on the operating table in the lithotomy position. The legs are strapped over sandbags. A Foley catheter is inserted into the bladder. An anal retractor is placed to retract perianal skin. The rectal mucosa is circumferentially incised using the cautery with a fine-tipped needle, approximately 5 mm from the dentate line, and the submucosal plane is developed. The proximal cut edge of the mucosal cuff is held with multiple fine silk sutures, which are used for traction (Fig. 40.6). The endorectal dissection is then carried out proximally, staying in the submucosal plane.

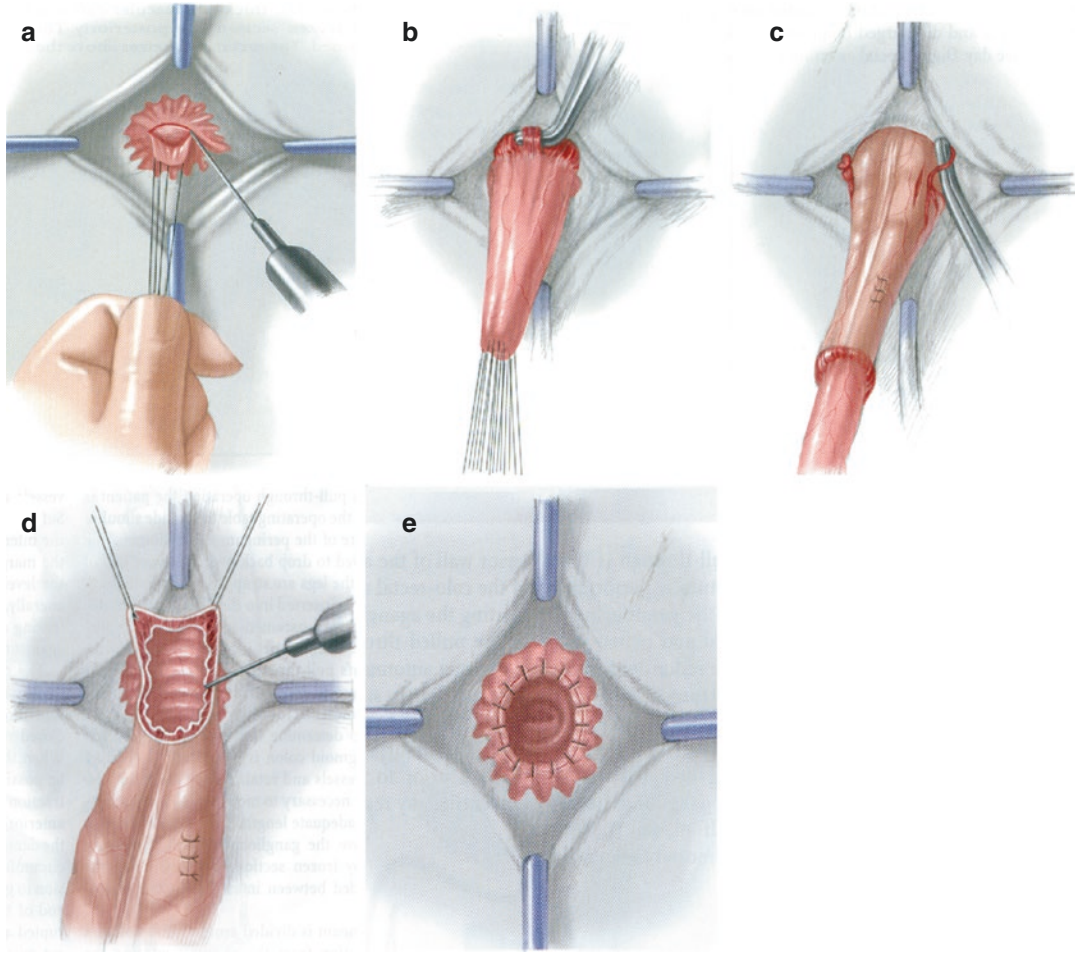


Fig. 40.6 Transanal endorectal pull-through operation: Rectal mucosa is circumferentially incised using the needle-tip cautery approximately 5 mm above the dentate line and the submucosa plane is developed (**a**). When the submucosal dissection is extended proximally for about 3 cm, the muscle is divided circumferentially, and the full-thickness of the rectum and sigmoid colon is mobilized out through the anus (**b**). On reaching the transition zone, full-thickness rectal biopsies are taken for frozen section to confirm ganglion cells (**c**). The colon is divided several centimeters above the most proximal biopsy site (**d**). A standard Soave-Boley anastomosis is performed (**e**)

When the submucosal dissection has extended for about 3 cm, the rectal muscle is divided circumferentially, and the full thickness of the rectum and sigmoid colon is mobilized out through the anus. This requires division of rectal and sigmoid vessels, which can be done under direct vision using cautery.

When the transition zone is encountered, full-thickness biopsy sections are taken, and frozen section confirmation of ganglion cells is obtained. The rectal muscular cuff is split longitudinally either anteriorly or posteriorly. The colon is then divided several centimeters above the most proximal normal biopsy site, and a standard Soave-Boley anastomosis is performed. No drains are placed. The patient is started on oral feeds after 24 h and discharged home on the third postoperative day. Digital rectal examination is performed 2 weeks after the operation. Routine rectal dilatation is not performed unless there is evidence of a stricture.

40.6.3 Postoperative Complications

Early postoperative complications which can occur after any type of pull-through operation include wound infections, anastomotic leakage, anastomotic stricture, retraction or necrosis of the neorectum, intestinal adhesions, and ileus. Late complications include constipation, enterocolitis, incontinence, anastomotic problems, adhesive bowel obstruction, and urogenital complications.

40.6.3.1 Anastomotic Leakage

The most dangerous early postoperative complication following the definitive abdomino-perineal pull-through operation is leakage at the anastomotic suture line. Factors responsible for anastomotic leakage include ischemia of the distal end of the colonic pull-through segment, tension on the anastomosis, incomplete anastomotic suture lines, and inadvertent rectal manipulation. If a leak is recognized in a patient without a colostomy, it is imperative to perform a diverting colostomy promptly, to administer intravenous antibiotics and to irrigate the rectum with antibiotic solution a few times daily. Delay in establishing fecal diversion is likely to result in an extensive pelvic abscess which may require laparotomy and transabdominal drainage.

40.6.3.2 Retraction of Pull-through

Retraction of a portion or of the entire colonic segment from the anastomosis can occur and is usually seen within 3 weeks after the operation. Evaluation under general anesthesia is generally necessary. In occasional patients, resuturing the anastomosis may be feasible transanally. For those with separation of less than 50% of the anastomosis, but with adequate vascularity of the colon, a diverting colostomy for approximately 3 months is necessary. For patients with wide separation at the anastomosis, early transabdominal reconstruction of the pull-through is recommended.

40.6.3.3 Perianal Excoriation

Perianal excoriations occur in nearly half of the patients undergoing pull-through operations, but generally resolve within 3 months with local therapy and resolution of diarrhea. It is helpful to begin placing a barrier cream on the perianal each movement for the first few weeks. Resolution of diarrhea will often hasten the clearance of perianal skin irritation.

40.6.3.4 Constipation

Constipation is common after definitive repair of HD and can be due to residual aganglionosis and high anal tone. Repeated and forceful anal dilations combined with botulinum toxin injection into the IAS under general anesthesia may resolve the problem. In some patients, a myectomy of the IAS may be needed. In patients with scarring, stricture, or intestinal neuronal dysplasia proximal to aganglionic segment, treatment consists of treating the underlying cause.

40.6.3.5 Enterocolitis

HAEC is a significant complication of HD both in the pre- and postoperative periods [140, 154]. It can occur at any time from the neonatal period onwards to adulthood and can be independent of

the medical management and surgical procedure performed. The incidence of HAEC ranges from 20 to 58% [140]. Fortunately, the mortality rate has declined over the last 30 years from 30 to 1%. This decrease in mortality is related to earlier diagnosis of HD and HAEC, rectal decompression, appropriate vigorous resuscitation, and antibiotic therapy. It has been reported that routine postoperative rectal washouts decrease both the incidence and the severity of the episodes of HAEC following definitive surgery. In episodes of recurrent HAEC, which can develop in up to 56% of patients, anal dilatations have been recommended. However, prior to commencing a treatment regime, a contrast enema should be performed to rule out a mechanical obstruction. Patients with a normal rectal biopsy may require a sphincterotomy.

40.6.3.6 Fecal Soiling

Soiling is fairly common after all types of pull-through operation. However, the precise incidence primarily dependent on how assiduously the investigator looks for it. The reported incidence of soiling ranges from 10 to 30% [8]. The attainment of normal postoperative defecation is clearly dependent on intensity of bowel training, social background, and respective intelligence of the patients. Mental handicap (including Down syndrome) is invariably associated with long-term incontinence [155]. Those patients with preoperative HAEC would also seem to have a marginally higher long-term risk of incontinence. In some patients in who soiling is intractable and a social problem, a Malone procedure may be needed to stay clean.

40.7 Long-Term Outcome

Most patients who underwent pull-through operation for HD generally have a satisfactory long-term outcome [141, 153, 156, 157]. A recent large multicenter study showed no significant differences in continence and stooling patterns after transanal compared with transabdominal approach [153]. However, some children have persistent postoperative problems such as constipation, enterocolitis, and soiling [158–160]. In order to identify and provide early treatment options for these problems, it is important to follow these patients closely, at least until they are through the toilet training process. The vast majority of residual bowel problems can be managed by non-surgical treatment such as laxatives, enemas or intrasphincteric botulinum toxin injection [157, 161, 162]. In one-third of all patients with HD, which require a redo pull-through operation, a retained aganglionic segment or transition zone bowel is the underlying cause for persistent abdominal distension and recurrent bowel symptoms [163]. But overall, adolescents and adults with HD usually have a relatively good quality of life, social satisfaction and sexual function [156, 164].

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Anorectal Malformations

41

Marc A. Levitt and Richard J. Wood

Abstract

Anorectal malformations (ARM) present across a range of defects, from isolated malformations with a good functional prognosis to complex malformations with associated defects, and a poor functional prognosis. The potential for bowel control can be predicted even in the newborn, which is the information that the parents are most concerned about.

Keywords

Imperforate anus • Anorectal malformations • Classification • Surgery Bowel management • Outcomes

Anorectal malformations (ARM) present across a range of defects, from isolated malformations with a good functional prognosis to complex malformations with associated defects, and a poor functional prognosis. The potential for bowel control can be predicted even in the newborn, which is the information that the parents are most concerned about.

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A newborn with ARM has no anal opening (Fig. 41.1) or has a visible fistula (Figs. 41.2 and 41.3). In males, meconium in the urine indicates a recto-urinary fistula, the most common defect. Usually there is no prenatal clue to an ARM diagnosis, but occasionally a dilated viscus is seen (Figs. 41.4 and 41.5) [1].

Associated problems such as cardiac conditions, esophageal atresia, duodenal atresia, urologic, and spinal defects, should be investigated in the first 24 h. The baby should remain NPO, and on IV fluids. A nasogastric tube manages gastric distension and also checks for patency of the esophagus. The newborn evaluation should include: an echocardiogram, an abdominal X-ray to check for duodenal atresia, AP and lateral films of the sacrum to assess sacral development (Fig. 41.6), a kidney ultrasound to check for hydronephrosis or absent kidney, a pelvic ultrasound in females with a single perineal orifice

P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_41

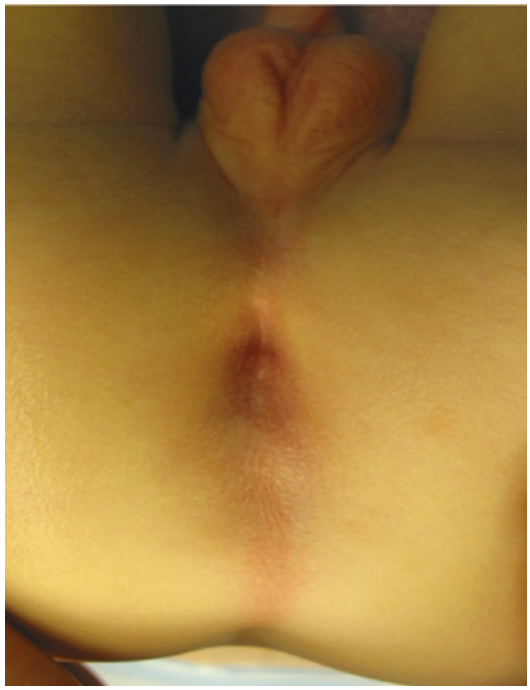

Fig. 41.1 Newborn male with ARM and no anal opening

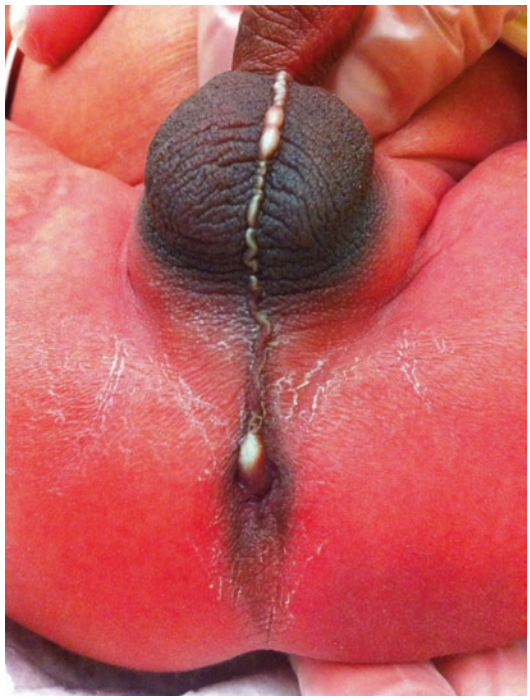

Fig. 41.2 Newborn male with ARM and visible fistula Seen as subepithelial mucous. From Peña A. Anorectal Anomalies. Sprincer Science + Business Media 2009; ebook; used with permission

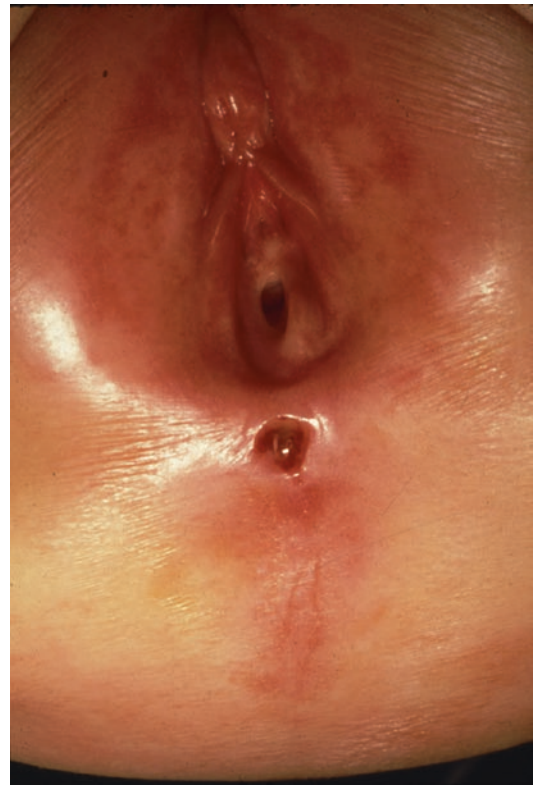

Fig. 41.3 Newborn female with ARM and visible fistula in the perineum, anterior to the center of the Sphincter. From Peña A: Anorectal Malformations. Seminars in Pediatric Surgery 4(1):35–47, 1995; Copyright Elsevier 1995; used with permission

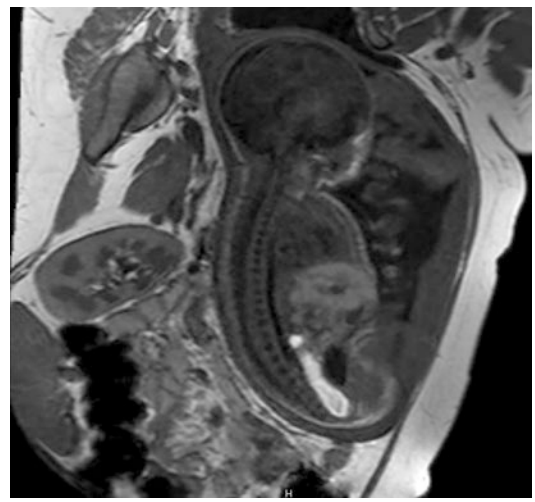

Fig. 41.4 Prenatal images on a fetal MRI of a dilated rectosigmoid in a patient with ARM. Levitt MA, Pena A. Ashcraft's Pediatric Surgery. Elsevier Ltd., Oxford UK; 2010, pp.:468–490. Copyright Elsevier 2010; used with permission

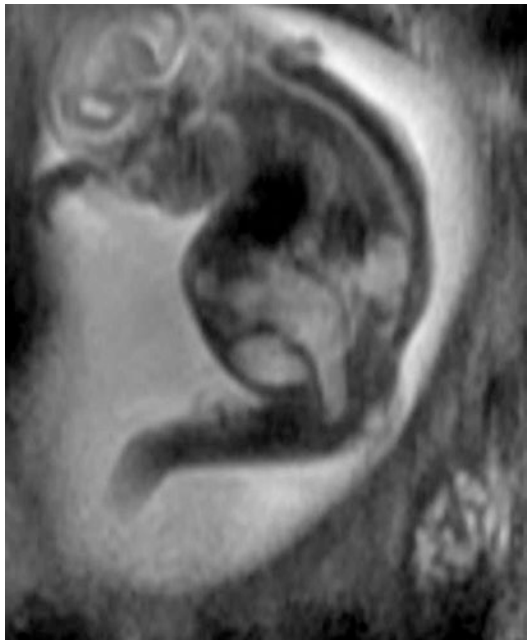

Fig. 41.5 Prenatal image of a cloaca with hydrocolpos

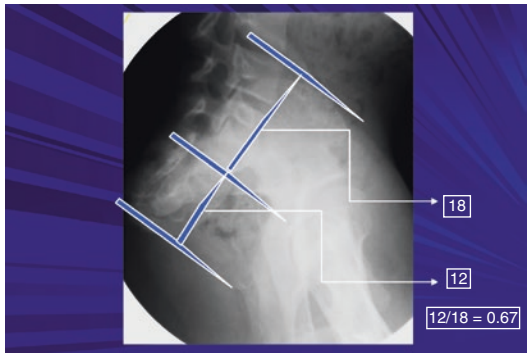

Fig. 41.6 Sacral ratio-lateral image of sacrum with sacral ratio measurements. The development of the sacrum is predictive of continence potential. It is ideally calculated after three months of age

to check for hydrocolpos, and a spinal ultrasound to evaluate for the presence of a tethered cord.

After 24 h, if no meconium is identified on the perineum or in the urine, in male patients, a cross fire film with the baby in prone position (Fig. 41.7) can show the gas of the distal rectum. Prior to 24 h, the bowel is not yet distended, and the rectum is therefore collapsed by the surrounding sphincter mechanism, so radiologic evaluations that are done too early will most likely show a falsely high rectum.

The next key decision for the surgeon is whether or not the newborn needs a colostomy.

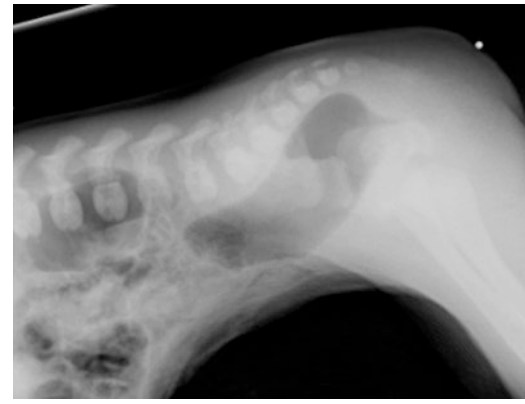

Fig. 41.7 Cross-fire film showing the height of rectal air column. In this case the distal rectum is too far away to reach in a newborn operation so a colostomy is indicated. From Peña A. Atlas of surgical management of anorectal malformations, Springer Verlag, New York 1989; used with permission

Figures 41.8 and 41.9 show the decision making algorithm for the newborn with ARM.

41.1 Males

41.1.1 Rectoperineal Fistula

With careful inspection of the perineum in this malformation, a perineal fistula is visible (Fig. 41.2). This is the lowest type of anorectal malformation. If the patient is stable and the surgeon has experience with this repair, a primary anoplasty can be done in the newborn period. If the patient is premature or has respiratory or cardiac issues, or if the surgeon choses to delay the repair, the fistula can be dilated and the surgical repair can be done within the first few months of life. This malformation has excellent prognosis for bowel control provided the patient receives a good operation, and the sacrum and spine are normal (Fig. 41.10). Associated malformations are rare in such cases. Constipation is common postoperatively and should be proactively treated [2].

41.1.2 Rectobulbar and Rectoprostatic Urethral Fistulae

Patients with rectourethral fistula might have meconium in the urine that can be identified

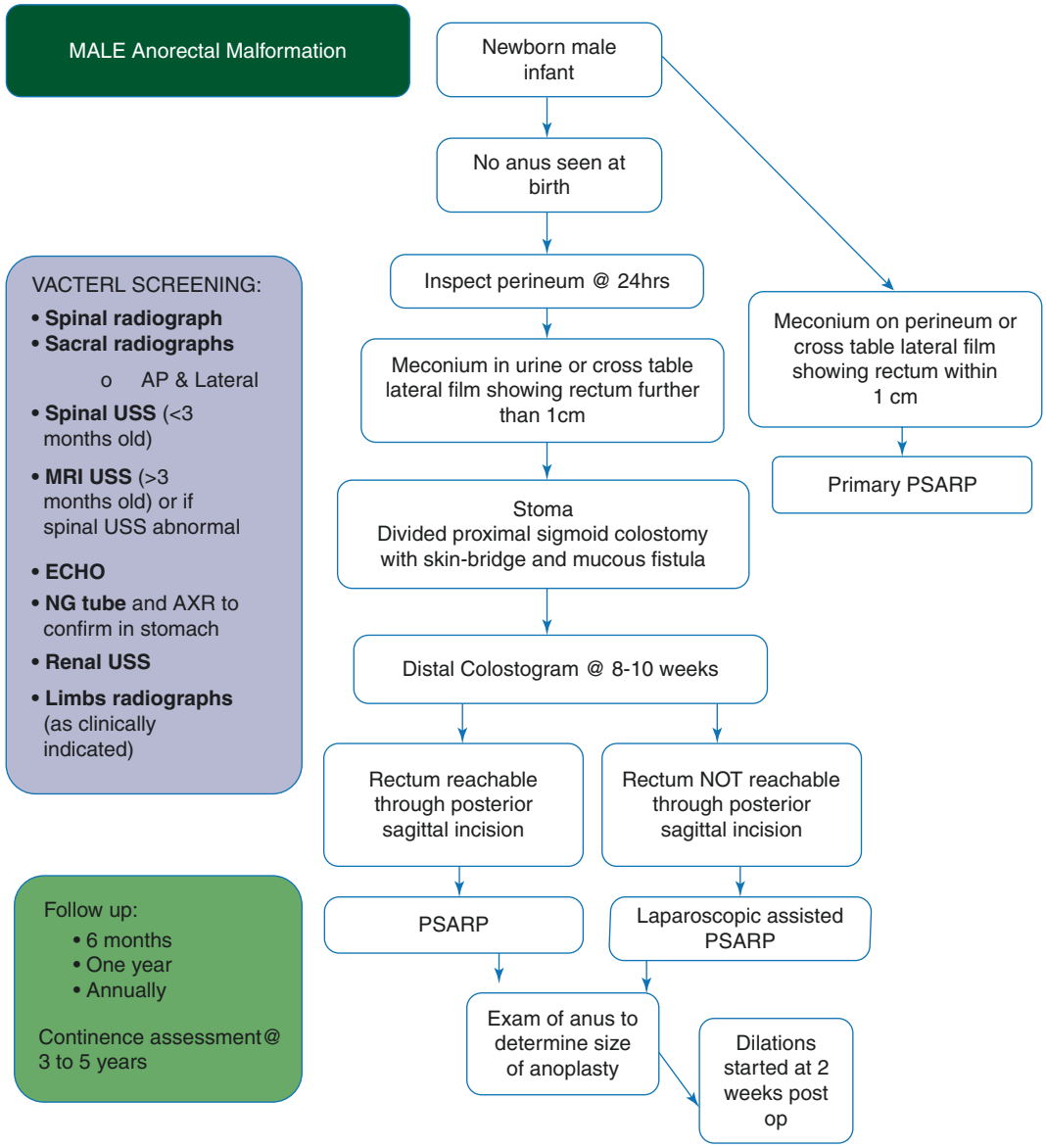

Fig. 41.8 Treatment algorithm for the newborn male ARM patient

on urinalysis or by placing a piece of gauze on the tip of the penis. There are two types: bulbar (Fig. 41.11) and prostatic (Fig. 41.12). Both require a colostomy in the newborn period, mainly because the precise location of the fistula can only be determined with a distal colostogram [3]. Without such a study a perineal exploration is risky and other midline whitish structures (bladder neck, vas deferens, seminal vesicles) can be found and injured.

Patients with rectobulbar fistula in general have excellent potential for bowel control, and patients with rectoprostatic fistula have a slightly lower chance of bowel control.

Characteristics in favor of a good prognosis for bowel control are: a lower malformation, a well-formed sacrum (sacral ratio >0.7), and the absence of a tethered cord or other spinal anomalies. Characteristics that indicate poor prognosis in terms of bowel control are: a higher malformation, poorly developed sacrum (sacral ratio <0.4), and the presence of a tethered cord or other spinal anomalies. These factors comprise the ARM continence index scorecard (Fig. 41.10).

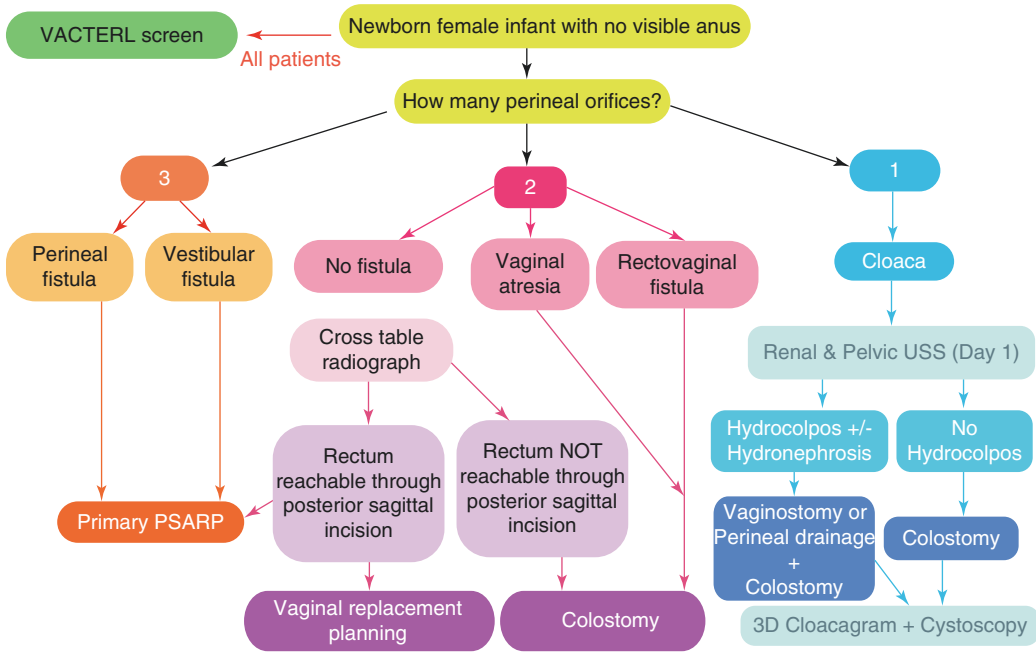

Fig. 41.9 Treatment algorithm for the newborn female ARM patient

1. ARM type –	
Rectal perineal fistula	
Rectal stenosis	
Rectal atresia	
Recto bulbar fistula	
Recto vestibular fistula	
Imperforate anus without fistula	
Cloaca <3 cm common channel	
Recto prostatic fistula	
Recto vaginal fistula	
Recto bladder neck fistula	
Cloaca >3 cm common channel	
Covered exstrophy	
Cloacal exstrophy	

3. Sacrum –	
Sacral Ratio	
Great than 0.7	
Between 0.4 and 0.69	
Less than 0.4	
Hemisacrum	
Presacral mass	
Sacral hemivertebra	

2. Spine –	
Termination (end) of the conus	
Normal	
Abnormally low termination	
Myelomeningocele	
Yes	
No	
Filum appearance	
Normal	
Abnormal - fatty thickening	
Myelomeningocele	

Fig. 41.10 ARM continence index

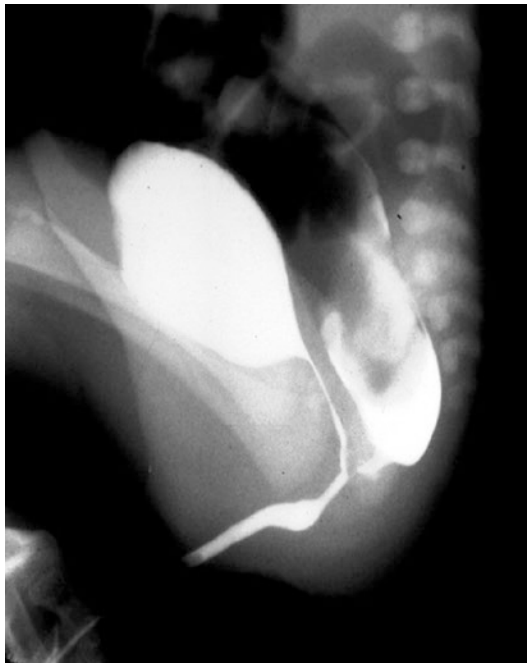

Fig. 41.11 Distal colostogram of a rectobulbar fistula. From Peña A. Atlas of surgical management of anorectal malformations, Springer Verlag, New York 1989, used with permission

Fig. 41.12 Distal colostogram of a rectoprostatic fistula. From Peña A. Atlas of surgical management of anorectal malformations, Springer Verlag, New York 1989; used with permission

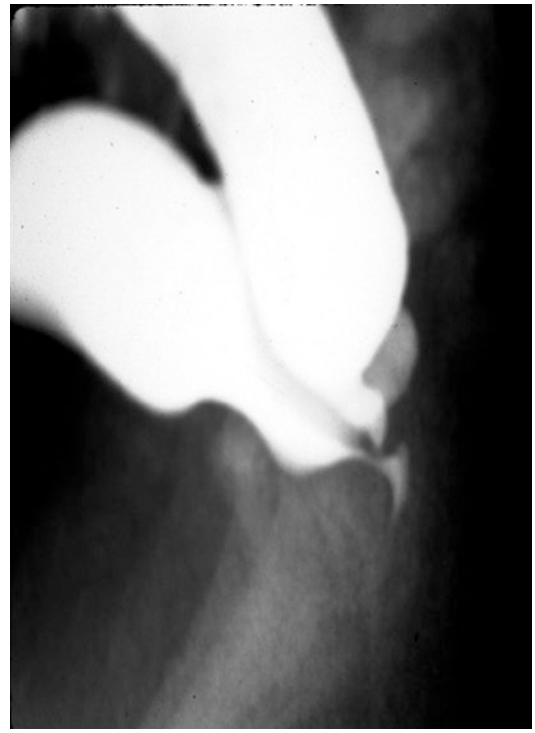

Fig. 41.13 Distal colostogram of a rectobladderneck fistula. From Levitt MA, Pena A. Ashcraft's Pediatric Surgery. Elsevier Ltd., Oxford UK; 2010, pp.:468–490. Copyright Elsevier 2010; used with permission

41.1.3 Rectobladderneck Fistula

The highest type of anorectal malformation in male patients is a rectobladder neck fistula (Fig. 41.13) which comprises 10% of cases. The prognosis for bowel control is usually poor. A colostomy is also required during the newborn period. Associated defects are common, particularly urologic. Delineation of these different types of urethral fistulas are represented by the schematic depicted in Fig. 41.14. The deltoid represents the location of a rectobladderneck fistula, the triceps represents the rectoprostatic fistula, and the elbow of the urethra or below marks the location of a rectobulbar fistula.

41.1.4 Imperforate Anus with No Fistula

In this type of malformation the rectum is blind and almost always is found at the level of the bulbar urethra. Rarely, the blind rectum is found in the pelvis. The functional prognosis is similar to

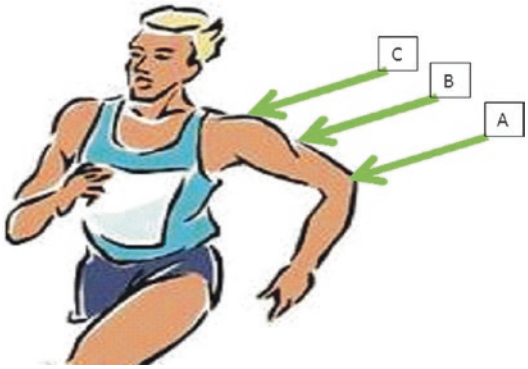

Fig. 41.14 Schematic of the three types of recto urethral fistula in males

that of rectourethral bulbar fistula cases. If the air column on a cross table lateral film is within 1 cm of the perineum, a newborn repair could be done, however the surgeon might not be able to differentiate this defect from a recto bulbar fistula case without a distal colostogram, and therefore, a colostomy is the safest first step. This malformation is particularly common in children with Down syndrome.

41.2 Females

41.2.1 Rectoperineal Fistula

In females, as in males, rectoperineal fistula (Fig. 41.3) is the lowest type of anorectal malformation. Potential for bowel control is excellent provided the patient receives a good operation, has a normal sacrum (sacral ratio >0.7) and no tethered cord or spinal anomalies. An anoplasty can be performed during the newborn period if the patient is stable; or Hegar dilation of the fistula can be done and the repair deferred for later, but best done prior to 3 months of age. Associated defects are rare. Confirmation of the presence of a vagina is vital and checked for visually by pulling out and separating the labia.

41.2.2 Rectovestibular Fistula

This is the most common defect seen in females and is one in which the rectum opens in the vestibule just below the posterior vaginal wall (Fig. 41.15) With a good operation, a normal sacrum (sacral ratio >0.7) and no tethered cord or spinal anomalies, potential for bowel control is excellent. A primary repair can be done in the newborn period or within the first 3 months. It is important to confirm the presence of a vagina and check whether there is a vaginal septum (which occurs in 5% of patients with vestibular fistula) [4].

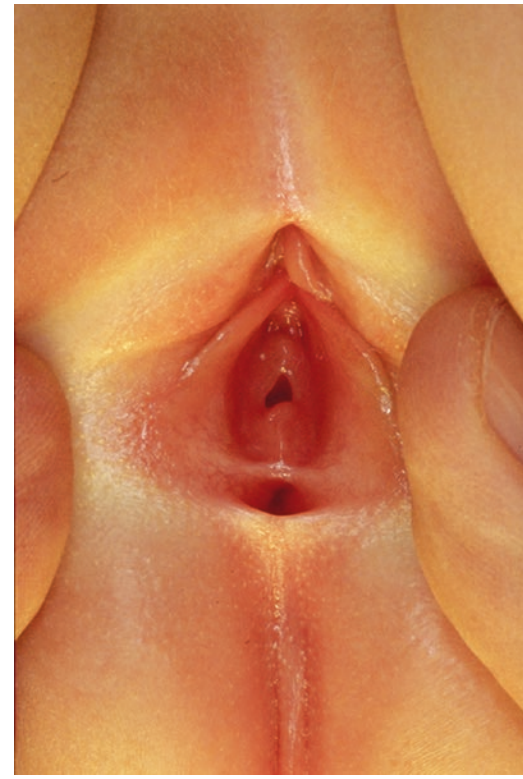

Fig. 41.15 Rectovestibular fistula

41.2.3 Cloaca

When the urethra, vagina, and rectum join together as a common channel that opens as a single orifice in the perineum, at the same location of the normal urethra, this malformation is called a cloaca. The newborn must be evaluated for hydronephrosis and a hydrocoplos (a distended vagina filled with urine and mucus) [5]. The hydrocolpos can compress the trigone of the bladder, and cause ureterovesical obstruction, megaureters, and hydronephrosis (Fig. 41.16). It can also get infected (pyocolpos) and can perforate. If detected during ultrasound

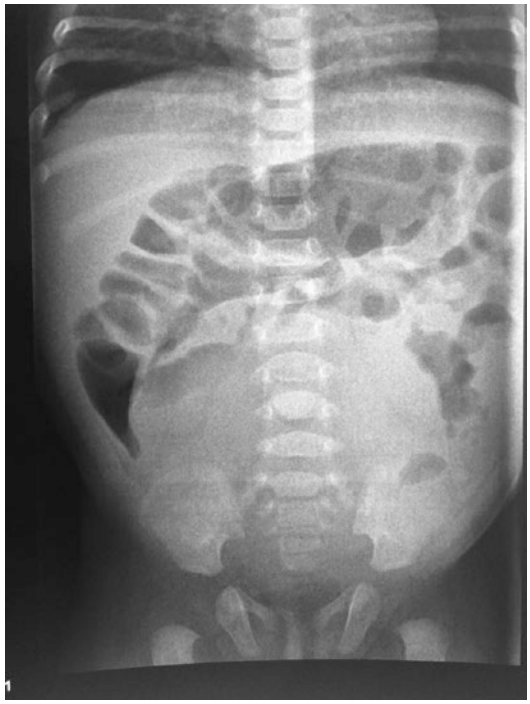

Fig. 41.16 Dilated vagina (hydrocolpos) seen as a pelvic mass on plain abdominal X-ray

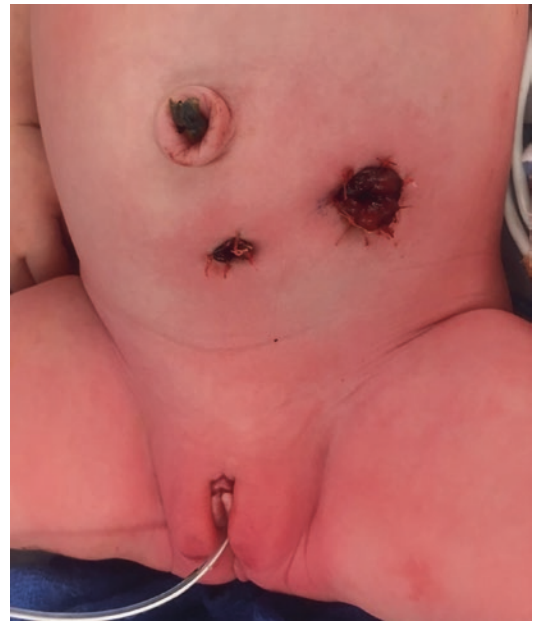

Fig. 41.17 Colostomy in a patient with ARM (Cloaca)

examination, it should be drained with perineal catheterization or with a trans-abdominal indwelling pigtail catheter or sutured to the abdominal wall as a tubeless vaginostomy.

This drainage should remain in place until the definitive cloacal repair. When draining a hydrocolpos if there is bilaterality, a window can be created through the common wall, allowing for a single tube to drain both hemivaginas.

These patients do not have a disorder of sexual development although this is erroneously suspected sometimes given the appearance of the genitalia. A prominent clitoris or phallus-like structure, in a patient with a single perineal orifice is a cloaca, needs to be contrasted with the same situation in a patient with an urogenital sinus and normal anus; who could have congenital adrenal hyperplasia.

The functional prognosis in patients with cloaca is related to the length of the common channel which can be anywhere from 0.5 to 7 cm. The operative plan is based on this length and also the length of the urethra from the urethral take off to the bladderneck [6]. Cloacas with a common channel less than 3 cm with good sacrum (sacral ratio >0.7), and normal spine have good prognosis for bowel and urinary control. A common channel longer than 3 cm usually suggests a more complex defect with less favorable prognosis, and is one that often needs complex maneuvers for urethral and vaginal reconstruction [7]. Duplication of the Mullerian structures (hemi-vaginas, a vaginal septum and two cervices) happens in about half of patients with cloaca [4].

Almost all patients with cloaca have an associated urological defect. If after draining the hydrocolpos the bladder still does not empty well and the hydronephrosis does not improve, then a vesicostomy is needed. All patients need a newborn colostomy (Fig. 41.17).

41.2.4 Imperforate Anus with No Fistula

The rectum ends blindly in this type of malformation at approximately 1–2 cm deep to the perineal skin, and is common in patients with Down syndrome. The prognosis is very good and a primary repair or colostomy during the newborn period are both appropriate options.

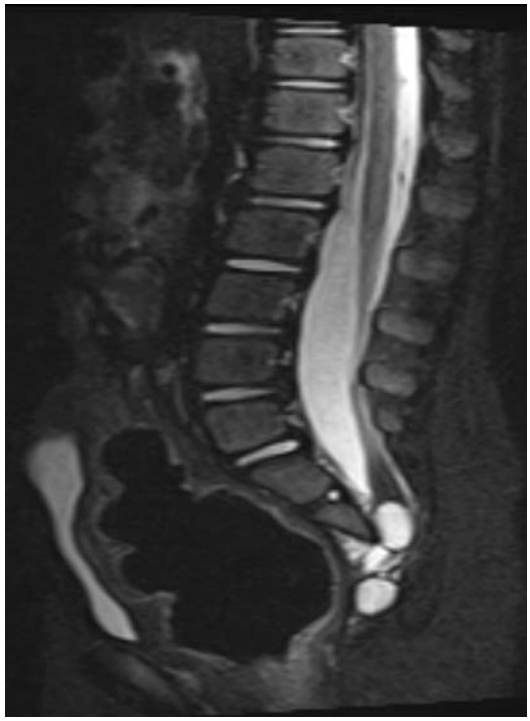

Fig. 41.18 MRI showing a presacral mass associated with anal stenosis

41.2.5 Rectal Atresia and Stenosis

These are rare defects occurring in only 1% of cases of anorectal malformations with the same characteristics in both genders. Unique to this defect is the presence of a normal anal canal. The obstruction or narrowing is located about 1–2 cm above the skin level. These patients have excellent prognosis for bowel control since the sphincter mechanism is normal as well as the anal canal. About one third of these patients have an associated presacral mass (Fig. 41.18). A colostomy is needed during the newborn period [8].

41.3 Colostomy

A colostomy decompresses the GI tract and diverts the stool. To avoid fecal contamination of the urinary system, the stoma is ideally completely diverting (Fig. 41.17). The proximal end is best located in the mobile portion of the descending colon, taking advantage of its attachments to the retroperitoneum, which helps to avoid stomal prolapse. Enough distal bowel must be left for the future pullthrough (Fig. 41.19). The proximal stoma should be matured and placed in the flat portion of the left quadrant equidistant from last left rib, the umbilicus, and the iliac crest (Fig. 41.17). This allows a colostomy bag to easily adapt to the abdominal wall. The distal stoma should be separated enough from the proximal one so that a stoma bag will not cover it, or the distal limb can be pursestringed closed until the time of the distal colostogram. In addition, the mucous fistula should be made small and flat to avoid prolapse, since it is only used for injection of contrast material. An important step during the creation of the colostomy is to irrigate the distal segment of the colon with saline until it is completely clean of meconium. Leaving meconium behind can lead to a fecaloma and contamination of the urine when there is a fistula between the rectum and the urinary tract.

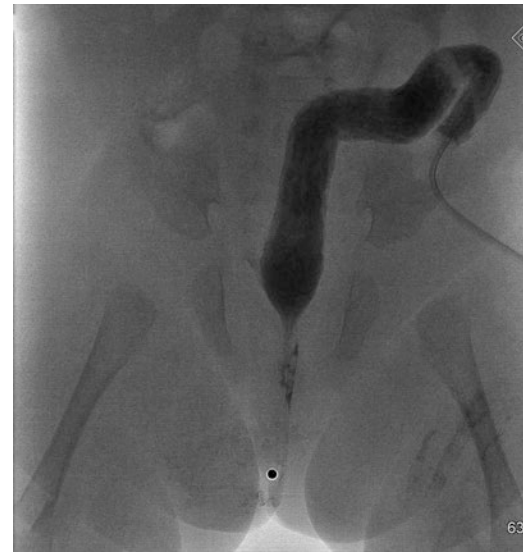

Fig. 41.19 Contrast study through an ideally located colostomy in the proximal sigmoid

41.4 Primary Repair for Females

In perineal fistulas and imperforate anus with no fistula the rectum is adjacent to the posterior vagina; in vestibular fistulas, the rectum shares a common wall with the vagina.

The operation proceeds with the patient in prone position, and the pelvis elevated [9]. Multiple silk sutures are placed around the fistula if one is present to exert uniform traction. A posterior sagittal incision (usually not much more posterior than the most posterior point of the sphincter mechanism) is made through the skin, subcutaneous tissue and the parasagittal fibers. The sphincter mechanism is divided in the midline. A white fascia surrounding the rectum is dissected, starting with the lateral walls and then anteriorly to the contiguous or common wall between rectum and vagina. The anterior plane is visualized by seeing the dissection already performed on the lateral planes. The rectum is lifted superiorly and the wall between rectum and vagina is completely dissected until the two structures are separated from each other and an areolar plane of separation is reached. If there is need to gain rectal length, the dissection is done as close as possible to the rectal wall, ligating with cautery the attachments and vessels on the posterior and lateral walls until the rectum reaches the perineum without tension. The perineal body is closed up to the anterior limit of the sphincter mechanism that is delineated with the use of an electric stimulator. The rectum is tacked to the posterior edge of the muscle complex up to the level of the skin. The reconstruction of the posterior sagittal incision reapproximates the ischiorectal fat, parasagittal fibers, subcutaneous tissue and skin and an anoplasty is performed with interrupted long-term absorbable sutures.

41.5 Primary Repair in Males

In perineal fistulas and imperforate anus with no fistula, the rectum is adjacent to the urethra. A Foley catheter is inserted, the patient is placed prone on the operating table with the pelvis elevated. Multiple silk stiches are placed in the fistula, if present, at the mucocutaneous junction. A midline posterior sagittal incision is made, staying perfectly in the midline, dividing the skin, subcutaneous tissue, parasagittal fibers, and muscle complex. The posterior rectal wall is identified. Silk stitches are placed in the posterior rectal wall which is then opened in the midline. More silk stitches are placed in the rectal wall edges as the rectum continues to be opened. The contiguous wall between the rectum and the urethra is carefully dissected, maintaining traction on the rectum. The lateral walls of the rectum should be cleaned in order to help to define the anterior plane. Once the rectum is completely separated from the urethra, rectal bands and vessels need to be ligated with cautery in order to gain length for a perineal anoplasty without tension. The posterior and anterior limits of the sphincter are delineated with the stimulator. The perineal body is then reconstructed up to the anterior limit of the sphincter, and the levator muscle edges are closed to each other. Sutures are placed in the posterior edge of the muscle complex, incorporating the posterior wall of the rectum. The posterior sagittal incision is closed up to the skin and an anoplasty is performed with long-term interrupted absorbable sutures. For bladderneck and high prostatic fistula cases, the repair begins with a laparoscopic dissection of the distal rectum. The rest of the operation is similar but is done supine.

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Part V

Liver, Biliary Tract, Pancreas

Biliary Atresia

42

Mark Davenport

Abstract

The first clear documented case of biliary atresia in English was reported in 1891 by the Edinburgh physician John Thompson. The child was jaundiced and was noted to have clay-coloured stool and dark urine throughout and ultimately died from liver failure or sepsis at a few months of age. The post-mortem drawings showed a normally formed but empty gallbladder two small bile filled cysts in the porta hepatis and an absence of the common hepatic duct.

Keywords

Biliary atresia • Classification • Aetiology and pathogenesis Portoenterostomy • Variant anomalies • Outcomes

42.1 History

The first clear documented case of biliary atresia in English was reported in 1891 by the Edinburgh physician John Thompson [1]. The child was jaundiced and was noted to have clay-coloured stool and dark urine throughout and ultimately died from liver failure or sepsis at a few months of age. The post-mortem drawings showed a normally formed but empty gallbladder two small bile filled cysts in the porta hepatis and an absence of the common hepatic duct.

Early reports of surgical intervention were unconvincing until William Ladd published a series in 1928 of 11 cases he had operated upon [2]. Though not all of these were biliary atresia, some appearing to be choledochal cysts and luminal blockages with inspissated bile, he was able to clear the jaundice in a majority using biliary reconstruction techniques such as hepaticojejunostomy with a Roux loop. However, as surgical experience increased with newborn surgical jaundice then it was realised that biliary atresia was actually usually "uncorrectable" by conventional means as no proximal bile-containing lumen could ever be identified.

Morio Kasai, working in Sendai, Japan in the late 1950s, adopted a much more radical approach to the biliary dissection, advocating complete excision of the extrahepatic biliary tree and anastomosis of the Roux loop to the denuded, transected,

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_42

albeit "solid" porta hepatis [3]. He recognised that actually most retained some communication with the intrahepatic bile ducts via microscopic biliary channels and exposure of these could restore bile flow in a proportion. This operation, now known as a Kasai portoenterostomy (KPE) does still fail in a high proportion but is still the main initial procedure in most and the only alternative to try and salvage the native liver.

The first liver transplant for a child with biliary atresia was attempted in 1963 in Denver, Colorado by Thomas Starzl [4]. Though unsuccessful as she died on-table from uncontrollable bleeding, it did mark a historical milestone. Liver transplant programmes emerged throughout the world in the 1960s, but all wilted in the face of ineffective immunosuppression and invariable recipient demise. Only with the discovery of cyclosporine at the end of the 1970s as an effective immunosuppressive agent did liver transplantation become a viable proposition for children with BA. The UK liver transplant programme for children began in the mid-1980s as the Kings College Hospital—Cambridge collaboration led by Sir Roy Calne and Alex Mowat.

42.2 Introduction

Biliary atresia (BA) remains a somewhat elusive disease, confined as it is to infancy but yet with its origin essentially unknown. It is potentially fatal; certainly if left to run its natural course, but can be treated effectively by expeditious surgery in a high proportion. For the remainder, liver transplantation is an option and indeed BA remains the single most common cause for this in the paediatric age-group.

42.3 Pathophysiology

BA is an *occlusive pan-ductular cholangiopathy* and thus affects both intra- and extrahepatic bile ducts [5]. The commonest classification divides BA into three types based on the most proximal level of occlusion of the extrahepatic biliary tree (Fig. 42.1). In Types 1 and 2 where there is a degree of preservation of structure of the intrahepatic bile ducts there is still blunting, irregularity and pruning (and absence of dilatation, even when obstructed). In the commonest, Type 3, the intrahepatic bile ducts are grossly abnormal with myriad small ductules coalescing at the porta hepatis. Where retrograde cholangiography is possible this is seen as a "cloud". In about 5% of cases, extrahepatic cyst formation (containing clear mucus or bile) can occur in the otherwise occluded biliary tree. Such cystic biliary atresia [6] is distinguishable clinical and histologically from simple obstruction in a cystic choledochal malformation, where there is preservation of an epithelial lining and retention of a normal and often dilated intrahepatic biliary tree.

42.3.1 Etiological Heterogeneity

BA is not a single disease, certainly not one with a single cause. In all probability it is a phenotype resulting from a number of different aetiologies [5]. Four groups can be defined clinically:

i. Biliary Atresia Splenic Malformation (BASM) syndrome [7, 8]
ii. Cystic BA [6]
iii. CMV IgM IgM +ve BA [9]
iv. Isolated BA

Other entities are fewer in number, but there seems to be a relationship with other gastrointestinal anomalies such as oesophageal atresia and jejunal atresia in a small proportion (<1% of large series) and occasional cases with a defined chromosomal abnormality (e.g. cat-eye syndrome and chromosome 22 aneuploidy [10].

Developmental biliary atresia is a term which we have used and includes (i) and (ii), where the onset is almost certainly prenatal, and evident by the time of birth [11]. The onset of occlusion in (iv) is much more contentious and some authorities hold that the bile duct can be normal and patent at the time of birth becoming occluded secondarily (by virally-mediated damage for instance).

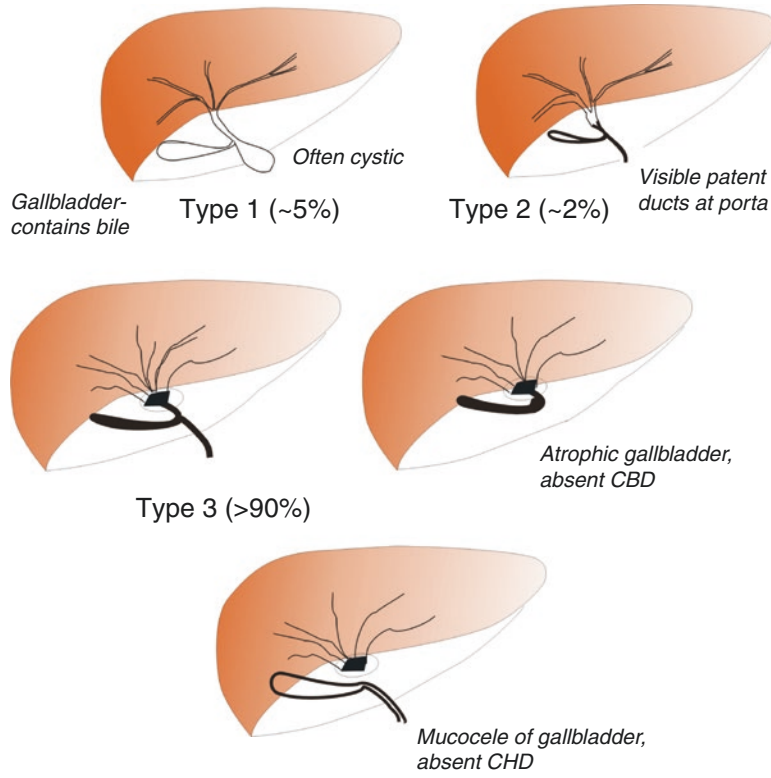

Fig. 42.1 Schematic illustration of biliary atresia classification

42.3.2 Biliary Atresia Splenic Malformation (BASM) Syndrome

While the association of BA with polysplenia had been recognised for some time, clarification of what constitutes BASM is only relatively recent [7]. The constellation of other anomalies is peculiar and the reasons for this still obscure. The common embryological insult may simply be timing (30–35 days) rather than a specific genetic defect. There are key genes which are important in both bile duct development (e.g. *JAG1* [12], *HNF-6*), and visceral and somatic symmetry (e.g. inv. [13], *CFC-1*), although correlation with the human condition is patchy. A possible genetic link has recently been reported by a French group who found an increased frequency of mutations in the *CFC-1* gene (on Chromosome 2), compared to controls [14].

42.3.3 Pathology

The macroscopic appearance of the extrahepatic biliary tree ranges from being inflamed, hypertrophic yet intact to an atrophic negligible remnant with absent parts. In about 20% of those with type 3 BA, there will be a patent CBD and relatively normal looking gallbladder containing clear mucus—a mucocele. In some, particularly those with the BASM syndrome the CBD will be completely absent and the gallbladder no more than a shrunken, atrophic remnant (Fig. 42.1).

The histological appearance within the liver appears more stereotypical, even reactive, with a time-dependent sequence to overt macronodular cirrhosis. BA is not simply a mechanical biliary obstruction (in which case there would be dilatation of the intrahepatic bile ducts) and there is a marked inflammatory component. Histologically, there is early portal tract inflammation and an obvious mononuclear cell infiltrate; and later

there appears to be bile-ductule plugging and re-duplication.

There is abnormal expression of Class II antigen and increased expression of the cell adhesion molecules, ICAM-1 and VCAM-1, on sinusoidal and biliary epithelium in BA infants [15, 16]. This is believed to facilitate the infiltration of circulating mononuclear cells which then become activated *in situ*. The mononuclear infiltrate is believed by a number of authors to be the specific destructive element of BA targeted at bile duct epithelium and therefore cholangiodestructive [16, 17]. Its composition can be ascertained by immunohistochemistry and appears predominantly CD4+ T lymphocytes (specifically Th1 and CD56+ (natural killer) NK cells). Infiltrating CD8+ cells do occur but some studies have suggested that they lack the normal markers of activation (e.g. perforin, granzyme B and Fas ligand) [18]. Most recently, increases in the Th17 (IL-17+) subset have been identified; principally in the mouse model [19] but also in clinical cases [20]. It is known that biliary epithelial cells possess an innate immune system consisting of the Toll-like receptor family and are able to recognize pathogen-associated molecular patterns (PAMPs). In some adult auto-immune diseases such as primary biliary cirrhosis, Th17 cells are implicated in the cholangiopathy and this too appears to be the case in BA [20].

The Th1 subset, regulatory T cells (Tregs) may also play a part in aetiology and defects have been shown in the mouse model [21, 22] although human evidence is patchy [20, 23]. The hypothesis is that there is an early perinatal absence of regulatory T-regs which are believed essential for suppressing and inhibiting NK cell expansion and which allows viral exposure to initiate a sequence of (auto) immune mediated bile duct damage.

That there is a potent systemic inflammatory process is reinforced by increased expression of the cytokines, sICAM-1 and sVCAM-1 in the circulation [24, 25], as is seen in other immunologically-mediated liver diseases such as primary biliary cirrhosis and sclerosing cholangitis; with levels of the sVCAM-1 at least being shown to be prognostic [25]. Increasing levels of various other cytokines (e.g. IL-2, TNFα and IL-18), can also be shown post-operatively but most discriminate poorly between those who would clear their jaundice or not, although, conversely some (e.g. IL-2, IFNγ, IL-4, IL-10, TNFα and sICAM-1) were better predictors of subsequent need for early transplantation [26].

Resident (Kupffer cells) or systemic/recruited macrophages seem to play a dual role in BA; as both the presenters of antigenic material in the first place and latterly as the initiating force for fibrosis in the development of chronic liver disease. Tracy et al. [27] first showed increases in resident macrophages (CD68+) with marked expression of the lipopolysaccharide receptor, CD14+. Increased levels of both CD68+ cells and its circulating markers (TNFα and IL-18) have also been shown impair prognosis post-KPE [26, 28].

42.3.4 Viruses and Biliary Atresia

It is possible to reproduce histological BA in particular strains of mice (Balb/c) by exposing the newly born pups to particular strains of hepatotropic viruses (e.g. Rhesus Rotavirus (RRV)) [29]. A group from Hannover has recently shown that this can be prevented by vaccination of the dams against RRV using either of two vaccines (RotaTeq® and Rotarix®) [30]. Thus although most offspring still developed cholestasis there was little subsequent development of actual BA.

Many groups have tried to identify either viruses or at least a trace of a virus in human BA. Initially serological techniques were used [31] but latterly increasingly sophisticated PCR techniques have been applied. The most comprehensive study has been that of Rauschenfels et al. [32], who looked at a panel of hepatotropic viruses in a series of 74 cases of BA at the time of diagnosis. The commonest viruses, identified by presence of DNA/RNA were reovirus type III (33%) and cytomegalovirus (11%). Interestingly, some children had PCR evidence of multiple viruses leaving the authors actually unconvinced that viruses really played any aetiological role, rather they suggested they were innocent bystanders in cholestatic infants.

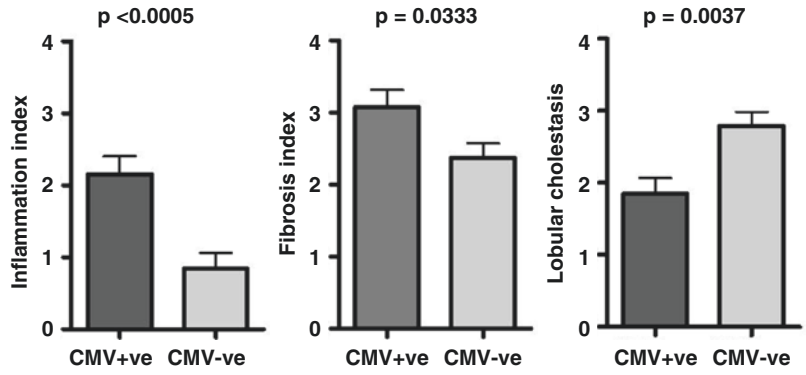

Fig. 42.2 Comparison of liver histology in infants with biliary atresia—CMV IgM +ve (n = 13) *versus* CMV IgM −ve (n = 54). Semiquantitive score (0–4) for inflammation, fibrosis and lobular cholestasis. [reproduced with permission from Zani A, Quaglia A, Hadzic N, Zuckerman M, Davenport M. Cytomegalovirus-associated biliary atresia: An aetiological and prognostic subgroup. J Pediatr Surg 2015; 50: 1739–45.]

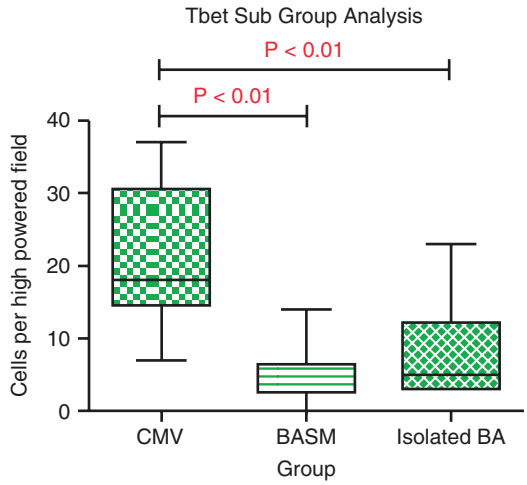

Fig. 42.3 Box and whisker chart showing significantly larger Th-1 cell (T_{bet} +ve) infiltrate in CMV patients compared with BASM (P < 0.01) and Isolated BA (P < 0.01) groups. (Reproduced with permission from Hill R, Quaglia A, Hussain M, Hadzic N, Mieli-Vergani G, Vergani D, et al. Th-17 cells infiltrate the liver in human biliary atresia and are related to surgical outcome. J Pediatr Surg 2015; 50:1297–303)

We have recently focused on those infants who have IgM +ve serological evidence of cytomegalovirus to try and prove a clinical link with viral exposure [9]. It is possible to differentiate these from infants with isolated BA (but CMV IgM–ve) both clinically (higher serum AST and bilirubin values, larger spleen sizes and a poor response to surgery), histologically (Fig. 42.2) and in terms of the composition of infiltrating mononuclear cells [9, 20] (Fig. 42.3).

42.3.5 (Auto)immune Response and Inflammation in Biliary Atresia

That there is a potent inflammatory reaction within the livers of infants with BA is unquestioned. Several groups have tried to link this presumably detrimental process with perinatal viral exposure though this has been based more on work in mice than in humans [33, 34]; with one group showing that adoptive transfer of hepatic T cells from BA mice into naïve immunodeficient recipients produces bile duct specific inflammation and injury [35]. In human tissue it has been shown that biliary epithelial cells have the potential to mount an antiviral response and to initiate apoptotic pathways in response to a synthetic double stranded RNA analog [36]. A recent intriguing observation has been of an increased prevalence of α-enolase antibodies in infants with BA, identified from work in the mouse model, with the speculation that there is a degree of molecular mimicry between antigens of viral origin and cholangiocyte antigens [37].

42.3.6 Biliatresone

There had been observations made that in certain circumstances sheep (to a lesser extent cattle) could develop biliary atresia by maternal grazing on land colonized by certain strains of weed (Red

Crumbweed, *Dysphania glomulifera*). Later work by Michael Pack in Pennsylvania isolated an isoflavonoid compound (now termed **biliatresone**) which retained the property of biliary tropism and consistently caused failure of bile duct development in both a zebrafish and a mouse model [38]. The relationship to human BA has not been shown but it does reiterate the concept of aetiological heterogeneity and allow the possibility of an environmental cause of this disease.

42.4 Clinical Features

The key features of BA are conjugated jaundice persisting beyond 14 days of age, acholic stools, and dark urine in an otherwise healthy term neonate. Indeed there is some evidence that conjugated jaundice is present from day 1 and 2 of life in most infants who later turn out to have BA [39]. Birth there is no difference in gestational age or birth weight between those with developmental compared to isolated BA and both cohorts demonstrate failure to thrive by the time they are admitted [11]. Fat malabsorption is the presumed mechanism for this and will also cause deficiency of the fat-soluble vitamins D, A, E and most importantly K. As a result some infants will present with a bleeding tendency and even an intracranial haemorrhage. Vitamin D is also remarkably low at presentation and even more so if they are of a non-Caucasian background, at least in those born in the UK [40].

Some infants with cystic BA will present with an abnormal maternal ultrasound scan, typically at around 20 weeks gestation [6, 41]. Clinicians need to recognise BA as a possibility for this scenario and facilitate a post-natal US and timely referral rather than assume these most all be choledochal cysts and that surgery can wait.

Liver fibrosis and cirrhosis are time-dependent features which seem to begin perinatally even in those infants with developmental BA [42]. Features such as obvious ascites, marked hepatosplenomegaly and a macronodular liver should therefore be late signs not seen before 80–90 days or so.

42.4.1 Diagnostic Workup

Liver biochemistry will show a conjugated hyperbilirubinemia, modestly raised transaminases (AST and ALT), and significantly raised γ-glutamyl transpeptidase (GGT) [5]. Protein and albumin levels are usually normal. Haemoglobin and white cell counts are normal although the platelet count may be raised. We now calculate an AST to Platelet ratio index (APRi), and use it as a surrogate marker of liver fibrosis. It does have a degree of long-term prognostic value but only if it is low (Fig. 42.4). Table 42.1 illustrates the medical and surgical differential of a conjugated jaundice [43].

The ultrasound examination is a key part of the protocol as it usually excludes other possible surgical diagnoses (e.g. choledochal malformation, inspissated bile syndrome etc.). All are characterised by intrahepatic or common bile duct dilatation. Ultrasound may be suggestive of BA as a diagnosis by showing an atrophic gallbladder with no evidence of filling between feeds. A more specific, albeit controversial, sign is the so-called "triangular cord sign" which was first identified

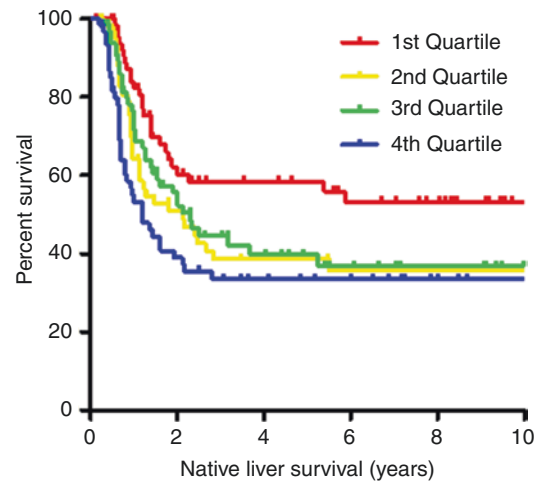

Fig. 42.4 Native liver actuarial survival curves of patients with biliary atresia based on AST-to-Platelet Ratio index (APRi) quartiles. Higher values suggest more liver fibrosis. 1st quartile: < 0.4; 2nd quartile 0.4–0.7; 3rd quartile 0.7–1.1; 4th quartile 1.1–11. (Reproduced with permission from Grieve A, Makin E, Davenport M. Aspartate Aminotransferase-to-Platelet Ratio index (APRi) in infants with biliary atresia: Prognostic value at presentation. J Pediatr Surg 2013; 48: 789–795)

Table 42.1 Differential diagnosis of conjugated hyperbilirubinaemia

Medical	Key investigation	Surgical	Key investigation
"TORCH" infections toxoplasma, cytomegalovirus, hepatitis, syphilis	Serology	Choledochal malformation	US and MRCP
α-1-Antitrypsin deficiency	Protein electrophoresis (PiMM is normal, PiZZ denotes A-1AT)	Inspissated bile syndrome	US and percutaneous transhepatic cholangiogram
Alagille's syndrome	Facies, echocardiography, Vertebral x-rays	Spontaneous perforation of bile duct	US and radio-isotope scan
Cystic fibrosis	Sweat test	Tumours	US and CT scan
Parenteral nutrition associated cholestasis	History, liver biopsy		
Progressive familial intrahepatic cholestasis	Liver biopsy, genetic analysis		
Metabolic causes e.g. galactosaemia	Gal-1-PUT level		

US ultrasound, *MRCP* magnetic cholangiopancreatography, *CT* computed tomography

by Park et al. in 1997 [44] and purports to represent the sonographic appearance of the solid proximal biliary remnant in front of the bifurcation of the portal vein. Some authors believe it to be highly accurate and specific for BA [45].

Radio-isotope (Technitium (Tc) labelled iminodiacetic acid derivatives) hepatobiliary imaging was formerly quite popular in showing absence of biliary excretion. However, it is rarely specific and there is considerable overlap with neonatal hepatitis.

Percutaneous liver biopsy, looking for histological features of "large-duct obstruction" as against those of "neonatal hepatitis", is safe and well-tolerated but needs an experienced pathologist to interpret. Currently it is this diagnostic method of choice in two out of the three English BA centres.

Direct cholangiography is certainly possible, either using ERCP [46] or at laparoscopy [47]. ERCP is technically challenging even with the right equipment, but can avoid laparotomy in larger infants. Laparoscopy and direct puncture of the gallbladder is relatively straightforward as an access point for a cholangiogram, though whether it is really advantageous is a moot point given you still have to surgical access the abdominal cavity for the umbilical camera port.

In some centres, particularly in Asia, simple placement of a naso-duodenal tube and luminal content aspiration over 24 h is the principle method of making the diagnosis. It has never caught on in North America or Europe.

42.4.2 Screening for Biliary Atresia

In order to diminish the time to definitive surgery, some countries have adopted a screening programme. The most well-developed has been that in Taiwan [48], where mothers are issued with colour coded cards and asked to compare their infant's stool. Recognition of pale stool prompts further investigation and referral. This certainly has lowered the time to surgery in that country but to no lower than we would expect in the UK where there is no such co-ordinated programme. Interestingly they do manage to avoid the very old infant with BA and overt cirrhosis which is still seen here in the UK.

42.5 Surgery: Kasai Portoenterostomy

The operation can be divided into various sections.

Confirmation of diagnosis: a limited (1 cm) right-upper quadrant muscle-cutting incision

allows access to the gallbladder and a cholangiogram (if possible). If there is no lumen then that, in itself, is evidence for BA. The cholangiogram should show the complete biliary tree and drain into the duodenum to exclude BA.

Mobilization of Liver: our practice suggests that complete porta hepatis dissection requires full mobilization of the liver by dividing the falciform, and left triangular ligaments. This allows it to be everted outside of the abdominal cavity. The anaesthetist needs to be aware of this manoeuvre as it reduces venous return and requires intravenous volume support. Alternatively, some surgeons leave the liver *in-situ* but sling the right and left vascular pedicles and use traction to expose the porta hepatis. There is a small risk of portal vein thrombosis with this technique.

Portal Dissection: The gallbladder is mobilized from its bed and the distal CBD divided and then dissected back towards the porta hepatis (Fig. 42.5 and Fig. 42.6). Ligate and divide small veins to the porta plate which facilitates downwards traction of the portal vein confluence and exposes the caudate lobe. On the left side, there is often an isthmus of liver parenchyma (from segment III to IV) which may need division by coagulation diathermy to open up the recessus of Rex (where the umbilical vein becomes the left portal vein)**.** On the right side, the division of right vascular pedicle into anterior and posterior should be visualized. The "width" of the transected portal plate should extend from this bifurcation and a small inominate fossa on the extreme right to the point where umbilical vein joins the left portal vein.

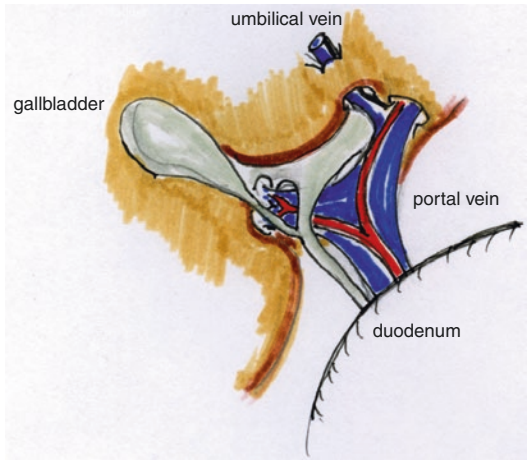

Fig. 42.5 Kasai portoenterostomy: anatomy of the region

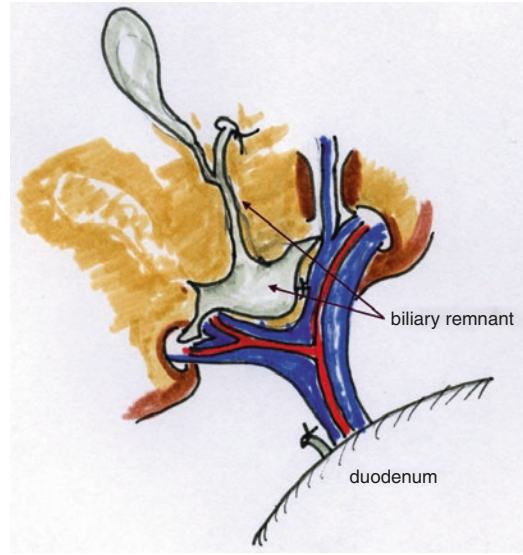

Fig. 42.6 Kasai portoenterostomy: division of common bile duct and mobilisation of gallbladder

Porta Hepatis transection: Excise remnants flush with the liver capsule by developing a plane between solid white biliary remnant and the underlying liver starting at the gallbladder fossa. Excising liver parenchyma itself does not seem to improve bile drainage and so-called "deep coring" adds absolutely nothing. All of the denuded area now needs to be incorporated into the Roux loop.

Roux Loop and Portoenterostomy: A standard retrocolic Roux loop measuring 40–45 cm should be constructed. The jejunojejunostomy lies about 10 cm from the ligament of Trietz and can be stapled or sutured. The proximal anastomosis must be wide (~2 cm) and end-to-side is appropriate. Fine precise, suturing (e.g. 6/0 PDS®) at the edge of the portal plate are satisfactory but remember most remnant ductules are concentrated in the right and left recesses of the dissection (Fig. 42.7).

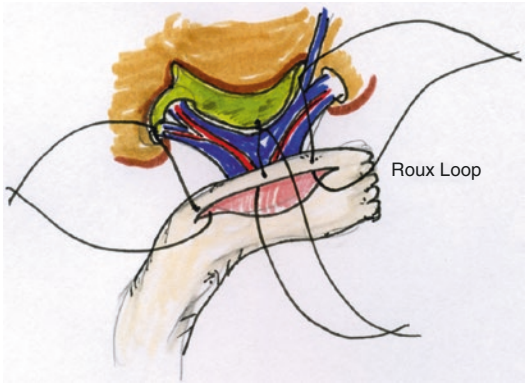

Fig. 42.7 Kasai portoenterostomy: resection of biliary remnants and anastomosis with Roux loop

42.5.1 Options and Alternatives

Patency of the native gallbladder and common bile duct might tempt one to consider a portocholecystostomy, as it does have the advantage of abolishing post-operative cholangitis. However, the anastomosis is not as flexible as a standard Roux loop and revisions for repeated biliary obstruction have been described with a poorer long-term outcome compared to a standard Roux loop [49].

Laparoscopic Kasai operations have been reported by minimally invasive enthusiasts [50] but this has not been taken up by the larger centres performing the standard KPE on a regular basis. It has become apparent that laparoscopic Kasai surgery doesn't offer anything advantageous to the child beyond a better scar and an adhesion-free abdominal cavity for the transplant surgeon. Results are certainly not better and rarely comparable and centres for instance in China and Germany have reverted to the standard open approach [51, 52]. This is likely to be due to the difficulties with portal plate dissection using currently available laparoscopic instruments. Radical resection of all extrahepatic biliary remnants from all biliary sectors and a wide portoenterostomy encompassing all the margins of that resection are the key features to maximize results and it can be a difficult, delicate dissection in the open without the constraints of videosurgery.

In some circumstances, the anatomy of the less common type 1 and 2 BAs, typically manifest as cystic biliary atresia, will allow a hepaticojejunostomy to be performed as there is still a bile duct to join to. However, this is tenuous at best and though these groups do have a better long-term outcome [53, 54] it is probably more sensible to dissect it higher and clear the portal plate as in a standard KPE.

42.5.2 Adjuvant Therapy for Biliary Atresia

Although a number of drugs have the potential to improve the outcome of KPE, there has been little published in the way of scientific data to provide unquestioned evidential support for any. Nonetheless two classes of drug deserve exposition.

42.5.2.1 Corticosteroids

Small, uncontrolled series have suggested benefit in terms of increased bile flow post KPE [55, 56] and post-operative steroids became popular. Our first prospective, double-blind, randomized, placebo-controlled trial using a low-dose of prednisolone (2 mg/kg/day) was published in 2007 [57]. This showed a significant increased rate of jaundice clearance (especially in young livers) in the steroid group but did not translate to a reduced need for transplant or improved overall survival. We followed this with an open-label designed study using contemporaneous controls and a higher dose (5 mg/kg/day) regimen [58]. This now showed statistical improvement in clearance of jaundice and correction of liver enzyme abnormalities but no change in need for transplant. A further randomized, placebo controlled trial (the START trial) from the USA failed to show a statistically significant difference in measures of outcome although the principle measure of jaundice clearance was the same as the aforementioned UK experience (15% improvement with steroids) [58, 59]. The most recent evaluation of the evidence has concluded steroid benefit [60]. All three UK centres continue to use high-dose steroids albeit different ones and for different durations.

42.5.2.2 Ursodeoxycholic Acid (UDCA)

This is widely thought to be beneficial, but only if surgery has already restored bile flow to a real degree. UDCA "enriches" bile and has a choleretic effect, increasing hepatic clearance of supposedly toxic endogenous bile acids and may confer a cytoprotective effect on hepatocytes. Willot et al. [61] assessed the effect of UDCA on liver function in children >1 year post-KPE in a crossover study in 16 children with BA who had undergone 'successful' surgery defined by resolution of jaundice 6 months after surgery. These patients were all treated with UDCA (25 mg/kg/day in three divided doses) for 18 months at which point treatment was stopped and their clinical and biochemical status monitored. Six months later only one had worsened clinically with recurrence of jaundice however, all but two had sustained significant worsening in liver enzymes. These were all then restarted on UDCA and 6 months later all of these had significant diminution in their liver enzymes.

42.5.3 Post-operative Complications

Ineffectiveness of the KPE and continuation of the natural history of BA is the most common problem leading to end-stage liver disease. Jaundice will worsen accompanied by abdominal distension and ascites with failure to thrive and malnutrition. Such infants require urgent consideration of liver transplantation. There are some specific complications which can occur independently of this process though.

42.5.3.1 Cholangitis

Restoration of a bilio-intestinal link predisposes to ascending cholangitis and is seen in up to 50% of large series [53, 62, 63]. This is much more likely to occur in those with BA compared to the those with choledochal malformations as the latter's bile flow is so much better than even the best KPE. The risk is apparent in the first 2 years post-surgery although the reason for this is obscure. Presumably there is some time-dependent change in local immunological defense.

Most children will present with pyrexia, worsening jaundice and a change in liver biochemistry and should be treated aggressively with broad-spectrum intravenous antibiotics effective against Gram−ve organisms (e.g. gentamicin, meropenem, Tazocin (piperacillin/tazobactam)).

42.5.3.2 Portal Hypertension and Oesophageal Varices

Portal venous pressure, when measured at KPE, is abnormally high in about 70% of BA infants and is caused by increasing liver fibrosis and correlates with age at KPE, bilirubin level and ultrasound measured spleen size [64]. It, however, is a poor predictor of outcome either in terms of response to KPE or even in those who will develop varices. This confirms the results of a previous study from King's College Hospital where original liver histology at KPE was graded and compared with variceal formation as assessed endoscopically in 77 children, some 2–4 years later [65]. The implication from both is that it is the result of the KPE in terms of clearance of jaundice and more importantly the abbreviation and perhaps attenuation of the hepatic fibrotic process, rather than the early state of the liver which determines variceal formation.

Varices take time to develop and bleeding is unusual before 9 months of age and usually occurs from 2—3 years. Using endoscopic surveillance about 60% of children surviving beyond 2 years will have definite varices and of these about 20–30% will bleed [66, 67]. Emergency treatment of bleeding varices specifically includes the use of vasopressin (e.g. terlipressin) or somatostatin analogues (e.g. octreotide) sometimes even a Sengstaken-pattern tube [68]. Most are treated endoscopically with banding or in the very young injection sclerotherapy. In those with reasonable restoration of liver function this should be all that is necessary; however those who are still jaundiced require transplant assessment. The role of propranolol in BA children with portal hypertension particularly those with cirrhosis has not been formalized.

42.5.3.3 Ascites

This is related to and caused by portal hypertension in part, but other contributory factors include hypoalbuminaemia and hyponatraemia. It predisposes to spontaneous bacterial peritonitis. Conventional treatment includes a low-salt diet, fluid restriction and the use of diuretics particularly spironolactone. Often seen in settings of malnutrition, due consideration should be given to naso-gastric feeding to try and increase calorie and protein intake.

42.6 Outcome and Results

According to the latest survey of outcome of the results of KPE in England and Wales, in 424 infants there was clearance of jaundice (to a bilirubin of ≤20 μmol/L) in 55%. As a consequence, the five and 10-year native liver survival estimate was 47 and 43%; with the overall survival estimate at 10 years being 90% [69] (Fig. 42.8). This compares well with data from other national surveys (e.g. Japan [70] France [71], Switzerland [72] and Canada [73].

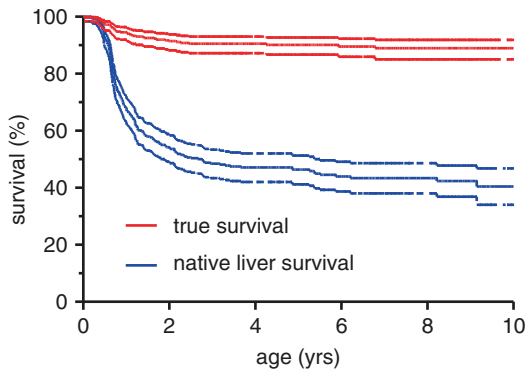

Fig. 42.8 Actuarial true and native liver survival curves [median (±95% CI)] for biliary atresia (n = 443) in England and Wales (1999—2009). (Reproduced with permission from Davenport M, Ong E, Sharif K, et al. Biliary atresia in England and Wales: results of centralization and new benchmark. J Pediatr Surg 2011; 46: 1689–94)

42.6.1 Prognostic Factors

The results of surgery of BA are largely unpredictable in individual cases though a number of factors can be identified as important.

42.6.1.1 Age at Kasai Portoenterostomy

The effect of age on outcome following KPE is still a contentious, complex issue—although not in its simplest expression. That is, if a bile-obstructed liver is left alone then delayed surgery will be associated with less good results; the liver ultimately becoming cirrhotic and unsalvageable.

But the effect is neither simple nor linear. For example, infants coming to KPE at King's College Hospital in the 1980s and 1990s were divided into age by quartiles and their subsequent native liver survival calculated. Only the oldest quartile had a worse outcome [74], even then not reaching statistical significance. However, when 225 infants from the 1990s, and 2000s were divided into specific age cohorts and by their putative aetiological group then a significant effect on outcome was shown but only for those where the BA was considered developmental (BASM and Cystic BA). For all those remaining infants with isolated BA, there was barely any discernable effect up until about 100 days of age [74]. Certainly there were no cut-offs. Dogmatic assertions that something specific happens at 6 or 8 weeks or 10 weeks really should be confined to the history books.

42.6.1.2 Surgical Experience

It has previously been shown in the UK that the more KPEs you do (as a centre, and arbitrarily >5/year), the better the outcome [75, 76]. This led to superspecialisation in England and Wales (and later Denmark [77] and Finland [78]) and an awareness of the need to improve collaboration and communication between centres in others (e.g. France, USA, Canada) [54, 73]).

42.6.1.3 Liver Histology and Biliary Remnant

There is improved outcome in types 1 and 2 compared to type 3 BA; and cystic BA compared to

non-cystic BA [6, 53, 54]. Almost certainly this is due to improved preservation of the connections between the intra and extrahepatic bile ducts and ductules. Infants with BASM also have a worse prognosis and appear at risk of sudden death in the first year following KPE. Whether this is due to an intrinsically worse liver disease, a smaller biliary remnant tissue or the effect of other anomalies (e.g. cardiac) is not known. Prospective evaluation of the macroscopic features of the hepatobiliary elements (hardness of the liver, presence of ascites etc.) was relatively poorly predictive of outcome with only actual size of resected biliary remnants being really discriminatory [79]. Microscopic examination of the transected bile duct remnant will show a varying amount of residual ductules. Older series suggested that only those showing large ductules (>300 μm) had a distinctly better outcome [80] but a later evaluation showed that minimal or no ductules in the remnant was also predictive of lack of effect of KPE [81].

Conclusion

In conclusion, although the cause of biliary atresia remains enigmatic a complementary system of surgical treatment has evolved over the past 35 years, which has improved the overall survival to adulthood in affected infants from a dismal 10 to about 90%. Not many surgical diseases can claim such a remarkable change in outlook.

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Choledochal Cyst

43

Naomi Iwai

Abstract

A choledochal cyst (congenital dilatation of the bile duct) shows extra and/or intrahepatic dilatation of the bile duct, and mainly cystic dilatation of the common bile duct. Although the etiology is unknown, it might be congenital. In 1936, Yotsuyanagi suggested a new etiological theory based on unequal epithelial proliferation at the stage of the physiological occlusion of the primitive choledochus. Thereafter, Babbit proposed an abnormal relationship between the common bile duct and pancreatic duct. However, Rustad and Lilly suggested that this abnormal relationship was simply a malformation associated with a choledochal cyst. Therefore, the etiology has not yet been established.

Keywords

Congenital disorders biliary tract • Choledochal cyst • Surgery • Outcomes

43.1 Introduction

A choledochal cyst (congenital dilatation of the bile duct) shows extra and/or intrahepatic dilatation of the bile duct, and mainly cystic dilatation of the common bile duct. Although the etiology is unknown, it might be congenital. In 1936, Yotsuyanagi [1] suggested a new etiological theory based on unequal epithelial proliferation at the stage of the physiological occlusion of the primitive choledochus. Thereafter, Babbitt [2] proposed an abnormal relationship between the common bile duct and pancreatic duct. However, Rustad and Lilly [3] suggested that this abnormal relationship was simply a malformation associated with a choledochal cyst. Therefore, the etiology has not yet been established. The estimated incidence in Western countries varies between 1 in 100,000 and 1 in 150,000 [4]. The incidence is higher in Asia and more prevalent in women, with a male to female ratio of 1:4.

With advancements in diagnostic imaging early diagnosis can be achieved within the infantile period. A surgical technique, Roux-en-Y hepaticojejunostomy after excision of the cyst, is feasible for the treatment of a choledochal cyst. The prognosis is favorable. However, long-term follow-up including the possibility of carcinogenesis is needed.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_43

43.2 Classification

In 1959 Alonso-Lej et al. [5] proposed three types of choledochal cyst:

- Type I: cystic or diffuse fusiform dilatation of the extrahepatic bile duct
- Type II: diverticulum of the extrahepatic bile duct
- Type III: the distal end of the common bile duct dilates cystically, which presses into the duodenum (called a choledochocele)

Type I is the most common, and Type II and III are extremely rare.

Since then, Todani et al. [6] further classified choledochal cysts mainly into five types, based on analyses of cholangiographic findings (Fig. 43.1).

- Type I. Common type: (a) choledochal cyst in a narrow sense; (b) segmental choledochal dilatation; and (c) diffuse or cylindrical dilatation.
- Type II: Diverticulum type in the whole extrahepatic duct.
- Type III: Choledochocele
- Type IV-A: Multiple cysts at the intra- and extrahepatic ducts
- Type IV-B: Multiple cysts at the extrahepatic duct only
- Type V: Intrahepatic bile duct cyst (single or multiple)

Type I is divided into three subtypes in view of morphologic findings and surgical treatment. Type IV is also divided into two subtypes. Type IV-A comprises multiple cysts that involve intra- and extrahepatic bile duct cysts, and Type IV-B also involves multiple cysts, but confined to the extrahepatic bile duct alone. Multiple intrahepatic cysts coexisting with fibrosis of the liver is referred to as Caroli's disease [7]. However, the etiology or pathophysiology is different from that of choledochal cysts.

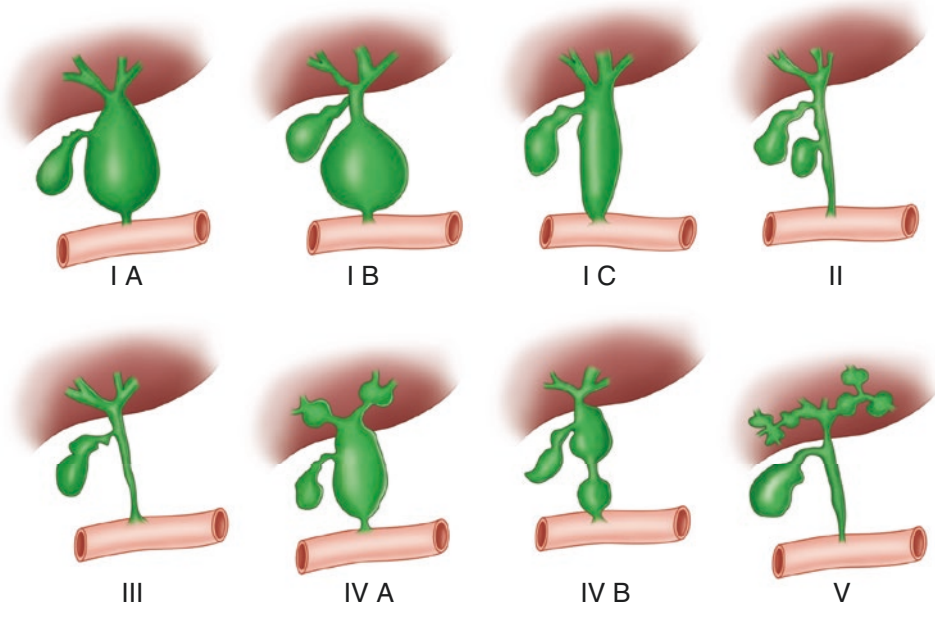

Fig. 43.1 Todani's classification of congenital bile duct cysts (choledochal cysts)

43.3 Prognosis

The prognosis after the excision of a choledochal cyst followed by hepaticojejunostomy with Roux-en-Y anastomosis is mostly favorable [8, 9]. Before resorting to cyst excision, carcinoma of the biliary tract occurred in 18 of 108 patients (16.6%) after internal drainage by cyst enterostomy [10]. After the excision of a choledochal cyst, we [11] encountered a case of local recurrence of adenocarcinoma arising from the distal end of the cyst 2 years postoperatively. Therefore, long-term follow-up is required, especially for the possibility of carcinogenesis.

In cases of preoperative hyperbilirubinemia, bile drainage with a T-tube is needed to relieve the symptom, and definitive surgery can be performed electively after the establishment of a favorable condition. Even after the successful excision of a choledochal cyst, Hori et al. [12] encountered six cases of liver transplantation for refractory hyperbilirubinemia caused by liver fibrosis, with good results.

43.4 Prenatal Diagnosis

Fetal diagnosis is possible by ultrasonography or magnetic resonance imaging in cases of choledochal cyst [13, 14]. Prenatal diagnosis using ultrasound has been performed at various intervals, ranging from 15 to 37 weeks. A cystic lesion at the hepatic portal region detected by ultrasonography commonly suggests the diagnosis of a choledochal cyst. Of these cystic lesions, however, we seldom encounter cases of Type-I cystic biliary atresia (Noncorrectable cystic type) [15].

A question regarding the optimal timing of definitive surgery has been raised when the prenatal diagnosis of a choledochal cyst is made by ultrasonography. As operative management in early infancy is safe, the early excision of a choledochal cyst is recommended. However, the precise timing of definitive surgery is different among investigators. Howell [16] and Lee [17] insisted that the early excision of a cyst in the newborn period was optimal because the grade of liver fibrosis increases with age and excision in the newborn period poses less of a risk to the patient than delayed surgery. On the contrary, Foo [18] reported that they performed definitive surgery at the age of 4 months as early excision of a choledochal cyst. Lugo-Vicente [19] also suggested that elective excision at 6 weeks of age was appropriate unless the patient was symptomatic. Therefore, no consensus has been reached on the best timing of definitive surgery when the diagnosis of a choledochal cyst is made prenatally. Accordingly, I would suggest that definitive surgery should be conducted within 2 months of age because there is a possibility not only of choledochal cyst but also of cystic biliary atresia, for which definitive surgery should be carried out within 2 months of age [20].

43.5 Clinical Presentation

Clinical signs and symptoms are highly dependent on two factors: the age at onset and reflux of pancreatic juice into the bile duct through the pancreaticobiliary maljunction [21]. Todani [22] reported the characteristics of a choledochal cyst in early infancy, aged less than 24 months. They are usually of the cystic type, and a huge abdominal mass and jaundice with acholic stools are typically found. Also, no symptom suggesting acute pancreatitis is observed. Davenport [23] also reported that choledochal cyst children with pancreatitis are older than those with painless jaundice (4.2 versus 1.5 years, respectively; $p = 0.005$).

In children aged more than 2 years with a choledochal cyst, they mainly complain of abdominal pain accompanied by nausea or vomiting, which might be confused with cyclic vomiting. The pattern of abdominal pain is similar to that of recurrent pancreatitis, and is examined based on the serum amylase level. Jaundice in this age group is intermittent and usually associated with pain in the epigastrium or in the right hypochondrium.

Jaundice is caused by inadequate bile drainage into the duodenum because of cholangitis. However, the jaundice is usually transient. Further, cholangitis occasionally causes liver dysfunction associated with elevations of AST

and ALT, in which biliary obstruction is complete at the papilla of Vater

43.6 Diagnostic Images

An abdominal plain film should be taken first, in which a diffuse shadow corresponding to a choledochal cyst might be found. Abdominal ultrasonography serves as an important tool for the differentiation of obstructive jaundice and abdominal pain in children [24]. Abdominal CT is further conducted after ultrasonography if it shows an abdominal cyst. ERCP (Endoscopic Retrograde Cholangiopancreatography) or MRCP (Magnetic Resonance Cholangiopancreatography) may be preoperatively employed to detect a pancreaticobiliary maljunction in a choledochal cyst. However, sedation or general anesthesia is required to perform ERCP or MRCP. Hepatobiliary scintigraphy is not necessarily mandatory for a preoperative diagnosis. However, it is useful for follow-up to observe bile flow after the operation.

43.6.1 Ultrasonography

Abdominal ultrasonography is a good initial screening method when diagnosing a choledochal cyst [25]. Such ultrasonography is noninvasive and can be performed at bed side without any sedation. It can provide us with information on the presence or absence of biliary and pancreatic ductal dilatation in addition to the status of the liver in terms of the density (Fig. 43.2).

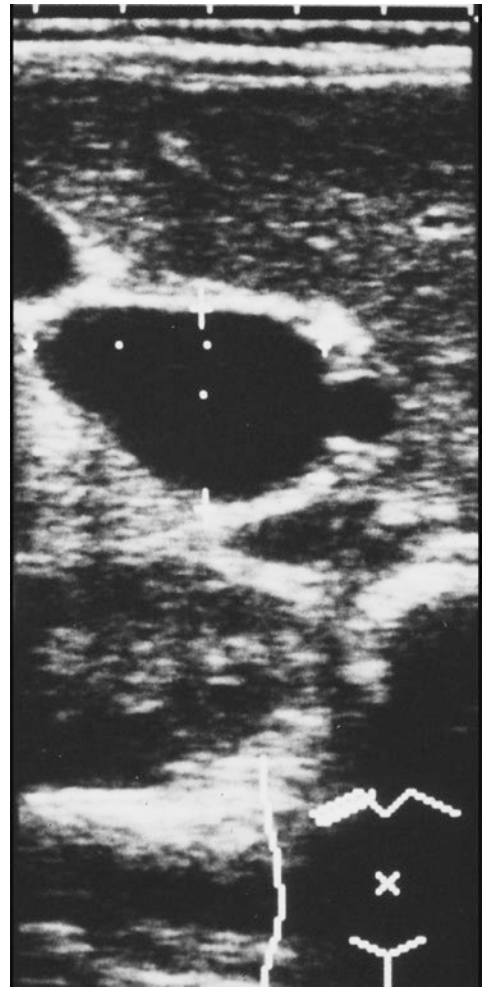

Fig. 43.2 Abdominal ultrasonography showing a cystic dilatation of the common bile duct in a 4-year-old girl

43.6.2 CT

The findings shown by abdominal CT are similar to those of abdominal ultrasonography. CT shows relationships among the biliary tract, pancreas, and gallbladder in the same slice. CT also provides an accurate diagnosis of a choledochal cyst with intrahepatic involvement (Fig. 43.3).

Computed tomography cholangiography (CTC) is also a noninvasive method for evaluation of the biliary system aside from radiation [26]. Bile duct imaging obtained using contrast material,

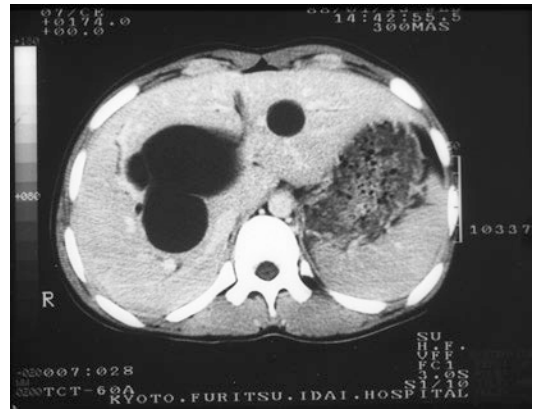

Fig. 43.3 CT of the abdomen in a 12-year-old girl at the hepatic hilum. The main locular lesion is a cystic dilatation of the common bile duct and the others are dilatations of the intrahepatic bile ducts

Biliscopin, yields extensive anatomical detail (Fig. 43.4). The emergence of multidetector-row CT (MDCT) is a major technological breakthrough that has markedly changed conventional CT.

43.6.3 ERCP

Otto et al. [27] and Paris et al. [28] reported an appraisal of ERCP for pancreaticobiliary disease in children, and that ERCP was useful and safe even in children. ERCP is capable of directly showing not only the dilatation of the bile duct, but also the presence or absence of an abnormal pancreaticobiliary maljunction (Fig. 43.5). Accordingly, ERCP is an essential investigative method in choledochal cyst management [29]. However, ERCP requires general anesthesia, and experience of ERCP for younger pediatric patients remains limited. Therefore, intraoperative cholangiography is occasionally done instead of preoperative ERCP to provide accurate anatomical information on the biliary ductal system, especially in younger pediatric patient.

43.6.4 MRCP

MRCP is widely used for hepatobiliary and pancreatic disease even in children. It allows the noninvasive and accurate detection of pancreaticobiliary maljunction without irradiation and avoids the life-threatening complications of ERCP. MRCP is capable of visualizing the pancreatic duct and pancreaticobiliary junction (Fig. 43.6). Therefore, this modality can be a viable alternative to ERCP in children with choledochal cysts [30]. However, MRCP in children is limited due to the need for sedation, high cost, and long scanning time required.

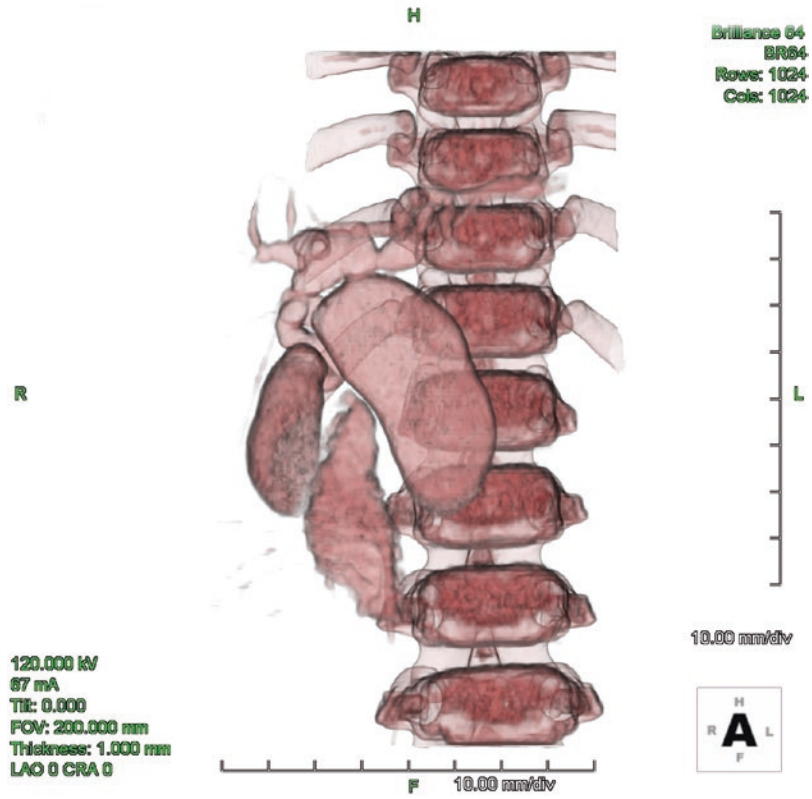

Fig. 43.4 CTC image of the biliary duct in a 2-year-old boy with choledochal cyst, providing a more anatomical detail of the biliary duct

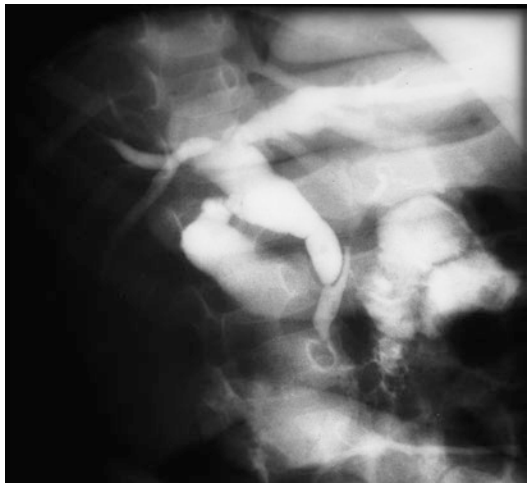

Fig. 43.5 ERCP image in a 3-year-old boy with the fusiform type of choledochal cyst, showing the presence of a pancreaticobiliary maljunction

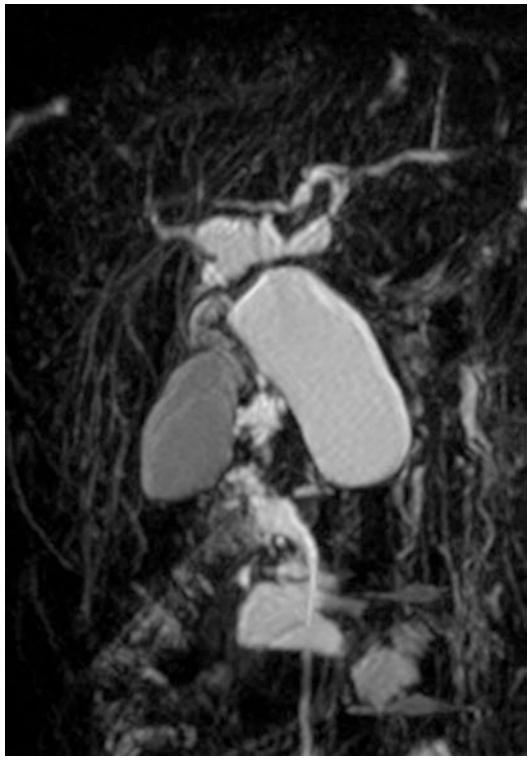

Fig. 43.6 MRCP image in a 2-year-old boy, showing cystic dilatation of the common bile duct and the presence of a pancreaticobiliary maljunction

43.7 Surgical Management

Before 1970, internal drainage without cyst excision was the norm. However, it became evident that the longer such patients were followed, the greater the number of complications, such as pancreatitis [31], calculus formation [32], or carcinogenesis [33]. In 1970, Kasai et al. [34] and Ishida et al. [35] reported favorable results of cyst excision with hepaticojejunostomy. Thereafter, choledochal cyst excision with subsequent hepaticojejunostomy has been widely accepted for this condition. Lilly [36] described a technique for total cyst excision using a plane of dissection between the inner and outer layers of the cyst. With the advancement of early diagnosis, we [37] have not recently experienced cases of severe pericystic inflammation to necessitate Lilly's technique, especially in infantile cases.

To decrease the incidence of ascending cholangitis, Todani et al. [38] suggested that a wide anastomosis at the hepatic hilum, allowing the free drainage of bile, is necessary in all patients with or without intrahepatic involvement to prevent cholangitis or stone formation. On the contrary, Miyano et al. [8] reported that hepaticojejunostomy at the hepatic hilum was indicated in only selected cases such as those with intrahepatic involvement. However, there was no significant difference in the morbidity associated with any of the procedures.

After cyst excision, we employ two biliary reconstructive procedures, Roux-en-Y hepaticojejunostomy or hepaticoduodenostomy. Most surgeons [39–41] prefer performing Roux-en-Y hepaticojejunostomy because, after this procedure, there is a low incidence of ascending cholangitis or stone formation. On the other hand, Todani et al. [42] and Santore et al. [43] preferred performing hepaticoduodenostomy after cyst excision. They suggested that hepaticoduodenostomy was more physiological and technically easier. However, hepaticoduodenostomy has been unexpectedly shown to often lead to bile reflux gastritis, so it is now superseded by Roux-en-Y hepaticojejunostomy [44].

Spontaneous perforation is a rare complication of a choledochal cyst which is difficult to diagnose due to its nonspecific clinical presentation [45, 46]. Vomiting and abdominal pain are the most common complaints. In cases of biliary pseudocyst formation, however, there is no overt sign of peritonitis [47]. The surgical treatment can be either single-staged cyst excision or a two-staged procedure with initial drainage followed by delayed cyst excision. The treatment strategy is based on the stability of the patient and grade of peritonitis.

The management of congenital dilatation of the intrahepatic bile ducts such as Caroli's disease [48] is difficult. The spontaneous course of this disease is dominated by biliary infection: cholangitis, septicemia, and intrahepatic and subphrenic abscesses. Ultrasonography and CT are useful for diagnosis and follow-up. Treatments consist of symptomatic treatment of cholangitis with antibiotics, and some endoscopic and surgical drainage procedures [49]. Partial hepatic lobectomy could be employed when the disease is localized and amenable to resection. The prognosis is fairly favorable unless recurrent cholangitis is present. Liver transplantation is the final treatment for this disease, and Hori et al. [12] reported that patients with refractory symptoms and complications secondary to liver failure are appropriate for liver transplantation.

43.8 Special Considerations

43.8.1 Carcinogenesis

Todani et al. [6] warned that cases of cancer arising from choledochal cysts were increasing. Ten percent of adults patients with an established diagnosis have malignancy of the biliary tract. We [11] encountered the youngest case of 12-year-old girl in whom an adenocarcinoma arose from the distal part of the choledochal cyst. According to the histopathological findings [50], papillary adenocarcinoma frequently occurs in the choledochal cyst wall. Therefore, we need to perform careful checks of children with choledochal cysts from the viewpoint of carcinogenesis.

A choledochal cyst is almost always associated with pancreaticobiliary maljunction, and is sometimes associated with biliary carcinoma. Ono et al. [51] pointed out that pancreaticobiliary maljunction was a major risk factor for biliary malignancy, and he also reported that hyperplastic change of the biliary epithelium leading to malignant degeneration had been triggered by chronic inflammation because of the reflux of pancreatic juice into the biliary tract in patients with pancreaticobiliary maljunction. In addition, Imazu et al. [52] reported that the incidence of mucosal hyperplasia of the gallbladder was significantly higher in the fusiform type than in the cystic type of choledochal cysts.

Bile duct cancer could develop even after the excision of a choledochal cyst. Ono et al. [53] reported the development of bile duct cancer 26 years after the resection of a choledochal cyst, and Watanabe et al. [54] also reported that the intervals between cyst excision and cancer detection ranged from 1 to 19 years (average: 9 years).

Therefore, patients must be followed up because of late complications such as malignant degeneration even after choledochal cyst excision. At each postoperative visit, the liver function and amylase levels in serum and urine must be checked. Ultrasonography of the liver and pancreas are also useful for follow-up. Those patients require close monitoring so that any recurrent carcinoma of the remnant bile duct can be found early.

43.8.2 Pancreaticobiliary Maljunction Without Choledochal Cyst

Recently, the presence of pancreaticobiliary maljunction without a choledochal cyst has attracted attention [55, 56]. However, the precise definition of a dilated common bile duct in children has not been fully established [57]. Miyano et al. [58] defined a nondilated type common bile duct as less than 8 mm in diameter (patients aged

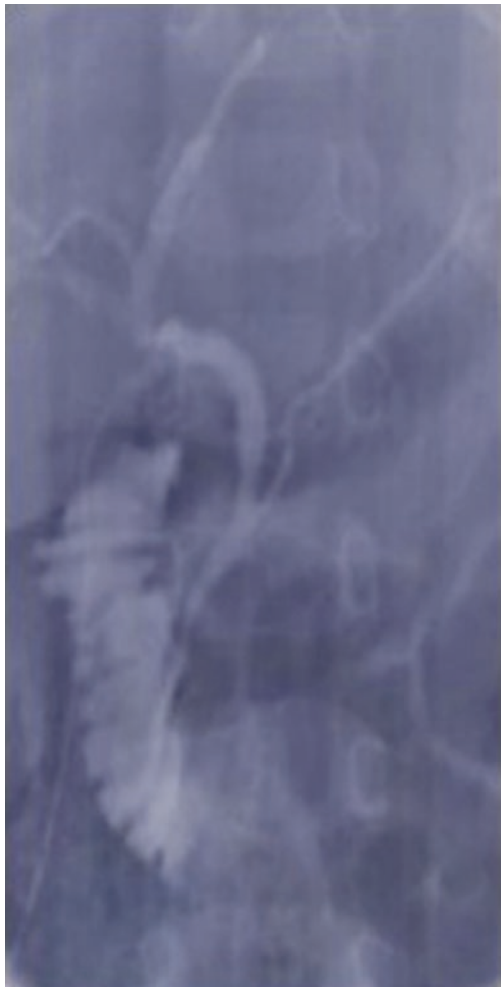

Fig. 43.7 Intraoperative cholangiopancreatography showing the presence of pancreatobiliary maljunction without choledochal cyst in a 2-year-old boy

1–7 years). According to our experience (Fig. 43.7) clinical symptoms are abdominal pain, vomiting, or jaundice, which are not different from those of a choledochal cyst [59].

Surgical indications in pancreaticobiliary maljunction in the absence of biliary dilatation are controversial. Some investigators [60, 61] have insisted that prophylactic cholecystectomy is sufficient, especially in adult patients. On the contrary, Miyano and Ando [62] adovocated excision of the common bile duct in addition to cholecystectomy for the prevention of pancreatic juice reflux into the bile duct. It is now suggested that the extrahepatic bile duct should be excised in pediatric patients with the nondilated type of pancreaticbiliary maljunction as well as in those with the dilated type (choledochal cyst).

43.9 Long Term Results

Most patients with a choledochal cyst have a favorable prognosis when diagnosed and treated early. Nonetheless, late complications and the long-term results of a series of patients who are older than 10 years after cyst excision with hepaticojejunostomy have scarcely been reported.

Our own series consisted of 56 patients with choledochal cysts and over a 10-year postoperative follow-up [63]. The dilatation of intrahepatic bile ducts persisted in the first 10 years, but all returned to normal thereafter.

Recurrent abdominal pain was encountered in two, one had pancreas divisum with a pancreatic stone, and one had adhesive small bowel obstruction. Two patients developed biliary tract malignancy even after excision of the choledochal cyst. Event-free and overall survival rates were 89% (50/56) and 96% (54/56), respectively. Saing et al. [64] reported the late results of 41 patients who underwent cyst excision with hepaticojejunostomy, and there was no mortality and they are all enjoying a good quality of life. Takeshita et al. [65] also reported two death cases out of the 137 with cyst excision as a long-term result. One died because of biliary cirrhosis and the other developed intrahepatic cholangiocarcinoma. Accordingly, long-term surveillance for the development of malignancy is still essential, especially if there is ongoing dilatation of the intrahepatic bile duct or biliary stone.

From the viewpoints of convenience and reliability, a combination of ultrasonography and CT once per year on an outpatient basis is therefore considered to be suitable for successive follow-up in patients with a choledochal cyst after excision of the cyst with hepaticojejunostomy [51].

43.10 Laparoscopic Surgery

Laparoscopic surgery for the resection of a choledochal cyst was initially reported by Ure et al. [66]. The laparoscopic technique included excision of the cyst and a Roux-en-Y anastomosis

was constructed after exteriorization of the small bowel via the infraumbilical trocar incision. Thereafter, laparoscopic surgery for children with a choledochal cyst has been gaining in popularity [67]. In some cases, however, conversion to open surgery was required due to oozing on cyst dissection. Urushihara et al. [68] reported total laparoscopic surgery comprising excision of the cyst and wide Rouex-en-Y hepaticojejunostomy with ductoplasty for a patient with stricture near the confluence of the hepatic ducts. Diao et al. [69] and Nguyen et al. [70] reported intermediate-term results of laparoscopic surgery for choledochal cysts and they concluded that the intermediate-term results were comparable to open surgery, and laparoscopic surgery was feasible and a safe procedure for a choledochal cyst.

However, none of those investigators reported the results of a series older than 10 years after laparoscopic cyst excision with hepaticojejunostomy, especially from the point of biliary tract malignancy. Therefore, the long-term follow-up of patients undergoing laparoscopic surgery is needed.

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Spontaneous Biliary Perforation, Liver Cysts, and Abscesses

44

Mark Davenport

Abstract

This is a peculiar condition which seems limited to the first few weeks of life whereby perforation occurs in the extrahepatic bile duct typically leading to bile in the peritoneal cavity, abdominal distension and jaundice. It should be distinguished from spontaneous perforation in a pre-existing choledochal malformation, said to occur in about 5–10% of all large series.

Keywords

Spontaneous biliary perforation • Liver cysts • Liver abscess

44.1 Spontaneous Perforation of the Bile Duct

This is a peculiar condition which seems limited to the first few weeks of life whereby perforation occurs in the extrahepatic bile duct typically leading to bile in the peritoneal cavity, abdominal distension and jaundice. It should be distinguished from spontaneous perforation in a pre-existing choledochal malformation, said to occur in about 5–10% of all large series [1].

Although at one time it was stated [2] to be the second commonest cause of surgical jaundice (after biliary atresia) this is clearly not the case. In our review of 171 consecutive infants with surgical jaundice, spontaneous perforation of the bile duct only accounted for about 2% of cases [3]. By comparison, infants with choledochal malformation (7%) and inspissated bile syndrome (8%) were much more commonly seen.

44.1.1 History

Dijkstra from the Netherlands first reported a case of spontaneous perforation of the bile duct in infancy in 1932 [4]. Thereafter only individual reports followed with the first real series of six cases being published in 1991 from King's College Hospital, London [5] and 11 infants seen over a 22 year period by Chardot et al. from Bicetre Hospital, Paris [6].

44.1.2 Anatomy and Pathogenesis

Why there should be spontaneous perforation in what appears to be a normal bile duct is not

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_44

known. Characteristically the perforation occurs at the junction of the cystic duct and common hepatic duct and this may be because it is structurally the weakest part of the extrahepatic biliary tree. Usually it is anterior and the bile then floods into the general peritoneal cavity. Occasionally it can be posterior and is therefore somewhat constrained with bile leaking into the lesser sac. Most authors assume there has been some obstruction in the bile duct leading to an acute rise in biliary pressure as the precipitating factor but actual evidence of this is rare.

The second commonest site of perforation appears to occur in the cystic duct [6].

44.1.3 Clinical Features

Most infants present from 1 to 16 weeks with insidious abdominal distension due to the accumulation of bile ascites. They are also usually jaundiced, possibly because of the biliary obstruction but also because of peritoneal reabsorption of bilirubin. Ascites often prompts development of a hydrocele or hernia and this leads to the characteristic sign of greenish discolouration of the skin overlying hernia (umbilical or inguinal) or hydrocele (Fig. 44.1). Vomiting will usually occur simply due to distension. In those with the posterior variant then symptoms can be vague and ill-defined. Sometimes the lesser sac only fills with bile leading to vomiting and at this age some have been explored on the basis of a diagnosis of pyloric stenosis [7].

44.1.4 Investigations

All infants should show a conjugated hyperbilirubinaemia with elevated mild elevations of the AST and γGT. Ultrasonography should show free fluid in most infants and probably some kind of ill-defined complex cyst or mass at the porta hepatis. Intrahepatic bile ducts may or may not be dilated. The diagnostic procedure of choice is the radioisotope scan which should show bile leakage into the peritoneal cavity. In those few centres with the capacity for ERCP, this may also be considered,

44.1.5 Management

All infants require resuscitation to a greater or lesser extent depending on the length of history. Usually the bile is sterile but intravenous antibiotic cover is essential from diagnosis through to definitive treatment.

There have been isolated cases where simple peritoneal drainage alone has been performed [8] however this is usually inadequate and most should come to laparotomy [5, 6]. There have been a number of surgical options put forward but invariably experience will be limited. On-table cholangiography is a key part of the assessment and should show whether there is any on-going distal obstruction. If there is no obvious occlusion then oversewing of the perforation can be contemplated. Alternatively a T tube (e.g. 6Fg) may be fashioned to lie within the bile duct

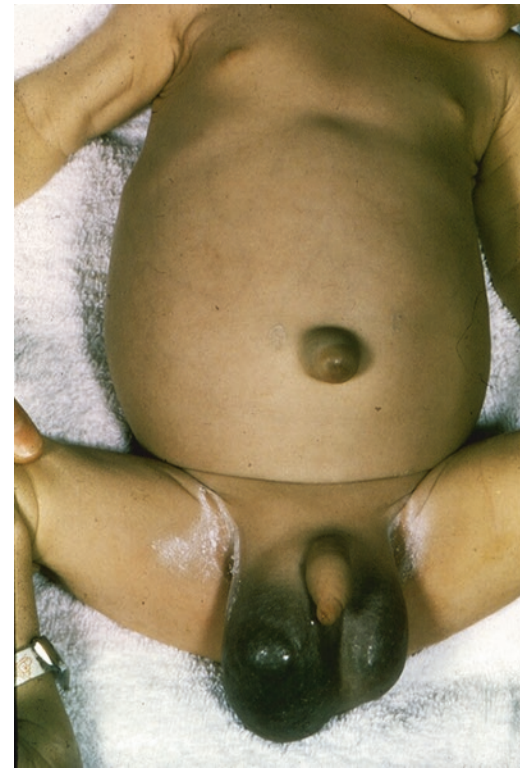

Fig. 44.1 Three-week old infant with spontaneous biliary perforation showing an obvious umbilical hernia and hydroceles. Skin pigmentation due to leaching of bile from peritoneal cavity

and provide a controlled biliary fistula to the skin [5]. It is then left in-situ for 2/3 weeks and if cholangiogram confirms biliary patency then it can be removed.

Dissection may show that there has been disintegration of the duct and in which case, cholecystectomy and hepaticojejunostomy should be performed as a biliary reconstruction. This is not an easy option because it's a relatively small duct to anastomose onto and the tissues will be oedematous and swollen. For those posterior perforations so far encountered we have chosen this option in the absence of an effective alternative and had good outcomes. Theoretically it might be possible to insert some kind of indwelling stent at ERCP to reflect the commonest option in adults. We have tried this and a percutaneous drain in one infant but the results was unconvincing and we resorted to laparotomy to correct it definitively.

Perforation confined to the cystic duct is relatively straightforward and should be treated by cholecystectomy.

44.1.6 Complications

Most post-operative complications, including death, revolve around failure to establish safe biliary drainage and on-going biliary obstruction leading to liver fibrosis and eventually cirrhosis. Some cases of what appear later to be an acquired form of biliary atresia may arise as a consequence of a sealed biliary perforation, periductal inflammation and stenosis [9]. Unlike typical biliary atresia these infants will have had a defined jaundice-free interval after birth.

Portal vein thrombosis appears to be a particular hazard for the posterior perforation and may simply be due to the irritant effects of leaking bile upon the neighbouring portal vein [7]. Usually this is only apparent some months after the acute event perhaps with increasing splenomegaly. Some authors have described a more acute presentation with early ascites [10] but this appears atypical. Chylous ascites is also possible and presumed to be due to damage to the periductal lymphatics ascending to the porta hepatis [11].

Post-operative follow-up should include serial liver biochemistry and ultrasonography at minimum but ideally would include a radio-isotope scan to show restoration of a normal biliary excretion pattern.

44.2 Parenchymal Liver Cysts

Congenital cysts arising within the parenchyma of the liver can be divided morphologically (unilocular or multilocular), histologically (simple parenchymal, mesenchymal hamartoma or rarely teratoma), or on the basis of content (typically bile-containing or not) [12].

The incidence is not known but one large Australian centre with 22,000 births per year identified three cysts of liver origin over 10 years [13]. In adults the incidence of simple liver cysts is much higher (3–18%) [14, 15].

Isolated intrahepatic bile cysts may be choledochal malformations but occur rarely and are not necessarily part of Caroli's syndrome [16]. Most can be left alone unless showing evidence of secondary infection, bile duct obstruction or stone formation.

The usual presentation for most liver cysts is antenatal detection in the second or third trimester and following birth can be shown to be entirely without symptoms. Occasionally cysts can be so large as to be palpable but it is rare that they obstruct either the bile flow (and hence become jaundiced) or the gastrointestinal tract [17].

Figure 44.2 suggests an appropriate diagnostic algorithm including ultrasound, CT & MR scan together with radio-isotope excretion imaging [18].

44.2.1 Management

Those adjudged to be simple parenchymal cysts can be left alone and followed up by serial US. The expectation is that they will diminish relatively in size over the years (Fig. 44.3). Those that appear to be mesenchymal hamartomas or teratomas require surgical excision. This usually involves partial hepatectomy although teratoma often have a thick-walled capsule which facilitates

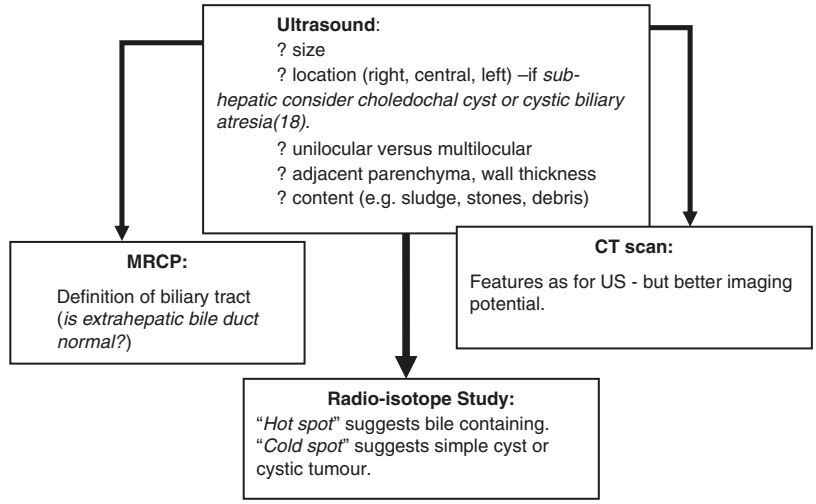

Fig. 44.2 Diagnostic approach to antenatally detected liver cyst

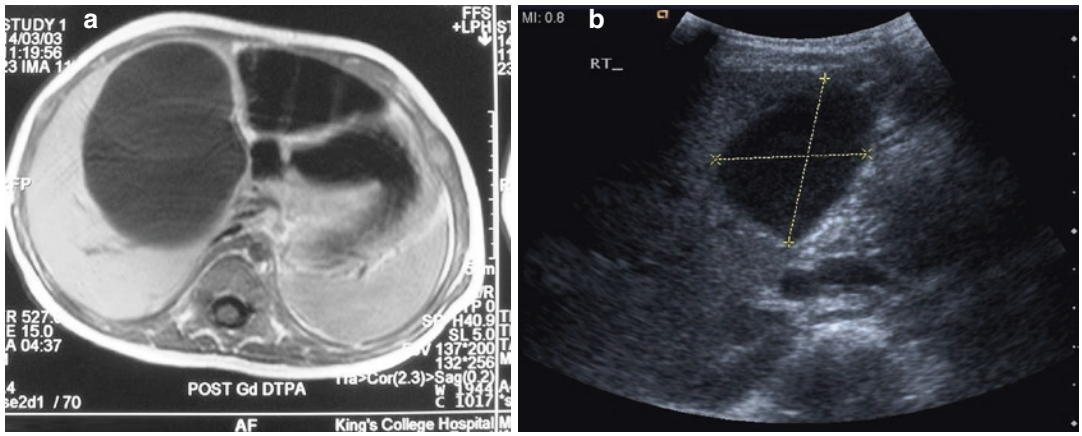

Fig. 44.3 Antenatally detected parenchymal liver cyst: measured at 22 mm diameter during CT scan in first week of life (**a**) and reaching 40 × 50 mm by ultrasound at 9 years (**b**)

enucleation. Simple aspiration of cysts either antenatally or postnatally has been reported [19, 20], however recurrence is highly likely. Large cysts may need to be treated and occasionally fenestration or marsupialisation could be considered if anatomically suitable. This can be achieved using a laparoscopic approach [21].

44.3 Parenchymal Liver Abscess

Infection and abscess formation within the liver are not commonly seen in the neonatal period, indeed less than 100 cases have been reported in the literature. Nevertheless it is certainly possible and may follow generalized sepsis, umbilical catheterization or ascending omphalitis. Other predisposing conditions included necrotizing enterocolitis, maternal infection and being an infant of diabetic mother or a immunodeficiency state such as HIV [22–24]. The problem is more often found in the preterm and those of low birth weight.

One well-described mechanism is the misplaced or infected umbilical vein catheter. This may lacerate portal vein or ductus venosus resulting in an intrahepatic haematoma or inadvertent intravenous fluid (typically high osmolar glucose solution) collection which becomes secondarily infected.

There is a wide spectrum of pathogenic organisms including bacteria (staphylococcal *spp*., enterobacter, Klebsiella *spp*. and E. coli) and fungi (Candida *spp*.) [24]. In some countries, tuberculosis has been reported as a pathogen in neonatal liver abscesses [23].

Investigations will show a neutrophil leucocytosis, raised C-reactive protein levels and abnormal liver biochemistry. A careful ultrasound should distinguish abscess from cyst although CT scan may be needed to show the contrast-enhancing rim of peri-abscess tissue. Percutaneous aspiration should be considered to identify organism and deduce sensitivities and can also be therapeutic.

Pyogenic liver abscess may also become complicated and discharge into adjacent spaces such as the pleura, peritoneum and even the pericardium. Later, venous thrombosis involving the portal vein (or more rarely the hepatic veins) may occur leading to portal hypertension and splenomegaly.

44.3.1 Management

Management is initially directed at the sepsis and is primarily aggressive broad-spectrum antibiotic (occasionally antifungal) therapy, which should be continued for at least 3–4 weeks. This is the only realistic option in multifocal abscesses (probably the majority) but in solitary collections other options may be considered. Lee et al. from Toronto described aspiration and/or catheter drainage (5Fg pigtail) in eight neonates with excellent results. Occasionally for solitary abscesses open surgery may be contemplated if there is no radiological alternative available. In which case, the key aim is to drain the contents of the cavity without initiating liver damage or inducing haemorrhage.

Infants with resolving collections require long-term serial ultrasonography to monitor resolution and detect any suggestion of portal vein thrombosis.

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Surgery for Congenital Hyperinsulinism

45

N. Scott Adzick and Pablo Laje

Abstract

Transient hypoglycemia in the newborn period is common and generally associated either with immaturity of the glucose regulatory pathways (which responds to frequent feeds and resolves spontaneously within hours), or with stress-associated hyperinsulinism (which responds well to hyperglycemic drugs and resolves spontaneously within the first few weeks or months of life). Congenital Hyperinsulinism (HI) is the most frequent cause of persistent, long-term hypoglycemia in newborns and infants, and can lead to severe and irreversible brain damage and developmental delay. It is a rare congenital disorder of the glucose metabolism that has an estimated incidence of 1–1.4 cases per 50,000 live births, leading to about 80–120 new cases in the United States each year. An incidence as high as 1 in 2500 live births has been reported in populations with high consanguinity like Arabians and Ashkenazi Jews. Inappropriate oversecretion of insulin is the hallmark of HI, and the genetic background is quite variable. Depending on the genetic mutation, babies with HI may be treated medically or may require surgery either as a palliative treatment or as a definitive cure.

Keywords

Congenital pancreatic disease • Congenital hyperinsulinism • Surgery

45.1 Introduction

Transient hypoglycemia in the newborn period is common and generally associated either with immaturity of the glucose regulatory pathways (which responds to frequent feeds and resolves spontaneously within hours), or with stress-associated hyperinsulinism (which responds well to hyperglycemic drugs and resolves spontaneously within the first few weeks or months of

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_45

life). Congenital Hyperinsulinism (HI) is the most frequent cause of persistent, *long-term* hypoglycemia in newborns and infants, and can lead to severe and irreversible brain damage and developmental delay. It is a rare congenital disorder of the glucose metabolism that has an estimated incidence of 1–1.4 cases per 50,000 live births, leading to about 80–120 new cases in the United States each year [1, 2]. An incidence as high as 1 in 2500 live births has been reported in populations with high consanguinity like Arabians and Ashkenazi Jews. Inappropriate oversecretion of insulin is the hallmark of HI, and the genetic background is quite variable. Depending on the genetic mutation, babies with HI may be treated medically or may require surgery as either a palliative treatment or as a definitive cure.

45.2 History

Congenital hyperinsulinism was first described by McQuarrie in 1954, who initially termed it "syndrome of idiopathic hypoglycemia of infants" [3]. At that time, assays for the accurate measurement of plasma insulin were not available. However, he suggested that there could be an association between the disease and a state of hyperinsulinism, and he also highlighted the "high incidence of a familial or genetic trait of the disease". The first pancreatectomy performed on a child with HI was reported in 1934 by Evarts Graham, 20 years before the disease was described. The pancreas was explored searching for an adenoma, but since no evidence of an adenoma was found, a near-total pancreatectomy [~90%] was performed, and the patient's hypoglycemia resolved [4]. The revolutionary development of an insulin radioimmunoassay in the late 1950s by Nobel Prize laureate Rosalyn Yalow confirmed that insulin oversecretion was crucial to the pathophysiology of HI [5]. For decades it was believed that insulin was secreted by an excessive number of islets resulting from *nesidioblastosis*, an abnormal postnatal budding of endocrine cells off the pancreatic ducts ("nesidion" = island). This theory, proposed by Yakovac et al. at the Children's Hospital of Philadelphia (CHOP), came from the histologic analysis of pancreatic specimens from HI cases stained with insulin-specific techniques. Later studies in the 1980s showed that nesidioblastosis was in fact a normal neonatal phenomenon, and the term "nesidioblastosis" has been abandoned [6, 7]. Advances in molecular biology and genetics led to our current understanding of the disease, which occurs due to a variety of genetic derangements that alter the regulatory mechanisms of glucose homeostasis.

45.3 Pathophysiology

Glucose homeostasis is complex and is influenced by a large number of factors. Plasma glucose levels are maintained within the normal range by mechanisms that respond to the postprandial and fasting states in opposite directions. During the postprandial state, the liver accumulates glucose in the form of glycogen (glycogenogenesis), while during the fasting state, the liver releases glucose by glycogenolysis. Multiple hormones and factors promote glycogenolysis and hyperglycemia: glucocorticoids, glucagon, catecholamines, somatostatin and others. However, insulin is the only endogenous hormone that reduces plasma glucose levels. Insulin inhibits glucose release from the liver and promotes glucose uptake in peripheral tissues. When the plasma glucose level rises, glucose enters the beta cell's cytoplasm through the high-capacity GLUT-2 transporter, which is followed by an increase in intracellular glucose metabolism. As a consequence, the intracellular concentration of ATP increases (as does the ATP/ADP ratio), and the ATP-dependent potassium channels (K-ATP channel) located in the cytosolic membrane of the beta cell become inactive and close. Potassium accumulates on the inner surface of the cytoplasmic membrane and depolarizes it. The depolarization generates the activation of voltage-dependent calcium channels and calcium accumulates in the cytoplasm, which eventually triggers a calcium-dependent insulin exocytosis (Fig. 45.1). When the K-ATP channel located in the cytoplasmic membrane is defective due to *loss-of-function*

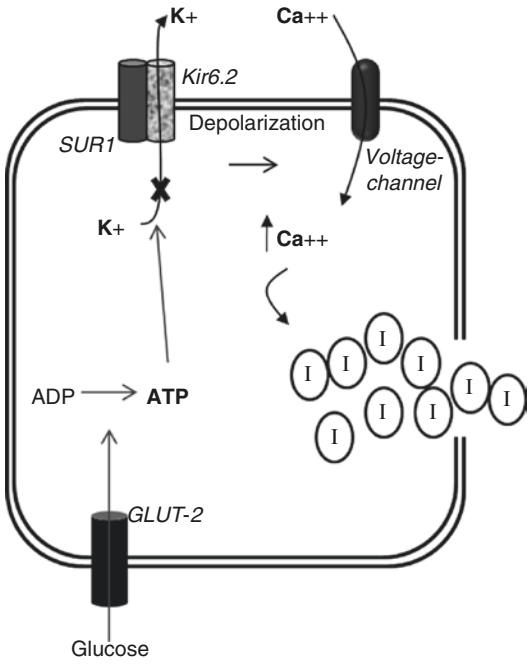

Fig. 45.1 Insulin release as a physiologic response to hyperglycemia. The ATP/ADP ratio increases as a consequence of the glucose metabolism. The ATP-sensitive potassium channel reacts to this by closing. The accumulation of potassium in the cytoplasmic surface of the beta-cell membrane depolarizes it. This event triggers an influx of calcium through voltage-sensitive calcium channels, which in turn generates a calcium-dependent insulin release. *SUR1* sulfonylurea receptor 1, *Kir6.2* inward-rectifier potassium ion channel 6.2, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *GLUT-2* glucose transporter 2, *I* insulin

genetic mutations, it remains inactivated at all times, regardless of the plasma glucose level, generating a non-regulated, persistent, insulin release that leads to unregulated hypoglycemia. This is the most common pathophysiologic mechanism of HI. The insulin levels, however, are never strikingly elevated in HI. The K-ATP channel is composed of 2 subunits: SUR1 (a sulfonylurea receptor, the regulatory subunit) and Kir6.2 (the ion pore), which are encoded by adjacent genes located in the short arm of chromosome 11. Less commonly, HI occurs due to genetic defects in other enzymes. Pancreatic glutamate dehydrogenase (GDH) is a mitochondrial enzyme that catalyzes the reversible oxidation of glutamate to alpha-ketoglutarate (and ammonia), which after a series of intermediate steps through the tricarboxylic acid cycle results in an elevation of the intracellular ATP/ADP ratio and consequently an insulin release. *Gain-of-function* mutations in the GDH gene lead to HI and hyperammonemia ("hyperinsulinism/hyperammonemia [HI/HA] syndrome") [8, 9]. Pancreatic glucokinase (GK) produces the phosphorylation of intracellular glucose to glucose-6-phosphate (G6-P), which is the first step of the glycolytic pathway that will ultimately increase the production of ATP and stimulate insulin release. GK has a low affinity for glucose and is not self-regulated by its end product G6-P. Gain-of-function mutations in the GK gene increase the affinity of GK for glucose so that more insulin is released at any given plasma glucose level, which in turn leads to HI (although most of these cases have a mild clinical course) [10, 11]. More recently, deficiencies in the mitochondrial fatty acid beta-oxidation enzyme "short-chain hydroxyacyl-CoA dehydrogenase" (SCHAD) have been identified as a rare cause of HI, and the mechanism appears to be a loss of the natural inhibitory effect that SCHAD exerts on the mitochondrial GDH [12].

45.4 Diagnosis

The diagnosis of HI is confirmed when all of the following metabolic criteria are present: (1) fasting *and* postprandial hypoglycemia with unsuppressed hyperinsulinism (neonatal hypoglycemia is generally defined as a glucose plasma level of <50 mg/dL after the first 24 h of life with an insulin level >36 pmol/L), (2) suppression of lipolysis and suppression of ketogenesis at the time of the hypoglycemia (lipolysis and hepatic ketogenesis are part of the normal physiologic response to hypoglycemia, and are physiologically inhibited by insulin), and (3) a positive hyperglycemic response to a dose of glucagon, which is a direct insulin antagonist (glucose must increase by 30–50 mg/dL after 0.25–1 mg of intravenous glucagon). Additionally, these criteria must be present for a prolonged period of time and outside certain clinical circumstances such as perinatal stress.

45.5 Classification

45.5.1 Histological Classification

There are two major histological forms of HI: *focal* and *diffuse*, which have a different genetic background and a different management strategy. Focal disease consists of a single focus of adenomatous islet cell hyperplasia surrounded by normal lobular pancreatic tissue. Focal lesions respect the limits of the pancreatic lobules, as opposed to insulinomas which are well demarcated and do not respect the limits of pancreatic lobules. The beta cells within the focal lesion have an enlarged cytoplasm and typically normal nuclei, although some can have nucleomegaly. They accumulate in central clusters, surrounded by non-beta islet cells. The proliferated endocrine cells in the focal lesions push the exocrine components toward the periphery, but there are always some exocrine acinar cells intermixed within the endocrine cells [13]. The size of a focal lesion is variable, from a few millimeters in diameter to much greater than a centimeter. It can be located in the surface of the pancreas, or deep within the organ. Superficial lesions can often be identified visually by subtle differences in color and/or by palpation, since focal lesions tend to be firmer than the normal pancreas. In our experience we have been able to identify the focal lesion by visualization and/or palpation in approximately two-thirds of the cases. Focal lesions can be located anywhere in the pancreas. In our series of more than 140 focal lesions treated by partial pancreatectomy, the distribution was 45% in the pancreatic head, 25% in the neck/body, 15% in the tail, and 15% had "other location", which included focal lesions unusually large that extended beyond a single pancreatic segment, and very rarely lesions that were present within ectopic pancreatic tissue [14]. In the diffuse form of the disease, most, if not all, beta cells are abnormal throughout the organ. The hallmark feature of the beta cells in diffuse HI is the nucleomegaly, which is defined as nuclei that occupy an area three times larger than the nuclei of the adjacent non-beta endocrine cells or four times larger than the nuclei of the adjacent acinar cells. Other nuclear abnormalities (e.g. abnormal shape, pseudoinclusions) may also be present. The total number of endocrine cells in pancreases with diffuse HI is not different than in pancreases from euglycemic age-match individuals. The distribution of the abnormal cells is not always homogeneous. In some cases, cells with clear nucleomegaly can be very concentrated in one area and very sparse in another area of the same specimen, intermixed with beta islet cells that do not look histologically abnormal [15].

Of *all* patients with HI, 30–40% have focal disease and 60–70% have diffuse disease. Among patients who have required surgery at CHOP (which represent approximately 60% of all HI patients), approximately 50% have focal disease and 50% have diffuse disease.

45.5.2 Therapeutic Classification

From a management standpoint, HI is divided in two groups: diazoxide-*responsive* and diazoxide-*resistant*. The initial drug in the management of HI is diazoxide, which inhibits insulin secretion by activating the K-ATP channel. Diazoxide binds to the SUR1 subunit of the channel, but in order to be effective both subunits must be structurally normal and functional. Since the most common causes of HI involve defects in the SUR1/Kir6.2 genes, the majority of HI patients do not respond to diazoxide and the only ones that do are those with mutations in the GK, GDH, SCHAD, or other genes. In our experience with more than 450 patients with HI, only 33% were diazoxide-*responsive,* whereas 67% were diazoxide-*resistant*. Most of diazoxide-*resistant* patients underwent surgery, although some were deemed not candidates for surgery due to a variety of reasons and were managed with different medical strategies [16].

45.6 Genetics

The development of genetic testing and diagnosis has allowed identification of a large number of mutations in patients with HI. To date, about 50%

of patients with HI have a known genetic mutation. The most frequent mutations cause a loss of function in the K-ATP channel of the cytoplasmic membrane of the pancreatic beta cells. This channel is composed of the subunits SUR1 and Kir6.2, which are encoded by two genes located next to each other in the p15.4 region of the chromosome 11: ABCC8 and KCNJ11. The *diffuse* form of HI occurs most frequently as a consequence of mutations of the SUR1/Kir6.2 complex inherited in a recessive manner [17]. There are currently more than 200 known mutations in the ABCC8 and KCNJ11 genes, and some of them have a remarkably high prevalence within certain populations [18]. Very rare mutations of the SUR1 gene inherited in a dominant manner have been identified as a cause of diffuse HI, but the clinical presentation of these patients is milder than patients with recessive disease and they respond partially to diazoxide. In addition, compound heterozygous mutations in the ABCC8/KCNJ11 genes have also been identified as a cause of diffuse HI, but their clinical course is milder [19–21]. Diffuse disease can also occur due to mutations in other genes. Gain-of-function mutations in the GK gene (located in the p15.3-p15.1 region of chromosome 7) inherited in a dominant manner can lead to diffuse HI. Several mutations have been identified already and all affect the same region of the enzyme [10, 11, 22, 23]. A variety of dominant gain-of-function, missense, single-nucleotide mutations in the GDH gene (GLUD1, chromosome 10, region q23.3) have been identified in patients with diffuse HI. These mutations in the GLUD1 gene, as a group, represent the second most frequent cause of HI. All identified mutations affect the GTP-binding site of the enzyme (GTP is the most potent GDH inhibitor) which makes the enzyme work at a higher basal rate [8, 9]. Diffuse HI has also been described as a consequence of recessive mutations in the mitochondrial enzyme short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD) gene located in the q22–26 region of chromosome 4. The mutations affect different regions of the protein which explains the heterogeneous clinical presentation of these cases [12, 24]. Over the last few years, cases of diffuse HI have been linked to mutations in three new genes: HNF4A (encoding the hepatocyte nuclear factor 4a; chromosome 20q12–13.1; dominant inheritance), SLC16A1 (encoding the monocarboxylate transporter; chromosome 1p13.2–p12; gain-of-function mutations; dominant inheritance), and UCP2 (encoding the mitochondrial uncoupling protein 2; chromosome 11, region q13; dominant inheritance). Their pathophysiologic mechanisms are not yet well understood, and their age at onset and clinical presentation is variable [25–28].

The *focal* form occurs when an individual with a constitutional paternally inherited mutation in the SUR1/Kir6.2 complex loses the normal maternal allele (an event called "loss of heterozygosity") in a group of pancreatic beta cells (a "two-hit" phenomenon), which not only will oversecrete insulin but will also develop an adenomatous hyperplastic proliferative pattern. The 11p15 region has several genes subject to genomic imprinting. The loss of the maternal 11p15 not only affects the expression of the ABCC8/KCNJ11 genes (not imprinted), but also affects the expression of the maternal tumor suppressor gene H19 and the cell cycle regulator $p57^{kip2}$ (region 11p15.5). The tumor suppressor gene H19 (strongly imprinted and of exclusively maternal monoallelic expression) exerts an antagonistic effect on the insulin-like growth factor 2 (IGF2) expressed exclusively from the paternal allele. The imbalance between IGF2 and H19 is the reason for the adenomatous proliferation of the affected cells. The loss of the maternal allele in a focal lesion can be evidenced by genetic testing and immunohistochemistry (decreased $p57^{kip2}$ staining within the focal lesion) [29]. With regard to the ABCC8/KCNJ11 genes, some cases have only the single abnormal paternal allele, whereas some patients have a duplication of the paternal abnormal allele, which is called uniparental paternal isodisomy.

When a baby is diagnosed with HI in the absence of a family history, the parents and the patient must undergo genetic testing. In cases of diazoxide-*responsive* disease, the genetic testing is not urgent and even with the newest technology can take several weeks. In diazoxide-*resistant* cases, which theoretically have a mutation in the

SUR1/Kir6.2 complex, the genetic testing becomes more critical because it can help in the differential diagnosis of diffuse versus focal disease, determine the need for imaging studies, and provide prognostic information.

45.7 Prenatal Diagnosis and Counseling

The prenatal diagnosis of HI based on the genetic analysis of known mutations in family members is possible, allowing immediate medical management at the time of birth. The genetic mutations that cause diffuse HI respond to the Mendelian inheritance laws with the exception of the *de novo* mutations. For the recessive forms of the HI, the chance of developing the disease in the offspring (homozygous for the affected allele) is 25% for each individual, whereas in cases of dominant inheritance the chance is 50%. Prenatal screening of all known mutations in all HI-involved genes in the general population is not justified by the overall low incidence of the disease, but prenatal diagnosis is justified and currently available for families with previously affected children [30]. While the inheritance of an abnormal ABCC8/KCNJ11 gene from paternal origin does respond to Mendelian laws, the occurrence of focal disease in subsequent siblings of an affected individual is unpredictable given the fact that the second event in the pathogenesis of the disease (the loss of the normal maternal allele) occurs as a random event in somatic cells. The likelihood of this occurrence is extremely low, but it has been described [31].

45.8 Medical Management

The first step in the treatment of newborns with HI is to provide enough glucose to maintain normoglycemia. This is usually achieved by a combination of a high-concentration glucose intravenous infusion plus frequent enteral feeds. The required glucose infusion rate (GIR), calculated as % dextrose × IV rate × 0.169/Wt in kg, can be as high as 25 mg/kg/min which is nearly three times higher than the physiological hepatic glucose release during fasting periods in newborns. Along with supportive glucose management, HI-specific drugs must be initiated. The first line drug is diazoxide. Diazoxide is an agonist of the K-ATP channel and is not effective in patients with recessively inherited mutations in the ABCC8/KCNJ11 complex and severe HI, but it is effective at variable levels in patients with dominant mutations in the ABCC8/KCNJ11 complex, patients with compound heterozygous ABCC8/KCNJ11 mutations, syndromic HI cases (e.g. Beckwith-Wiedeman syndrome) and patients with mutations in most of the other HI-related genes of dominant inheritance known to date. The dose of diazoxide is 5–20 mg/kg/day divided in three oral doses. After 5 days of treatment the response to diazoxide is evaluated by a fasting test, off intravenous glucose and off any other hyperglycemic medications (Fig. 45.2). Patients with the ability to maintain a plasma glucose level >70 mg/dL for at least 12 h are considered diazoxide-*responsive*. For these patients, an adequate feeding regimen is established and they are discharged home on long-term diazoxide treatment. The adverse effects of diazoxide are sodium and fluid retention which can be problematic in patients with concomitant pulmonary or cardiac diseases but can be controlled with the simultaneous administration of diuretics, and hypertrichosis which can be disturbing for the parents but is a benign condition. Patients who cannot maintain glucose levels above 70 mg/dL for 12 h are presumed to have recessively-inherited disease and are considered diazoxide-*resistant*. In these patients, diazoxide is discontinued, the glucose infusion is re-established immediately, and preoperative planning starts. A variety of alternative drugs can be tried in these patients, but mainly as stabilizing agents prior to surgical intervention. Octreotide is a synthetic long-acting somatostatin analog that inhibits insulin secretion by a direct inhibition of voltage-dependent calcium channels. It is generally administered subcutaneously every 6–8 h, but can also be given in a continuous intravenous infusion. The starting dose is 2 μg/kg/day, but it must always be titrated up due to rapid tachyphylaxis. The maximum dose is 15 μg/kg/day. Patients with a partial response to diazoxide

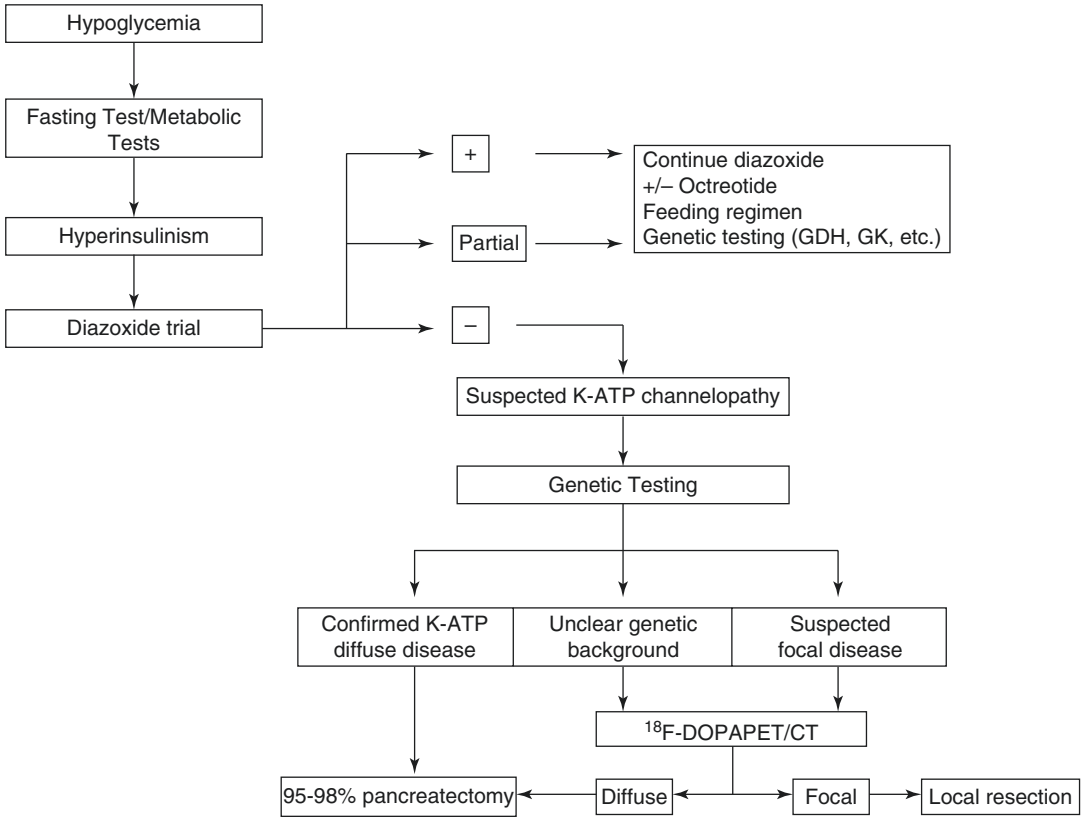

Fig. 45.2 Current algorithm for the management of patients with hyperinsulinism

and some patients with persistent hypoglycemia after a near-total pancreatectomy have been successfully managed at home by a combination of long-term subcutaneous octreotide (twice daily) and a very strict feeding regimen via a gastrostomy. However, octreotide is not recommended for long-term treatment due to its many potential adverse effects (some of which can be life-threatening [e.g. necrotizing enterocolitis]) and its rapid desensitization [32]. Glucagon is a natural insulin antagonist that elevates the plasma glucose levels by activating the enzyme phosphorilase A, which catalyzes the degradation of glycogen. It can be used preoperatively as a continuous intravenous infusion to help maintaining adequate glucose levels or as an intravenous bolus to rescue patients from severe hypoglycemic episodes, but it is not suitable for long-term management. Other drugs, like the calcium channel blocker nifedipine, have been used in the past in the long-term management of patients with HI but their effectiveness is very limited and their use is currently not recommended.

45.9 Preoperative Management

The most relevant aspect of the preoperative planning in patients with diazoxide-*resistant* HI is to differentiate between *diffuse* and *focal* disease, because the surgical strategy is radically different between the two, as is the clinical outcome. Genetic testing is the first step. In the ideal situation, two K-ATP channel mutations are found (one from each parent) confirming diffuse disease, or only one mutation of paternal origin is found, possibly consistent with focal disease. There are situations, however, in which the genetic analysis is difficult to interpret. Sometimes no mutation is found, or in other instances an identified genetic variant is not

disease-causing but simply a rare polymorphism. Additionally, the identification of a mutation in the paternal line does not exclude the possibility of a disease-causing postzygotic mutation on the maternal line (resulting in diffuse HI) not reflected in peripheral blood leukocytes [33].

Patients with genetically confirmed recessive K-ATP-related diffuse disease do not need preoperative imaging and should undergo a near-total pancreatectomy if they cannot be safely managed with medical therapy. The resection of less than 95% of the pancreas is associated with a higher need for another resection and is not recommended [34]. All other patients need preoperative imaging to localize the suspected focal lesion or to help in the differential diagnosis of focal versus diffuse disease when the genetic background is unknown or unclear.

45.10 Imaging Studies

All conventional non-invasive image studies (ultrasound, computerized tomography, magnetic resonance) have been used to try to distinguish between focal and diffuse disease or to localize genetically suspected focal lesions, but these radiologic tests are not helpful. Invasive interventional tests were developed in the late 1980s and were used until 2004 [35, 36]. The Arterial Stimulation with Venous Sampling (ASVS) test measures insulin in the hepatic veins after injecting calcium (a stimulant of insulin release) selectively in the arteries that supply the different regions of the pancreas. An immediate rise in insulin from stimulation in only one artery suggests focal HI in the corresponding area of the pancreas (gastroduodenal artery: pancreatic head; superior mesenteric artery: uncinate process and neck; splenic artery: pancreatic body or tail), whereas an insulin rise in all three areas suggests diffuse HI. The Transhepatic Portal Venous Sampling of the pancreatic veins (THPVS) measures insulin levels in the small pancreatic veins that drain the different regions of the organ to determine if there is an area of higher concentration, consistent with focal disease, or not, consistent with diffuse disease. These techniques take several hours to be performed, are technically very demanding, and their sensitivity and specificity for distinguishing between focal and diffuse disease are limited [37]. They have been largely replaced by what is now considered the gold-standard imaging study: ^{18}fluoro-L-3–4 dihydroxyphenylalanine positron emission tomography merged with a low-radiation computerized tomography (^{18}FPET/CT). The study was originally developed in the late 1990s for the detection of tumors of neuroendocrine origin in adults, and has been used in HI patients since 2004 [38–40]. Islet cells of the pancreas, like all other neuroendocrine cells, take up L-dihydroxyphenylalanine (L-DOPA), convert it to L-dopamine by the enzyme DOPA decarboxylase, and store it in vesicles. Similarly, these cells can take up ^{18}fluoro-L-3–4 dihydroxyphenylalanine (18FDOPA), convert it into ^{18}fluoro-dopamine and store it in vesicles that can be tracked by their gamma radiation. At CHOP, the isotope ^{18}FDOPA is administered in children under an FDA-approved Investigational New Drug (IND) protocol and the approval of the Institutional Review Board. The isotope has a half-life of 110 min, so it is manufactured on the day of the study in the Cyclotron Facility of the University of Pennsylvania, and used at a dose of 0.08–0.16 mCi/kg (slow intravenous infusion) within 2–3 h of its preparation. All glycemic medications must be stopped prior to the study. The study is done under general anesthesia in a hybrid scanner that initially captures the nuclear signal (γ-radiation) and then generates low-dose (x-radiation) CT scan of the abdomen without changing the patient's position. The nuclear signal is captured at 10-min intervals during only the first 50 min post injection because after that time the tracer accumulates in the liver, gallbladder, biliary tree and duodenal lumen, which can lead to false positive images. Focal lesions are seen as bright spots over a darker background, whereas in cases of diffuse disease the tracer is homogeneously distributed throughout the organ (Fig. 45.3). In our experience with more than 160 studies, the sensitivity of the ^{18}FPET/CT to detect a focal lesion has been 84%. In the 16% that were erroneously diagnosed as diffuse disease, the focal lesions were particularly

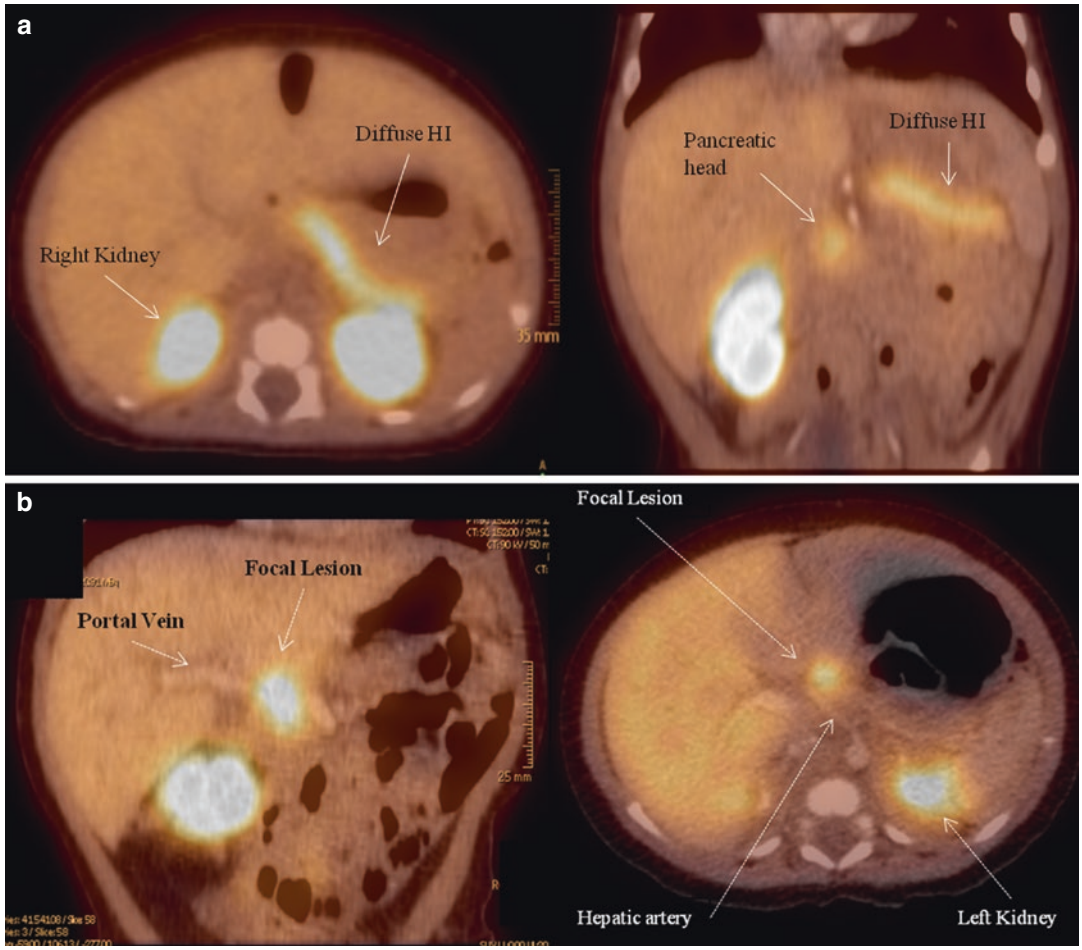

Fig. 45.3 ^{18}Fluoro-L-3–4 dihydroxyphenylalanine positron emission tomography merged with a low-dose radiation computerized tomography (^{18}F-PET/CT). (**a**) Diffuse disease: the entire pancreas uptakes the tracer homogeneously. Coronal and axial views. (**b**) Focal disease: the lesion is a discrete bright spot in the pancreatic head over a darker background. Merging the PET images to the CT images helps to determine the exact location of the focal lesion and its relation to surrounding structures

small (although the size of the lesion does not always correlates with the intensity of the signal), had an unusual shape, or were an atypical case in which the focal lesion occupied most of the pancreas [41]. The ^{18}FPET/CT is also sensitive in the detection of the very rare ectopic focal lesions [14, 42]. When a focal lesion is identified on the ^{18}FPET/CT, the correlation with the actual location determined during the surgery is nearly 100%. In cases with subtle differences in the signal intensity throughout the organ, we do a quantitative activity analysis using the ratio between the peak intensity at the point of interest to the intensity at the background. A ratio $\geq$1.5 is considered diagnostic of focal disease.

45.11 Surgical Management

All open operations are approached using a transverse supraumbilical laparotomy. The pancreas is completely exposed by an extended Kocher maneuver, entry into the lesser sac, and mobilization of the inferior border. It is not necessary to mobilize the spleen. The pancreas is inspected under 3.5X loupe magnification in an attempt to

visualize a focal lesion, and it is also thoroughly palpated. If no focal lesion is identified, then 2-3 mm biopsies are taken from the pancreatic head, body, and tail. Patients with diffuse HI confirmed by intraoperative frozen analysis undergo near-total pancreatectomy. Near-total pancreatectomy (95–98%) involves the resection of the entire pancreas with the exception of a tiny residual piece of pancreatic tissue between the common bile duct and the duodenal wall. The intrapancreatic segment of the common bile duct (CBD) must be completely dissected to perform an for an adequate near-total pancreatectomy. To help with the dissection of the CBD, we place a vessel loop around the extrapancreatic distal CBD and then swing it within the duodenal C-loop to trace the CBD through the head of the pancreas until it enters the duodenum. This maneuver is not needed if the CBD follows a course posterior to the pancreatic head. In children with diffuse disease treated by near-total pancreatectomy, a gastrostomy tube is also placed to provide enteral access for glucose or overnight feeds if needed. When the intraoperative biopsies demonstrate normal pancreatic histology, a further search for the focal lesion using the preoperative localization data is conducted. Intraoperative high-resolution ultrasound has been reported to provide some help in localization because focal lesions may be hypoechoic, but we have been unable to confirm the utility of this radiologic modality [43]. Additional biopsies of suspicious areas are obtained until the focal lesion is identified by frozen section. Expert pediatric pathologic interpretation is vitally important.

Focal lesions tend to be less than 10 mm in diameter (although they can be much larger) and frequently are irregularly shaped. Some lesions have octopus-like extensions that make imperative the intraoperative confirmation of clear margins by frozen section analysis. Focal lesions often have subtle differences in their appearance compared to normal tissue, or may feel firmer than the surrounding normal pancreas. The preoperative PET/CT study greatly facilitates the search. We have been able to identify by visualization and/or palpation approximately two-thirds of all focal lesions. Focal lesions, however, can be buried within the pancreas and be impossible to see or feel. Once the focal lesion is identified, a partial pancreatectomy is performed using frozen sections of margins to ensure a complete resection. Small and superficial lesions in the body or tail can be treated by simple resection. Deep periductal lesions in the body and tail usually are treated by distal pancreatectomy. Superficial and small lesions in the head of the pancreas can also be treated by simple resection. On the other hand, deep pancreatic head lesions close to the common bile duct and pancreatic duct can be tricky to excise completely, particularly if there are tentacles of diseased tissue that emanate from the lesion. To ensure complete lesion resection in these challenging cases, we remove most or all of the pancreatic head, and follow with a Roux-en-Y pancreaticojejunostomy to drain the pancreatic body and tail. By doing this, the endocrine and exocrine functions of the remaining normal pancreas are preserved. In our experience, this approach has been needed in about 40% of focal lesions within the pancreatic head. The end of a retrocolic, 25 cm-long Roux-en-Y jejunal limb is meticulously anastomosed to the capsule of the pancreatic body (just *beyond* the cut surface of the pancreas) with fine interrupted 5-O monofilament suture to effectively tuck the cut end of the pancreas into the jejunal lumen (Fig. 45.4). The posterior aspect of the anastomosis is performed first, with all sutures placed first and then tied serially leaving the knots on the inside of the anastomosis, and the anterior aspect is performed last, in the same manner, but leaving the knots on the outside. The omentum is then freed from the transverse colon, wrapped around the anastomosis and sutured into place for additional security. Rarely, a focal lesion in the head will extend into the duodenal wall in which case a Whipple procedure may be needed. In cases of near-total or pancreatic head resections it is important to preserve the gastroduodenal artery as well as the vessels supplying the third and fourth portion of the duodenum (superior and inferior pancreaticoduodenal arteries) to avoid duodenal ischemia [16]. We do not use drains after any pancreatic resection for HI.

We have used laparoscopic surgery in patients with HI. In cases of focal disease of the body or

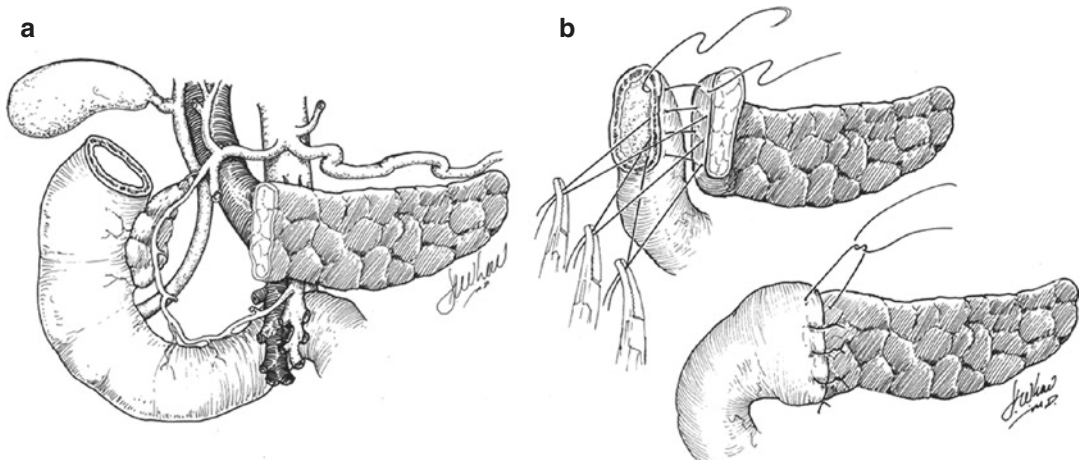

Fig. 45.4 To ensure complete lesion resection of deep pancreatic head lesions close to the common bile duct and pancreatic duct, we remove most or all of the pancreatic head followed by Roux-en-Y pancreaticojejunostomy to drain the remaining pancreatic body and tail to preserve the endocrine and exocrine functions of the remaining normal pancreas. The end of a retrocolic, 25 cm-long Roux-en-Y jejunal limb is meticulously anastomosed to the capsule of the pancreatic body (just *beyond* the cut surface of the pancreas) to effectively tuck the cut end of the pancreas into the jejunal lumen. The posterior aspect of the anastomosis is performed first, with all sutures placed first and then tied serially leaving the knots on the inside of the anastomosis, and the anterior aspect is performed last, in the same manner, but leaving the knots on the outside. From Laje P, Stanley CA, Palladino AA, et al. Pancreatic head resection and Roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism. J Pediatr Surg, 2012;47 [1]:131–135; used with permission

tail, the approach is straightforward. To facilitate pancreatic body and tail exposure during laparoscopy, it is useful to sew the stomach up to the anterior abdominal wall using 2–3 transabdominal sutures to the anterior gastric wall close to the greater curvature (Fig. 45.5). The carbon dioxide pneumoperitoneum further suspends the stomach anteriorly and also helps to expose the pancreatic body and tail. The laparoscopic procedure is performed via four 3–5 mm ports, and this permits biopsies, complete resection of a visible peripherally located focal lesion, or a distal pancreatectomy if needed. The major drawback to the laparoscopic approach is that there is little tactile feedback to help locate a non-visible focal lesion. Near-total pancreatectomies and pancreatic head resections are significantly more demanding by laparoscopy than by open surgery, and while they are technically feasible, their complication rate such as bleeding and common bile duct injury is higher. The effectiveness of this approach is currently not as good as the open approach given that most reported cases are actually 75—90% pancreatectomies because the CBD is not dissected [44–46]. Perhaps an intraoperative laparoscopic ultrasound probe could facilitate visualization of the CBD to allow precise dissection of this structure.

45.12 Postoperative Management

Postoperative pain is managed by an epidural infusion of bupivacaine, which is kept for 3–4 days, and intravenous narcotics if needed as a continuous infusion or rescue boluses. Patients are kept NPO until bowel function resumes. The intravenous GIR is re-started at a low dose (2 mg/kg/min) because the stress of the surgery induces hepatic glycogenolysis. The GIR is advanced to 5 mg/kg/min 12–18 h after the surgery and to 8 mg/kg/min (equivalent to the physiological hepatic glucose release during fasting periods) 24—36 h after the surgery. Plasma glucose levels are measured hourly in the beginning and spaced out as they become stable. If the plasma glucose levels are excessively high (>400 mg/dL) we assess the presence of ketonic bodies in the urine, and if they are present, an intravenous insulin

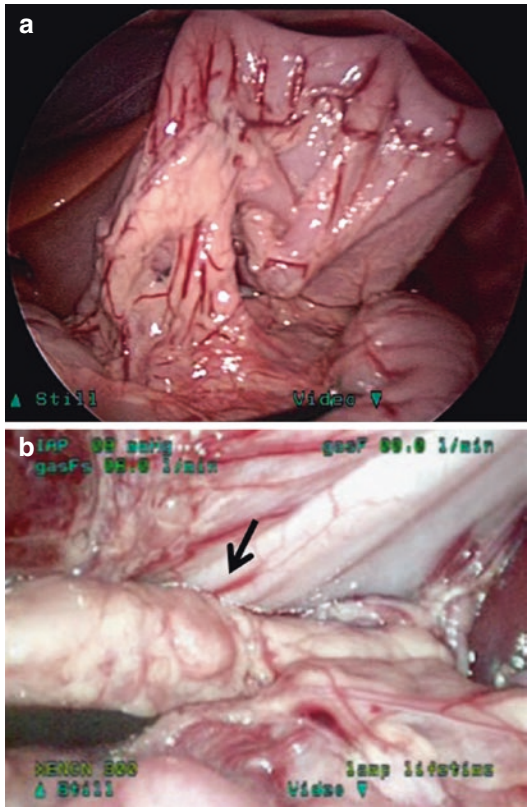

Fig. 45.5 Laparoscopic pancreatectomy. (**a**) To facilitate pancreatic exposure, the stomach is tacked up to the anterior abdominal wall using transabdominal sutures to the anterior gastric wall close to the greater curvature. (**b**) A focal lesion is clearly seen on the anterior-inferior aspect of the pancreatic body. Notice the difference in color between the lesion and the adjacent normal pancreas

infusion is started. The immediate postoperative oscillations in the plasma glucose levels are not reflective of the eventual long-term outcome, because factors like surgical stress and pain can alter glucose homeostasis. When bowel function is evident, enteral feeds are restarted. We start with 1/3 of the goal volume and advance daily by thirds. Simultaneously, the GIR is gradually weaned as the feeding volume increases. When patients are exclusively on enteral feeds, a "cure" fasting test is performed. If patients are able to maintain euglycemia for 18 h, they are considered completely cured. If the time to hypoglycemia is less than 18 h the next step is to determine a regimen of frequent feeds and short fasting periods that will allow the patient to be managed safely at home. Patients that are unable to be weaned from the intravenous glucose infusion rate are obviously not cured and will need further assessment.

45.13 Postoperative Complications

Our overall surgical complication rate after pancreatic surgery for HI is low. General potential complications are bowel obstruction due to adhesions and small intestine to small intestine intussusception (which occurs within the first 2 postoperative weeks) [47]. Specific complications include chyle leaks, pancreatic leaks, and CBD injuries, all of which are very rare in our experience.

45.14 Long-Term Outcomes After Surgery

In our experience with more than 300 pancreatectomies, about 95% of patients with focal disease are cured after surgery. The remaining 5% require some degree of support that is usually consists of a strict feeding regimen, and these cases are presumed to be secondary to microscopic residual disease. In cases of diffuse HI, approximately 50% of cases continue to have hypoglycemia after surgery and may require supportive management with octreotide and frequent feeds, and 25% develop diabetes requiring insulin. These patients, despite not being cured, are much easier to manage than before the surgery. Finally, approximately 25% of diffuse HI cases are well controlled with no medications. Long term follow-up is mandatory since insulin-dependent diabetes can develop even a decade, or more, later.

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Part VI

Abdominal Wall Defects

Gastroschisis and Exomphalos

46

Basem A. Khalil and Paul D. Losty

Abstract

The earliest description(s) of exomphalos date from antiquity though credit is linked with the French surgeon Ambrose Pare for providing the first accurate account of the malformation and its grave prognosis in the sixteenth century. Exomphalos was considered universally fatal until success with surgical treatment was published in the early 1800s. Scarpa (1814) later emphasized a spectrum of malformation severity. In 1899 Ahfield introduced the concept of conservative management by applying alcohol dressings to the exposed sac. This method was modified by Grob some 60 years later with the introduction of mercurochrome. Creation of a 'skin silo' by mobilising abdominal wall skin to cover the intact sac in large exomphalos lesions was advocated by Olshausen (1877), Williams (1930) and later Robert Gross at Children's Hospital Boston in 1948.

Keywords

Exomphalos • Omphalocoele • Gastroschisis • Human embryology Surgical management • Silo • Staged closure • Outcomes

46.1 History

The earliest description(s) of exomphalos date from antiquity though credit is linked with the French surgeon Ambrose Pare for providing the first accurate account of the malformation and its grave prognosis in the sixteenth century. Exomphalos was considered universally fatal until success with surgical treatment was published in the early 1800s. Scarpa (1814) later emphasized a spectrum of malformation severity. In 1899 Ahfield introduced the concept of conservative management by applying alcohol dressings to the exposed sac [1]. This method was

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_46

modified by Grob some 60 years later with the introduction of mercurochrome [1, 2]. Creation of a 'skin silo' by mobilising abdominal wall skin to cover the intact sac in large exomphalos lesions was advocated by Olshausen (1877), Williams (1930) and later Robert Gross at Children's Hospital Boston in 1948 [1–4].

Early descriptions of gastroschisis ('belly cleft') by teratologists in the nineteenth and early twentieth century had links with exomphalos (or ruptured sacs) [1]. Moore and Stokes (1953) later suggested the term gastroschisis should be strictly reserved for index cases in which the exposed viscera without a sac covering and abdominal wall defect lay adjacent to a normally inserted umbilical cord. Watkins in 1943 was the first to report surgical success [5, 6].

Staged abdominal wall closure with prosthetic materials was popularised by Schuster (1967) for management of exomphalos [7]. Intravenous nutrition heralded significant advances in survival of newborns with abdominal wall defects and gut related dysmotility notably in babies with gastroschisis [8]. Fetal medicine with prenatal imaging has now permitted accurate diagnosis, in utero monitoring, delivery planning and early surgery [9, 10]. Today many strategies are available for the paediatric surgeon to manage even the most challenging cases with the availability of preformed silos, tissue expander devices and artificial biomatrix materials to support skin grafting/abdominal wall closure [11–15]. In the modern era of care 95% survival is achievable in newborns with gastroschisis [16]. Exomphalos has also witnessed modest improvements in outcome(s) with 60–80% survival possible in selected cases (even with congenital heart disease) and those without major chromosomal anomalies.

46.2 Epidemiology

Exomphalos is estimated to occur in 1:3000–4000 births in Western countries [16]. In Japan the prevalence reported by the Japan Association of Obstetricians and Gynecologists Birth Defects Registry was 1:2500 births [17]. Gastroschisis has an incidence of 3–4.5 cases per 10,000 live births [18]. For reasons not fully understood abdominal wall defects have been observed to be increasing steadily in prevalence in the UK, Europe and North America [19, 20]. A 2011 EUROCAT report showed a rising prevalence particularly of gastroschisis [20]. Young maternal age with teenage pregnancy appears to be a risk factor. Low socioeconomic group status, poor nutrition, smoking and illicit substance abuse have also been cited [21, 22]. Clustering of index cases of gastroschisis within defined geographic regions suggests potential role(s) for environmental teratogens and pollutants [23]. Only 1%–2% infants with gastroschisis will have chromosome abnormalities [24]. By contrast exomphalos carries a significant risk, up to 30–40%, for presence of chromosomal lesions—trisomy 13, 18 or 21 [24, 25].

46.3 Embryology

During the 6th week of early human development the intestines with rapid growth herniate through the umbilical ring contributing to the 'physiological umbilical hernia'. By the 10th week the midgut then begins the process of returning to the abdominal cavity undergoing a 270° counterclockwise rotation fixing the gut in a normal axis of rotation [26, 27]. Exomphalos results from failure of the physiological hernia/gut loops to return to the abdominal cavity through an insult likely occurring to the lateral embryonic folds that fail to fuse in the midline. The lesion occupies a central location on the abdominal wall and can vary greatly in size from a small minor defect—2 cm diameter to a major malformation 5 cm or greater with liver and bowel loops herniated from the abdominal cavity and contained in a membranous covering sac composed of peritoneum, Wharton's jelly and amnion—(Fig. 46.1) The thoracic cavity may be maldeveloped also leading to significant restriction(s) on lung, airway growth, and diaphragm function contributing to pulmonary hypoplasia and bronchomalacia [28, 29]. Defects of the lower sternum and adjacent diaphragm may moreover contribute to co-existent anterior diaphragmatic hernia defects with pericardial

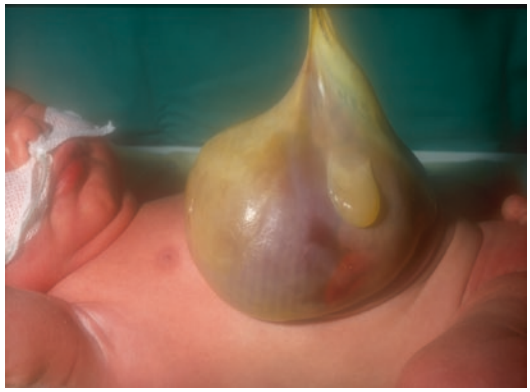

Fig. 46.1 Exomphalos—a major defect. A large sac can be seen covering the liver and intestines. The cord structures are evident at the apex of the sac

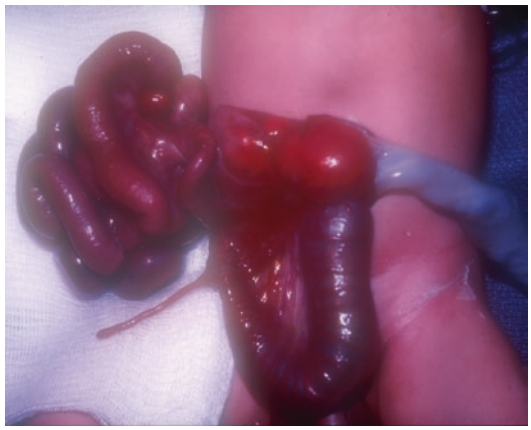

Fig. 46.2 Newborn with gastroschisis. The gut can be clearly seen herniated through an abdominal wall defect to the right side of the umbilical cord. In this case the bowel is in a healthy condition without any evidence of matting or peel formation

sac and cardiac anomalies as seen in infants with 'Pentalogy of Cantrell' syndrome [30].

Gastroschisis is characterized by the herniation of intestinal loops through an abdominal wall defect to the right side of a normally sited umbilical cord—(Fig. 46.2). Various theories regarding pathogenesis are proposed. These have included in utero rupture of the 'physiological hernia' from weakness occurring on the right side of the umbilical cord (Devries 1980) [31]. Stevenson (2009) also recently hypothesized gastroschisis may result from failure of the yolk sac and vitelline structures to be incorporated into the umbilical stalk leading to gut herniation [32]. Alongside visceral herniation testes and ovaries, fallopian tubes and bladder may also be visibly extruded through the defect.

46.4 Prenatal Diagnosis

Exomphalos and gastroschisis are readily diagnosed in over 90% cases from antenatal ultrasound imaging performed in the late first and second trimester periods of pregnancy [9, 24]. Maternal serum alphafetoprotein levels may also be raised [33]. First trimester prenatal diagnosis of exomphalos is associated with a greater than 50% risk of chromosomal abnormalities in addition to other major anomalies notably involving the cardiac and central nervous system(s). Distinguishing the abdominal wall defects is crucially important as fetal karyotyping should be routinely offered to pregnant women with a suspected diagnosis of exomphalos [24]. Fetal echocardiography and screening for other structural anomalies is additionally indicated as these greatly influence prognosis. Gastroschisis is not considered to have associations with chromosomal disorders though some 10–15% babies may have other anomalies notably co-existent intestinal atresia(s) [24]. A major focus of prenatal diagnosis in the current era has been the accurate identification of predictors of postnatal outcome that may influence parental counselling, timing of delivery and surgical management. Ultrasound and/or MRI may provide valuable information on risks of pulmonary hypoplasia developing in fetuses with giant exomphalos lesions by measuring the lung/thorax transverse area ratios (L/T) [28]. Some authors have also cited the value of measurement of largest exomphalos diameter compared to abdominal circumference in an effort to predict the need for primary versus staged closure, risk(s) of respiratory insufficiency and survival [29]. For many infants with exomphalos timing of delivery is scheduled near term with vaginal birth permissible for small lesions not containing liver. By contrast caesarean section is advised in those fetuses with the larger size defects containing herniated liver to avert hepatic injury occurring exiting the birth canal. In fetuses with gastroschisis much attention

has focused on prenatal risk factors such as bowel dilatation and the potential risk(s) of intestinal damage to exposed bowel loops from amniotic fluid exposure [34, 35]. Several authors proposed amnioexchange based on experimental work on animal models. The rationale for amniotic fluid volume exchange derived from evidence linking inflammatory mediators in the liquor fluid to bowel injury. However, Midrio and colleagues carefully evaluated the role of amnioinfusion in a series of human fetuses with gastroschisis which then showed no benefit from amnioexchange in terms of reduction of intestinal injury and postnatal outcome [35]. Amnioinfusion though would still appear to have a potential valuable role as prenatal therapy in restoring liquor volume in those maternal cases complicated by severe oligohydramnios [35]. Bowel dilatation in utero has been cited as an adverse risk factor in fetuses with gastroschisis [36–38]. Specifically of concern is reference to progressive dilatation of the contained intra-abdominal loops which may indicate the existence of intestinal atresia and worse postnatal outcomes. These sonographic findings have led fetal medicine specialists to advocate more frequent surveillance ultrasound imaging to assure wellbeing.

More recent studies including a comprehensive systematic review have now challenged these observations by failing to show convincing evidence to indicate an increased risk of adverse postnatal events in fetuses with the presence of prenatal bowel dilatation [36]. Timing and mode of delivery has been widely debated in the fetus with gastroschisis [39]. Among many published studies (including a Cochrane review), none have convincingly shown outcome benefits for—(1) early preterm delivery <36 weeks, (2) caesarean section versus vaginal delivery unless specific obstetrical factors (fetal and/or maternal distress) prevail [39, 40]. Current evidence therefore strongly supports spontaneous or induced vaginal delivery of prenatally diagnosed gastroschisis fetuses after 36 weeks [40, 41]. It is self evident that all fetuses with a prenatally diagnosed abdominal wall defect should be delivered in obstetrical centres with appropriate expertise and access to a multidisciplinary team of NICU specialists and surgeons.

46.5 Newborn Management

Immediate management of a newborn with exomphalos or gastroschisis requires fluid replacement, gut decompression via passage of an NG tube, avoidance of hypothermia and local care to the exomphalos sac or herniated viscera—(Fig. 46.3). Cardio-respiratory support may also be indicated in babies with giant exomphalos lesions due to associated lung hypoplasia and/or congenital heart lesions. In infants with gastroschisis the bowel should be carefully inspected to ensure the gut is not injured/perforated, twisted or constricted by a narrow ring or band at the base of the abdominal wall defect. Testes, ovaries, fallopian tubes and bladder may be sometimes herniated through the defect also. The exposed viscera should be protected by wrapping a layer of transparent cling-film/cellophane bag over the gut and torso. Alternatively the gut may be placed in large medical grade plastic bag with drawstrings. The bowel should be always visible to the primary care team and the infant positioned with the exposed gut supported to avoid kinking the mesentery or strangulating the lesion at the base of the defect. It is often therefore best to advise that newborns are nursed on their right side (protecting gut perfusion/no mesentery kinking) whilst being transported by a retrieval team to a surgical facility. In infants with exomphalos inspection of the quality of the

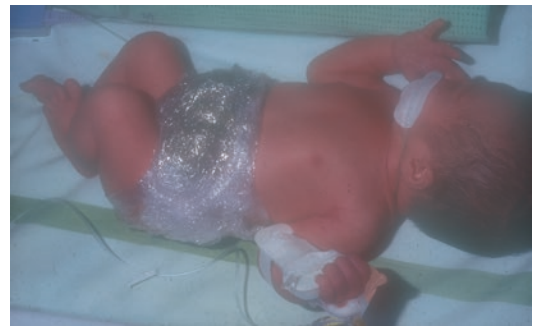

Fig. 46.3 Newborn with gastroschisis on arrival to the surgical unit following transport. Note the exposed viscera covered with a cling-film torso wrap to protect the gut and reduce heat loss. A nasogastric tube in situ facilitates gut decompression and reduces the risks of aspiration. An intravenous line allows delivery of crystalloid fluids and administration of antibiotics

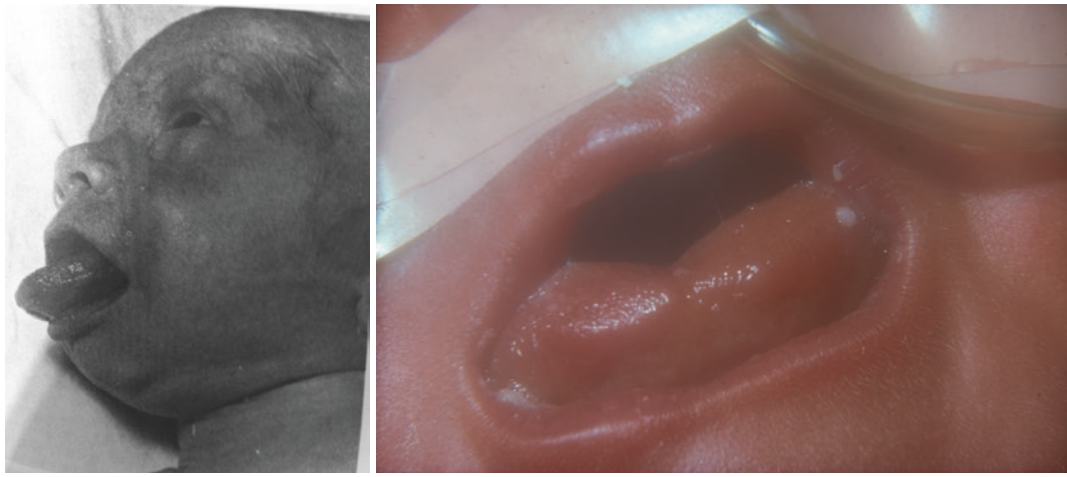

Fig. 46.4 Beckwith-Wiedemann syndrome in newborn with exomphalos. Note the coarse facial features and large tongue—'macroglossia'

exposed sac is important looking for tears or rupture that may greatly influence subsequent management. Contents may be clearly visible notably liver and/or gut defining the complexity of the lesion as a 'major' or 'minor' defect. All infants should be fully examined to exclude syndromic associations particularly in those with exomphalos where for example the presence of a large protruding tongue 'macroglossia' may indicate Beckwith-Wiedemann syndrome—(Fig. 46.4) [42]. Such infants are prone to neonatal hypoglycaemia and require glucose supplementation. Vascular access via a peripheral vein is secured with isotonic crystalloid fluids containing 10% dextrose and sodium chloride delivered to ensure adequate tissue perfusion and urine output. Nasogastric losses should be replaced with 0.9% normal saline. Fluid boluses are administered as indicated by low urine output. As heat is rapidly lost with exposed viscera newborns with abdominal wall defects should be nursed in a thermoregulated controlled environment to avert hypothermia.

46.6 Surgical Management

Surgical management of exomphalos is largely dictated by the size and complexity of the lesion and patient status [24]. An intact sac is protective to the underlying viscera and liver. Operation should not be delayed beyond 24 h for small defects <5 cm in size containing intestine with minimal liver herniation as primary fascial closure with or without prosthetic abdominal wall patch insertion can be accomplished. Commencing with sac excision care should be taken as the membrane covering is dissected from the bowel loops and liver. In the vicinity of the liver, sac may be adherent and should be left in place. Additionally the liver often encroaches occupying the midline plane such that the hepatic veins may be superficially located and injured if appropriate care is not taken. At the time of primary exomphalos operation where possible the surgeon should inspect the diaphragm for an anterior defect (Pentalogy of Cantrell) as this will additionally require repair or a prosthetic patch [30]. We have managed several cases where diaphragm defects have been undetected at exomphalos repair with chest film radiology weeks or months later revealing a defect. Stretching of the abdominal wall will facilitate viscera reduction and primary fascial closure. Likewise lateral flank relieving incisions can aid skin closure. Management of newborns and premature babies with large lesions (>5 cm) /giant exomphalos defects poses considerable challenges because of (1) lack of abdominal domain and/or (2) associated pulmonary hypoplasia with ventila-

Fig. 46.5 Conservative management exomphalos major. The sac was treated with a topical agent silver sulfadiazine to promote healing

tor dependency. Conservative therapy is advocated here allowing the exposed sac to epithelialize. Several agents may accelerate and promote this process. This was successfully accomplished in the past using mercurochrome based compounds or povidone iodine solutions with toxicity problems later apparent which also included thyroid metabolic dysfunction [43–45]. Experience with burn wound care promoted the wider use of topical silver sulphadiazine which achieves excellent results with eschar formation aiding new skin cover and creating a ventral hernia defect—(Fig. 46.5) [46]. Staged ventral hernia repair can be scheduled in later years when the patient's medical status is improved. Conservative management may involve a lengthy hospital stay requiring dedicated nursing care to prevent sac infection. Trauma to the sac including tears and rupture can also occur. Sepsis if it develops can be difficult to eradicate despite antibiotic therapy which may then require emergent sac excision. In these challenging cases where primary closure or prosthetics cannot be deployed we have successfully utilised skin substitutes i.e. Integra artificial skin, which provides a collagen matrix as a temporary scaffold for subsequent native mesh skin grafting—(Fig. 46.6) [15]. Finally, tissue expanders are also a novel option to consider when confronted with giant exomphalos lesions to facilitate staged defect closure [13].

In newborns with gastroschisis primary closure of the defect can be achieved in some 75%

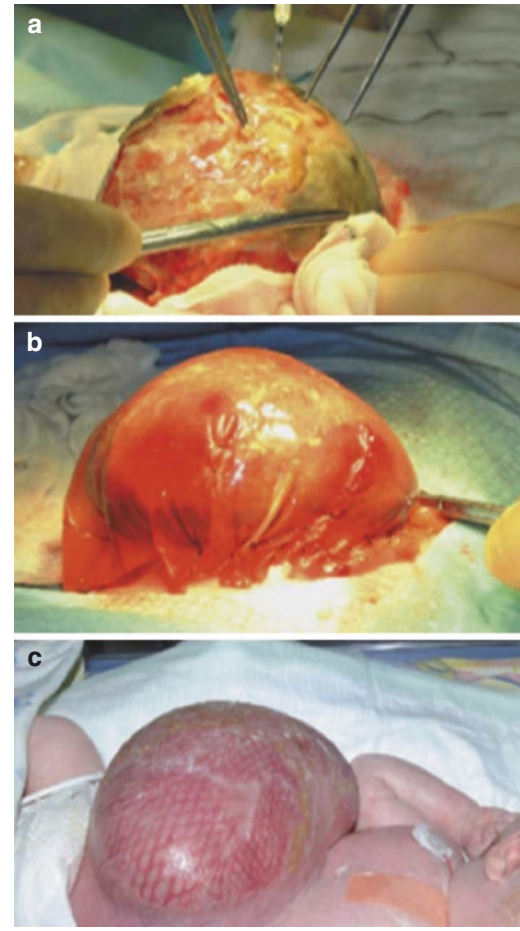

Fig. 46.6 Use of Integra artificial skin substitute as a rescue therapy to facilitate subsequent skin grafting in a 38 week gestation 2.8 kg newborn with giant exomphalos and cardiac anomaly. In this case primary conservative management was complicated with sac infection and systemic sepsis. Integra provided and created a scaffolding platform for native mesh skin graft placement after several days. The patient now a healthy teenager underwent uncomplicated staged ventral hernia repair as a toddler. Panels show (**a**) excision of infected sac day 15 after birth (**b**) Integra artificial skin substitute in place day 19—the composite material consists of a bovine porous collagen matrix covered by a thin sheet of silastic (**c**) Appearance after mesh skin grafting on week 11 after birth

cases with timely emergent operation [24, 41, 47]. To achieve these goals it is crucial cases are transported with some urgency after maternal delivery to the surgical team. Undue delay results in the infant's herniated bowel becoming matted and oedematous making silo placement and staged repair more likely.

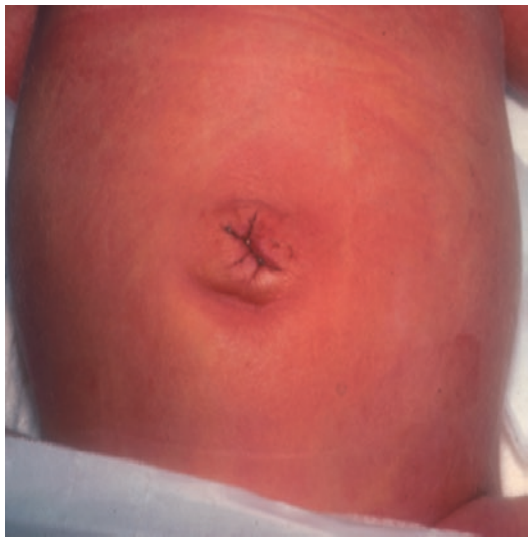

Fig. 46.7 Newborn with gastroschisis following primary repair with umbilicoplasty

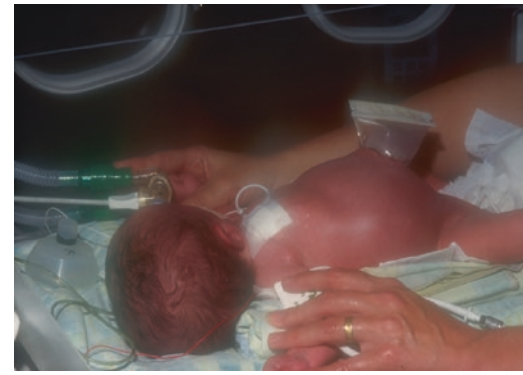

Fig. 46.8 Silo (reinforced silastic) creation in a newborn with gastroschisis and associated viscero-abdominal disproportion. The silo pouch was placed in this case to avert development of abdominal compartment syndrome. The silo is sutured to the fascial layers of the abdominal wall with interrupted monofilament sutures. Staged closure was later accomplished in 10 days

At operation the surgeon should carefully inspect the quality and integrity of the bowel particularly looking for intestinal atresia(s) seen in 10–15% cases. Where the gut appears healthy, stretching of the defect ring with retractors and/or a cephalad fascial incision will facilitate gentle bowel reduction. Primary fascial closure with preservation of the native umbilical cord or purse string creation of an umbilicus with cord excision 'umbilicoplasty' is desirable—(Fig. 46.7). Close co-operation between surgical and the anaesthetic teams is vital to ensure physiological safety of primary closure and avoidance of abdominal compartment syndrome characterized by ventilatory compromise, intestinal and renal ischaemia and impaired lower limb perfusion. The authors routinely assay arterial blood lactate levels during the procedure therefore to guide surgical management. Increased requirements for ventilation notably raised ventilator pressure(s) indicating impaired lung compliance may indicate the safer option of placing a silo and scheduling staged repair. In circumstances where bowel is extensively matted and oedematous and in premature babies with little abdominal domain, a silo should be fashioned by the surgeon permitting gradual staged visceral reduction with delayed repair. Debate exists with regard management of intestinal atresia at primary operation [48, 49]. Where the bowel appears very healthy some surgeons would elect to perform resection and primary anastomosis. In circumstances when bowel is inflamed, matted and oedematous a stoma may be created or the abdominal wall defect repaired with the aim to undertake atresia resection several weeks later. Silo placement likewise with delayed defect repair may be indicated with or without creation of a stoma. Several techniques may be deployed when electing to create a silo and plan staged repair. Traditionally reinforced silastic sheeting or prolene mesh may be sutured to the abdominal wall fascial layer at operation to create a 'silo pouch' protecting the gut—(Fig. 46.8). Some authors have also promoted the use of bedside spring-loaded silos in primary management of gastroschisis [11, 12]. At presentation to the newborn surgical unit the silo is placed over the exposed bowel without anaesthesia with the aim to undertake delayed staged repair some days later. Opinion is widely divided on the merits of this approach. Perhaps the real advantage here may be the 'out of hours' emergent care surgical residents can deploy to protect the infant's exposed bowel on the ward with the opportunity to undertake primary defect closure in normal working hours. Sutureless gastroschisis closure i.e. 'awake reduction' with

umbilical capping in newborns without anaesthesia or silo placement was first proposed by Bianchi and Dickson [50]. Early reports steered some enthusiasm for this technique which was largely applicable in a select group of newborns with healthy bowel that could be easily reduced into the abdominal cavity. Whilst feasible great care is needed in decision making as the procedure is not without risk(s) indeed some authors have cited poor outcomes [51]. A meta-analysis concluded that infants managed by primary defect closure have much improved outcomes [52]. In the postoperative period infants with gastroschisis require ventilation for a number of days (primary closure vs. silo), antibiotics and total parenteral nutrition (TPN) delivered via a Broviac central venous line (or peripheral long line) until gut function normalises. Trophic enteral feeding (breast milk or formula) is commenced when NG bile aspirates diminish in volume to minimise TPN associated liver disease. The severity of the gastroschisis lesion will greatly influence hospital stay (4 weeks average—many months) as factors here to consider include intestinal dysmotility, risk(s) of development of necrotising enterocolitis, short gut syndrome, presence or absence of intestinal atresia(s) in 'complex' cases and staged repair [24, 51–56]. Feed intolerance should alert the surgeon to consider 'missed' atresia lesion, adhesive obstruction or a dysmotility syndrome which may require upper and lower GI contrast imaging to facilitate diagnosis.

46.7 Long Term Outcome(s)

Overall survival for newborns with gastroschisis in the current era is now well over 90–95% cases [24, 41, 47]. Factors determining survival here include 'simple' or 'complex' gastroschisis defects, 'vanishing lesions' with risks of non viable gut/extreme short gut, morbidity from TPN dependency and dysmotility, staged repair, adjunct procedures i.e. tapering, intestinal lengthening and 're-do' operations for necrotising enterocolitis, adhesive obstruction or volvulus [54–56]. The need for surgery beyond the neonatal period may be significant with a study showing that 25% of patients required operation for a gastroschisis related complication most commonly bowel obstruction in the first year of life [55]. The most severely affected patients with gut failure may ultimately require intestinal transplantation [24, 54]. Growth in early years may be suboptimal but many children 'catch up' milestones [57]. Neurodevelopmental outcomes are generally good with equivalence to aged match cohorts [58]. In boys with gastroschisis one-third may be noted to have undescended testes on office follow up visits. Spontaneous descent is observed to occur in almost half with orchidopexy required in a minority [59]. Dissatisfaction with abdominal wall scarring and absence of a 'normal umbilicus' is a significant aesthetic issue for many young people and older patients [60, 61]. Quality of life and physical functioning as adult survivors is perceived as equal to the general population [60, 62].

Outcomes of exomphalos survivors show a spectrum of illness severity linked with associated anomalies [24, 62, 63]. Respiratory and feeding problems are prevalent including ventilator dependency in the first year of life secondary to pulmonary hypoplasia, bronchomalacia and diaphragm malfunction [63, 64]. Studies have shown survivors can also develop reactive airway disease, pulmonary and systemic hypertension [24, 64, 65–67]. Neurodevelopmental outcomes are impaired in those requiring a high burden of intensive care in early life i.e. ventilation, tracheostomy, supplemental feeding [24, 68]. Further operations in early years may be required to manage adhesive bowel obstruction, staged ventral hernia repair, groin hernia(s), undescended testes, including surgery for gastroesophageal reflux [24, 59, 61, 68–70]. Quality of life for many adult survivors is perceived as equivalent to the healthy population [62, 63].

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47 Omphalomesenteric Duct and Urachal Remnants

Nada Sudhakaran and Bruce Okoye

Abstract

The umbilical cord remnant usually separates in the neonatal period and its persistence beyond the first couple of months is considered abnormal.

Umbilical abnormalities may present with failure of the umbilical cord to separate, omphalitis, mass lesions, or discharge. The commonest umbilical lesion in the neonate is an umbilical granuloma. Other abnormalities are umbilical polyps, omphalomesenteric duct and urachal remnants. It is essential to distinguish between these conditions in order to initiate appropriate treatment.

Keywords

Human embryology • Umbilical disorders • Meckel's diverticulum Urachal abnormalities

47.1 Introduction

The umbilical cord remnant usually separates in the neonatal period and its persistence beyond the first couple of months is considered abnormal [1].

Umbilical abnormalities may present with failure of the umbilical cord to separate, omphalitis, mass lesions, or discharge. The commonest umbilical lesion in the neonate is an umbilical granuloma [1, 2] Other abnormalities are umbilical polyps, omphalomesenteric duct and urachal remnants. It is essential to distinguish between these conditions in order to initiate appropriate treatment.

47.2 Omphalomesenteric Duct Remnant

47.2.1 History

Fabricius Hildanus was the first to report this congenital anomaly in 1598 [3, 4]. Morgagni further defined the anatomy and clinical presentation of Meckel's diverticulum [5–7].

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_47

In 1809 Johann Friedrich Meckel, described the embryology and the clinical features of this condition. His study of 22 paediatric cadavers gave rise to his description of the various forms of omphalomesenteric duct remnants namely, omphalomesenteric fistulas, omphalomesenteric cysts, umbilical sinuses and mesodiverticular bands. Meckel deduced that these malformations arose from the incomplete obliteration of the omphalomesenteric duct [4, 8, 9].

47.2.2 Epidemiology

The commonest Omphalomesenteric duct (OMD) remnant is the Meckel's diverticulum (MD). MD is also the commonest congenital abnormality of the gastrointestinal tract. It is referred to as the disease of "2s": It occurs in 2% of the population, arises 2 feet from the ileocoecal valve (adults), is about 2 in. long, about 2 cm in diameter, symptoms are often seen before the age of 2 and males are reported to be twice more likely to present with clinical symptoms [10, 11].

Meckels diverticulum is sporadic, but its presence is reportedly increased in children with Hirschsprung's disease, Down syndrome, esophageal atresia, duodenal atresia, malrotation, and congenital cardiac abnormalities [1].

47.2.3 Embryology

The yolk sac, is an extra embryonic extension from the primitive mid gut. This is formed by the 4th week of gestation. As the cranial and caudal body of the embryo folds, the neck of the yolk sac narrows. The lateral edges of the embryonic disk then start to fuse in the midline. The ectoderm covers the entire embryo, except where the yolk sac and connecting stalk emerge.

By the 6th week of gestation, the yolk sac is narrowed to a slim stalk now, known as the vitelline duct, omphalomesenteric duct or the yolk stalk [12] (Fig. 47.1).

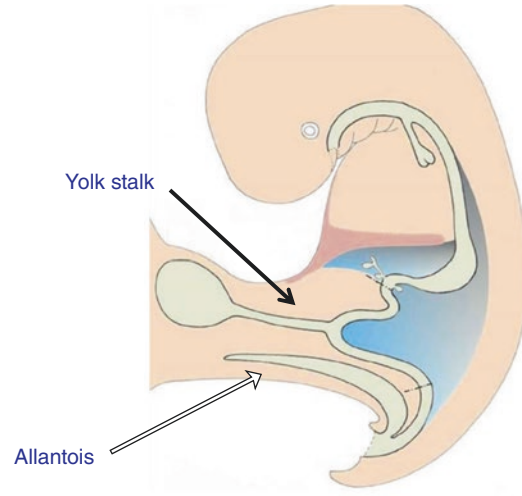

Fig. 47.1 Diagram of a fetus. *Black arrow*: Yolk stalk attached to the yolk sac on the left and the developing midgut on the right. *White arrow*: The allantois, which later becomes the urachus

The yolk stalk is thought to provide nutrients from the yolk sac to the developing embryo [13] After the 6th week, the yolk sac and yolk stalk disappear, along with the vitelline arteries [14]. Failure of this regression, creates the various forms of omphalomesenteric remnants. Although a number of other OMD anomalies can occur, MD is by far the most common.

As the yolk sac is continuous with the developing intestine, it contains all the layers of the intestinal wall as does a MD. Approximately 55–70% of MD contain ectopic tissue, usually either heterotopic gastric or pancreatic mucosa [15, 16]. The exact cause for this ectopic tissue in the diverticulum is unknown [17–19]. There have been suggestions that small buds of the pancreas are left on the foregut prior to its fusion, which then moves with the elongation of the gut onto the MD [20, 21]. There have been case reports of other ectopic tissues such as, colonic, duodenal, jejunal, hepatic, and endometrial, however these cases are rare and are isolated findings [22–25].

47.2.4 Anatomy

Meckels diverticulum is usually located on the antemesenteric border of the ileum [26]. It contains all five layers of the small intestine and is supplied by the vitelline artery (Fig. 47.2). This feature distinguishes it from a duplication cyst. The vitelline artery arises directly off the aorta [13, 27–30]. In addition to the mesenteric location of the ileum, MD has also been reported involving the proximal jejunum and the rectum [31]. The MD may be free (74%) or attached (26%) by fibrous bands to the umbilicus [32].

47.2.5 Clinical Presentation

Omphalomesenteric duct (OMD) remnants present clinically with a complication at an incidence of 4—6% [26, 33]. It has been noted that this incidence decreases with age. Clinical presentation is very varied and is related to the degree and pattern of patency or obliteration of the OMD. This may range from a completely patent omphalomesenteric duct at the umbilicus communicating with the bowel to a variety of lesser remnants, including the MD.

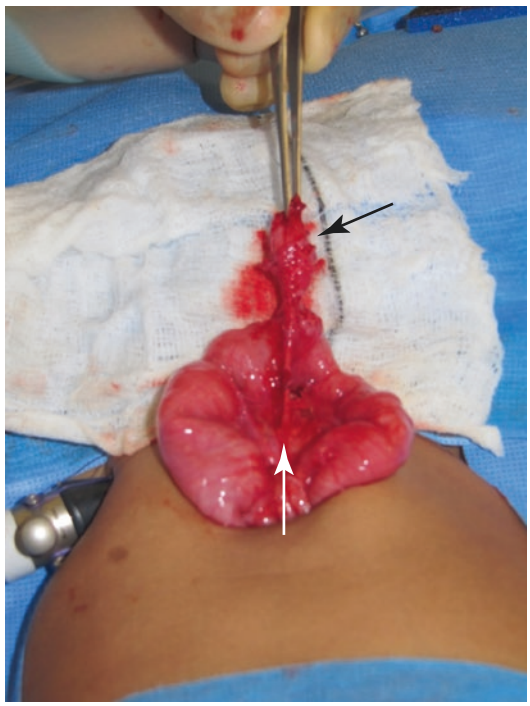

Fig. 47.2 *Black arrow*: Meckel's diverticulum; *White arrow*: vitelline artery arising from the mesentery, supplying the MD

Omphalomesenteric duct remnants may present with the persistent discharge of bowel content or mucus from the umbilicus, intussusception, prolapse of ileum at the umbilicus, intestinal obstruction, melena, anaemia and peritonitis [2].

Symptoms occur most frequently during childhood years (especially in the first 2 years of life) [34] The commonest modes of presentation are obstruction (30%), bleeding (27%), intussusception (19%), omphalitis (1%), and others (23%) [11, 35]. In the neonatal period MD may present with perforation, intussusception, ileal volvulus and less commonly, bleeding [2, 11].

Bowel obstruction is usually due to a mesodiverticular band, which is a fibrous remnant of the vitelline artery. This band, extending from the mesentery into the diverticulum, may trap a portion of the bowel [4, 36, 37]. In addition, volvulus of the bowel may occur around a persistent vitelline duct or band which connects the diverticulum to the umbilicus [16]. This may lead to bowel obstruction, perforation and peritonitis. Less commonly, an axial torsion of the MD may also occur. This occurs around its base when it is attached to either the umbilicus or ileal mesentery [26, 38]. Perforation of the MD may occur due to distal intestinal obstruction such as with Hirschsprungs disease or distal atresia [39].

Gastrointestinal bleeding is an important clinical presentation of MD. The incidence of bleeding in childhood has been recorded as high as 70% [4]. Bleeding occurs due to the presence of gastric or pancreatic tissue within the MD. Gastric tissue tends to be the more prevalent of the two, seen in 60–65% of cases, with pancreatic tissue seen in 5% of cases [15, 16]. The acidic secretions of the gastric tissues and alkaline secretions from the pancreatic tissues cause ulcerations to the adjacent normal ileal mucosa at the base of the MD, often upstream. This ultimately leads to the early detection of the diverticulum and may

explain why it is most commonly found in children [22, 25]. The bleeding is often bright red fresh bleeding if large in volume or may be darker in colour. Melaena is unusual. The painless bleeding can be catastrophic, sometimes requiring urgent blood transfusion [4].

Ileo-ileal intussusception results when the MD, an aperistaltic segment of ileum, is pushed into the adjacent ileum or when the MD falls into the bowel lumen becoming a lead point for the intussusception. The intussusception may progress into the colon becoming ileo-colic [4].

MD have also been reported within inguinal or umbilical herniae (Littres hernia) [36, 40].

A small proportion of OMD may present with omphalitis, often, due to an infected OMD cyst. These cysts are what remains when the umbilical and bowel margins of the OMD obliterates but the central portion remains patent. Inflammation within an MD may occur but is unusual in the neonatal period. In addition, OMDs may present as an umbilical sinus, an unconnected collection of ectopic mucosa of ileal or gastric origin or pancreatic tissue at the umbilicus [10].

47.2.6 Management

Management varies with clinical presentation. Most importantly, following acute presentation such as bleeding, bowel obstruction, intusscusception or peritonitis, adequate rescusitation is the key priority. Crystalloid, blood products and antibiotics should be administered as needed with insertion of a naso gastric tube to aid bowel decompression and prevent pulmonary aspiration.

In some cases, such as with bowel volvulus, obstruction or peritonitis, the diagnosis will only be made following emergency laparotomy or laparoscopy. Surgery in cases of peritonitis or suspected bowel ischaemia must not be delayed in an attempt to obtain a precise diagnosis. Differential diagnoses in such cases will include the full spectrum of possible causes of acute abdomen or obstruction in the neonate such as malrotation, intussusception or bowel atresia.

In a stable child with an uncertain diagnosis further investigation may include plain radiography, ultrasonography, or imaging of the small and large bowel through contrast follow through or enema.

Obvious umbilical lesions with prolapsed intestinal mucosa would require surgical resection. If the baby presents with omphalitis or a mass under the umbilicus, then an ultrasound scan can be done prior to surgery. If the diagnosis is still unclear following radiological investigations in a stable child, diagnostic laparoscopy may be useful. Laparoscopy is increasingly used in both the diagnosis and treatment of MD. The diverticulum can be exteriorized via a periumbilical incision allowing either diverticulectomy or segmental resection and reanastomosis [41–45].

A "well" baby presenting with significant rectal bleeding will require a Meckel's scan. This scan utilizes Tc99 sodium pertechnetate given intravenously. The presence of ectopic gastric mucosa is highlighted by scintigraphy (Fig. 47.3).

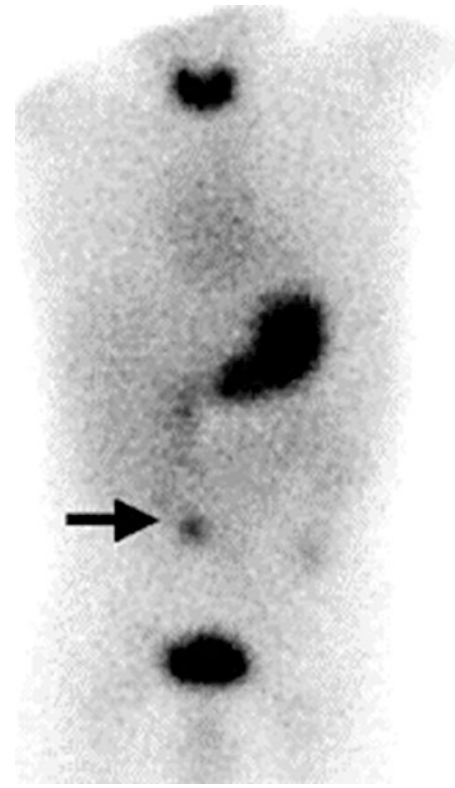

Fig. 47.3 Meckels Scan using Tc99 sodium pertechnetate, the arrow showing an area of ectopic gastric mucosa. Also highlighted are the thyroid gland, stomach and the urinary bladder

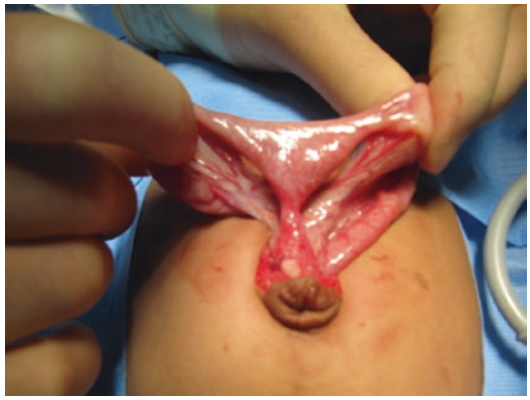

Fig. 47.4 Meckel's diverticulum attached to the umbilicus

The isotope has a high affinity for parietal cells of gastric mucosa. The residual isotope is concentrated in the urinary bladder. A positive scan shows abnormal uptake of the isotope outside the stomach and urinary bladder. The Meckel's scan has a reported sensitivity of 25–92% [41, 46–50]. Prescribing pentagastrin, histamine-2 (H-2) blockers and glucagon, have been reported to increase the diagnostic yield of the Meckel's study [33, 51]. In view of the wide variation in the sensitivity of the meckles scan, consideration should be given to early laparoscopy or laparotomy in children with suspicious clinical presentation (Fig. 47.4).

MD presenting with intestinal bleeding should have a segmental ileal resection along with the MD as the bleeding is often form ulcerated ileal mucosa adjacent to the MD. In addition, the heterotropic tissues may be found at the base of the MD. Hence a simple diverticulectomy is insufficient. A wedge excision or a segmental ileal resection would ensure complete resection of abnormal tissue [33].

47.2.7 Incidental Finding of Meckel's Diverticulum

Meckels diverticulum may be found incidentally during laparotomy or laparoscopy. There is varying opinion regarding the need to resect the MD in this situation. It has been suggested that diverticuli less than 2 cm in length, with no heterotopic palpable mucosa, constitute a lower risk group [52]. There are concerns that resecting an MD in a "clean" operation potentially converts it into a "dirty" or contaminated one. In addition, it is argued that the risk of the MD becoming symptomatic is small and that resection could result in a longer hospital stay with a risk of anastamotic leaks bowel obstruction, or infection [17, 53].

Proponents of resection suggest that the morbidity or mortality of the primary procedure may not be increased and that the palpable characteristics of the diverticulum may be unreliable [54, 55]. Tumors have rarely been reported within MD. These may be benign, such as lipoma, neuromuscular and vascular hamartomas, or malignant with carcinoids making up the majority of such cases [4, 56].

Two large studies looking at 50 years of data have shown an approximately 6% risk of complications arising from MD. Diverticulectomy performed in the presence of complications carries an operative mortality and morbidity of approximately 2% and 12% respectively [51, 57]. However, this risk must be weighed against the risks of complications from an incidental resection, a morbidity figure of around 1—2% [51, 57].

47.3 Urachal Abnormalities

The urachus is a fibrous, midline, tubular structure that extends from the dome of the bladder to the umbilicus. It represents an incomplete regression of the allantois. Urachal remnants may be completely asymptomatic but can also cause significant morbidity.

47.3.1 Epidemiology

Urachal remnants are considered rare. In pediatric autopsy studies, an incidence of 1 in 7610 cases for patent urachus and 1 in 5000 cases for urachal cysts has been documented [58]. However the incidence of symptomatic presentation with a urachal remnant is significantly smaller with the most common abnormality being urachal cysts [59].

In one review of 56 children with urachal abnormalities, about half were identified incidentally [60]. Babies with umbilical discharge and a patent urachus usually present at birth while non discharging anomalies usually present before 5 years of age [61, 62].

47.3.2 Embryology

The allantois is a finger like projection, connected to the cloaca of the primitive hindgut. The cloaca separates to form the urogenital sinus anteriorly and the rectum posteriorly [63–66] (Fig. 47.1).

The fetal bladder descends from the umbilicus into the pelvis around the fourth or fifth month of gestation. The allantois, which is attached to the dome of the bladder, stretches and progressively narrows down. It forms an epithelialized fibromuscular tube, the urachus. The urachus obliterates by fibrosis and forms the median umbilical ligament by about the 4th or 5th month of gestation [66, 67]. The precise aetiology of urachal anomalies remains undefined, however its presence has historically been attributed to bladder outlet obstruction. This "pop-off" anatomic theory is not well supported in the literature. One study reports up to 14% of patients with urachal abnormalities had evidence of bladder outlet obstruction, this finding is disputed in larger series [68, 69]. Urachal remnants can present as Umbilicourachal sinus (an incomplete tract from the umbilicus) or a complete one (patent urachus), urachal cysts or a vesicourachal diverticulum (Fig. 47.5). The most common abnormality, urachal cyst, can occur anywhere between the bladder and umbilicus and mostly occur in the distal third of the urachus. Vesicourachal diverticuli are rare, consisting of outpouchings of the bladder at the insertion of the urachus [69]. Other genitourinary conditions such as vesico-ureteric reflux, hypospadias and crossed renal ectopia are associated with urachal anomalies [70, 71].

47.3.3 Anatomy

The urachal remnant remains as a fibrous band lying in the retropubic, preperitoneal, perivesical space between the transversalis fascia and the parietal peritoneum, extending from the dome of the bladder to the umbilicus [65, 67] (Fig. 47.6). Its length varies from 3 to 10 cm and from 8 to

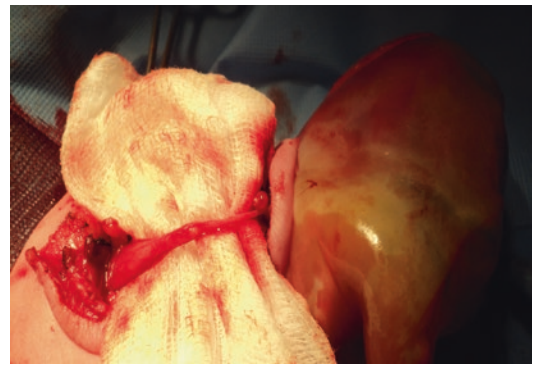

Fig. 47.6 Patent urachus attached to the bladder on the left, extending into an omphalocoele sac

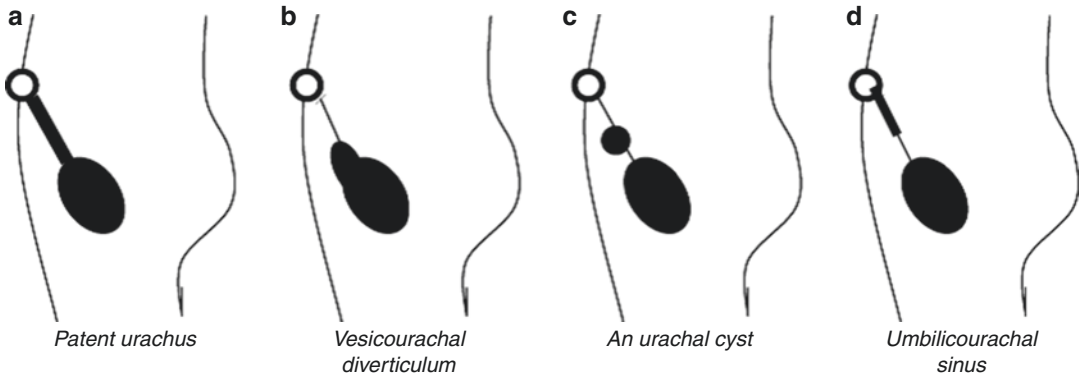

Fig. 47.5 Different forms of urachal remnants

10 mm in diameter [72, 73] Coexistence of a vitelline and urachal remnant is also uncommon, although reported [74].

47.3.4 Clinical Presentation

A patency of the embryologic urachal remnant after birth may give rise to various clinical problems. These include umbilical discharge, local infection, lower abdominal pain, and urinary tract infection. They may also be asymptomatic and be discovered incidentally [61, 62]. In a recent series, with 56 patients, the presentation was as follows: umbilical discharge (43%), umbilical infection (43%), and palpable cysts or masses associated with pain (14%). In this same group of patients, further investigations revealed that 14% had an associated genitourinary abnormality including vesico-ureteric reflux, a duplicated collecting system, hypospadias, meatal stenosis, bladder diverticulum, periurethral polyp, and renal dysplasia [69]. A patent urachus is estimated to account for about 10–15% of urachal anomalies [75]. These may sometimes present as a pseudocyst of the cord in the antenatal/fetal period [76].

As urachal remnants are rare, the literature on presentation in the neonatal period consists largely of case reports. These include prolapse of the urinary bladder, giant umbilical cord or with an omphalocoele [77–80]. There is a report of urinary ascites following trauma to a urachal remnant during umbilical artery catheterisation [81]. A subtle clinical sign of the presence of urachal remnant is the retraction of the umbilicus during voiding. This is often associated with pain [82]. Some urachal cysts are identified on ultrasound scan for another indication [83].

In an older child or young adult, infected urachal cysts can present with signs mimicking appendicitis, this is often an unsuspected finding at operation [84, 85].

47.3.5 Management

Clinical management depends on the mode of presentation. If the baby presents with an infected urachal cyst or urinary tract infection, it is important to treat the acute condition, with antibiotics, and appropriate fluid resuscitation. Ultrasound scan will assist with confirming the diagnosis and planning definitive treatment [86]. The presence of an abscess is traditionally managed in two stages: initially with antibiotics and drainage (either surgical or via interventional radiology), followed by delayed resection once the infection has resolved [86–89].

A micturating cysto-urethrogram (MCUG) may not always provide the diagnosis of a urachal remnant, especially if there is no connection with the bladder. However it may be informative in patients with a patent urachus and in whom a posterior urethral valves are a consideration [61, 69, 90]. A recent large study of 66 children with urachal remnant, from the Mayo clinic showed that of those who had a MCUG, 71% had grade 3 or less of vesico ureteric reflux and 12% had grade 4/5 reflux [91].

There have been reports of a patent urachus closing in the early newborn period. Some centres would advocate following some of these asymptomatic urachal remnants with serial ultrasound scans and conservative management [60, 75, 92]. However the long term risks of leaving these urachal remnants are stone formation and malignancy. The risk of future cancer in urachal remnants is well recognized. Urachal cancers account for 1–10% of adult bladder cancers, with a 10-year disease-free survival of about 50% [93, 94]. There have also been reports of cancers arising from urachal remnants in adolescence [95]. Urachal cancers are usually adenocarcinomas, although transitional cell, squamous cell and sarcomas have been reported [96–98].

For these reasons, the treatment of choice should be surgical resection. The tract along with the cyst and a small cuff of bladder at the insertion are removed. Mucosa should not be left at the umbilicus because of the concern that the urachal remnant may harbour a future carcinoma. This procedure can be performed by either open techniques or via laparoscopy. An open procedure may be performed via a curvilinear umbilical incision in infants. A transverse incision midway between the umbilicus and the pubis provides better exposure in older children [43–45, 99–101].

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The Exstrophy Complex: Bladder and Cloacal Exstrophy

48

Peter P. Stuhldreher and John P. Gearhart

Abstract

The care of a newborn with the exstrophy-epispadias complex presents a formidable challenge to the pediatric surgical community. The approach to these children is a multi-disciplinary effort involving multiple subspecialties including urologists, surgeons, orthopedists, pediatric anesthesiologists and specialty nurses. Advances in the basic and clinical sciences in the past two decades have yielded insight into the embryologic, genetic, and the physiology of exstrophy. Despite multiple approaches to the surgical management of the exstrophic patients are used throughout the world, the critically important part of the surgical care is a successful primary closure. The best long-term outcomes can only be achieved with a successful primary closure, and each failure decreases a patient's chance at voided continence. This chapter aims to examine all aspects of the exstrophy patient including the surgical management and long term prognosis.

Keywords

Bladder exstrophy • Cloacal exstrophy • Embryology • Surgical management • Outcomes

48.1 Introduction

The care of a newborn with the exstrophy-epispadias complex presents a formidable challenge to the pediatric surgical community. The approach to these children is a multi-disciplinary effort involving multiple subspecialties including urologists, surgeons, orthopedists, pediatric anesthesiologists and specialty nurses. Advances in the basic and clinical sciences in the past two decades have yielded insight into

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_48

the embryologic, genetic, and the physiology of exstrophy. Despite multiple approaches to the surgical management of the exstrophic patients are used throughout the world, the critically important part of the surgical care is a successful primary closure. The best long-term outcomes can only be achieved with a successful primary closure, and each failure decreases a patient's chance at voided continence. This chapter aims to examine all aspects of the exstrophy patient including the surgical management and long term prognosis.

48.2 History

Interestingly, the first description of exstrophy dates back to 2000 BC, and is documented in the British Museum archives on an ancient Assyrian tablet [1]. The first recorded us of ureterosigmoidostomy in an exstrophy patient was by Syme in 1852 [2]. Followed in 1871 by Maury who successfully used abdominal and scrotal skin flaps to cover the exstrophy bladder and in 1885 by Wyman who is credited with the first successful neonatal primary bladder closure [3]. The use of osteotomy was introduced by Trendelenburg in 1892 starting with bilateral sacroiliac osteotomy to close the pelvis and fix the bladder, leading to subsequent operative refinement and its eventual integration as a mainstay in exstrophy closure [4]. Hugh Hampton Young was the first surgeon to perform a successful bladder exstrophy closure that resulted in a continent patient in 1942 [5]. The patients with the most severe end of the spectrum, cloacal exstrophy, frequently died in infancy or childhood, and it was not until 1960 that Rickham and Johnston in Liverpool reported the first long-term surviving case of cloacal exstrophy [6]. This successful management of the exstrophy and cloacal exstrophy patient led to significant advancements in the 1970s and 1980s in improved surgical techniques and strategies, including the advent of the modern staged repair by Jeffs, that led to the continence rates in exstrophy patients improving four-fold to 70–80% [7–9].

48.3 Classification

The exstrophy-epispadias complex (EEC) presents as a spectrum of disorders from epispadias to bladder exstrophy (BE) to cloacal exstrophy (CE). Depending on the point where embryologic development is disrupted, exstrophy can present from its milder forms to its more severe variant, the omphalocele-exstrophy-imperforate anus-spinal defect (OEIS) complex, otherwise known as CE [10].

Epispadias, the mildest variant in the EEC, typically presents with a urethra that is open on its dorsal aspect, and depending on the degree of severity, mildly separated pubic rami and rectus muscles. In more severe variants, the external urinary sphincter may be involved resulting in incontinence. This defect can be only glanular or extend to the bladder neck. Classic BE is the most common form of the defect and is characterized by an exstrophic bladder with the bladder mucosa exposed on the abdominal wall, a widened pubic diastasis, laterally rotated bony pelvic halves, divergent rectus muscle and fascia and an epispadiac phallus or bifid clitoris. Figures 48.1 and 48.2 illustrate these findings in both a male and female infant respectively. Cloacal exstrophy, now commonly referred to as the OEIS complex is the severest variant in the EEC. In addition to an exstrophied bladder template, the bladder halves are often separated, and a hindgut remnant is herniated in the midline. Spinal defects, omphalocele, extreme pubic diastasis, amorphic

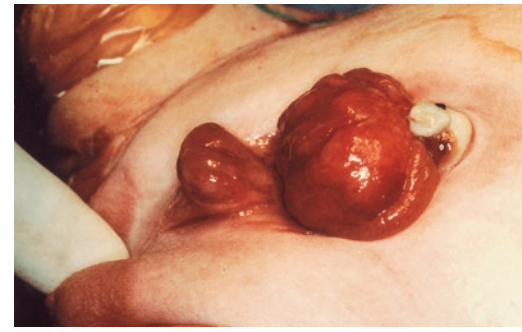

Fig. 48.1 Newborn male infant with classic bladder exstrophy

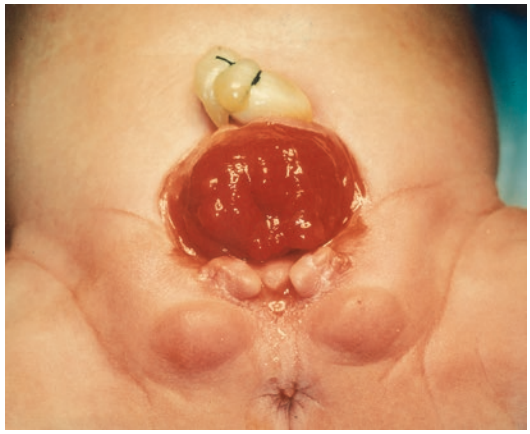

Fig. 48.2 Newborn female infant with classic bladder exstrophy

bony pelvic and hip anomalies, imperforate anus, and renal anomalies also accompany this variant of the EEC [11].

48.4 Prognosis

The published exstrophy literature is rife with different measures of success, and different prognostic factors that either lead or contribute to these outcomes. The universal tenets of successful neonatal repair of bladder exstrophy are: (1) a secure abdominal wall and bladder closure; (2) functional and cosmetic genital reconstruction; (3) achievement of urinary continence; and (4) preservation of renal function [12]. The principles for cloacal exstrophy closure are similar with the addition of: (5) neurosurgical stabilization of any spinal defects; (6) prevention of short bowel syndrome; and (7) achievement of fecal continence [13]. The literature on the exstrophy complex primarily consists of retrospective reviews, which is complicated as exstrophy is historically treated with several different techniques in multiple centers, injecting modest amounts of bias into the outcomes. Overall, the prognosis and outcome of the surgical reconstruction of the EEC can be evaluated in three major subcategories: physiological function, cosmetic appearance and psychological health [14].

48.5 Epidemiology

The incidence of bladder exstrophy in the general population is estimated in the literature to be 1 in 10,000 to 1 in 50,000 live births [15]. This is supported from data from the International Clearinghouse for Birth Defects monitoring system which quotes the incidence to be 3.3 in 100,000 live births [16]. There is a male preponderance noted in the exstrophy population in most contemporary series; the ratio is reported at 5:1–6:1 male-to-female exstrophy births [15, 16]. However, a recent epidemiological study based off of a national inpatient databank in the United States estimates that the male to female ratio may be equivalent [17]. The risk of recurrence of bladder exstrophy in a family with a child born with BE is approximately one in 100 [16]. Offspring of individuals with bladder exstrophy and epispadias having a recurrence of exstrophy recurrent is one in 70 live births, a 500-fold greater incidence than that in the general population [18]. Three isolated trends are noted that lead to increasing the incidence of bladder exstrophy: (1) decreasing maternal age; (2) high-parity pregnancies; and (3) in-vitro fertilization assisted pregnancy [16, 19].

The OEIS complex is found to occur in one in 200,000 to one in 400,000 live births according to published reports [20]. However, the incidence increases to 1:10,000 to 1:50,000 when stillborn infants are included in the analysis [21]. Similar to what is historically noted in BE, there is an increased incidence in the male population with a twofold higher incidence over the female population [22]. The only predilection data comes from an epidemiological study from New York where the incidence of OEIS was highest in Hispanic mothers and lowest in black, non-Hispanic mothers [23].

48.6 Genetics

Due to the rarity of the condition, genetic studies have been carried out on small populations of patients and no strong studies exist. One study

looking for chromosomal anomalies revealed several abnormalities such as 47,XXX; 47XXY; 47XYY; and 45, XO/46,XX mosaicism in a group of 20 patients. The ultimate conclusion is that none of these chromosomal aberrations were causative of the EEC, although interestingly six of these patients also had Down's syndrome [24].

Insufficient folic acid intake during the antenatal period and deficient folate metabolism in pregnant mothers is a known risk factor for several midline birth defects [25]. The effects of folate on the development of the EEC have mixed results in the literature. In 2005, Mills et al. suggested that one polymorphism of metabolism in a DNA synthesis pathway resulted in an unstable protein that showed an increased risk ($p = 0.035$) for the development of omphalocele [26]. However, a family-based association study of that specific genetic polymorphism in the EEC showed no significant deviation in the exstrophy population from random transmission [27]. This was further supported in a study of 214 cases of EEC where folate supplementation showed no protective effect in preventing formation or decreasing the severity of the variant of EEC [28].

Recent advances in DNA technologies have allowed for significant discoveries in the alterations that may lead to the EEC. Genome wide association studies (GWAS) have shown strong evidence for variations in the *ISL1* gene being the candidate gene for bladder exstrophy, with the most significant SNP marker found to date being rs9291768 [29]. This has been supported by follow up studies showing rs9291768 as a strong candidate susceptibility locus for CBE [30]. Murine models support these findings as ISL1 is expressed in the critical time frame for CBE development, and expressed in the peri-cloacal mesenchyme and urorectal septum [31]. Continued study of the *ISL1* gene in the bladder exstrophy population is ongoing, and may lead to a better understanding of the pathogenesis of the EEC.

48.7 Animal Models

Animal models of the EEC are primarily mechanically induced and not transgenic or spontaneous animal models [11]. Naturally occurring cases of the EEC complex in animals are rare and are scantly described in the literature, with only isolated references to a feline occurrence in 1832 and a rhesus monkey with CBE in 2002 [32, 33]. Muecke was the first to report cloacal membrane maldevelopment in chicks resulting in exstrophy [34]. Subsequent studies on pig and chick embryos have demonstrated that disruption of the cloacal membrane leads to anorectal malformations and even cloacal exstrophy [35, 36]. Several other animal studies have been performed including embryological studies of the EEC on a rat model, a lamb model, and a female dog model [37–39]. However, all of these models share the same limitation as they are all mechanically and not genetically induced.

48.8 Embryology

The embryology of the EEC has been attributed by Muecke to the failure of the cloacal membrane to be reinforced by in-growth of mesoderm [34]. The cloacal membrane is situated caudally in the embryo, and is a double layer of tissue the makes up the infra-umbilical abdominal wall. Mesenchymal ingrowth between the ectodermal and endodermal layers of the cloacal membrane normally forms the bony pelvis and muscles of the lower abdominal wall. Once the mesenchymal grows inward, the urorectal septum grows downward and splits the cloacal cavity into anterior (bladder) and posterior (rectum) cavities. Paired genital tubercles will then migrate in a medial fashion to fuse in the midline cephalad to the dorsal membrane before spontaneous perforation of the cloacal membrane occurs. If the cloacal membrane is subject to premature rupture or is impeded from migration during development, the EEC may result. Depending on how far along during development the embryo is when membrane rupture occurs determines if epispadias, BE, or CE will result [40].

Multiple theories have been proposed, but Marshall and Muecke maintain that the primary etiology of the defect is an abnormal overdevelopment of the cloacal membrane. This subsequently, prevents medial migration of the mesenchyme and inhibits proper lower abdominal wall and pelvic development [41].

48.9 Associated Anomalies

Exstrophy is part of a spectrum of anomalies involving the urinary tract, genital tract, musculoskeletal system, the gastrointestinal tract, and the neurologic system.

48.9.1 Bladder Exstrophy

The musculoskeletal system in patients with bladder exstrophy is characterized by a widening of the pubic symphysis caused by malrotation of the innominate bones of the pelvis. Bony pelvic findings include a mean external rotation of the posterior aspect of the pelvis of 12° bilaterally; the acetabula of the hip are retroverted, the anterior pelvis is outwardly rotated by a mean of 18° and the pubic rami are 30% foreshortened [42]. These rotational deformities of the pelvic skeletal structures contribute to the short, pendular penis seen in bladder exstrophy. Additionally, this rotation also accounts for the increased distance between the hips, waddling gait, and the outward rotation of the lower limbs in these children. The sacroiliac joints are also externally rotated, the pelvis is rotated inferiorly, and the pelvic volume in exstrophy patients is larger than normal controls [43]. However, reports by Stec et al. have shown that fetal bony histology in the exstrophy child is identical to controls and bone development occurs at an equivalent rate [44].

In addition to the bony structures of the pelvis being laterally rotated, the large muscle groups constituting the pelvic floor are also flattened and laterally splayed. The pelvic floor covers a twofold greater surface area in the exstrophy complex and each levator ani half is outwardly rotated 38° from midline. The levator ani complex is more flattened and only 32% of the puborectal sling is located anterior to the rectum for pelvic support as compared to 50% in controls [45]. MRI studies on the pelvic floor musculature have demonstrated one additional caveat: the degree of pubic and bony diastasis does not solely account for all of the derangements in the pelvic floor anatomy [46].

The abdominal wall is characterized by a fascial defect that is limited inferiorly by the intrasymphyseal band, representing the divergent urogenital diaphragm. This band connects the bladder neck and posterior urethra to the pubic ramus on while the anterior sheath of the rectus muscles fans out behind the urethra and bladder neck to inserts into the intrasymphyseal band. In exstrophy, the distance between the umbilicus and the anus is foreshortened, an umbilical hernia is usually present, and the incidence of inguinal hernia is high, occurring in 81.8% of boys and 10.5% of girls [47].

Anorectal defects are common as the perineum is short and broad, with the anus situated directly behind the urogenital diaphragm, displaced anteriorly. The divergent pelvic floor musculature may distort the anatomy around the external sphincter and contribute to varying degrees of anal incontinence and rectal prolapse.

The male genital defect may be severe with wide separation of the crural attachments, prominent dorsal chordee, and a shortened urethral groove. Magnetic resonance imaging (MRI) has demonstrated that the anterior corporal length in male patients with bladder exstrophy is almost 50% shorter than that of normal controls [48]. Female genital defects include a vagina that is shorter than normal, hardly greater than 6 cm in depth but of normal caliber. The vaginal orifice is frequently stenotic and displaced anteriorly; the clitoris is bifid. The labia, mons pubis, and clitoris are divergent depending on the severity of the phenotype. Typically, the uterus enters the vagina superiorly so that the cervix is in the anterior vaginal wall and the fallopian tubes and ovaries are normal.

The urinary tract is abnormal, with the bladder mucosa exstrophied on the abdominal wall. The bladder mucosa may appear to be normal, however hamartomatous polyps may be present on the bladder surface [49]. The upper urinary tract is usually normal, but anomalous development does occur. Horseshoe kidney, pelvic kidney, hypoplastic kidney, solitary kidney, and dysplasia with megaureter are all encountered in these patients. The ureters run through an abnormal course in their termination; the peritoneal pouch of Douglas between the bladder and the rectum is unusually deep, forcing the ureter down laterally in its course across the true pelvis. The distal

segment of ureter approaches the bladder inferiorly and laterally, enters the bladder with little obliquity and therefore vesicoureteral reflux in the closed exstrophy bladder occurs in 100% of cases [50].

48.9.2 Cloacal Exstrophy

The above noted defects seen in the bladder exstrophy complex are all generally present in the OEIS complex, however they usually present as much more severe variants (Fig. 48.3). The gastrointestinal issues are usually the most profound addition to the spectrum with an ileocecal exstrophy, omphalocele, hindgut remnant and imperforate anus being the most common [51]. Omphaloceles are present in 88—100% of cases and may contain portions of small bowel or even liver depending on their size [52]. Short bowel syndrome and absorptive defects are commonly observed while other defects such as duplication anomalies, gastroschisis, anal ectopia, malrotation and exstrophied colonic segments may also be present [53].

The central nervous system typically is abnormal with spinal anomalies such as myelomeningocele, or tethered cords presenting in 64–100% of cases [21, 54]. Routine screening of neonates with OEIS is recommended. The innervation of the hemi-bladders arise from a pelvic plexus around the rectum, travelling along the posteroinferior surface of the rectum and extending out laterally to the bladder halves, placing them at risk for iatrogenic injuries at time of closure [55].

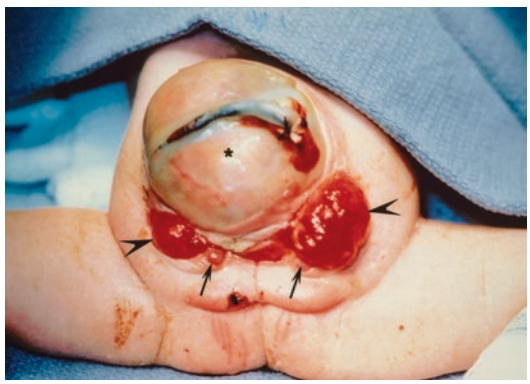

Fig. 48.3 Newborn infant with cloacal exstrophy

The OEIS complex is characterized by more profound bony abnormalities than bladder exstrophy. Spinal issues such as kyphosis, scoliosis, and abnormal vertebrae are present in 22–60% of the reported series [51, 53]. The pelvis is deformed with widely separated iliac wings, an extreme pubic diastasis, and vastly asymmetric pelvic halves [42]. Lower extremity malformations are also commonly seen in cloacal exstrophy. Club foot, equinovarus deformities, limb hypoplasia, absence, split foot, and additional digits are all noted within the complex at a rate of 17–26% [56].

Again, genitourinary aberrations are much more commonly seen in cloacal exstrophy. Upper urinary tract malformations such as renal agenesis, pelvic kidney and hydronephrosis may be observed in 1/3 of patients. Additionally, fusion anomalies, horseshoe kidney and ureteral abnormalities may also be found [52]. Testes in the male are frequently undescended with scrotal and labial halves widely separated. The phallus or clitoris is almost always bifid, underdeveloped or potentially absent. Inguinal hernias are common. In females, uterine duplication, vaginal duplication and vaginal agenesis are also reported in 25–95% of cases [21, 52].

48.10 Antenatal Presentation

48.10.1 Bladder Exstrophy

With modern prenatal ultrasound, it is possible to diagnose classic bladder exstrophy in the antenatal period [57, 58]. Two major criteria exist on prenatal ultrasound to suggest the diagnosis of bladder exstrophy: (1) the absence of a normal fluid-filled bladder on repeat examinations; and (2) a mass of echogenic tissue on the lower abdominal wall [58]. Furthermore, in a retrospective review of 25 prenatal ultrasound examinations resulting with the birth of classic bladder exstrophy, several observational findings were made: (1) absence of bladder filling; (2) a low-set

umbilicus; (3) widening of the pubic ramus; (4) diminutive genitalia; and (5) a lower abdominal mass which increased in size as the pregnancy progressed [59].

48.10.2 Cloacal Exstrophy

Ultrasound is also the mainstay in the prenatal diagnosis of cloacal exstrophy, although it still is not 100% accurate. First described in 1985, major findings on prenatal ultrasonography include inability to visualize a full bladder, a large midline lower abdominal mass, and possible myelomeningocele [60]. An identifier that differentiates cloacal and bladder exstrophy is the trunk-like appearance of the exstrophied ileocecal segment that can be detected on ultrasound [61]. Further characterization of this issue has led to major criteria (occurring in >50% of cases) for prenatal diagnosis: non-visualization of the bladder, large anterior midline abdominal wall defect, cystic midline structure, omphalocele, and myelomeningocele; minor criteria (occurring in <50% of cases) include: lower extremity defects, renal anomalies, ascites, widened pubic rami, hydrocephalus, a single umbilical artery, and a narrow thorax [62]. When the prenatal diagnosis of the OEIS complex is obtained, consideration for termination of the pregnancy is an option for discussion with the parents [63].

48.11 Clinical Presentation, Diagnosis, and Postnatal Care

In the absence of prenatal diagnosis, the exstrophy complex can be diagnosed by physical examination at the time of birth. Typically children with exstrophy are most often born at term and in no particular distress. In BE, the exstrophic bladder template is visible as a circular patch of reddened mucosa from which the ureteral orifices will actively drain urine. Hamartomatous polyps may be present, the pubic symphysis is open and the diastasis between the two sides is palpable. The appearance of the genitalia is variable, with the urethra in males lying open on the dorsal surface of the corporal bodies with the penis splayed open dorsally. In females, the pubic diastasis results in an absence of a mons pubis with a bifid clitoris and lateral displacement of the labia. In CE, the above mentioned findings are present, however the bladder halves may be separated with a hindgut remnant located in the midline; the pubic diastasis may be extreme, and an omphalocele and/or myelomeningocele may be visible. Typically the abnormal vertebral defects and lower limb defects are visibly apparent in the newborn.

No immediate laboratory information is required, except in children who will undergo immediate surgery where a type and screen with baseline CBC, serum electrolytes and coagulation studies will assist preoperatively. Additionally, karyotyping should be performed in cases of the OEIS complex to better delineate chromosomal sexual determination. Imaging should be performed in the immediate postnatal period including a plain abdominal radiograph for precise measurement of the pubic diastasis, and characterization of the pelvic and vertebral defects. A renal ultrasound and spinal ultrasound allow for identity of baseline renal characteristics and to rule out spinal anomalies and tethered chord. The use of CT or MRI in the newborn is currently for academic and investigational purposes and is considered optional.

Postnatal care is similar for both BE and CE; starting in the delivery room, the umbilical cord should be tied with 2-0 silk sutures close to the abdominal wall so that the umbilical clamp does not traumatize the exposed mucosa. The bladder may be covered with a non-adherent film of plastic wrap (i.e. Saran Wrap) to prevent the mucosa from sticking to clothes or diapers. In addition, each time the diaper is changed the plastic wrap should be removed, the bladder surface irrigated with sterile saline, and a new square of plastic wrap placed. Consultation of surgical teams with expertise in the exstrophy complex should be obtained including a pediatric urologist or pediatric surgeon, an orthopedist, and in cases of OEIS

a pediatric surgeon and a neurosurgeon when necessary. Cardiopulmonary and general physical assessment can be carried out in the first few hours of life. A thorough neonatal and subspecialist assessment may have to be deferred until transportation to a major children's medical or exstrophy center can be arranged.

48.12 Surgical Management of Bladder Exstrophy

48.12.1 Primary Bladder Closure

Over the past three decades, improved techniques in the functional bladder closure have contributed to higher success rates and improved long term outcomes in the exstrophy population. The objective of primary closure, whether as an infant or older, is to convert a patient with an exstrophic bladder into one with complete epispadias with incontinence. This allows for a low posterior urethral outlet resistance and ensures preservation of renal function. Typically epispadias repair is now performed between 6 and 10 months of age. In some very select cases, surgeons may elect to combine the bladder closure and epispadias repair into one procedure in the newborn. Initial repair is of paramount importance as it has been demonstrated that a successful closure of a good quality bladder template in a newborn is the single most important predictor of eventual voided continence [64].

Preoperatively it may be evident that a bladder template may be small and fibrotic and is not elastic or contractile enough for the usual closure procedure (Fig. 48.4). Examination with the patient under anesthesia may be required to assess the bladder adequately, particularly if edema, excoriation, and polyps are present on the mucosal surface (Fig. 48.5). The suitability of a bladder for closure or the need to perform a delayed closure should only be made by experienced surgeons as a failed closure may be catastrophic in the long term, while it has been shown in small series that delayed closure can have comparable continence outcomes long term to immediate primary bladder closure [65].

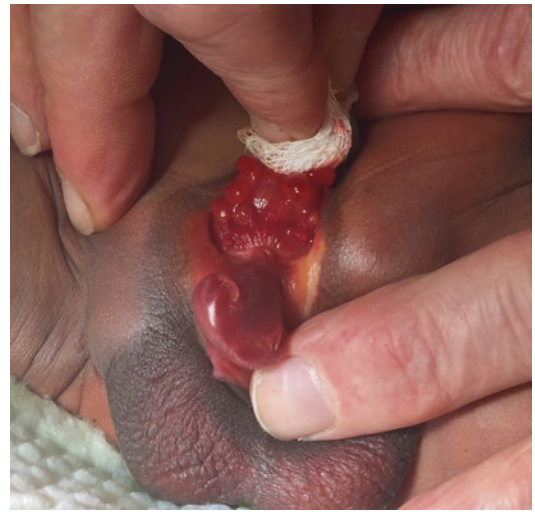

Fig. 48.4 Bladder template on a newborn with classic bladder exstrophy deemed too small for primary closure during the newborn period

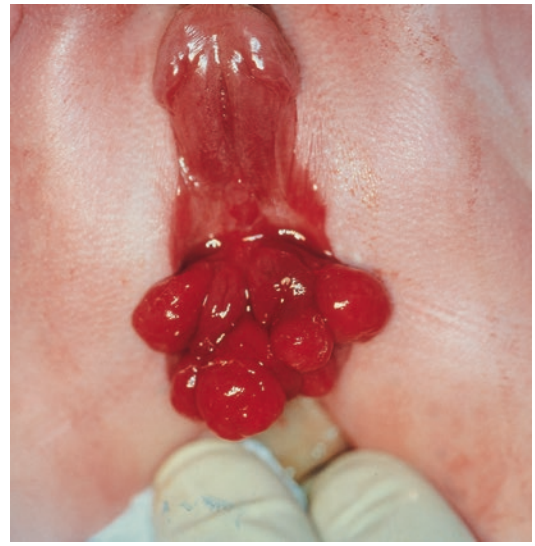

Fig. 48.5 Fibrotic bladder filled with hamartomatous polyps deemed unsuitable for primary closure during the newborn period

48.12.2 Pelvic Osteotomy

If primary closure is undertaken within 72 h of birth, majority of times the pelvic bones are not completely calcified and are malleable. At the beginning of the closure procedure, if the pelvis can be manually manipulated and closed without

significant tension, then one may choose to forgo a formal pelvic osteotomy. In this case the pubis is re-approximated later in the procedure and the child is immobilized post-operatively with traction. If the closure is being performed after 72 h of life, if the pelvis is not malleable, or if the pubic diastasis is over 4 cm, then osteotomies should be performed at the time of primary bladder closure. If osteotomy is not utilized in the primary closure, postoperatively the infant is immobilized in modified Bryant's traction in a position in which the hips have 90° flexion for 4 weeks [66].

A pelvic osteotomy provides security to the closure as it brings the pubic symphysis together, diminishes tension on the abdominal wall closure, facilitates placement of the vesicourethral junction deep within the pelvis, and brings the pelvic floor musculature more anterior in the pelvis. A well performed osteotomy will add extra time under anesthesia for the infant; however security of the closure is paramount to prevent the procedure from failing.

Multiple techniques and approaches exist for performing pelvic osteotomy; however the technique that enjoys the most published results is the bilateral transverse innominate and vertical iliac osteotomy. Osteotomy should be performed as the initial step prior to attempting bladder closure [67]. The osteotomy may be performed with the infant in the same position required for bladder closure with the same whole body surgical prep. The pelvis is approached from the anterior body wall and exposure is gained from the iliac wings inferiorly to the pectineal tubercle and posteriorly to the sacroiliac joints. Both the transverse innominate osteotomy and the posterior iliac osteotomy may be performed through this anterior approach. Two fixator pins are placed in the inferior osteotomized segment and a single pin is placed in the wing of ileum superiorly. Radiographs are obtained to confirm pin placement, the soft tissues are closed, and the urologic portion of the procedure may then be performed. At the end of the procedure, an external fixator is applied and the patient is placed in Buck's traction for 4 weeks to prevent dislodgement of tubes and destabilization of the pelvis. Postoperatively, in newborns that undergo closure with-out osteotomy in the first 48–72 h of life, the baby is immobilized in modified Bryant's traction in a position in which the hips have 90° flexion. When modified Bryant's traction is used, the traction is employed for 4 weeks.

48.12.3 Bladder, Posterior Urethral, and Abdominal Wall Closure

The patient is given broad-spectrum antibiotics in an attempt to convert a contaminated field into a clean surgical wound. The various steps in primary bladder closure are illustrated in Figs. 48.6 and 48.7. The initial incision is created from just above the umbilicus and carried down around the bladder and paraexstrophy skin to approximately the level of the urethral plate. To ensure later posterior urethral and prostatic closure, a mucosal strip 2 cm wide is marked out from the trigone to just below the verumontanum in the male and the vaginal orifice in the female patient as seen in Fig. 48.6a, b. Male urethral length is typically sufficient and no longer are urethral transection and paraexstrophy skin flaps recommended in the modern repair.

The posterior plane behind the bladder template is entered just above the umbilicus and is established between the rectus fascia and the bladder. Each umbilical vessel is doubly ligated and incised allowing the peritoneum to be peeled off the dome of the bladder (Fig. 48.6c). The peritoneum should be separated from at least 50% of the bladder at this point allowing the bladder to be placed deeply into the pelvis at the time of closure. This plane of dissection is continued laterally in a caudal direction between the bladder and the rectus fascia until the urogenital diaphragm fibers are encountered (Fig. 48.6d). The pubis will also be encountered at this juncture and it should be retracted laterally allowing for the incision of the urogenital diaphragm fibers. This step facilitates the radical mobilization of the bladder neck and posterior urethra from the pubic bone (Fig. 48.7a).

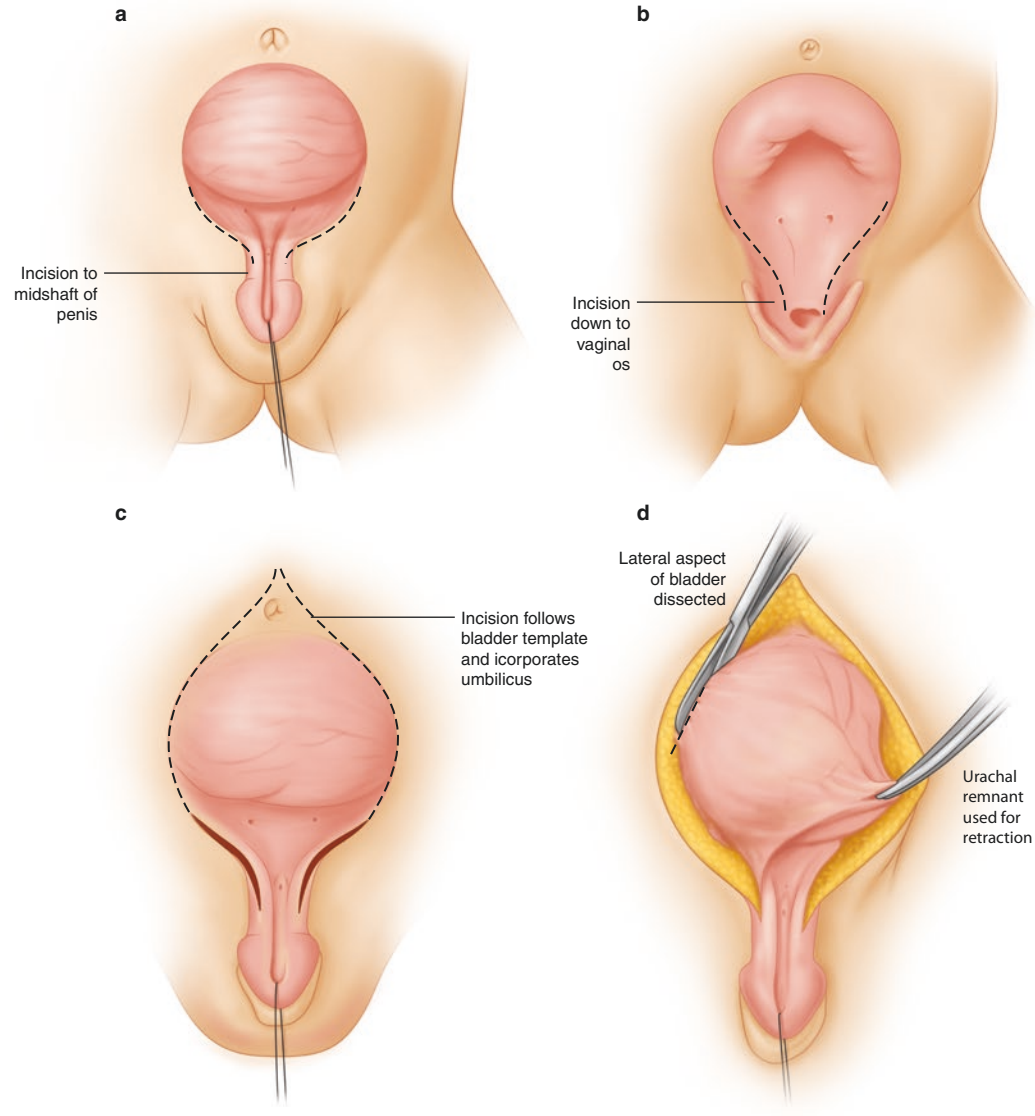

Fig. 48.6 Initial steps in primary bladder exstrophy closure. (**a**) Outline of initial incisions in a male exstrophy patient, (**b**) Outline of initial incisions in a female exstrophy patient, (**c**) Periumbilical incision and initial bladder dissection, (**d**) Further bladder dissection into the retropubic space and division of lateral bladder attachments

Gentle traction on the glans of the penis at this point will show the insertion of the corporal body on the lateral inferior aspect of the pubis. Care should be taken to avoid radical mobilization of the corpora as their blood supply may be aberrant in the exstrophy complex. The corporal bodies are not brought together at this juncture, as the epispadias repair will be performed as a second stage procedure around 6 months of age. The urogenital fibers are then incised with electrocau-

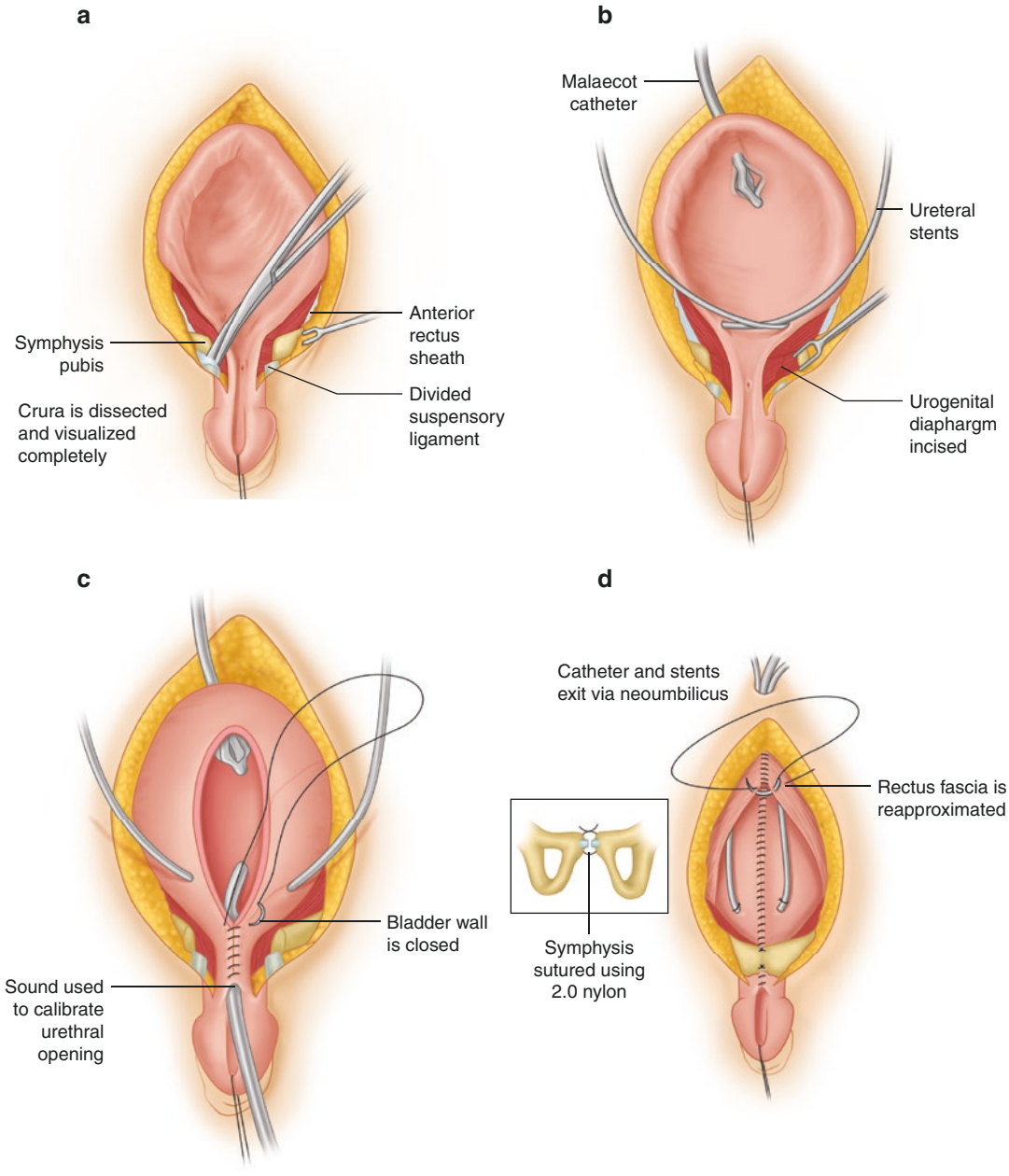

Fig. 48.7 Continued steps in primary bladder exstrophy closure. (**a**) Freeing of the urogenital diaphragm from the pubis, (**b**) Incision of the urogenital diaphragm fibers and placement of a suprapubic tube, (**c**) placement of ureteral catheters and bladder wall closure, (**d**) Fascial closure following reapproximation of the pubic symphysis

tery down to the pelvic floor in their entirety. This step is crucial in allowing the vesicourethral junction to be placed as deeply in the pelvis as possible. If the urogenital fibers are left intact, when the pubic bones are re-approximated, the posterior vesicourethral unit will be brought anteriorly in an unsatisfactory position.

After their incision, the wide band of fibrous and muscular tissue representing the urogenital diaphragm is detached subperiostally from the pubis bilaterally (Fig. 48.7b). At this stage the bladder should be freely mobile from surrounding structures while its postero-lateral blood supply is preserved. Paraexstrophy skin may then be discarded if not required during the repair. The mucosa and muscle of the bladder, and the posterior urethra are then closed in the midline anteriorly. This urethral orifice should calibrate to 12–14 French allowing enough resistance to aid in the bladder adaptation while avoiding increased outlet resistance and potential upper tract damage. This sized urethral opening will also primarily preventing prolapse through the urethra. If possible, a second layer closure with local tissue should be performed over the posterior urethra and bladder neck (Fig. 48.7c).

A suprapubic non-latex Malecot catheter is left in the bladder and ureteral stents are left in the ureters for 4 weeks to promote maximal urinary drainage. Ureteral stents allow for free renal drainage as swelling in the bladder floor may induce temporary ureteral obstruction. Urethral stents are avoided to prevent necrosis and accumulation of secretions in the neourethra.

Following bladder closure and drainage tube placement, the pubis is then re-approximated. If osteotomies have been performed, the fixator pins may be used to manipulate the pelvis closed, otherwise pressure over the greater trochanters bilaterally allows the pubic bones re-approximated in the midline. Horizontal No. 2 nylon mattress sutures are placed in the pubis and tied with a knot away from the neourethra (Fig. 48.7d).

An umbilicoplasty is then performed and the ureteral stents and suprapubic tube are brought out through the neoumbilicus. The author's primarily use a V-shaped flap of abdominal skin at the orthotopic umbilical location tacked down to the abdominal fascia in the method described by Hanna [68]. The abdominal fascia is closed with interrupted sutures. Care should be taken so that the drainage tubes exit the abdominal fascia superiorly with minimal tunneling under the skin to prevent erosion of the skin. The subcutaneous tissue and skin are then closed. The infant is then placed in traction, extubation is attempted is possible and the patient is transported to the intensive care unit for monitoring.

48.12.4 Combined Bladder Closure and Epispadias Repair

This surgical technique for complete primary exstrophy closure (CPRE) combines both the bladder closure and epispadias reconstruction into one procedure on the newborn. This technique was first described by Lattimer and Smith for primary closures and in 1991 for failed exstrophy closures [15, 69]. Today, renewed international interest exists in using a combined procedure on newborn patients, and the critical steps of the procedure have been outlined by Grady and Mitchell [70]. Initially, a similar dissection is performed to isolate the bladder, beginning superiorly and carried out inferiorly. Once the bladder template is dissected free, the penile dissection begins ventrally. Dissection of the corpora progresses medially and the penis is completely disassembled with care being taken to ensure the urethral plate preservation [71]. Deep proximal dissection frees the vesicourethral unit from the intrasymphyseal ligaments. The bladder is then closed, the penis is reassembled anatomically with a hypospadiac urethral opening (in 70% of patients) and the abdominal wall and skin closure is completed [70]. However, with this approach there have been several reports of significant soft tissue (glans and corporal) loss with this technique [72].

48.12.5 Radical Soft Tissue Mobilization (The Kelly Repair)

Another surgical option for a staged repair of exstrophy is the Kelly repair, or radical soft tissue mobilization. Briefly, this is a multi-staged

technique that closes the bladder and abdominal wall without osteotomy after birth. Several months later a radical soft tissue surgical mobilization of the urogenital diaphragm from its periosteal attachments is performed to allow closure of the pelvis and pelvic floor. The penis is made hypospadiac and later penile repair is performed. Osteotomy is not routinely used in this repair [73].

48.13 Surgical Management of Cloacal Exstrophy

Cloacal exstrophy presents a much more complex treatment plan than bladder exstrophy. In the OEIS complex, spinal anomalies and myelomeningocele frequently occur. In the situation with a concomitant neurological issue, neurosurgical consultation and closure of the defect should be performed as soon as the infant is medically stable to undergo the procedure. The remainder of the surgical closure requires a coordinated effort by both a pediatric urologist and a pediatric surgeon. As both bowel and bladder are exstrophic and intertwined and the degree of severity is varied, individualized treatment strategies for each patient result in the best long-term results [74]. Most importantly, the pediatric surgeon and pediatric urologist should have a unified management plan regarding initial closure of both bowel and bladder with a long-term treatment plan for subsequent surgical reconstruction as the child ages [75].

A newborn cloacal exstrophy is typically brought to the operating room within 48–72 h of life for a closure procedure and abdominal exploration from the multi-disciplinary team. Various algorithms have been proposed as to single stage versus multi-stage procedures for initial repair, however all approaches emphasize several basic tenets: (1) omphalocele repair; (2) separation of the cecal plate from the bladder halves; and (3) hindgut preservation [13, 76]. The goal of urologic repair is to preserve and possibly close the two bladder halves while providing minimal opportunity for renal compromise [77]. The gastrointestinal objectives are to identify and quantify all available intestinal components, assess their continuity and ensure preservation of all intestinal length [78]. Individual steps of each procedure will not be detailed, but the guiding tenets of each portion of the repair and the optional treatment steps will be outlined in further detail.

The omphalocele defect in cloacal exstrophy ranges in size and may contain small bowel and even other solid abdominal viscera depending on its size. In almost all circumstances, attempts should be made to close the omphalocele at the time of the initial closure procedure as this facilitates successful closure of the abdominal wall. In most series this can be performed successfully after the abdominal exploration, bladder realignment and fecal diversion are performed. In cases of extremely large defects, alternatives are occasionally required instead of primary closure [54]. If the omphalocele cannot initially be reduced, a silo device may be employed with slow gradual reduction of the defect until it is small enough for closure. Alternatively, the omphalocele may be allowed to epithelialize creating a controlled ventral hernia for which repair may be deferred until the child has undergone some longitudinal growth [79]. Despite the availability of alternatives, most exstrophy experts attempt to close the omphalocele primarily in the initial surgical foray.

The cecal plate must be separated from the bladder halves. Once the entire hindgut remnant is free from the urinary tract, an attempt at bladder closure may be made if deemed appropriate. If performed, the bladder halves may be joined back in the midline with care to identify the ureteral orifices at the time of realignment. The bladder closure technique described above for bladder exstrophy may be used as the guiding principle for repair. If a complete closure is performed, then osteotomy may be employed in these patients at the same time however in the malformed pelvis of these infants, the task is difficult. At the author's institution, it is preferred to rejoin the bladder halves on the anterior abdominal wall and leave the bladder exstrophied. Subsequently in a delayed fashion around 1 year of age, the bladder may be closed with a staged osteotomy to close the pelvis if there is an extreme diastasis (>6 cm) [80, 81]. Additionally, the staged approach to bladder closure is supported by the increased incidence of tethered cord as well as the extensive dissection to close the bladder and pelvis through areas that innervates

the bladder potentially placing the upper urinary tracts at unnecessary risk to justify one stage procedures [82]. However, in rare cases with a small omphalocele, good sized bladder template, and narrow pubic diastasis, a single staged closure can be safely performed.

The goal of gastrointestinal (GI) reconstruction at the time of primary closure is to characterize existing bowel, free it from the urinary bladder, divert the fecal stream and preserve all available bowel length. The typical anatomic presentation of the GI tract is to have the ileocecal segment of the gut exstrophied on the abdominal wall with the herniated ileum protruding out like an elephant trunk. In addition there may be hindgut a hindgut remnant or other detached colonic segments distally not in continuity with the intestinal stream [78]. Majority of patients (96%) in a large series have been found to have between 2 and 20 cm of total colonic length with the remainder having greater than 20 cm. Typically small bowel length is preserved and is close to normal in these infants [83]. The initial step is to mobilize the cecal plate from the bladder halves. This cecal plate must be tubularized so care needs to be taken to ensure adequate width to allow for tubularization. This step must be followed by careful inspection of the abdomen to identify any remaining segments of large intestine that are distal to or attached to the cecal plate. If any segments are discontinuous, continuity of the bowel should be reestablished by re-anastomosing the segments. The distal end of the large bowel segment is then brought out to the skin as a colostomy to divert the fecal stream. Careful attention to the GI reconstruction at this initial surgical closure procedure attempts to minimize short gut syndrome and maximize intestinal length for the consideration of future reconstruction [84].

48.14 Complications and Special Considerations

48.14.1 Primary Bladder Closure Failure

Regardless of the technique chosen to close the exstrophic bladder, the goals are the same: successful closure of the abdominal wall, pelvis and bladder; preservation of the urogenital soft tissues, and protection of the upper tracts from outlet obstruction and pyelonephritis. Primary bladder closure can fail in three primary ways in the postoperative period, either through dehiscence of the abdominal wall and bladder, prolapse of the bladder through the urethral opening, or the development of outlet obstruction [85].

Dehiscence of the abdominal wall and bladder is one of the primary reasons for failure of a closure procedure in the immediate postoperative setting. Dehiscence presents as opening of the abdominal wall and fascia and re-exposure of the exstrophic bladder mucosa on the abdominal wall; dehiscence is handily diagnosed on physical examination of the surgical wound. Dehiscence is mainly attributed to tension on the abdominal wall, bladder and pelvic closure. Tension must be minimized by good closure of the bony pelvis, deep placement of the bladder within the pelvis, and proper post-operative care including immobilization, sedation, proper urinary drainage, and avoidance of abdominal distension.

Bladder prolapse and outlet obstruction are problems that occur at the vesicourethral junction or the urethral opening following a primary closure procedure. Bladder prolapse can be partial or complete and is identified by the reddish bladder mucosa protruding through the urethral orifice. Incomplete closure of the pelvis or pelvic floor or creation of a neourethral segment that is considerably wider than 12 French can result in lack of support leading to prolapse through a capacious orifice. Additionally, avoidance of increased abdominal pressure or distension should be protective [86]. This can be accomplished through pain control measures to minimize unnecessary or abrupt movement of the infant, urinary drainage to keep the bladder decompressed, and avoidance of early postoperative abdominal distension from early feeding and avoidance of ileus.

Outlet obstruction, that can lead to upper tract deterioration stems from stricture of the neourethra, either from over-tightening of the neourethra or from erosion of the pubic stitch into the

urethral channel [87]. This predisposes both the bladder and the upper urinary tracts to stress, dilatation and renal damage. This ultimately may result in recurrent pyelonephritis, renal insufficiency and detrusor muscle fatigue [88]. Both prolapse and outlet obstruction obviates the surgeon to perform a re-closure procedure or reconstructive procedure to open the bladder for urinary drainage.

Wound infections in the post-operative period are the enemy of any reconstructive surgery. Prophylactic antimicrobials are recommended for the postoperative period to prevent surgical site wound infections, which have been attributed as causative factors in wound dehiscence and scar tissue formation. Additionally, antimicrobial prophylaxis prevents urinary tract infections while drainage tubes are indwelling in the ureters and bladder [89]. During the post-operative period when the suprapubic tube and ureteral stents are in place, keeping them secure is of significant importance as early dislodgement of urinary drainage tubes has also been implicated as reasons for early surgical failures [90].

48.14.2 Genitourinary Soft Tissue Loss

The complete primary repair of exstrophy (CPRE), where epispadias repair is performed on the infant in the same surgical setting as primary bladder closure, has a unique series of complications reported with the loss of urethral, penile and glanular soft tissues [72]. The mechanism of injury is hypothesized to be ischemic in nature, with either compression of the pudendal blood vessels at time of pelvic closure or direct injury to the blood supply due to aggressive dissection compromising the already tenuous blood supply to the lower GU tract [91]. In capable hands at major exstrophy centers this complication can be avoided, however large referral centers internationally are reporting this complication with greater frequency [92, 93]. Unfortunately at this time, loss of glanular and corporal tissues are not replaceable and pose grave risks to future genital reconstructive efforts.

48.14.3 Bowel Complications in Cloacal Exstrophy Reconstruction

Primary bowel complications in the immediate post-operative period are rare, but the long term developmental issues and reconstructive issues are directly related to the primary procedure. Careful preservation of all intestinal length is of paramount importance as in 25% of the cases of children born with the OEIS complex, short bowel syndrome has been reported [20, 22]. If proper handling of the bowel is performed in infancy, potential exists for these children to have their colostomy reversed later on during childhood. Candidacy for an intestinal pull through procedure depends on both the ability to form solid stool and development of adequate perineal musculature and function. Careful dissection around the pelvic floor and preservation of bowel length at initial and subsequent reconstructive procedures maximizes the potential for anatomic reconstruction of the cloacal exstrophy child's distal GI tract later in life [94].

48.15 Quality of Life and Long-Term Outcomes

Urinary continence is a primary measure of long term outcome in both bladder and cloacal exstrophy reconstruction. In the bladder exstrophy patient population, volitional voided continence is achievable and well reported in the literature following surgical reconstruction. Rates of continence following reconstruction are reported as ranging from 18 to 83% [14]. The single most agreed-upon determinant of potential volitional voided continence is the success of the primary surgical bladder closure procedure [64]. Some reports of continence being achieve by primary closure or complete primary repair alone do exist, but most series acknowledge that the exstrophy child will eventually require a bladder neck reconstruction or outlet procedure [95]. Following bladder neck reconstruction, in patients who had a successful primary repair, continence rates have been

reported as high as 83% in large series [96]. In infants that have had a failed re-closure procedure, the volitional continence rates only approach the 50% range. Many of these children ultimately have to go augmentation cystoplasty and continent catheterizable channels to become dry of urine [97]. In cloacal exstrophy, the reports of volitional voided continence are rare although some reports utilizing a complete primary repair at birth or through bladder neck reconstruction are reported [54, 98]. It is generally accepted that majority of patients with the OEIS complex will undergo a continent urinary diversion at some point during reconstruction to achieve urinary dryness [99].

Fecal continence is expected in the bladder exstrophy population. Several reports exist of exstrophy patients having long-term pelvic floor compromise and issues with partial fecal incontinence [100, 101]. Hypothesized theories for these issues are compromised pelvic floor muscular anatomy in the exstrophy complex and long term fatigue or stress on the pelvic floor manifesting earlier in life than in the healthy adult population. In cloacal exstrophy fecal continence is directly correlated to the ability of the remaining large intestine to form solid stool and the development of the perineal musculature in the children as they age. Decisions for eventual intestinal pull through procedures are made by a pediatric surgeon after longitudinal assessment of these two variables during infancy and childhood.

The psychological impact on children and adolescents with the exstrophy complex are a significant and chronic health condition that is similar to that seen in other major congenital birth defects [102]. Exstrophy patients are challenged in life and relationships and must cope with anxiety stemming from their physical differences potentially numerous operative procedures [103]. The quality of life of children with exstrophy is in many ways determined by their ability to develop essential coping mechanisms; however reports of increased post-traumatic stress and suicidal ideations are a cause for significant concern. Active surveillance of these children's' mental health by their pediatric surgeon and urologist is essential as in many cases these physicians serve in a primary care capacity for this patient population. When recognized, psychological or psychiatric referral should be obtained for those felt to be in need [104].

Long-term sexual outcomes of both male and female health are the source of ongoing studies. The male phallus is typically functional and suitable for intercourse; anatomically the penis will be shorter but wider than average with some degree of dorsal chordee or upward deflection [48]. Female patients with the exstrophy complex are the best characterized to date. The exstrophic female vaginal canal and internal genitalia are reasonably normal. The vaginal orifice may be stenotic, but vaginal depth is sufficient for intercourse and internal vaginal caliber is typically normal. The appearance of the external genitalia is dependent upon the surgical reconstruction. A series of 42 women with the exstrophy complex demonstrated that 34 engaged in vaginal intercourse; however 30 required either modified episiotomy or vaginoplasty to obviate the stenosis frequently encountered at the vaginal introitus [105]. Sexual desire has also been found to be appropriate and consistent with the unaffected population, at least in the bladder exstrophy population [106].

The fertility of patients in bladder exstrophy is primarily based on retrospective studies and observations. Males with bladder exstrophy are thought to have difficulty with antegrade ejaculation however a recent series of adult male exstrophy patients who underwent a single stage repair have shown achievable antegrade ejaculation in 94%. In these patients however, sperm quality was severely diminished [107]. The advancements in modern infertility treatments, such as intracytoplasmic sperm injection and IVF have made reproduction a viable possibility for the exstrophy male [108]. Several series have documented adult females with exstrophy who have become pregnant via vaginal insemination, who then carried and successfully delivered children [105]. Females however due to the widened pubic diastasis and weakened pelvic floor are particularly prone to vaginal and rectal prolapse; for this reason, delivery by Caesarian section is typically recommended in the exstrophy female population [106].

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Part VII

Nervous System

Hydrocephalus

49

Jawad Yousaf, Stephano R. Parlato, and Conor L. Mallucci

Abstract

The term Hydrocephalus relates to the presence of an excessive amount of cerebrospinal fluid (CSF), which may cause an increase in intracranial pressure with or without associated abnormal enlargement of the cerebral ventricles. Hydrocephalus is not a single pathological disease entity rather it is secondary to a variety of pathological processes or insults that cause an imbalance between the production and absorption of CSF.

Keywords

Hydrocephalus • Pathophysiology • Classification • Venticulo-peritoneal shunt • Ventriculostomy

49.1 Introduction

The term Hydrocephalus relates to the presence of an excessive amount of cerebrospinal fluid (CSF), which may cause an increase in intracranial pressure with or without associated abnormal enlargement of the cerebral ventricles. Hydrocephalus is not a single pathological disease entity rather it is secondary to a variety of pathological processes or insults that cause an imbalance between the production and absorption of CSF. The estimated prevalence of congenital and infantile hydrocephalus is between 0.5 and 0.8 per 1000 births (live and still) [1–3].

The treatment of hydrocephalus has been revolutionized since the advent of shunts in 1950s. This transformed a usually fatal condition into a manageable disease. While CSF shunting remains the mainstay of treatment for neonatal hydrocephalus, endoscopic third ventriculostomy is an important surgical treatment option in certain disease entities. Better understanding of CSF dynamics and pathophysiology and technological advances in neuro-imaging, neuro-navigation and shunt hardware have allowed for a patient specific approach in management of this complex pathological entity. Early diagnosis and treatment is warranted to limit pathological damage, maximise neurological development and improve patient outcome.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_49

49.1.1 CSF Physiology

The total CSF volume, on average, is 140 mL and this is divided between the ventricular system (25% or 35 mL), spinal canal (30—70 mL) and the cranial subarachnoid space [4–9]. In young children the total amount of CSF is smaller, around 70 ml, divided between the various compartments in a way similar to adults. The three components influencing CSF dynamics are production, circulation and drainage. Most CSF is produced by a highly vascular ingrowth through the ependymal lining of the ventricles known as the choroid plexus (Fig. 49.1). CSF is derived by adenosine triphosphate (ATP) dependant active secretion from cerebral arterial blood across epithelial walls. Mean CSF production in humans is 0.36 mL/min (approximately 20 mL/h, or 500 mL/day) although in young children the total daily production is smaller than in adults, possibly half [5–8, 10–14]. The choroid plexus has a blood supply ten times that of the cortex, and can produce CSF at a rate up to 0.21 mL/min/g tissue, a rate higher than any other secretory epithelium. The current widely accepted view is that CSF circulation is via bulk flow [15]. CSF is produced mainly within the lateral, third and fourth ventricles. Net bulk flow occurs from the lateral to the third ventricle via the foramen of Monro, on into the fourth ventricle via the aqueduct of Sylvius, and then out of the fourth ventricle via the midline foramen of Magendie, and the lateral foramina of Lushka into the subarachnoid space [16] (Fig. 49.2). Once produced, CSF circulation is limited by the cells, membranes, and junctional barriers lining the ventricular and subarachnoid spaces. The dynamics of CSF flow are in part governed by these anatomical configurations, and hence abnormalities within the system can affect CSF flow. The subarachnoid space comprises of an interconnecting network of basal CSF cisterns. CSF rapidly moves around the basal cisterns, and then moves more slowly into the subarachnoid space on the cortical convexity and to a lesser extent the spinal subarachnoid space, until reabsorption into the systemic circulation occurs via the venous system at the arachnoid

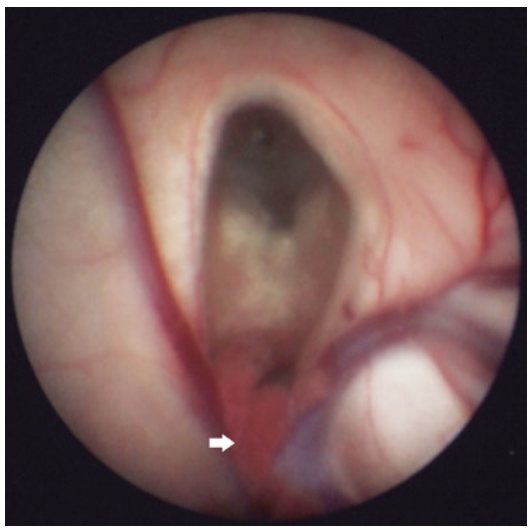

Fig. 49.1 Endoscopic view of the right foramen of Monro showing the choroid plexus (*white arrow*)

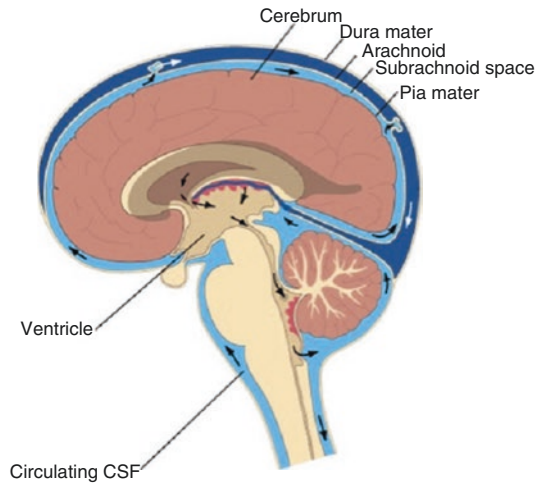

Fig. 49.2 CSF drainage pathways. A schematic section through the brain and spinal cord showing the drainage pathways for CSF. The CSF is formed by the choroid plexuses of the lateral ventricles with a small portion derived from fluid exudate from the cerebral parenchyma. Once formed the CSF passes through the foramina of Monro into the third ventricle. CSF then flows through the cerebral aqueduct of Sylvius into the fourth ventricle, which has a single-sided sheet-like plexus. From there fluid exits into the various basal cisterns and then into the subarachnoid space through paired foramina of Luschka and the single foramen of Magendie. CSF flows through SAS over the surface of the cortex. Some fluid drains back into the blood via the arachnoid granulations into the superior sagittal sinus, some via the spinal nerve roots and the remainder via the olfactory tracts

granulations in the superior sagittal sinus, the lymphatics across the cribiform plate, and the nerve root subarachnoid angles [17].

49.1.2 Classification

The classification of hydrocephalus remains a source of continued discussion due to our evolving understanding of pathogenesis and treatment of hydrocephalus. Hydrocephalus can be classified as Obstructive (block proximal to arachnoid granulations) and Communicating (block at arachnoid granulations) or Congenital and Acquired (see Box 49.1).

49.1.3 New Concepts

Recently Rekate [18] has defined hydrocephalus as "an active distention of ventricular system of the brain resulting from inadequate passage of cerebrospinal fluid and its point of production within the cerebral ventricles to its point of absorption into the systemic circulation". This concept assumes all hydrocephalus to be obstructive and defines hydrocephalus as an active process with a mismatch between CSF production and absorption. Rekate classification is based on point of obstruction and developed on a mathematical model. Figure 49.3 shows different points of obstruction along the CSF pathway.

Box 49.1 Common causes of hydrocephalus

Congenital causes

- Chiari malformation or spina bifida
- Danday-Walker complex
- Atresia of foramen of Munroe
- Aqueduct stenosis (X-linked)
- Congenital arachnoid cysts

Acquired causes

- Haemorrhage
- Infection
- Traumatic head injury
- Tumour

49.2 Causes of Hydrocephalus

49.2.1 Post-haemorrhagic

Intraventricular haemorrhage (IVH) is one of the most serious complications in premature infants and an important cause of mortality and long-term neurological sequelae in this group.

When infants are born prematurely, they are essentially arrested at a gestational stage during which the development of the highly vascularized germinal matrix in the brain is ongoing. Because the capillary network of this structure is still anatomically immature in these infants, the vessels are especially fragile and susceptible to rupture in the face of fluctuating cerebral blood flow or cerebral venous pressure, both common in premature babies, especially during periods of respiratory distress. If these vessels rupture, it can result in bleeding into the germinal matrix and subsequently into the ventricles of the brain [19]. The subsequent development of hydrocephalus is usually ascribed to fibrosing arachnoiditis, meningeal fibrosis and subependymal gliosis, which impair flow and resorption of cerebrospinal fluid (CSF).

IVH is characterized by a spectrum of lesions amenable to classification by grade of severity. The first classification scheme, proposed by Papile et al. [20] was based on computerized tomography (CT) scan findings of the extent of bleeding and recognizes four grades of IVH that are cumulative and numbered from mild to severe:

- Grade I: germinal matrix hemorrhage (GMH) only
- Grade II: GMH + IVH with no ventricular distension
- Grade III: GMH + IVH + ventricular distension
- Grade IV: GMH + IVH + intraparenchymal hemorrhage

Mild IVH (grades I and II) is generally benign [21], while grade III and particularly grade IV may be related to early complications, such as posthemorrhagic hydrocephalus (PHH) with

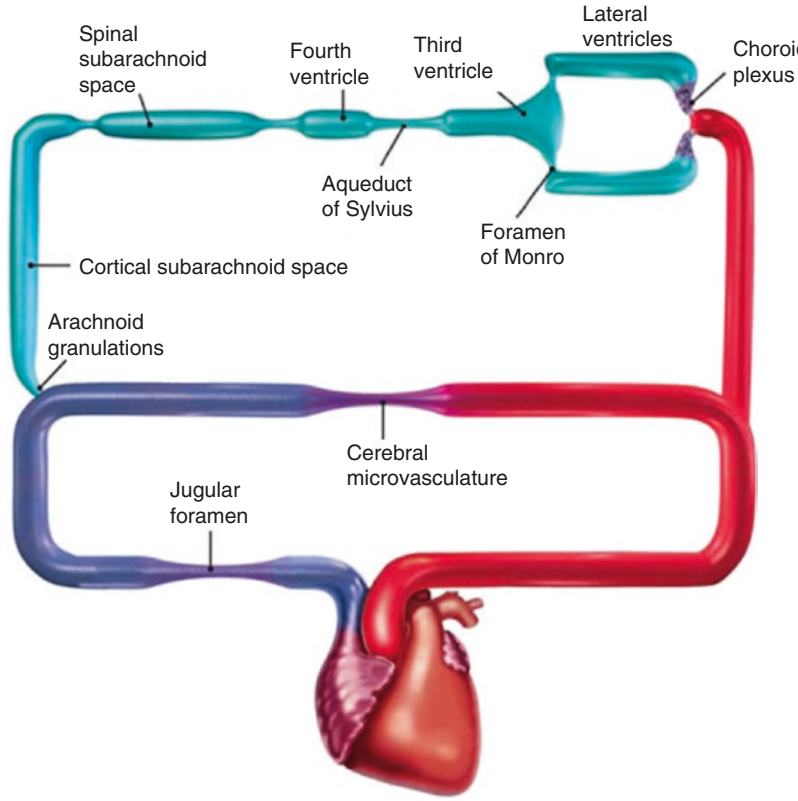

Fig. 49.3 Intracranial hydrodynamics represented as a circuit diagram with a parallel pathway of CSF flow and cerebral blood flow [18]

concomitant neurodevelopmental disabilities and high mortality. Grades II and III include intraventricular hemorrhages of variable severity as judged by the percentage of ventricle that contains blood or by the presence or absence of ventricular enlargement. IVH occurs in approximately 80% of cases with germinal matrix bleeding [22]. If the hemorrhage is large, it may even extend into adjacent parenchymal tissue [20], where the degree of injury dramatically impacts the neurological outcome. The correlation between the development of IVH and the actual gestational age at birth is thus dependent upon the stage of anatomical development of the germinal matrix, with the occurrence of IVH relatively uncommon after week 32. Estimated frequencies of germinal matrix bleeding and IVH range from 50 to 75% for infants born at less than 26 weeks, decline sharply after the 30th week of gestation, and decrease to less than 5% among unselected full-term infants [23].

The term post-hemorrhagic hydrocephalus (PHH) is generally applied when there is progressive accumulation of cerebral spinal fluid (CSF) under pressure with ventricular ballooning (ventriculomegaly or VM) and accompanying enlargement of the head [19, 24] (Figs. 49.4 and 49.5). VM typically develops 1–3 weeks following the initial intraventricular bleed [25, 26] in 55–80% of the IVH population, with 26–85% of these cases progressing to PHH. PHH should be suspected whenever IVH of grade II or higher is diagnosed.

PHH typically presents with symptoms of rising ICP, including apnea, vomiting, and abnormal posture, as well as rapidly increasing head circumference that crosses over the initial percentile or enlarges over 1.5 cm per week, a bulging anterior fontanel, and separation of the cranial sutures. However, the measurement of an enlarged head circumference is not sufficiently sensitive to aid in the diagnosis of hydrocephalus in the premature infant because ventricular dilatation can occur days to weeks prior to a detectable increase in the rate of head growth [27]. For the majority (65%) of newborns with PHH, the

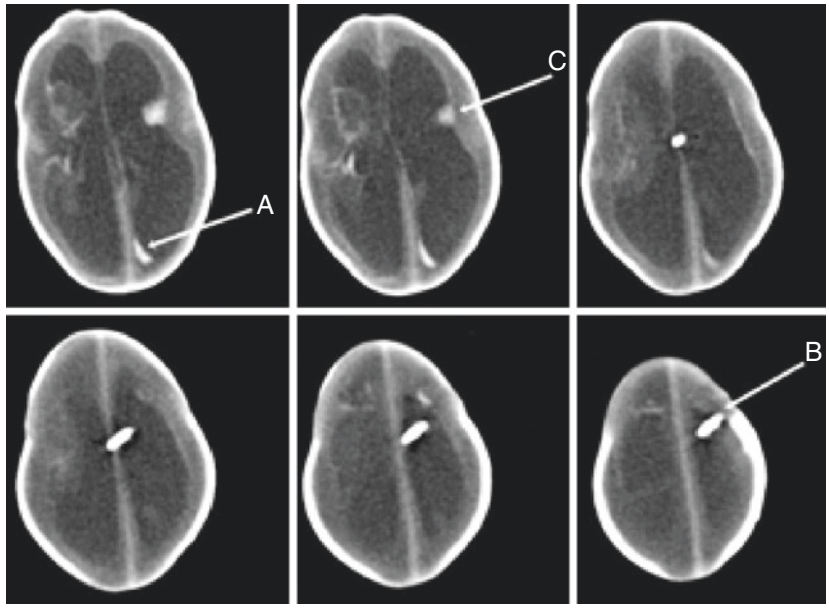

Fig. 49.4 Non-contrast axial CT (corrected age 29 weeks) images demonstrating the presence of a small amount of intraventricular hemorrhage (layering posteriorly within the occipital horn of the left lateral ventricle) (*A*), ventriculomegaly and the left frontal ventricular catheter portion of a ventricular catheter-reservoir (*B*). Small regions of thrombus are present within the lateral ventricles (*C*)

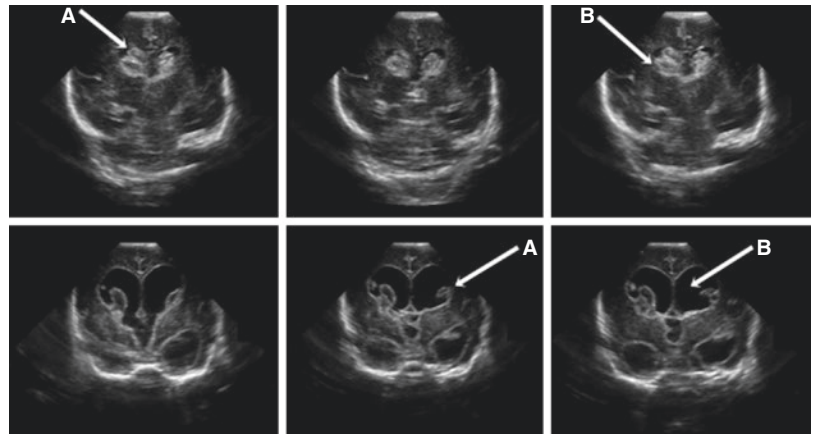

Fig. 49.5 *Upper panel*: Coronal cranial ultrasound images (corrected age 27 weeks) demonstrating the presence of bilateral IVH (*A*), right caudate nucleus hemorrhage (*B*) and ventriculomegaly. *Lower panel*: Subsequent cranial ultrasound images (corrected age 29 weeks) show evolving IVH (*A*) and progressive ventriculomegaly (*B*)

condition resolves spontaneously within a month, either regressing or stabilizing at an acceptable ICP (<approximately 80–110 mmH_2O), and these patients never require medical or surgical intervention [22]. Therefore, if the monitored progression continues at a slow rate, surveillance alone is the most appropriate management program. However, if close monitoring reveals rapid progression (increase in serial head circumference measurements of 2 cm/week with a full fontanel and split sutures) or if the slow progression persists beyond 2–4 weeks, interventions are indicated [28, 29].

The risk of IVH in the pre-term infant has been significantly reduced by measures that may indirectly ameliorate fluctuations in cerebral blood flow such as surfactant to reduce pulmonary hypertension and antenatal steroid administration [30, 31]. Some also advocate that premature infants should be maintained on paralytics and sedation for the first 72 h following birth to reduce the risk of IVH [31]. Once PHH

has been diagnosed radiologically, temporising interventional methods may be employed as some patients may either be too unstable for surgery or their hydrocephalus resolves with degradation of the IVH without obvious lasting imbalance to the CSF dynamics. Most cases of PHH occurs 3–4 weeks after IVH but it is important to note that many of these cases are clinically silent and early detection requires a high index of suspicion and serial radiological monitoring. Of those that develop PHH, over 50% become shunt dependant with a high rate of neurodevelopmental disabilities.

More recently, the DRIFT trial has suggested reduction in cognitive disability at 2 years in premature neonates with PHH treated with continuous ventricle washout and intraventricular infusion of Tissue Plasminogen Activator [32]. The treatment did not have any impact on the incidence of shunt dependence. Medical and surgical management options for PHH are discussed in the proceeding sections of this chapter.

49.2.2 Post-infectious

Post infectious hydrocephalus (PIH) is an important cause of hydrocephalus is the developed world and is most common cause of hydrocephalus in the developing world. Intrauterine infection can cause hydrocephalus when they involve the central nervous system. Infection not only impairs CSF flow and absorption but also compromise parenchymal development. These infections include Toxoplasmosis, cytomegalovirus, mumps and syphilis. Postnatal meningitis may result from amniotic infection where the membranes have been ruptured for a prolonged period. In the first 2 weeks of life, the organism is usually Escherichia coli and other Gram-negative enteric bacilli. In the second 2-week period, the pathogens are more likely to be Gram-positive cocci, Listeria and Pseudomonas [33–35]. In low birth weight neonates, pathogenic organisms include coagulase negative staphalococci, gram positive cocci and Candida species. In the developing world B-haemolytic streptococci and tuberculosis remain important causes of neonatal hydrocephalus. PIH typically occurs 2–3 weeks following diagnosis of bacterial meningitis and studies have shown that associated complications include abscess formation, ventriculitis and subsequent CSF loculations and intraventricular septations [35, 36]. The management is difficult and frequently requires multiple shunt placements and revisions with associated poor developmental outcome and high morbidity and mortality rates.

49.2.3 Chiari Malformation and Spina Bifida

Chiari malformations are a group of conditions with different etiologies which involve abnormalities in the posterior fossa and craniovertebral junction. These abnormalities are often associated with the presence of hydrocephalus due to changes they cause in cerebrospinal fluid (CSF) flow at the level of the craniovertebral junction. The Chiari I malformation (CM I), or hindbrain herniation syndrome, consists of downward herniation of the cerebellar tonsils through the foramen magnum into the cervical spinal canal [37, 38]. The degree of displacement is typically greater than 5 mm below the plane of the foramen magnum on sagittal magnetic resonance image (MRI) [38–42]. The vermis, fourth ventricle and brainstem are relatively normal. Syringomyelia occurs in 45–68% of cases [41, 43, 44]. It is associated with scoliosis in 42%, abnormal retroflexed odontoid process in 26%, and basilar invagination in 12% [39, 40, 42, 45–47]. The average age of onset is in the mid 30s, but it can occur in those as young as 3 months [45].

Chronic tonsillar herniation in CM I is most likely secondary to underdevelopment of the occipital bone and overcrowding of the cerebellum in a small posterior fossa. The fundamental defect is thought to involve underdevelopment of the occipital somites originating from the paraaxial mesoderm.

The most common symptom, occurring in up to 81% of patients, is suboccipital headache that is worsened with head dependency and valsalva-type maneuvers such as coughing, straining and exertion [48–50]. Over 70% of patients present with either ocular disturbances (such as diplopia,

blurred vision or retro-orbital pain), or otoneurological disturbances (such as dizziness, disequilibrium, tinnitus or ear pressure). Lower cranial nerve, brainstem and cerebellar findings include dysphagia, sleep apnea, dysarthria, tremors, impaired gag reflex and poor coordination. Permanent nocturnal central hypoventilation requiring ventilation has been reported [51]. Sensory and motor findings due to spinal cord dysfunction are common, especially when associated with syringomyelia. Over 90% of patients with syringomyelia present with spinal cord disturbances such as paresthesias, pain, burning dysesthesias or anesthesia, weakness, spasticity, atrophy, incontinence, trophic phenomena, impaired position sense, or hyperreflexia [52]. Scoliosis, which can occur in children with Chiari I—related syringomyelia, has been shown to improve following craniovertebral decompression.

The Chiari II malformation (CM II) is intimately associated with myelomeningocele, and involves vermian herniation with descent of the brainstem and fourth ventricle through a widened foramen magnum (see Fig. 49.6). The vermian "peg" may descend as low as the upper thoracic level [52–54]. Other findings include cerebellar inversion with absent cisterna magna ("banana sign" on ultrasonography), hypoplastic tentorium that inserts very low placing the torcular herophili just above the foramen magnum, and a medullary "kink" in two thirds of patients due to posterior displacement of a relatively mobile medulla along with a fixed spinal cord [52–54]. CM II is associated with many brain anomalies. Skull findings include enlarged foramen magnum, craniolacunia, scalloping of the petrous bones, jugular tubercles and frontal bone (known as the lemon sign on ultrasound), increased concavity of the basioccipital clivus, low inion and sometimes basilar impression and assimilation of the atlas [52, 55, 56]. Cerebral findings include enlarged massa intermedia, polygyria, and agenesis of the corpus callosum. Below-average intelligence occurs in over half of patients [57]. Other findings include prominent anterior commissure, absence of the falx with interdigitation of the occipital and parietal lobes, agenesis of the olfactory tract, absence of the cingulate gyrus, heterotopic gray matter, fusion of the colliculi (tectal beaking), cranial nerve nuclei malformation, and decreased cerebellar volume with dysplastic or absent folia. In CM II, cranial and upper cervical nerves display an upward course [52].

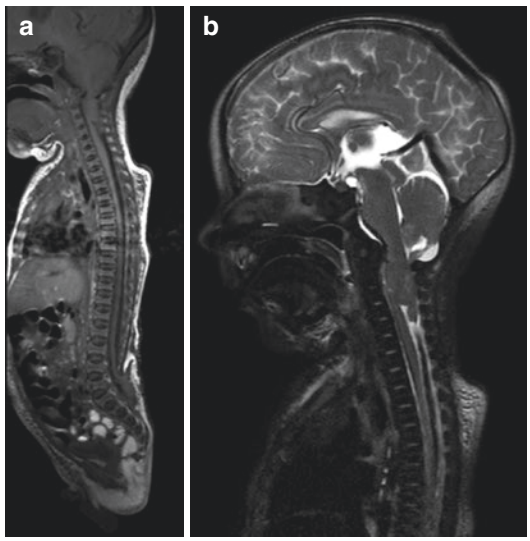

Fig. 49.6 Sagittal T1 (**a**) and T2 (**b**) weighted MRI images obtained following closure of lumbosacral myelomeningocoele demonstrating Chiari II malformation

CSF flow abnormalities are abundant in CM II. Hydrocephalus is seen in approximately 90% [52] (see Fig. 49.7). Other common ventricular abnormalities include a small, elongated low lying fourth ventricle that can be displaced into the cervical canal, with outwardly projecting choroid plexus (embryological location), small aqueduct, "shark tooth deformity" of the third ventricle (anterior diverticulum), colpocephalic lateral ventricles, "beaking" of the frontal horns, occasionally absent inferior medullary velum and occasionally absent foramen of Magendie [52]. Development of the CM II is likely associated with the open neural tube defect and drainage of CSF through the central canal during development [58]. Without ventricular distention, the posterior fossa does not develop normally. This theory also explains the development of hydrocephalus, due to blocked CSF outflow at the foramina of Lushka and Magendie [58]. Nearly every patient with CM II presents initially with an open neural tube defect. Frequently, the diagnosis is made in utero.

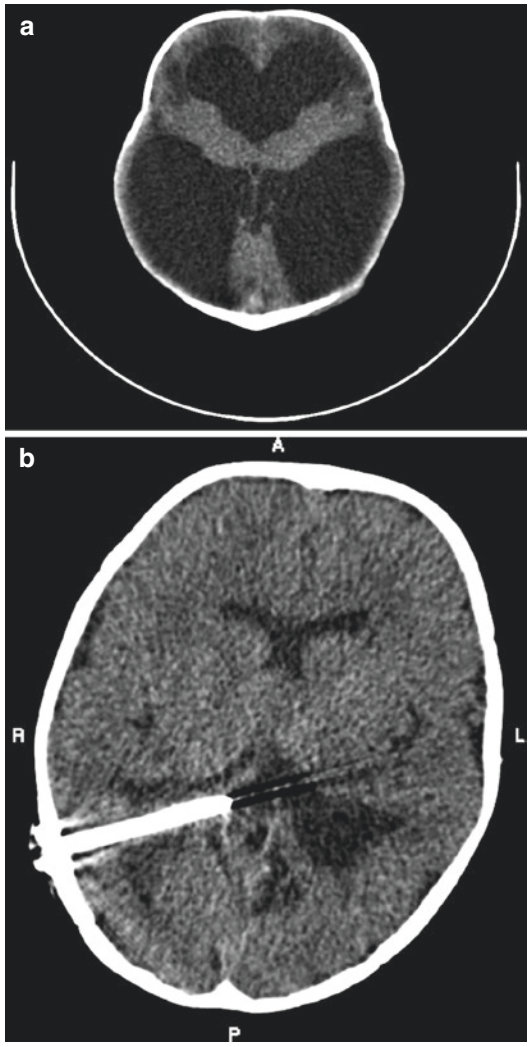

Fig. 49.7 Axial CT images demonstrating ventriculomegaly (**a**). The hydrocephalus was treated with insertion of ventriculoperitoneal shunt with resolution of ventriculomegaly as demonstrated on the CT scan obtained 1 year after shunt insertion (**b**)

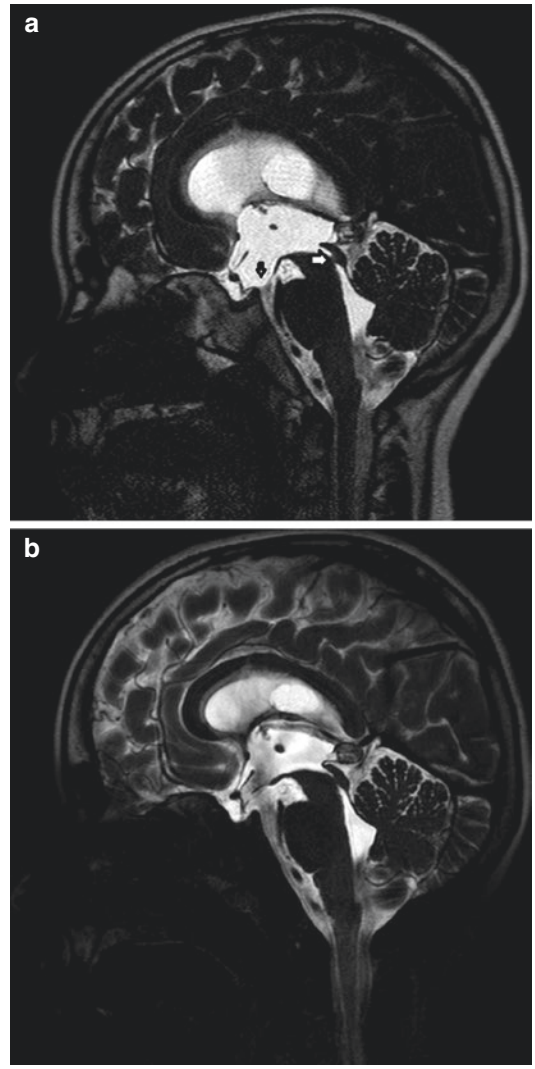

Fig. 49.8 CINE sequence sagittal MRI images demonstrating membranous occlusion of the aqueduct with dilatation of the proximal part of the aqueduct (*white arrow*) and depressed floor of the third ventricle (*black arrow*) indicating hydrocephalus (**a**). This was treated with endoscopic third ventriculostomy. Post operative CINE sequence MRI image demonstrates restoration of the normal architecture of the third ventricular floor and a flow void in the prepontine CSF cistern demonstrating patent third ventriculostomy (**b**)

Symptoms attributable to CM II vary with age. In all age groups, symptoms are worsened with the presence of hydrocephalus.

49.2.4 Aqueduct Stenosis

Aqueductal stenosis is responsible of 6–66% of cases of hydrocephalus in children (more than 50% presenting in the first year of life) [59–61] (Fig. 49.8). Ceddia and co-workers reported an incidence of congenital hydrocephalus of 0.3–2.5/thousand born alive, 20% associated to aqueduct stenosis [62]. There is a mild male prevalence and there are two peaks of distribution for age including one in the first year of life [59]. In about three quarters of patients with aqueduct

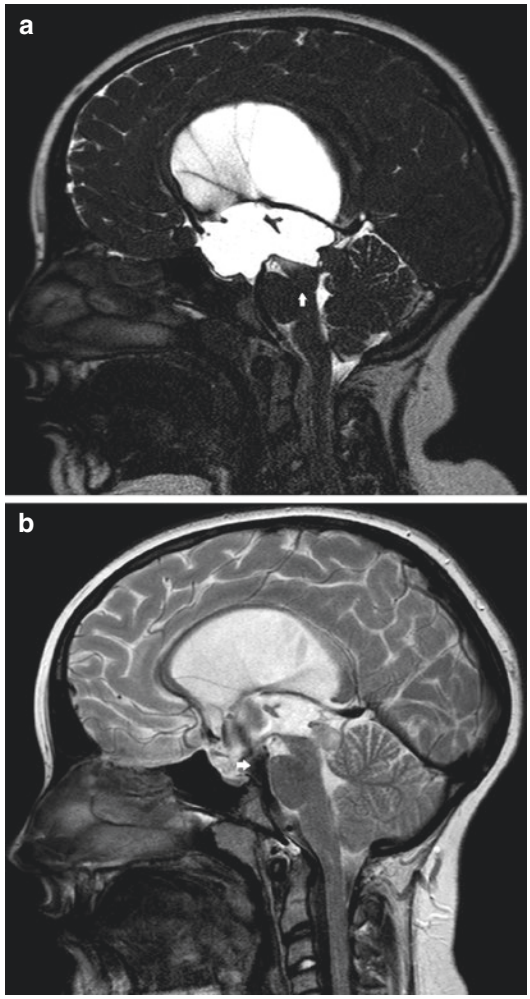

Fig. 49.9 Pre-operative (**a**) and postoperative (**b**) CINE sequence sagittal MRI images demonstrating hydrocephalus secondary to a tectal plate tumour (*white arrow*) causing aqueduct stenosis. Again note the depressed floor of the third ventricle in (**a**). This was treated with Endoscopic third ventriculostomy. Note the flow void through the ventriculostomy (*white arrow*) in (**b**)

stenosis the etiology of the disorder is not known [60]. In remaining cases it can be attributed to different causes including rare X-linked syndromic cases, infectious, haemorrhagic, neoplastic (e.g. tectal tumours) (Fig. 49.9), and vascular (Vein of galen aneurysms). Aqueductal stenosis has also been reported in association with different CNS malformations, such as Spina Bifida, Dandy-Walker complex, retrocerebellar and supracollicular cysts [60, 63, 64].

49.2.5 Dandy Walker Complex

The classic Dandy Walker Malformation (DWM) is defined by the presence of a large median posterior fossa cyst (diverticulum) widely communicating with the fourth ventricle, associated with a rotated, elevated and hypoplastic or aplastic cerebellar vermis contacting an upwardly displaced tentorium and similarly displaced transverse sinuses. There is in addition posterior bossing of the posterior fossa contributing to its enlargement and antero-lateral displacement of normal or hypoplastic cerebellar hemispheres [65]. The cystic dilatation of the fourth ventricle fills the posterior fossa and extends into the cisterna magna, which is compressed between the dilated fourth ventricle and the posterior fossa dura. The cystic CSF collection in the posterior fossa does not communicate freely with the basal cisterns (Fig. 49.10).

Dandy Walker Complex (DWC) was described by Berkovich et al. to denote a spectrum of disorders including classic DWM at one extreme all of which include a cyst communicating with the fourth ventricle [66]. The crucial point according to Barkovich et al. is to assess the axial images at the mid-fourth ventricle level; no vermian tissue interposed between the fourth ventricle and the cyst indicates a Type A DWC which is either a classic DWM or a 'Dandy Walker Variant' (DWV). The Dandy Walker Variant being, effectively, the same widely communicating cyst without all of the features of a classic DWM, particularly the enlargement of the posterior fossa. If vermis is interposed between the cyst and the fourth ventricle at the level of the mid-fourth ventricle then this is referred to as a type B DWC lesion, the equivalent, traditional term being mega cisterna magna (MCM).

Dandy walker complex accounts for around 4% of all cases of hydrocephalus with the incidence of the order of 1:25,000–1:30,000 live births [67–69]. The majority of foetuses with prenatally diagnosed DWM or DWV will not survive to term [70].

The Dandy Walker Complex can arise in the context of mendelian disorders, chromosomal disorders (trisomies, deletions and duplications)

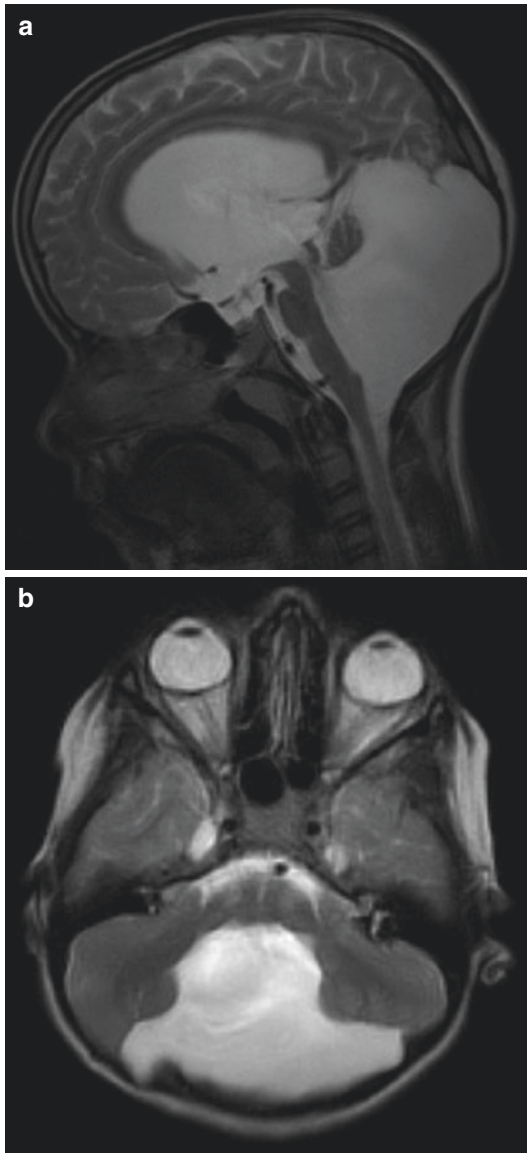

Fig. 49.10 Dandy Walker Malformation (DWM). T2 W MR images in the midsagittal (**a**) and mid-fourth ventricle axial (**b**) plains show the salient features of the classic DWM namely the rotated and partially agenetic vermis, the high insertion of the torcular, the enlarged posterior fossa and the wide communication between the fourth ventricle proper and the 'cyst'. Note the widely patent aqueduct with flow void

and with teratogen exposure (alcohol, viral infection, drugs). In addition the DWC may be associated with other brain malformations in 68% of cases [71] including aqueduct stenosis, callosal agenesis and neural tube defects. In addition significant extracerebral malformations; particularly of the heart, the kidneys, the palate, the perineum and the vertebrae, are present in about 45% [67, 68]. For these reasons it is imperative that every new case of the DWC is assessed by a clinical geneticist and other abnormalities identified.

49.2.6 Craniosynostosis

Craniosynostosis is an uncommon cause of neonatal hydrocephalus. The pathogenesis of hydrocephalus in craniosynostosis involves mechanical obstruction of CSF outflow due to crowding of the posterior fossa [72] and impaired CSF absorption resulting from venous outlet obstruction [72].

49.2.7 Uncommon Congenital Malformations

49.2.7.1 Encephalocoele

The term encephalocoele is used to describe all congenital cranial herniations. Traditionally encephalocoeles are divisible into posterior and anterior encephalocoeles. Posterior lesions are commoner and classified into parietal and occipital lesions with the occipital lesions including supra and infratorcular subtypes. These are cystic swellings with variable skin coverage. A significant subgroup of these includes the atretic encephalocoele, which is usually flat and non-cystic. The rarer anterior encephalocoeles are herniations through the anterior skull base and they are classified as, sincipital, where the herniation is through the foramen cecum anterior to the cribriform plate or basal where the herniation is through the sphenoid bone and sinus.

Posterior encephalocoeles are associated with very significant brain abnormalities including hydrocephalus, agenesis of the corpus callosum, DWC, grey matter heterotopias and venous drainage anomalies (Fig. 49.11). Parietal lesions are

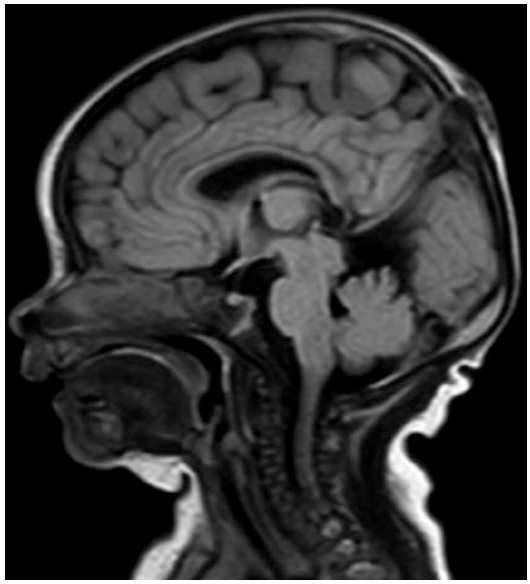

Fig. 49.11 Sagittal T1-weighted MRI scan of a new born with a midline occipital lump covered with tuft of hair. The lesion was resected and histology confirmed it to be an encephalocoele. Note the aberrant straight sinus

particularly associated with dorsal interhemispheric cysts which may communicate directly with the ventricular system, in extreme cases they may be associated with holoprosencephaly. MRI is mandatory before exploring these lesions to delineate other abnormalities and MRV may help delineate venous anatomy which is frequently abnormal. The incidence of hydrocephalus in encephalocoeles is variably reported with the association reportedly higher with posterior encephalocoeles.

49.2.7.2 Agenesis of Corpus Callosum

The corpus callosum is the major commissural structure and its complete or partial agenesis is a common brain malformation with a prevalence of 0.5–70 per 10,000 in children with developmental delay. It is rarely isolated and is often associated with other serious brain malformations i.e., DWC, Chiari malformations, holoprosencephaly and interhemispheric cysts [73] (Fig. 49.12).

A large survey of the aetiology of congenital hydrocephalus indicated that agenesis of the

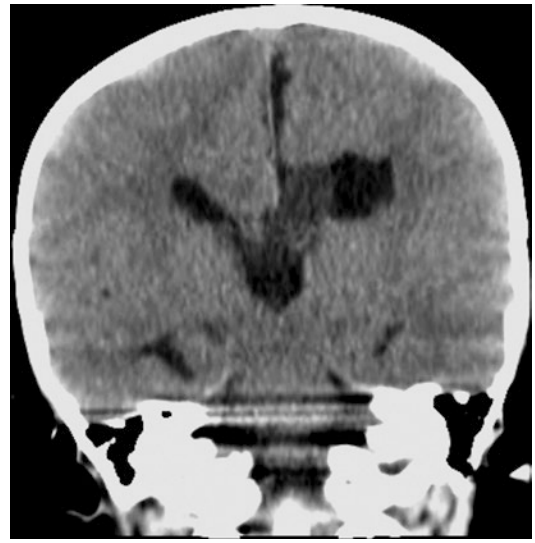

Fig. 49.12 Coronal CT image showing partial agenesis of the corpus callosum and an associated cyst

corpus callosum was a relatively common cause of foetal and to a lesser extent infantile hydrocephalus [74]. In a large literature review encompassing 705 cases of agenesis of the corpus callosum (ACC) hydrocephalus was present in some 23%, often associated with distinct syndromic states (Aicardi, Acrocallosal, Andermann and Shapiro syndromes) [75]. More recently it has been realised that X-linked hydrocephalus overlaps with X-linked agenesis of the corpus callosum and a number of other conditions resulting in a spectrum of disorders which include all or some of: corpus callosum hypolpasia, mental retardation, adducted thumbs, spastic paraplegia and hydrocephalus. It has gained the acronym CRASH syndrome and they are related to mutation in the L1 cellular adhesion molecule gene [76]. ACC can be associated with the finding of interhemispheric arachnoid cysts which again may be related to hydrocephalus.

49.2.7.3 Hydrancephaly

Hydranencephaly describes a severe brain malformation in which, although remnants of nonfunctional cortex may be present, there is an extensive reduction in brain parenchyma that has

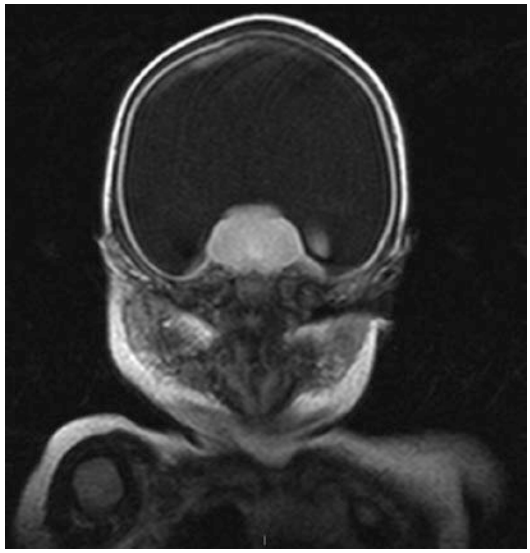

Fig. 49.13 Coronal T1-weighted MRI scan demonstrating hydrancephaly

been replaced with CSF (Fig. 49.13). The aetiology is variable and infants have a limited lifespan. Ventriculoperitoneal shunts have been inserted to control head size in infants and although the literature is sparse there are reports of relatively prolonged survival [77]. Children with hydranencephaly never gain consciousness or awareness regardless of shunt insertion but with aggressive nursing care can have prolonged survival and control of head size reduces the incidence of cranial pressure sores [78].

49.2.7.4 Holoprosencephaly

Holoprosencephaly (HPE) is a complex, congenital brain malformation the essence of which is the failure of the forebrain to split into two hemispheres; it is associated with facial anomalies. It occurs in 1:250 pregnancies approximately but only 3% of foetuses will survive to term so the live birth prevalence is of the order of 1 in 10,000 [79–81].

The incidence of hydrocephalus increases in the more severe forms of the malformation and an important guide is that the majority of children with HPE have microcephaly, when it is not present the child should be investigated for potential hydrocephalus [82]. Although the functional status achieved by children with severe forms of HPE is very limited insertion of a ventriculoperitoneal shunt can make nursing care easier [83].

49.2.8 Neoplasms

Neoplasms are uncommon but important cause of hydrocephalus in neonates. Hydrocephalus can arise from obstruction at various points of CSF pathway. Neoplasm associated hydrocephalus can be further subdivided according to tumour location into three types, supratentorial, infratentorial and spinal. The commonest types in newborns are often of neuroectodermal origin and are more commonly supratentorial.

49.2.9 External Hydrocephalus

This controversial pathological entity is also linked to or referred to as ‘pseudohydrocephalus’, ‘benign subdural effusion’, benign enlargement of the subarachnoid spaces’ and ‘benign pericerbral effusion’. Its etiology and pathophysiology in relation to CSF dynamics is uncertain but include abnormal collections of fluid in the subarachnoid or subdural space overlying the cerebral convexity. The condition occurs while the cranial sutures are open. Although most cases do not require intervention and maintain a benign course some patients present with features related to mass effect and raised intracranial pressure and in rare cases may require management with a subdural-peritoneal shunt.

49.2.10 Overproduction

Choroid plexus papillomas are rare intraventricular tumours that may cause overproduction of CSF resulting in massive ventricular enlargement. They are most often found in the lateral ventricle and appear as homogenously enhancing lesions on MRI. They are vascular lesions and resection of the tumour may be curative if the tumour is benign.

49.3 Clinical Presentation of Hydrocephalus in Neonates

The clinical presentation of hydrocephalus is remarkably similar despite the varied etiology and is related to signs and symptoms of localised or generalised raised intra-cranial pressure (see Box 49.2).

An increase in head size is the major feature of hydrocephalus in the neonate, with an increasing deviation of head circumference from the normal centiles for age. Incremental plotting of head circumference is essential in this regard, using a centile chart such as that produced by Gairdner and Pearson, allowing for gestational age at birth [84]. It should be noted that there are causes for head enlargement other than hydrocephalus (e.g. a familial tendency for a large head, osteofibromatosis, macrocephaly or intracranial cysts). The head-shape may also be abnormal.

Box 49.2 Symptoms and signs of raised intracranial pressure in newly diagnosed hydrocephalus or shunt malfunction in the infant and young child

- Irritability
- Impaired level of consciousness
- Vomiting
- Failure to thrive
- Poor feeding
- Developmental delay
- Increasing head circumference crossing centiles
- Poor head control
- Tense anterior fontanelle
- Dilated scalp veins
- "Setting sun" sign (combination of upper eyelid retraction and failure of upgaze)
- Bradycardia
- Apnoeic spells
- Seizures

Bulging of the anterior fontanelle with a variably open posterior fontanelle, separation of the suture lines and dilatation of superficial scalp veins (due to venous reflux from cerebral sinuses) are classical feature of raised intracranial pressure in hydrocephalus. "Setting sun sign", an upward gaze palsy may be seen with the superior sclera visible. The component parts of this phenomenon consist of downward rotation of the eyeballs and retraction of the upper eyelids and may be accompanied by brow raising. It may be intermittent, disappearing when ICP is reduced. However, this sign can also be seen and elicited though rarely in normal infants. Sixth nerve palsy can be seen as this nerve is most sensitive to pressure due to is long intracranial course. Papilloedema, decreased level of consciousness and other focal neurological deficit can be presenting signs too. Opisthotonic posturing, bradycardic and apnoeic episodes are critical signs of raised intracranial pressure suggesting brainstem compromise and requires emergent neurosurgical assessment and treatment.

Other important presenting symptoms of hydrocephalus in the infant are related to raised intracranial pressure such as irritability, lethargy, poor feeding, vomiting, failure to thrive, and delayed motor development. The clinical presentation may also include features specifically related to the associated causative pathology.

49.4 Imaging and Investigations

Skull X-rays may shows signs of raised intracranial pressure however they are largely obsolete and are not used as part of the standard diagnostic workup and management of hydrocephalus in the newborn. Historically, widening of the sutures beyond 3 mm can be seen with associated *lacunar* skull defects ("copper beating") and erosion of posterior clinoids at the dorsum sella.

Ultrasonography is exceptionally useful as a non-invasive technique [85–87] (Fig. 49.5) Antenatal sonography can detect hydrocephalus in utero and is the screening procedure of choice in patients under the age of 18 months.

Measurements of both the ventricle size and the cortical mantle are possible. Serial ultrasonography has not only improved the ability to detect hydrocephalus, but has also resulted in more prompt treatment of this condition and has proved extremely useful in detecting IVH and hydrocephalus in premature infants. It is considered the initial investigation of choice for neonates with hydrocephalus and can be performed at the bedside. It is worth noting that although ultrasound is sensitive and specific for the diagnosis of hydrocephalus, clarification of its aetiology usually necessitates subsequent CT or MR imaging.

Computed topography (CT) is widespread, rapid and easy to interpret tool. CT diagnosis of hydrocephalus is based on ventriculomegaly including ballooning of frontal horns of lateral ventricles and periventricular low density suggesting trans-ependymal absorption of CSF secondary to raised pressure (see Fig. 49.7). CT however is less efficient in defining the pathoanatomical substrate as compared to Magnestic resonance imaging. In addition it exposes the child to radiation the cumulative doses of which can be significant through the lifetime of treatment.

Magnetic resonance imaging (MRI) is the gold standard for diagnosing hydrocephalus related causative pathology and demonstrates the ventricular and CSF anatomy in exquisite detail. Pathological entities such as aqueduct stenosis, Chiari malformations and neoplastic lesions are readily identifiable. MRI also allows for detailed surgical planning when considering the options of endoscopic third ventriculostomy, shunting, posterior fossa surgery and so forth. MRI T1 and T2 weighted dynamic flow sequences can highlight the relevant ventricular, periventricular and CSF flow with remarkable clarity [88]. This is particularly useful when assessing the anatomy of the third ventricle and aqueduct in relation to determining the surgical procedure of choice. Volume data-sets for both CT and MRI are now readily obtainable which are compatible to bespoke three-dimensional neuronavigation workstations for shunting and neuroendoscopic procedures. MRI is increasingly used for antenatal investigation and is valuable in both outlining congenital malformations and haemorrhage [89].

Postoperative imaging to assess ventricular size after shunting or neuroendoscopy can be performed with both CT and MRI. However after a third ventriculostomy, phase contrast dynamic MRI sequences are required to identify CSF flow through the ventriculostomy and is best visualised on sagittal images [88, 90]. Invasive pressure measurements such as fontonometry are less often justified as they are unreliable when compared with modern methods of imaging.

An antibody screen should be carried out if an intrauterine infection is considered. CSF analysis is indicated where infection or haemorrhage is suspected, as these factors may influence the subsequent clinical management. A raised protein level, or indeed bloodstained CSF, is not necessarily a contraindication to shunting but is taken into consideration when determining the timing of shunt placement. It may be appropriate to delay surgery until the protein count and/or the blood in the CSF clears to an acceptable degree. If active infection is suspected then a temporising external ventricular drain would be preferred before a permanent shunt can be implanted once the infection has been treated and confirmed with sterile CSF samples.

49.5 Management Options

The complications associated with surgery in the low-birth weight neonate or neonates with co-existing unstable medical conditions raises the need to explore non-surgical means of managing hydrocephalus. The additional possibility of occasionally self-limiting conditions such as PHH may only require temporising management options. However, pharmacotherapeutic agents such as acetozolomide, frusemide and steroids have not been shown to be effective in reducing the rate of shunting and cannot be recommended [91, 92]. Although historically a common practice, serial lumbar punctures should probably no longer be used. A published meta-analysis concluded that no evidence of benefit was demon-

strated with a significant risk of secondary infection [93]. Similarly serial multiple percutaneous ventricular taps have been abandoned by most large tertiary neurosurgical centres due to the numerous associated complications such 'puncture porencephaly', infection and encephalomalacia [94, 95].

Surgery remains the overwhelming mainstay of treatment for hydrocephalus in the newborn. CSF Shunting has converted hydrocephalus from an almost exclusively fatal disease to a frequently curable condition. The first permanent CSF diversion for hydrocephalus was performed by Mikulicz in 1893 in the form of a ventriculosubarachnoid-subgaleal shunt [96]. This procedure was also simultaneously the first intrathecal ventriculostomy. Since then virtually every anatomical cavity has been utilised as a potential reservoir or conduit for CSF drainage with varying degrees of success. These include subcutaneous tissues of the scalp, atria, pleura, ureters, gallbladder and thoracic duct. Most of these are no longer considered in standard 'first line' practice in newborn hydrocephalus. This section outlines the most common surgical techniques in newborn hydrocephalus surgery.

49.5.1 External Ventricular Drainage

EVD has been widely used in the temporary treatment of hydrocephalus for several decades. The frontal and occipital horns of the lateral ventricles are the site of choice via a single burr-hole and the CSF is drained into a sterile closed circuit system which can be continuously controlled by a simple gravity based outflow valve. In situations of acute symptomatic hydrocephalus secondary to operable or potentially operable lesion, EVD can be employed to provide necessary control until such time as to allow further assessment and definitive treatment of hydrocephalus. It is of particular use in the presence of active infection whereby a permanent shunt system cannot be placed until the infection has been successfully treated and also until a high related CSF protein level (as seen in some peri and post infectious settings) normalises to allow shunt placement. It also allows for the direct administration of intrathecal antibiotics into the infected CSF space. EVD is also potentially useful in IVH or PHH as a temporising measure before either persistent hydrocephalus has been confirmed or the blood load has reduced. In PHH, EVDs have also been used in several studies for administration of intraventricular fibrinolytic therapies and CSF irrigation however these have not translated to proven clinical practice and remain experimental [95, 97].

Potential complications associated with EVDs include infection and catheter dislodgement. Recent introduction of antibiotic impregnated EVD systems have reduced the risk of infection however it remains the major source of EVD related patient morbidity.

49.5.2 Subcutaneous Reservoir Ventricular Catheter Placement

This device comprises of a frontal subcutaneous reservoir with a catheter entering the ventricle (Figs. 49.14, 49.15, and 49.16). It is

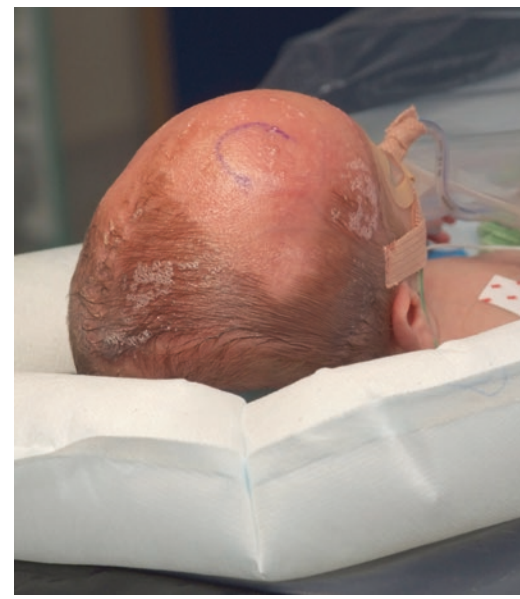

Fig. 49.14 Preoperative skin marking for insertion of a right frontal subcutaneous CSF reservoir

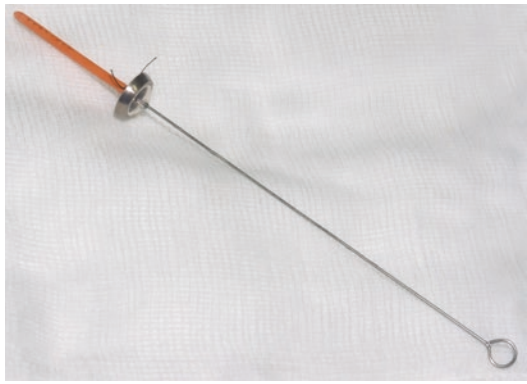

Fig. 49.15 Intraoperative image of ventricular catheter connected to subcutaneous reservoir. (A stylet has been inserted through the reservoir and the catheter to aid insertion)

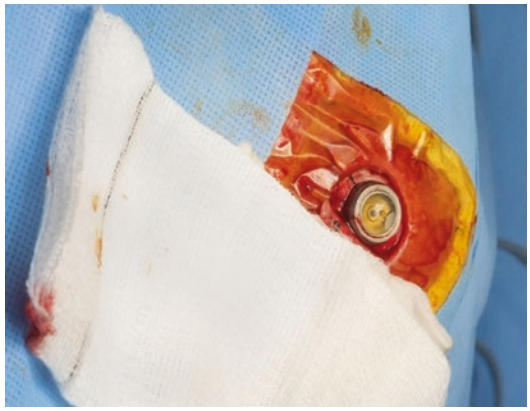

Fig. 49.16 Intraoperative image following insertion of subcutaneous CSF reservoir. The stylet shown in Fig. 49.15 has been removed. Note the xanthochromic fluid in the reservoir typical of post haemorrhagic hydrocephalus

mainly used in neonates with symptomatic hydrocephalus whose low birth weight and/or the potential for spontaneous arrest of the hydrocephalus preclude the immediate need for a permanent shunt. It is a viable option in PHH. The reservoir allows repeated bedside aspiration of CSF, has lower infection rates compared to EVD and also allows access for administration of intraventricular antibiotics. Complications and limitations include skin erosion and only intermittent intracranial pressure control.

49.5.3 Ventriculoperitoneal Shunt

49.5.3.1 Overview

Ventriculoperitoneal shunt is the most common form of implantable CSF shunts. The method was first described in 1908 and was initially less favoured than the ventriculo-atrial (VA) or ventriculopleural shunt [96]. The peritoneum has since become the drainage site of choice due to complications with VA shunts such as sudden death from pulmonary embolism, endocarditis and nephritis were noted. Another recognised problem in many VA shunts in the neonate is the need to lengthen the lower end as the child grows and the catheter pulls up out of the atrium. This can be obviated with VPS in the neonate with a longer intraperitoneal catheter. VPS hardware includes a ventricular catheter, CSF reservoir, a one way shunt valve and distal peritoneal catheter.

The choice of valve type remains a personal choice and a regular source of debate within the neurosurgical community as there is no high quality evidence favouring one type over another. Valve types include differential-pressure, flow-regulating, gravity-actuated and programmable valves. All the valve types only allow unidirectional flow of the CSF. An anti-siphon device may be included in the system to prevent over-drainage. In practice some factors that may influence decision making include valve size and profile in relation to newborn/premature neonate scalp skin, cortical mantle thickness, cost and individual surgeon experience. Some authors advocate a flow control valve for shunts in the newborn to avoid the later complication of slit ventricle syndrome. This is related to chronic over-drainage and is seen most commonly in patients who have a shunt implanted in the first 2 years of life [98]. Over-drainage and development of subdural haematomas in newborns with large ventricles and thin cortical mantle may be avoided with high-resistance valves [99].

The catheters are usually made from synthetic silicone rubber. The use of antibiotic impregnated and silver coated shunt tubing with in-vivo antibacterial activity is gaining popularity and

may confer a protective benefit against infection, particularly in the neonatal setting [100]. Further randomised studies are required to confirm this.

Both frameless, and frame-based neuronavigation systems have been utilised to reduce the incidence of poorly sited ventricular catheters and recent studies have shown benefit in catheter placement accuracy but it remains to be seen if this relates to a significant reduction in shunt revision rates in the long-term [101]. With the bespoke electromagnetic (EM) frameless neuronavigation system no rigid head fixation, pins or screws is required and this confers a significant advantage for neonatal shunt surgery. Previous studies on endoscopic versus non-endoscopic catheter placement have not demonstrate any difference in shunt revision rates [102].

49.5.3.2 Surgical Technique

Routine preoperative preparations such as blood parameters are a necessity. The patient is positioned whilst under general endotracheal anaesthesia. Antibiotic prophylaxis is recommended such as a cephalosporin e.g. Cefotaxime at the time of induction. The head is rotated to the opposite side to the shunt with the neck extended to create a straight line between the scalp and abdominal incision. The site of the burr-hole and abdominal incision should be marked prior to skin preparation and draping. (Fig. 49.17) Occipital burrholes are usually 3–4 cm from the midline along the lambdoid suture. Frontal burrholes are 2–3 cm along the coronal suture from midline. It is vital to tailor the burr-hole to the ventricular morphology on imaging so as to ensure optimal ventricular catheter placement. In infants with splayed sutures, access can be achieved via an opening of the sutures. The site of burrhole is of surgeon's preference as there is little evidence showing advantages of one over the other. Occipital burrholes are traditionally used as they are more cosmetically acceptable. Durotomy is made and the brain pia is cauterised. Dural opening should be kept minimal to reduce the risk of CSF escape around the ventricular catheter and hence promoting CSF leak.

The abdominal incision is usually performed on the same side either upper midline or paraumbilical site, however the site is unimportant. The most prudent part is to be sure the peritoneum space is opened. Open technique, use of trocar [103] and more recently laparoscopic assistance have been described [104]. The distal catheter is tunnelled subcutaneously from the burrhole site to the abdominal opening, or vice versa (Fig. 49.18). If a frontal burrhole is used, an intervening incision is made at the occiput.

The ventricular catheter is introduced mounted on a stylet. The trajectory is determined according to external landmarks. From the occipital burrhole, a target at the midpoint of the forehead at the hairline so that the lateral frontal horn will be entered. From a frontal burrhloe, aim for a target of the intersecting planes midpupillary line and the external auditory meatus. Intraoperative ultrasonography or image guided stereotaxy (for example EM guidance) [101] can be used for

Fig. 49.17 Intraoperative image during insertion of right parietal ventriculoperitoneal shunt after skin preparation and draping

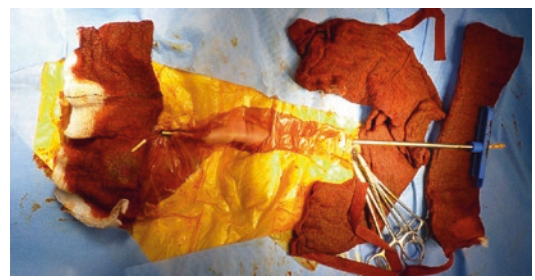

Fig. 49.18 Intraoperative image during insertion of ventriculoperitneal shunt. The tunneller has been passed from the abdomen to the right parietal incision

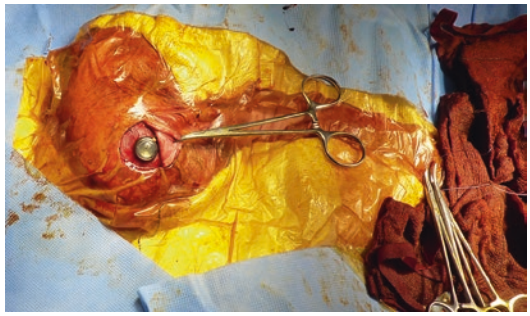

Fig. 49.19 Intraoperative image during insertion of ventriculoperitoneal shunt. The right parietal burrhole seated reservoir is visible with the attached distal catheter

more accurate positioning of the catheter. CSF Pressure may be measured at this point and a sample of CSF taken for biochemical and microbiological examinations. The proximal catheter is connected to the distal catheter via a reservoir (Fig. 49.19) and a valve system, depending on what type is being used.

The distal end is examined to ensure that there is free flowing CSF. The distal catheter is placed within the peritoneum. The peritoneum is closed using absorbable sutures, the muscle layers and skin are then closed.

49.5.3.3 Image Guided Placement of Ventricular Catheter

Both frameless and frame-based neuronavigation systems have been utilised to reduce the incidence of poorly sited ventricular catheters and recent studies have shown benefit in catheter placement accuracy but it remains to be seen if this relates to a significant reduction in shunt revision rates in the long-term [101]. With the bespoke electromagnetic (EM) frameless neuronavigation system no rigid head fixation, pins or screws is required and this confers a significant advantage for neonatal shunt surgery. Previous studies on endoscopic versus non-endoscopic catheter placement did not demonstrate any difference in shunt revision rates [102].

49.5.3.4 Complications

Complications of VPS most commonly includes infection, malposition of the ventricular catheter, mechanical failure leading to suboptimal drainage or blockage, overdrainage, shunt migration/disconnection and less commonly intra-abdominal sequelae such as bowel perforation, hernias, hydrocoeles, appendicitis and peritonitis. Shunt complication rates are significantly higher in the newborn and studies have shown low-birth weight to be linked to a higher incidence of shunt infection and revision rates [105]. If the CSF is sterile on insertion, the usual organisms causing postoperative shunt infection are skin commensals such as Staphylococcus epidermidis (Coagulase negative Staphalococcus). Where infection has been proven, the removal of the entire system and temporary CSF diversion via an EVD and concomitant intrathecal antibiotic administration is usually necessary. The treatment of shunt infections has been reviewed extensively by Bayston et al. [106].

Unfortunately despite advances in neuronavigation and shunt tubing material, shunt failure remains a considerable source of morbidity for hydrocephalus patients with up to 40% of shunts failing in the first year [107]. Indeed, shunt failure remains an almost inevitable consequence during a patient's life up to 80% of shunts requiring revision after 12 years [108].

49.5.4 Ventriculoatrial Shunt

Ventriculo-atrial shunts are indicated in patients with intraabdominal pathologies precluding the use of peritoneum as a drainage site. These include necrotising enterocilitis, peritonistis and adhesions secondary to extensive abdominal surgery.

These may be performed in a similar fashion to ventriculo-peritoneal shunts except for the lower incision which is over the right side of the neck. The objective is for the shunt tip to lie in the superior vena cava just rostral to the tricuspid valve. The two most common methods are open versus percutaneous insertion. Access to the jugular vein can be achieved by exposing the common facial vein, which is tied proximally and held with a stay suture at the venotomy site, the distal catheter is fed into the superior vena cava. Intra-operative fluoroscopy or X-rays are helpful

in achieving the ideal position. Throughout the procedure, the anesthiologist should inform you of any cardiac alterations or rhythm changes. A purse-string suture is closed around the catheter sufficiently to prevent hemorrhage, but not so tight as to cause obstruction to the catheter. Percutaneous methods into the jugular or subclavian veins can be achieved with the aid of ultrasound guidance and fluoroscopy [109–111].

Complications include the need to repeatedly lengthen the distal catheter as the child grows, higher risk of bacteremia and sepsis and specific vascular complications including thrombosis, micro-emboli with secondary pulmonary hypertension and corpulmonale, macroemboli with pulmonary embolism and vascular perforation.

49.5.5 Ventriculopleural Shunt

Ventriculo-pleaural shunts are only used in cases where peritoneum and right atrium cannot be used as sites for CSF diversion. It is rarely performed in neonates or indeed infants and not recommended in this age group as the pleural cavity cannot cope with the benign pleural effusion that results from CSF drainage.

The proximal approach is identical to the ventriculo-peritoneal shunt placement. The pleural space can be entered at a variety of sites however along the anterior axillary line in the fifth intercostal space is both convenient and safe. Intercostal muscle layers are split on the upper border of the rib to avoid the neurovascular bundle to reveal the pleura. It is then opened, the distal catheter is then introduced into the space gently to avoid entering the lung parenchyma. The muscle is closed to avoid further air entry into the pleural space. Distal catheter placement may be aided by thoracoscopy [104]. Contraindications for this technique include previous thoracic surgery, acute or chronic pulmonary disease and poor pulmonary function. CSF will usually accumulate as benign pleural effusion, however if this is progressive it may lead to respiratory distress and therefore vigilance for this complication is important. This technique however is rarely applicable in newborns or indeed infants as the pleural cavity cannot cope with the CSF load at this age. The technique is thus usually reserved for very rare cases where few options for the distal catheter remain in older children.

Other contraindications include previous thoracic surgery, acute or chronic pulmonary disease and poor pulmonary function.

49.5.6 Post Operative Care of Shunted Patients

Post operative scans are obtained and act as a reference to future surgery and shunt positioning. Continual monitoring of head circumference is required.

49.5.7 Endoscopic Third Ventriculostomy

Endoscopic third ventriculostomy has re-emerged in the past 30 years and introduced a new dimension to management of hydrocephalus. Open third ventriculostomy was first performed by Dandy in 1922 [112] and later as an endoscopic procedure by Mixter in 1923. Advances in fiber-optic camera technology combined with high resolution MRI have been chiefly responsible for emergence of ETV as a therapeutic option for hydrocephalus.

The aim of ETV is to re-direct CSF through a "short-cut" from the third ventricle into the subarachnoid space to allow circulation and natural absorption of CSF. This re-route allows for natural absorption of CSF as opposed to external re-routing via a shunt.

49.5.7.1 Indications

The obvious advantages of shunt independence have made this an attractive surgical option however current evidence suggests that patient selection is crucial to outcome success rates. ETV in obstructive hydrocephalus with maintained CSF absorption such as in congenital aqueduct stenosis is associated with the highest success rates. ETV is seldom successful in hydrocephalus sec-

ondary to IVH and meningitis which account for the majority of cases of neonatal hydrocephalus. This is due to a difference in aetiology with the obstruction being at the level of the subarachnoid space secondary to scarring and inflammation and possibly also involving failure of CSF absorption. While in older children, the indications for endoscopic treatment have been relatively well defined, much debate continues on the value of this treatment in the first few months of life [113–115]. While various studies have reported differing success rates there remains a lack of consensus on the value of third ventriculostomy in infants and neonates.

The role of ETV as a secondary treatment option after initial or multiple shunt failures is gaining popularity with encouraging success rates [116]. This is relevant to the newborn with PHH or PIH who may benefit from a primary shunt (where primary ETV is ineffective) and then be considered for a secondary ETV when presenting with a future shunt failure.

ETV may also have an important role in the treatment of hydrocephalus in developing countries [117]. The lack of a follow-up service for children in developing countries having permanent shunt implants re-inforces the obvious advantage of a shunt-free therapeutic option—ETV. PIH accounts for up to 60% of hydrocephalus cases in certain developing countries [117]. In keeping with results published for developed country ETV success rates in infants, success rates in a relatively large series of patients treated in a developing country in the under 1 year group was lower than in the older child. Nevertheless, up to a 60% shunt avoidance rate has been reported in developing country infants presenting with PIH aqeuduct stenosis undergoing ETV [117]. The challenge posed by the lack of a shunt follow-up service in developing countries and the consequent impetus for ETV as a treatment modality had also potentially leads to a clinical situation in which ETV may be performed on a patient whose CSF absorption capability has not recovered sufficiently. Whereas these patients would probably have been treated with a shunt in a developed country. The combination of ETV and choroid plexus cauterization (CPC) may be a viable option in temporarily reducing the rate of CSF production until the absorptive function potentially returns. Results from a study employing this management technique on patients in the developing world reported a success rate of over 70% in infants under 1 year with PIH and an open aqueduct [118].

Other applications of neuroendoscopy include aqueduct stenting for isolated fourth ventricle enlargement, multiloculated hydrocephalus requiring communication of CSF spaces via septum pellucidotomies, cyst fenestrations and as an adjunct to shunt surgery by aiding shunt placement under direct endoscopic vision.

49.5.7.2 Surgical Technique

The technique involves a single paramedian coronal burrhole to gain access into the lateral ventricle. The ventricle is then cannulated using a 10 or 12 Fr cannula which then acts as a conduit for rigid or flexible endoscope. The endoscope is then introduced and navigated through the enlarged foramen of Munroe into the third ventricle (Fig. 49.1). The landmarks on the third ventricle floor are identified including the mammillary bodies and pituitary red spot. A midline fenestration is then made in the thinnest part of the third ventricle floor avoiding critical structures including the basilar artery (Fig. 49.20). The endoscope is then advanced through the fenestration to identify and fenestrate any further obstructive membranes thereby ensuring that an effective communication is achieved between the third ventricle and the inter-peduncular and prepontine subarachnoid CSF cisterns. Upon completion, the endoscope and the cannula are withdrawn and no hardware is left in situ.

Although a safe procedure in well trained and experienced hands the complications of neuroendoscopy can be devastating. Severe haemorrhage, cardiac arrest, cerebral infarction, diabetes insipidus and damage to the fornices resulting in memory deficit have all been reported [119]. In addition it is important to mention the rare but potential risk of sudden post ETV death due to closure of the ventriculostomy [119].

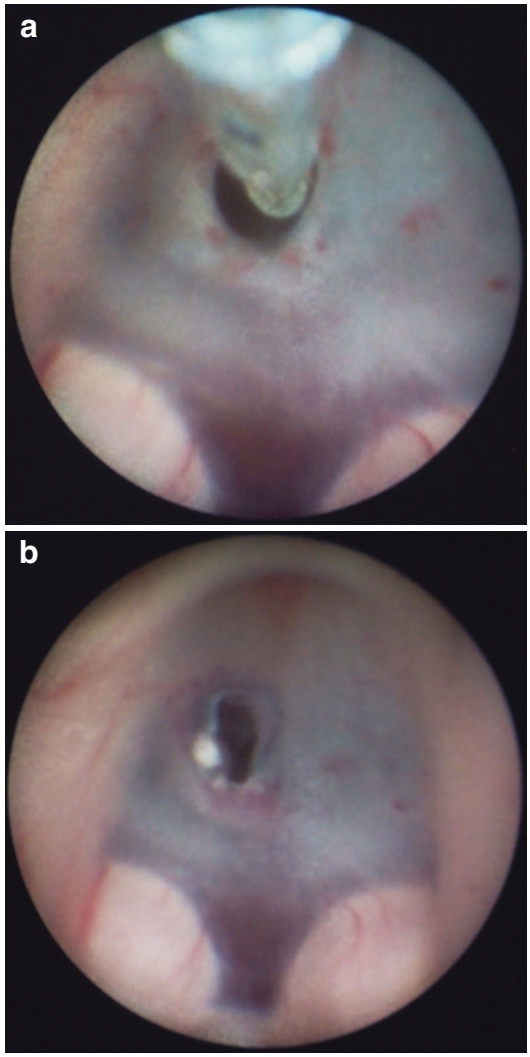

Fig. 49.20 Intraoperative images (obtained during endoscopic third ventriculostomy) demonstrating passage of the balloon through the floor of the third ventricle. Note the pituitary *red spot* is upper half and the mammillary bodies in the lower half of the picture (**a**) The balloon tip cab be seen across the stoma. (**b**) The stoma after the balloon has been withdrawn

49.5.8 Fetal Surgical Therapy

In utero diagnosis of hydrocephalus by fetal ultrasounds has raised the possibility of prenatal intervention and treatment of hydrocephalus. Extensive experimental work and certain human studies have been performed in countries where abortion is legally banned but thus far the results are poor and majority of patients who underwent fetal surgery for hydrocephalus required VPS insertion after birth. This method of management is therefore not currently recommended [120].

More recently the MOMS (Management of Myelomeningocoele study) trial [121] has shown that prenatal repair of myelomeningocoele reduced the need for shunting from 82 to 40% and improved motor outcomes at 30 months albeit at an increased risk of fetal and maternal complications. This is therefore a viable management option in countries where abortion is legally banned and expertise for prenatal intervention is available.

49.6 Outcome

The outcome of hydrocephalus is ultimately determined by the underlying causative pathological entity. Other factors influencing outcome include the treatment selected and avoidance of the treatment related complications. Historically, successful hydrocephalus treatment was defined as satisfactory ventricular catheter position on cranial imaging, absence of postoperative complications (such as infection or haemorrhage) requiring further surgery, and relief of symptoms of raised intracranial pressure. Such measures are however crude and an absence of shunt failure does not necessarily equate to success. In a cohort of UK patients with spina bifida followed from birth, patient reported outcomes indicated a poor prognosis for independent living into adulthood [122]. More recently small prospective case series have evaluated the role of neuropsychological testing in patients with spina bifida and showed that reading and writing function remain deficient into adulthood and that memory status is positively correlated with functional independence [123]. These tests are time consuming to administer and interpret but provide an indication of the potential for independent living for patients.

Several researchers have developed objective outcome measures that are primarily aimed at paediatric cohorts and patients with spina bifida living into adulthood. These tools range from

prospective lifestyle and health assessment questionnaires (patient reported outcomes) to objective measures of physical, social-emotional, and cognitive function (the hydrocephalus outcome questionnaire). The hydrocephalus outcome questionnaire has been validated and can be administered to children older than 5 years who are shunt dependent to measure development and the effects of episodes of shunt malfunction on neurological development and social integration [124].

49.7 Ongoing Research

Research into the pathophysiology of hydrocephalus continues and is beyond the scope of this chapter. One such current research is the study by J. Miyan at the University of Manchester to investigate the role of CSF in developmental of cerebral cortex and developmental defect associated with fetal-onset hydrocephalus and neural tube defects. The study is based on the results of rat hydrocephalus model and aims to determine if the imbalance in a folate enzyme (10-formyltetrahydrofolate dehydrogenase), Transforming Growth Factor-beta, Brain Derived Neurotropic Factor and Basic Fibroblast Growth Factor concentrations that is present in rat model of hydrocephalus is also present in the CSF of human infant with hydrocephalus.

Ongoing surgical research trials aim to further improve the management of hydrocephalus. The International Infant Hydrocephalus Study (www.iihsstudy.org) is a multicentre trial randomising infants with defined aqueduct stenosis and triventricular hydrocephalus to receive either endoscopic third ventriculostomy or CSF shunting. This study was initiated under the aegis of the International Study Group for Neuro-endoscopy and the International Society for Paediatric Neurosurgery and aims to provide long term outcome analysis on shunt dependence and a more comprehensive analysis of treatment effect and patient outcome (including various aspects of quality of life such as hospitalisation or other sickness time and neurodevelopmental evaluations over the course of 5–7 years).

British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts is a multi-centre randomised controlled trial (BASICS trial) funded by the National Institute for Health Research. The trial is led by the departments of neurosurgery in Alder Hey Children's Hospital and the Walton Centre for Neurology and Neurosurgery in Liverpool and aims to compare standard silicone, antibiotic impregnated and silver impregnated catheters in the incidence of shunt infections.

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Neural Tube Defects

50

Martin T. Corbally

Abstract

Neural Tube Defects (NTD) or Spina Bifida are disorders of neural tube development and closure and include a wide variety of abnormalities ranging from spina bifida occulta to anencephaly. Although the incidence of neural tube defects is less common today (0.5–1/1000 live births in some reports) and is falling, NTDs remain the most common congenital central neural system developmental disorder. The factors contributing to this decreasing incidence are in some part geographic and related to antenatal screening and termination of pregnancy but also relate to improved nutrition and folic acid supplementation. Improved standards of living and a falling birth rate have also impacted on a declining incidence. Despite this Spina Bifida is a cause of major morbidity with significant implications to the quality of life of the child but which also impacts significantly on the wellbeing of the family unit as a whole. Not surprisingly the management of these children involves a multi-disciplinary team approach with significant input from specialist paediatric surgeons, neurosurgeons, urologists, orthopaedic surgeons, paediatricians (especially rehabilitation) social workers, nursing, physiotherapy and child psychology.

Keywords

Neural tube defects • Spina bifida • Encephalocoele • Surgical management Outcomes

50.1 Introduction

Neural Tube Defects (NTD) or Spina Bifida are disorders of neural tube development and closure and include a wide variety of abnormalities ranging from spina bifida occulta to anencephaly. Although the incidence of neural tube defects is less common today (0.5–1/1000 live births in some reports) and is falling, NTDs remain the

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_50

most common congenital central neural system developmental disorder [1]. The factors contributing to this decreasing incidence are in some part geographic and related to antenatal screening and termination of pregnancy but also relate to improved nutrition and folic acid supplementation. Improved standards of living and a falling birth rate have also impacted on a declining incidence. Despite this Spina Bifida is a cause of major morbidity with significant implications to the quality of life of the child but which also impacts significantly on the wellbeing of the family unit as a whole. Not surprisingly the management of these children involves a multi-disciplinary team approach with significant input from specialist paediatric surgeons, neurosurgeons, urologists, orthopaedic surgeons, paediatricians (especially rehabilitation) social workers, nursing, physiotherapy and child psychology.

An unexpected diagnosis of NTD can have devastating consequences for the family and great support is necessary from birth onwards. The objective of management is to achieve early back closure, deal with hydrocephalus if required and to provide a meaningful structure for the child and family to allow as good a quality of life with normal or near normal integration into society as possible. There is no immediate cure for this often severe congenital deformity but modern techniques of back closure combined with precise hydrocephalus management enable the paediatric surgeon or paediatric neurosurgeon deliver not only life saving initial surgery but also provide a more holistic individualised management plan that improves not only the child's life quality but also that of the immediate family. This involves regular review at a dedicated Spina Bifida clinic which aims to minimise the disruption to family life by providing a multidisciplinary team presence (paediatric and orthopaedic surgery, social workers, specialist nurse and experts in paediatric rehabilitation) at each follow up.

It is important that each clinic visit focuses not only on identified problems e.g. posture control, mobility and hip issues with correction of talipes but also monitors potential problems such as the neuropathic bladder and its consequences especially long-term renal damage. A "one stop" properly structured clinic is a resource of great value to parents managing a child with a NTD and enables not only the medical and surgical aspects to be addressed but can focus on social and housing issues and on integration into mainstream education.

This chapter will focus briefly on the embryology of neural tube defects, the types commonly seen and their management including closure. For descriptive reasons most emphasis will be placed on the treatment of myelomeningocoele as this is the commonest type of NTD seen.

50.2 Embryology and Pathogenesis

Spina Bifida is a congenital abnormality affecting growth and development of the spine in which development and fusion of the vertebral arches and overlying skin and muscle has failed with or without protrusion and dysplasia of the spinal cord and its meninges.

The neural tube begins to form at around 14 days of age by the formation of the neural plate which is derived from the ectodermal tissue. Longitudinal in-folding of the plate (neurulation) (Fig. 50.1) proceeds from the mid portion (cervical) of the tube in a cephalad and caudal direction. The precise control of neurulation is not fully understood but the notochord which lies deep to the neural plate probably induces in-folding. The two ends of the neural tube are the last to close and these are called the anterior and posterior neuropores with the anterior or cranial neuropore closing at 24 days. Failure of closure of either neuropore can explain anencephaly or Myelomeningocoele. Alternatively the neuropores could close normally but failure of CSF drainage through the fourth ventricle causes hydrocephalus which ruptures the newly formed and delicate neural tube.

At this stage of development there are two layers of ectodermal tissue one more medially placed which on closure forms the neural tube and the more laterally placed ectoderm provides complete neural tube closure. By 21 days the neural tube has formed and the mesodermal elements begin to arrange into the vertebra and dura.

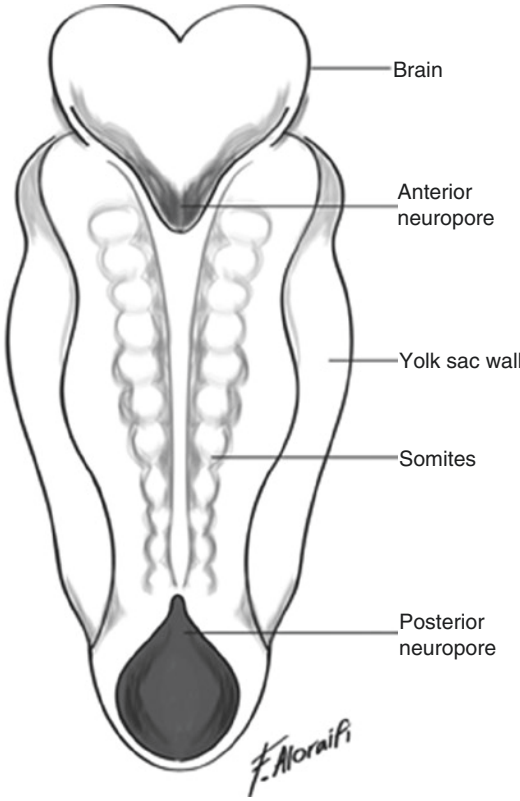

Fig. 50.1 Neurulation is proceeding and the anterior and posterior neuropores are visible

This occurs by migration of mesodermal elements into the notochord area to begin the formation of vertebra and intervertebral discs. Abnormalities of mesodermal arrangement or inclusion or persistence of some totipotent cells can result in other abnormalities such as diastematomyelia, lipo-myelomeningocoele abnormal vertebrae, sacro-coccygeal teratoma. If the notochord splits and the yolk sac herniates then the result can be the split notochord syndrome sinus or a fistula with ectopic bowel.

50.3 Aetiology

While we have significant insight into the development of the neural tube we do not know the precise aetiology of NTDs. A variety of factors have been suggested some of them genetic, some nutritional and some teratogenic.

50.3.1 Nutritional Factors

There is sufficient data to support a causal relationship between myelomeningocoele and folic acid metabolism. This may reflect environmental factors interacting with a genetic predisposition. Whatever the reason, there is substantial evidence now that peri-conceptual folic acid in a dose of 0.1–0.4 mg/day will reduce the incidence of NTDs in all pregnancies with or without added or existing risk. The Medical Research Council Vitamin study in1991 reported on the results of a randomised double blind trial in 33 centres in 7 countries in women at risk and demonstrated a significant reduction in the incidence of NTD in such pregnancies [1, 2]. Periconceptual folic acid is now recommended for all women whether or not there is a perceived genetic risk. In women at risk the dose of peri conceptual folic acid is 4–5 mg/kg per day. The incidence seems to be higher in women who have preconception obesity and diabetes with poor glucose control.

50.3.2 Genetics

The incidence of Spina Bifida continues to decline and its real incidence is hard to define especially when considered against the rates of termination for the condition. While the NIH list the condition as rare there are over 240 live births per year in the USA but over 4000 pregnancies with an antenatal diagnosis of NTD the majority of whom do not reach term. In the UK the overall incidence is about 5.7/10,000 births. While there are clear genetic associations the exact mode of inheritance is not known, and it is likely that there is a multifactorial hereditary predisposition. This is suggested by ethnic variation (more common in Caucasians and Hispanics), females more likely affected, familial tendency and increased incidence in parental consanguinity. If there has been a previous pregnancy affected by NTD the risk is of the order of 1 in 20–25 of a subsequent pregnancy being affected. This increases to 1 in 8 if there are two children with a NTD. The risk if one parent had an NTD is 1 in 200.

50.3.3 Teratogens

Foetal exposure to Sodium Valproate and Carpamazine carry a 1.2% risk of NTD while hyperthermia and certain viruses have also been associated with increased risk.

50.4 Historical

The earliest cited reference to an NTD abnormality may be that of Casper Bauhin (1605) from a work by Morgagni in1761 [3]. However the term spina bifida dorsi was introduced by Talpius in 1641 who also attempted to excise the sac with fatal results. Similar surgical efforts were invariably fatal as were attempts to aspirate the sac. Although there were some reports of successful surgery in the latter part of the nineteenth century it was not until techniques were developed to effectively deal with hydrocephalus in the late 1950s that real improvements in survival and outcome were seen. Earlier attempts had attempted to reduce CSF production by choroid plexus ablation. It was not until the introduction of the Spitz-Holter valve that the management of these children was revolutionised and a more aggressive approach to primary back closure acceptable [4]. Longterm survival of these children was now the norm and necessitated the progression of strategies to deal with neurogenic bladder and orthopaedic issues.

However survival of greater numbers of children who were severely incapacitated with a poor life quality prompted a re-appraisal of an aggressive attitude and sentinel works by Lorber and Schofield [5] and others suggested that in selected patients aggressive surgical management was not appropriate. Major ethical dilemmas were raised which called into question the decision to select infants in this way and to with hold primary back closure in those regarded as having poor outcomes. Patients born with thoracolumbar lesions, severe kyphosis, gross paraplagia, severe hydrocephalus (>90th centile by 2 cm) and other significant associated congenital lesions were considered to be incompatible with survival or good quality of life and primary operative closure was not advised. Conservative management of these infants with demand feeding and sedation was recommended after discussion with parents. While it achieved time for parents to consider the recommended treatment it also became apparent that many infants managed in this way survived and that their quality of life may have been adversely affected by the decision to manage them without primary back closure [6].

Today the majority of infants with Spina Bifida are managed operatively but this nevertheless accepts that treatment in all such infants should be individualized. Of course the widespread use of antenatal Ultrasound and prenatal counseling allows for early termination, if legislated and based on parental request, and is based on an assessment of severity of the lesion. Parents must be fully informed about the anticipated quality of life potential if they decide against termination. This clearly contributes to fewer children being born with severe lesions.

50.5 Classification and Types

NTD defects vary from anencephaly to spina bifida occulta but the most commonly seen is myelomeningocoele and for the most part it will form the basis of this chapter.

A. Brain
   1. Encephalocoele. is a herniation of brain (anterior or posterior) through a congenital defect of the skull which is covered by meninges and skin.
   2. Anencephaly is a uniformly fatal congenital NTD defect where the brain is very severely malformed with poor skull and soft tissue development
   3. Exencephaly is extremely rare with no skin or skull coverage

B. Brain and Spine
   Craniorachisis involves both the brain and the spine

C. Spine (Spina Bifida Cystica)
   1. Myelomeningocoele. (Fig. 50.2) is the commonest form of spina bifida and presents as a cord defect anywhere from the

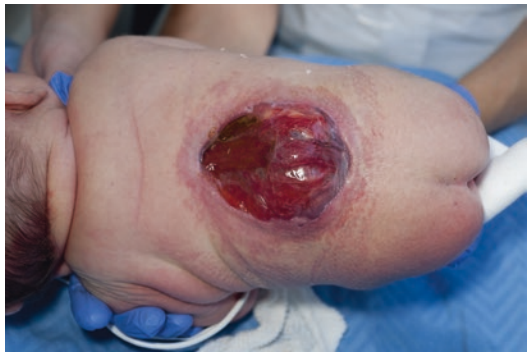

Fig. 50.2 Typical thoracic-lumbar myelomeningocoele showing exposed meninges and neural plaque

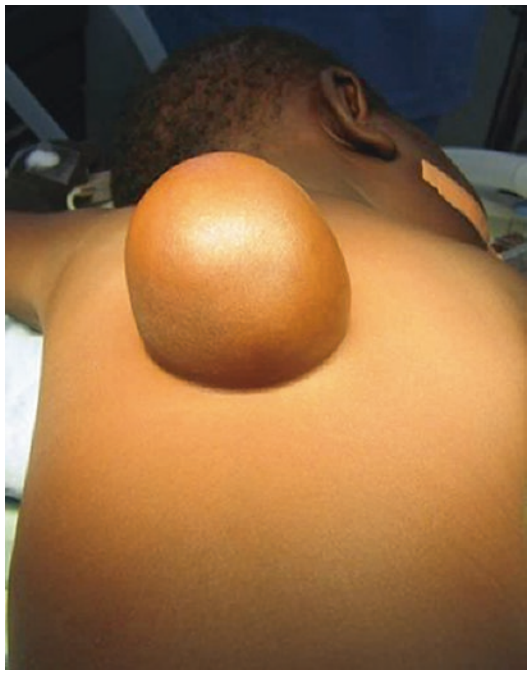

Fig. 50.3 Intact skin covering sac of investing meninges

cervical to sacral region. The defect may have a flimsy attenuated meninges and partial skin covering or partially covering a centrally placed neural plaque.

2. Meningocoele (Fig. 50.3) is a defect in the vertebra and muscle but the skin is intact. Generally the cord is covered by a meningeal sac.
3. Spina Bifida Occulta. The skin is intact but there are absent vertebral components (spinous processes) and there is usually a large tuft of hair or there may be an associated tethered cord, haemangioma or lipoma.

50.6 Antenatal Diagnosis

It is more likely today that antenatal scans will have detected a neural tube defect and termination is possible if that is both legal and in keeping with parental wishes. Maternal alpha feto-protein (AFP) can be used as a screening test in early pregnancy and will be raised with open NTDs as early as 16–18 weeks gestation. This should prompt more detailed investigation either by ultrasound and or MRI scan especially if persistently raised at this stage of pregnancy. 3-D ultrasonography is more sensitive than 2-D U/S and more widely available than foetal MRI scan with a reported sensitivity of 94% [7]. It does need significant training however and all abnormal scans should be the subject of detailed multidisciplinary discussion before any decision is reached on management.

Antenatal ultrasound allows appropriate discussion and planning of delivery if the parents decide not to terminate the pregnancy. Discussions should involve the Obstetrician, Paediatric Surgeon or Paediatric Neurosurgeon and should present as realistic a view as possible considering the level and size of the lesion. This discussion should highlight the main areas of concern which with any spinal NTD will include mobility, presence or absence of hydrocephalus and likelihood of a ventriculo-peritoneal shunt, intellectual ability or disability, long term bladder and bowel issues and the likelihood of multiple surgeries and morbidity. When the decision is made to carry to term a decision should be reached about the mode and place of delivery as most would advocate planned Caesarean section which may positively affect functional outcome as well as facilitating team readiness for the child's delivery. Ideally such infants are best delivered close to a paediatric surgical hospital or a paediatric neurosurgical unit. There is as yet no clear benefit of foetal in-utero surgery to allow lesional coverage.

50.7 Initial Management

Following delivery the infant is assessed as regards site of the lesion and whether it is covered or not. Skin covered lesions require no urgent intervention but open lesions should be covered with cling film and a rapid assessment made of associated problems. It is important that the medical team looking after the infant have a series of discussions with the parents and provide as much information as possible at this time. This should include a frank but empathetic discussion of the clinical severity of the lesion, the assessments needed and the likely clinical plan. It is clearly helpful if parents have had an opportunity to meet the surgeon prior to delivery and the news is not so catastrophic for them. A plan of management needs to be developed that includes a structured imaging protocol and a full sensorimotor evaluation. This often demonstrates a flaccid paralysis and is best quantified by an experienced physiotherapist and is most useful when subsequently compared to post-operative function [8].

In addition to the obvious spinal lesion, patients with NTDs can have many other associated problems and these must be documented. Talipes, congenital hip dislocation and other spinal abnormalities are common and need the input of a paediatric orthopaedic surgeon and paediatric physiotherapist.

Most patients with a myelomeningocoele will have a patulous anus and some may have neonatal rectal prolapse. The majority of patients with myelomeningocoele will have features of a neuropathic bladder (decreased bladder compliance and sphincter dysfunction) causing a high pressure bladder with consequential risk of urinary stasis and Vesico-Ureteric Reflux with renal scarring. However these are rarely seen at birth apart from bladder dribbling and can be monitored by regular screening and earlier introduction of clean intermittent catheterisation as indicated by recurrent infection or renal damage on radioisotope (DMSA) scan. A baseline renal Ultrasound is performed and is generally normal at this stage.

Head circumference and a cranial U/S are performed to assess the degree of Hydrocephalus. Approximately 90% of myelomeningocoele patients will require a Ventriculo-Peritoneal shunt for increasing Hydrocephalus within the first 4 weeks of birth [8].

It is advisable that all spinal NTD patients have a cranio-spinal MRI scan performed at some stage to rule out any associated cord abnormalities such as a tethered cord (Figs. 50.4 and 50.5), the ubiquitous Arnold Chiari malformation (Fig. 50.6) or a cord syrinx (Figs. 50.6 and 50.7). Approximately 70% of NTD patients will also

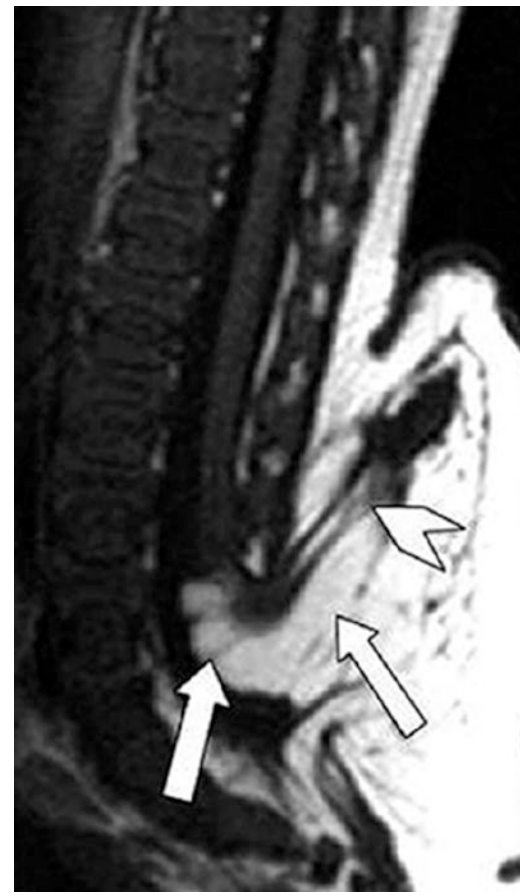

Fig. 50.4 Newborn male infant with a lipomyelomeningocoele. Sagittal T1 weighted image of the lower spine showing the low lying cord tethered by the filum (*white arrow head*) to the large lipomatous malformation (*white arrows*) that is contiguous with the subcutaneous fat through the posterior dysraphic elements

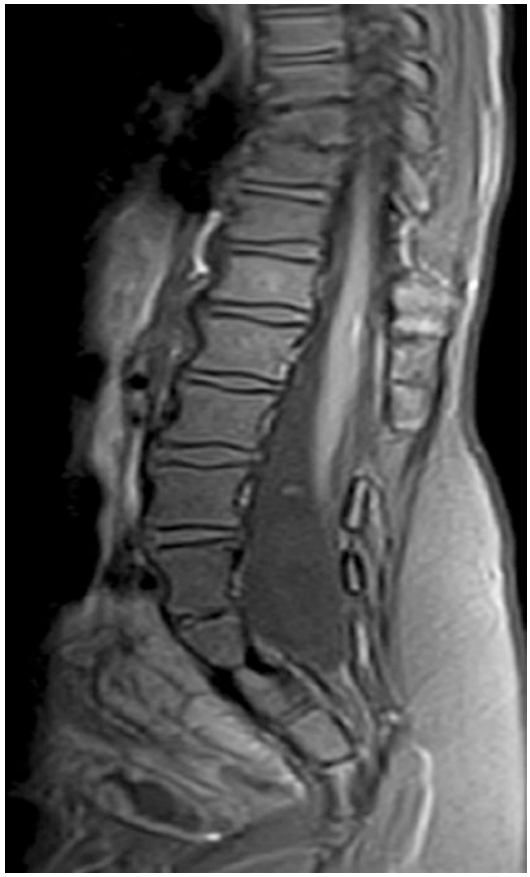

Fig. 50.5 Saggital T2 weighted image of the lower spine, showing the cord tethered at the level of L4 with a short syrinx above this

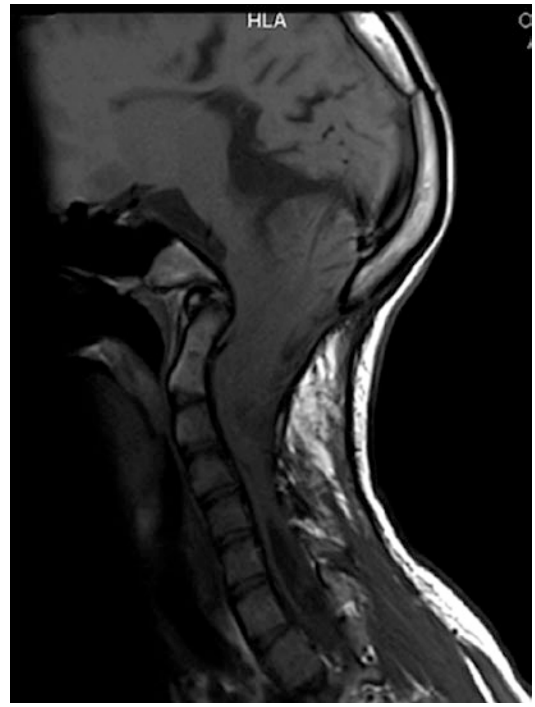

Fig. 50.6 Sagital T1 weighted image of the craniocervical junction showing a typical Arnold Chiari malformation, a small posterior fossa, large funnel shaped foramen magnum and herniation of cerebellar contents into the cervical canal behind the medulla. A large syrinx is also seen

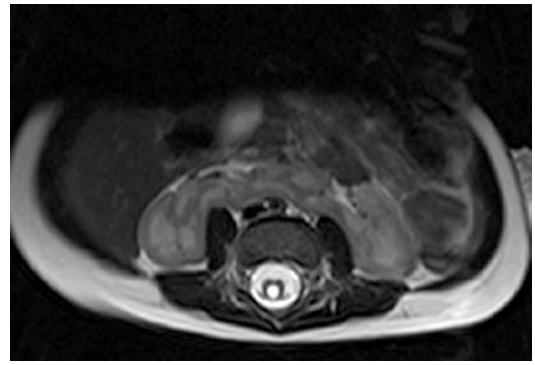

Fig. 50.7 Showing an axial T2 weighted image through the lower cord showing a central syrinx and a horseshoe kidney

have an abnormality of the corpus callosum. Spinal U/S is extremely sensitive to these abnormalities when performed from birth to 4/6 weeks postnatal.

Other investigations required are an X-ray of the spine to document the extent of the bony defect and also the degree of kyphosis (Fig. 50.8) which may require an osteotomy to facilitate closure. An orthopaedic opinion is obtained to assess and treat Talipes and dislocated hip if present. In general both of the latter abnormalities are managed conservatively.

It is important to provide support at all times to the parents, especially if there has not been an antenatal diagnosis, who can be and generally are shocked by the entire process. In general most infants undergo closure within 24–36 h unless there is a severe lesion or serious major associated abnormality. The objective of early closure is to prevent further neural deterioration from infection and prior to closure the lesion should be

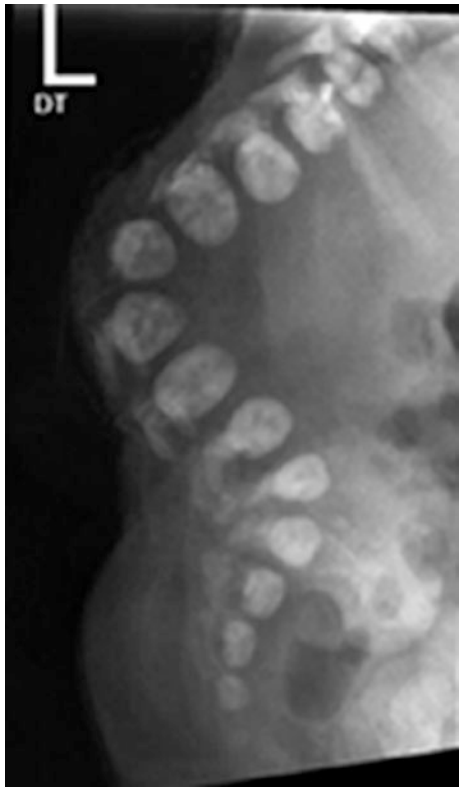

Fig. 50.8 Severe lumbar kyphosis associated with a myelomeningocoele. This lesion may require an osteotomy prior to complex soft tissue closure

protected with a Chorhexidine sponge and cling film over. Consideration should also be given to a broad spectrum antibiotic.

Most closures are well tolerated but occasionally closure can result in accelerated hydrocephalus which is generally compensated well with an open anterior fontanelle. Shunting will be required when the head circumference exceeds two standard deviations over the 90th centile or when there is rapid increase in hydrocephalus. It is also necessary if there is persistent CSF leakage from the closed back lesion.

50.8 Operative Details of Closure (As per Myelomeningocoele)

Following general anaesthesia and insertion of an endotracheal tube the patient is turned prone and cotton (Gamgee) supports placed under the pelvis and chest. It is important to place additional supports beneath each foot. It is not necessary to have blood available for this procedure but most would have a group and hold order with the laboratory. A neonatal diathermy pad is usually applied to the abdomen or chest. A warming bear hugger is routinely used. Bipolar diathermy should be used throughout. A swab for culture may be obtained at this point.

The skin is prepped with a povidone iodine solution and the lesion with chlorhexidene and draped with generous margins to facilitate additional skin dissection if required. An incision is made at the lowermost portion of the sac using a sharp scissors. This incision is carried cranially staying away from the neural plaque, which should not be handled where possible, and close to the sac-skin junction. Incision into the sac results in a release of CSF and some bleeding which is easily dealt with using bipolar diathermy. Nerve roots and blood vessels are now seen traversing the sac and disappearing anteriorly through the dural layer, and they should be preserved. The dural layer is clearly visible as a whitish fibrous layer. The sac is elevated taking care not to traumatise the neural plaque and the sac excised completely from the plaque. Bleeding from the neural edge is dealt with using biloar diathermy and with minimal handling of the plaque itself. At intervals chlorhexidene soaks may be applied to the area. Tubal reconstruction of the plaque is rarely indicated [8, 9].

The plaque will now be seen to lie on an easily recognisable dural layer. This fibrous layer is incised as far laterally as possible and the layer carefully dissected from the underlying fascia. This dissection is carried medially until the nerve roots come into view. Epidural veins may proof difficult at this point but these can be controlled by bipolar diathermy.

The mobilized dural layer is now tubularised over the exposed neural plaque using a running suture of 6/0 maxon on a 9 or 11 mm round bodied needle. A watertight closure is the expected aim. Occasionally it is not possible to complete the dural tube completely and a small portion of vertebral fascia is used to achieve closure. This

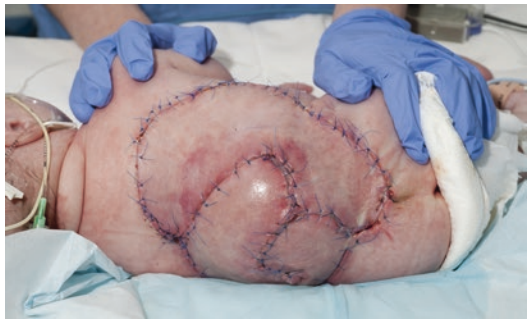

Fig. 50.9 Complex rotational flap repair in baby with severe kyphosis

is preferable to compromising the plaque. A small suction drain is placed to lie lateral to the dural lube and exited far laterally. This deals with any leakage of CSF which is usually short lived. Troublesome leakage usually responds to the insertion of a Ventriculo Peritoneal shunt. Where possible the dural tube is re-inforced using an additional fascial covering obtained by mobilising the fascia from the underlying muscle. It is usually impossible to cover the dural tube completely with fascia especially at the lower end.

The subcutaneous layer is approximated using a 3/0 absorbable suture. It is nearly always possible to close the skin layer using interrupted (4/0) sutures, but very rarely this requires considerable skin undermining or the use of lateral releasing skin incisions or complex flap repairs (Fig. 50.9). The skin closure is supported with wound strips and a dressing applied.

50.9 Post-Operatively

The baby is nursed prone or in a lateral position. Careful attention is paid to keeping the area clean. Feeds are not restricted. Weekly estimates of head circumference are performed and this is supplemented with cranial ultra-sound to monitor progress of the associated hydrocephalus. A Ventriculo-peritoneal shunt is inserted when the head circumference rises precipitously or when the Ventricular diameter increases beyond 50–60% of the diameter of the skull.

50.10 Other Considerations

Associated vertebral kyphosis may occasionally require an osteotomy to facilitate closure in the primary setting (Figs. 50.8 and 50.9). This is more likely with lesions treated conservatively initially and back closure performed as a secondary event

It is worth remembering that infants with NTDs may become sensitised to Latex rubber and that this should be avoided where possible even at the time of initial closure.

Encephalocoeles account for less than 10% of all neural tube defects and occur as a defect in the cranium through which the brain or part of the brain herniates. They are typically posterior and occipital but fronto-nasal may be more common in Asia. They may occur in other sites such as parietal. They are obvious at birth although fronto nasal lesions may be mistaken for dermoid cysts. Their size and complexity relate to the amount of brain tissue in the encephalocoele. The rest of the brain may abnormal also and there may be hydrocehalus. Imaging is with MRI and treatment is generally by excision unless there is a very significant amount of brain in the lesion in which case they may be, by necessity, managed conservatively.

50.11 Outcome

Patients with spina bifida pose serious problems to the family and the medical, nursing and allied professions. They need a multidisciplinary approach for their management with special emphasis on monitoring renal and bladder function, provision of physiotherapy services both in the community and hospital, proper evaluation of hearing and visual acuity, orthopaedic review and assistance with mobility either using calipers or a modified wheelchair. In addition the mobilisation of local paediatric and medical services with input from social services is vital to optimise their ultimate quality of life. Quality of life in these patients can be actively enhanced using clean intermittent catheterisation and bowel washout programmes.

The majority of meningomyelocoele patients have a neurogenic bladder and less than 10% are truly continent [8, 9]. Increased detrusor pressure is rarely a problem in the neonatal period and most infants empty with a dribbling stream. Over time urinary stasis and a high pressure system can be associated with vesico-ureteric reflux and be the cause of recurrent urinary tract infection and renal scarring. Consequently frequent renal tract imaging, cultures and urodynamics are required to determine whether or not there is a need for prophylactic antibiotics or early institution of bladder catheter drainage as in intermittent catheterisation (CIC). CIC may be introduced at a later time to confer social continence in the majority (>75%) and the remainder by a combination of pharmocology (anticholinergics) and surgery [10]. It is essential that the urinary tract is frequently monitored using Ultrasound and radionuclide imaging to ensure that silent renal damage does not occur or progress unnoticed.

The majority of myelomeningocoele patients have an active internal anal sphincter and tend to have a degree of constipation. This is considerably easier to manage with diet, fluids and laxatives as needed. Rectal retrograde washouts using systems like the Willis washout are largely effective although some degree of tolerance to the washout can occur over time. Antegrade washouts as in an antegrade colonic enema procedure may restore social faecal continence in these cases.

While virtually every NTD patient will have the Chiari malformation only a minority will have symptoms referable to brainstem compression such as cranial nerve palsies, headache. MRI scan is indicated to evaluate the need for foraminal decompression in selected symptomatic patients. A problem arises with regard to cord tethering which is a common finding in repaired myelomeningocoele. The issue is whether a tethered cord in itself warrants surgery since in all probability it will probably simply recur. A more rational approach is to monitor progress and reserve surgery for situations of neurological deterioration, change in ambulation (gait or toe clawing) or urinary function, the latter perhaps directed by deterioration on urodynamics. MRI is the investigation of choice to detect significant anatomical cord tethering (Figs. 50.4 and 50.5).

In general patients with lesions at L3 will be non-ambulatory while those at L5 will ambulate normally. Patients with lesions between these areas will require considerable support to walk and may spend intermittent periods in a wheelchair. However less than 1/3 patients are ambulatory in long term studies. Some of these may relate not to an inability to walk but to a personal choice as many find the wheelchair more acceptable and easier to use. Living circumstances must be reviewed constantly as the child grows older with interaction with social workers and occupational therapy.

Over 90% of myelo-meningocoele patients will require CSF shunting and these patients need constant review to ensure there is no shunt malfunction. Shunt series allow diagnosis of catheter fracture but a CT scan is needed to gain more useful information especially when the fontanelle has closed after 16 or 18 months of age.

NTD patients may have a variety of cognitive impairments especially if associated with shunt malfunction and episodes of infection. Shunt infection rates should be less than 3% using a no touch insertion technique. It is important that early remedial education is available and that these children are supported in mainstream schools as early and as far as possible.

50.12 Summary

Spina Bifida is a congenital disorder of neural tube closure that may occur anywhere from the cranium to the sacrum and vary from a life threatening condition to a mild and unnoticed defect. While the pattern of inheritance is not clear it is certain that there are both nutritional and genetic factors that weigh together to influence the occurrence of a neural tube defect. Antenatal diagnosis both by imaging and maternal Alpha Feto-protein (AFP) has changed the incidence of NTD dramatically in jurisdictions where medical terminations are legal. There has also been a real reduction in the overall population incidence however which appears to be independent of this and may relate to better overall nutrition. The addition of peri-conceptual folic acid has been shown to decrease incidence

when given in doses of 0.1–0.4 mg/kg/day. Post natal management of NTD babies presents serious and complex ethical considerations if the lesion is severe and survival is questioned, especially if it is considered that a conservative approach is justified on the basis of quality of life. Most patients however are considered for early back closure and or Ventriculo Peritoneal Shunt insertion. Timing of surgical intervention may impact on variables such as mobilty and intellectual ability with early closure perhaps conferring a positive effect on these variables. Most patients will need Ventriculo-peritoneal shunting and all require lifelong surveillance to ensure preserved renal function. Issues surrounding bladder and renal function and continence with mobility, educational and psychosocial concerns are lifelong matters that require significant professional input. With modern interventional techniques and an all encompassing multidisciplinary approach, the majority can enjoy a good quality of life.

Acknowledgments Sincere thanks to Mr. John Caird, Consultant Paediatric Neurosurgeon and Dr. Claire Brenner, Consultant Paediatric Radiologist for permission to use their clinical photographs and Dr. Fatima AlOraifi, MRCSI, PhD for the art work.

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Neonatal Brain Tumours

51

Chris Barton, Jothy Kandasamy, Benedetta Pettorini, Conor L. Mallucci, and Barry Pizer

Abstract

Neonatal brain tumours (NBT) are a rare but important group of neoplasms within the field of paediatric neuro-oncology as they present particular technical and physiological challenges to the neuro-surgical team. Contemporary management requires the application of appropriate multimodal individualised therapeutic approaches.

Neonatal brain tumours (NBT) are a rare but important group of neoplasms within the field of paediatric neuro-oncology as they present particular technical and physiological challenges to the neuro-surgical team. Contemporary management requires the application of appropriate multimodal individualised therapeutic approaches.

Keywords

CNS tumours • Newborn brain tumours • Management • outcome

51.1 Epidemiology and Aetiology

Neonatal brain tumours represent a rare and heterogeneous group of neoplasms with an incidence of 1–3.5 per 100,000 newborns [1]. Central Nervous System (CNS) tumours diagnosed in the first year of life represent 7.2–10.9% of all perinatal tumours [2], but account for up to 20% of deaths from neoplastic disease within the neonatal age bracket [3]. The rarity and sporadic nature of many of these tumours means that case series tend to be small, with reporting over long periods during which investigations, diagnostic criteria and treatments may have changed, affecting epidemiological, clinical and survival data. Furthermore, it can be difficult to extract data

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_51

regarding particular age ranges (e.g. <28 days or <1 year) from some reports, complicated further by the analysis of data within age ranges specific to the treatment strategy being considered (e.g. 0–3 years in protocols delaying radiotherapy).

51.2 Causative Factors

A higher incidence of infant brain tumours is seen with familial genetic conditions such as Gorlin Syndrome, Li-Fraumeni and Tuberose Sclerosis [1] (Fig. 51.1). Overall congenital abnormalities are seen in around 15% of neonatal tumours in general, suggesting an association with genetic defects [4].

Observational, biological, environmental and demographic studies have investigated potential relationships between causative factors and particular tumour subtypes or histotypes, with in utero exposure associations even more difficult to elucidate. Proposed factors include smoking, diet, racial characteristics, maternal age, maternal viral infections, pesticides and medications, with inconsistent, inconclusive and even contradictory findings from studies [1, 5].

51.3 Clinical Presentation

Obstetric complications of NBT include reduced foetal movements, polyhydramnios, enlarged uterinal dimensions and premature labour, and tend to be vague, non-specific findings [3, 6]. While the widespread use of antenatal ultrasound as a routine tool in the monitoring of pregnancy has seen an increase in antenatal detection of intracranial lesions [6], in most cases this is as an incidental finding [2]. None the less, up to 18%

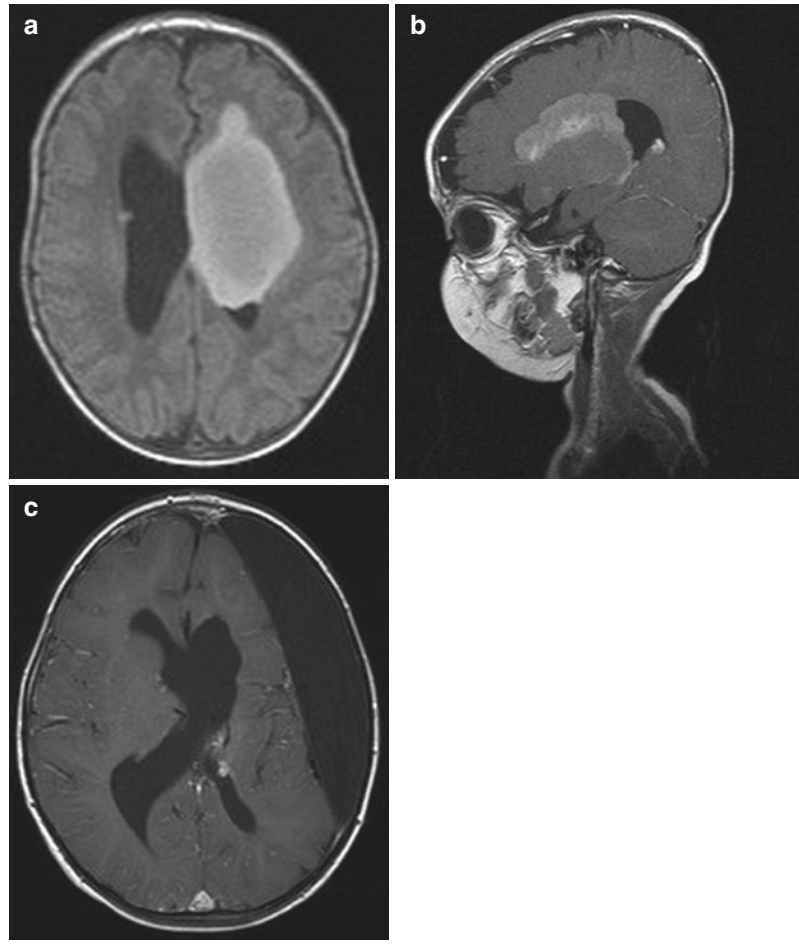

Fig. 51.1 (**a**) Axial and (**b**) sagittal T1 weighted MRI scans of a newborn child demonstrating a large intra-ventricular tumour. This tumour had been first diagnosed on the antenatal 22 week maternal ultra sound scan. A diagnosis of tuberose sclerosis was subsequently confirmed and the tumour was confirmed as a giant cell astrocytoma, which is pathognomic for tuberose sclerosis. The lesion slowly progressed on serial imaging leading to resection of the lesions at 6 months of age. (**c**) T1 weighted post-contrast study of the postoperative MRI scan showing complete resection of the lesion with associated asymptomatic subdural hygroma

of brain tumours presenting in the first year of life are diagnosed antenatally [2]. In utero magnetic resonance imaging (MRI) can help to elucidate further clinical information, and allow for better informed planning of delivery through the anticipation of peripartum problems such as dystocia.

The peripartum presentation of brain tumours includes dystocia, breech, stillbirth, and poor condition at birth [3]. Some of these correlate with neonatal presentations including macrocephaly, hydrops, hydrocephalus, seizures, nystagmus, apnoeas, cranial nerve lesions (e.g. hemifacial spasm) seizures and intracranial haemorrhage [3, 6, 7]. It must be appreciated that increased head circumference can manifest pre-, peri- or postpartum, and can significantly complicate the birthing process.

After birth, NBT can be insidious in their growth and presentation, and can reach a significant size before clinical manifestation. Subsequently, slowly progressive intracranial lesions can be obscured by normal growth, further complicated by the pliability of infant skull plates and potential to accommodate increasing intracranial pressure and masses. Common presentations include bulging fontanelles, rapidly increasing head circumference, separating sutures, prominent scalp veins, hydrocephalus [8], and optical manifestations such as sundowning [8] and nystagmus [7–9]. Other presentations include disordered growth e.g. failure-to-thrive (FTT), centile discrepancy (e.g. head/length/weight), lethargy, vomiting and seizures, with less commonly described presentations including irritability, head tilt, facial palsy, ptosis, hypotonia, incontinence and parapesis [7–9]. The association of particular symptoms with tumour types in infancy is also well established e.g. hypothalamic hamartoma and gelastic epilepsy (Fig. 51.2).

51.4 Neuroimaging

The anatomical locus of a tumour, apparent morphology (e.g. cystic, nodular, solid etc.), homogeneity and size, as identified from radiological findings can give an idea of a potential underlying diagnosis. As such, effective radiological input is key to the multidisciplinary management of NBT. Using non-ionising radiation, MRI is the modality of choice, posing less risk to the immature brain than computed tomography (CT), whilst offering clearer, higher resolution imaging of tumour morphology and anatomical relations. In the neonatal period, images can frequently be successfully acquired after infants have fed however MRI under general anaesthetic may be necessary to ensure imaging is of an adequate quality. Furthermore, the frequent presentation of some tumour types with leptomeningeal and subarachnoid spread means imaging of the entire CNS axis is required [6].

The higher water content and decreased myelination of the neonatal and infant brain decreases the differential appearance of white versus grey matter relative to the more mature brain of older children and adults. Subsequently, infant specific imaging protocols have been developed that not only address the time constraints of imaging, but also the specific technical challenges that arise [10].

CT does however haves a definite role in the further characterisation of some tumours, for example in determining the extent of calcification within tumours, and determining the extent of haemorrhage within lesions [1, 6]. Where surgical intervention has required the insertion of devices such as ventriculo-peritoneal (VP) shunts for the management of hydrocephalus, CT is the preferred modality for the investigation and monitoring of potential complications.

Newer advanced radiological techniques such as MRI spectroscopy are finding increasing application in clinical practice. The biochemical spectroscopic profiles of molecules such as choline, creatinine, amino acids and N-acetyl aspartate within normal brain tissues and lesions are measured relative to one another whilst non-specific profiles are common, differences can help to distinguish between different disease processes (e.g. tumour vs. abscess) and suggest possible tumour grade and types [1].

Alongside the initial investigation and management of disease, radiological modalities are find-

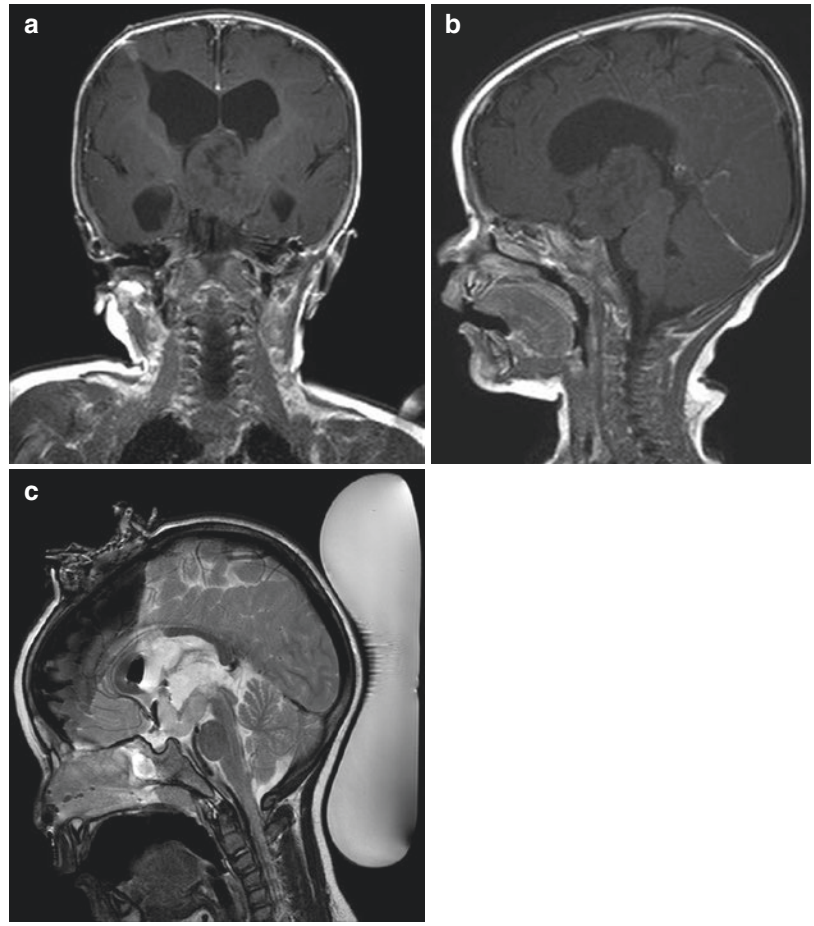

Fig. 51.2 (**a**) Coronal and (**b**) sagittal T1 weighted images demonstrating a large hypothalamic mass in a newborn child presenting with intractable gelastic epilepsy. The tumour had actually been diagnosed on antenatal ultrasound and MRI. Management initially consisted of observation only after an endoscopic biopsy confirmed a hypothalamic hamartoma. (**c**) The patient progressed to have medically intractable epilepsy, and at age 3 she had a subtotal resection of the hypothalamic hamartoma. The figure demonstrates the intra-operative MRI (sagittal T2) of the lesion during surgery

ing increased applications in preoperative and intraoperative planning. The anatomic relationship of a tumour and surrounding functional neurological and vascular structures can be mapped for preoperative planning, and imported into a surgical navigation system for intra-operative guidance.

51.5 Surgical Management

Despite an increasing incidence, NBT remain rare, and represent a highly heterogeneous group of diseases. Surgical management in specialised centres is essential to facilitate the frequent and cumulative exposure of clinicians to new cases in all age ranges and populations. With modern neurosurgical techniques, there is increasing evidence linking gross total tumour resection in various histological types to improved outcomes and progression free survival in older children. The data for neonatal surgery remains less well defined.

Surgical intervention usually incorporates the following objectives: (1) control of raised intracranial pressure due to hydrocephalus by diversion of CSF, (2) obtaining tissue for pathological diagnosis; (3) attempted curative resection of benign lesions and (4) improving survival for malignant tumours. Other important factors to consider are surgeon experience, expectations of the family with regard to treatment outcomes, and accessibility of the underlying lesion. Obtaining a histopathological diagnosis to guide the surgical objective and management strategy is vital to providing such patients with optimal care.

Relative to the size of the neonatal and infant brain, NBT can often occupy several cranial

compartments, accounting for a significant portion of the intracranial vault [1]. Even with such extensive development, NBT may only manifest in the first instance as the result of an acute change or deterioration. Intratumoural haemorrhage, reflecting the increased vascularity of large tumours is common, and the sudden, spontaneous rapid growth of biologically "benign" tumours is well recognised. This increased vascularity of neonatal tumours also complicates surgery, greatly increasing the risk of intraoperative bleeding. The reduced circulating volume seen in neonates increases their susceptibility to hypovolaemia and associated problems such as haemocoagulative disorders [11, 12], complicated further by difficulties regulating metabolic homeostasis and temperature regulation in this population whilst under general anaesthetic.

The size constraints of the infant head impose highly restrictive dimensions on the operative field, and the fragility of the infant brain often limits the extent of surgery that can be planned. Alongside this, the anatomical site of an NBT is a determinant factor in the appropriateness and nature of planned surgery. Fundamental to this is whether the site is supratentorial (cerebral) or infratentorial (cerebellar), with approximately 60% of IBT supratentorial in nature, a figure seen in numerous case series (Serowka et al., 2010: n = 33, 63% supratentorial [8] and Young and Johnston, 2004: n = 16, 62.5% supratentorial [9]).

The location of NBT relative to the tentorium has significant practical implications, implicit in differential diagnoses, surgical accessibility (and hence potential complications and morbidity), and the long-term clinical implications of tumours resistant to treatment (i.e. continued growth and infiltration into surrounding structures). Neonatal tumours demonstrate a predilection for midline and periventricular loci, probably as result of the neoplastic transformation of physiologically proliferating primitive cell populations within these regions [1]. Midline locations such as the optic-hypothalamic region and brainstem make gross total resection impossible in certain cases, and the infiltration of normal brain structures in malignant tumour types contributes significantly to poor resectability.

Improvements in neurosurgical techniques, imaging (including intraoperative MRI) and importantly perioperative care in regional specialist centres have led to a more aggressive surgical strategy with radical or wide surgical resections sometimes the goal. Frameless and wireless neuronavigation as well as the use of intraoperative evoked potentials may further increase the safety and effectiveness of neurosurgical procedures even in these very young patients. Minimally invasive procedures such neuroendoscopic surgery (burr-hole transventricular approaches) can be used to obtain tumour samples, where present, simultaneously treat associated hydrocephalus via CSF diversion procedures such as an endoscopic third ventriculostomy [6].

Nevertheless, the rate of radical tumour excision remains relatively low compared to older children and adults [13]. The International Society for Pediatric Neurosurgery survey (1991) reported on 876 children with brain tumors of the first year of life with a gross total tumour resection rate of 44% [14]. A staged-surgery strategy is adopted in many centres to allow the surgeon to remove large neonatal brain tumours in two or more operating sessions. In theory this may reduce surgical risk by having multiple shorter operations, thereby allowing for easier maintenance and control of intraoperative metabolic and thermal homeostasis, reducing intraoperative blood loss, and reducing postoperative complications resulting from sudden intracranial decompression e.g. subdural fluid collections secondary to cranio-encephalic disproportion. Intraoperative bleeding which can cause physiological imbalances in the neonate can be further reduced by means of thrombin based haemostatic agents, intraoperative isovolemic haemodilution and intraoperative blood recovery to help in decreasing the risk of haemotransfusion [15].

Preoperative endovascular embolization of the tumors such as choroid plexus papilloma and carcinoma has been reported as a valid option to decrease the risk of severe intraoperative haemorrhage [16]. Furthermore, some authors have reported the successful use of neoadjuvant chemotherapy to allow for tumour shrinkage and

reduction of vascularity before planning surgical resection. The use of preoperative chemotherapy has been reported for choroid plexus tumors, posterior fossa malignant glioma, optic-hypothalamic glioma and unresectable brainstem gliomas [1].

It is important to understand that all the published series on neonatal brain tumours report on a sizable group of infants who do not undergo any surgical resection. The reasons are not necessarily clearly outlined in the published literature but factors that are considered will include clinical and ethical considerations with regards to survival and prognosis, situations where there is agreement on the radiological diagnosis with no possibility of successful resection and/or adjuvant therapy. These decisions are best made in conjunction with a specialist paediatric neuro-oncology multidisciplinary team.

Nevertheless, new surgical techniques continue to develop, as do strategies to support surgical procedures and planning. Intraoperative MRI and ultrasound have improved the safety of operative techniques and helped to maximise the extent of resection through real time analysis of resected tumour relative to surrounding tissues. Distinct from this, the use of 5ALA, a dye that when applied to tumour cells, glows red under an ultraviolet light, potentially allows the intraoperative assessment of any residual tumour burden, also aiming to maximise the extent of resection [17]. Robot assisted neuroendoscopy systems continue to be refined, aiming to minimise the risk of damage to intracranial structures, as distinct from the development of techniques that allow optical imaging of brainstem nuclei and nerve tracts, that enable safer surgery in difficult regions such as the brain stem.

51.6 Adjuvant Therapies

Irradiation of the developing brain is associated with considerable long term morbidity, including learning difficulties, attention and concentration disorders, short term memory deficits, social adjustment and personality disorders, disorders of speech, language and communication, and physiological problems such as pituitary and hypothalamus related growth disturbance [18]. Subsequently, its avoidance until well beyond the infant period has become a standard in the design of most neonatal and infant brain tumour treatment protocols, ideally extending this period to the fourth year of life where possible.

51.7 Chemotherapy

As with all chemotherapy, therapeutic benefits have to be considered against the considerable toxicity profiles of chemotherapeutic agents, and long-term or late effects such as second malignancies. No chemotherapy protocols have been developed specifically for the management of neonatal brain tumours, although a number of so-called ‘baby brain’ protocols have been developed with the aim of using prolonged relatively low-intensity chemotherapy schedules to delay of avoid the use of radiation therapy [19–21].

With regard to designing such protocols, a number of fundamental pharmacokinetic differences between infants and older children/adults need to be considered [22]. These include significant differences in drug transport, drug metabolism and increased half-life arising from altered renal function, immature gastrointestinal systems and decreased glomerular filtration rate, with a greater body water composition and decreased plasma concentrating ability, as well as altered end organ differences such as decreased myelination [22, 23].

51.8 Multidisciplinary Management

The rarity and heterogeneity of NBT, alongside difficulty in their accurately classification and diagnosis demands multidisciplinary case review and management, involving histopathology, neurosurgery, neurooncology, radiology, endocrine, clinical oncology and neurology amongst others. With the significant morbidity associated with neurosurgical procedures, and long terms problems associated with chemotherapy, an extended MDT including dietetics, social workers, clinical

psychology and physiotherapy is often required. In the case of NBT, primary health services, and in particular health visitation is fundament with the potential for deranged growth and development, and significant long-term disability.

51.9 Genetic and Biological Characterisation of Tumours and Risk Stratification

Putative biological, genetic and molecular markers of tumour biology and behaviour are increasingly finding clinical application, in the staging and classification of tumours, in some instances determining treatment courses. The presence of certain phenotypic or genotypic markers has been validated as determinants of whether specific tumours need more or less intensive surgical intervention or chemotherapy. For example, a tumour with more aggressive profiles, with metastasis on investigation may warrant more radical surgery, or more intense chemotherapy, whereas lower risk lesions demand less intensive therapy, if long term health risks can be reduced without compromising survival.

The prime example of this new knowledge is in medulloblastoma, which is now sub-categorised into four molecularly distinct sub-groups [24]. Further research has demonstrated that probing alterations in tumour DNA is able to define a so-called CIMP-positive subtype of posterior fossa ependymoma that clearly has a poorer outcome than CIMP-negative tumours [25]. Similar genetic sub-typing is being demonstrated in high grade glioma, atypical teratoid/rhabdoid tumour and others.

51.10 Prognosis/Survival/Outcomes

Due to the rarity of NBT, published literature tends towards being small cases series, limited to considering a heterogeneous group of tumours with distinct individual anatomical characteristics [9]. The small numbers can also mean that series can be from an extended periods, during which diagnostic methods, surgical techniques and treatment protocols may have changed [9]. This impacts greatly on the already difficult task of trying to generate survival data, and when counselling parents about the prognosis of diagnosed conditions.

The outcomes measured when considering survival following infant brain tumours, as with tumours at other loci include 5-year survival and 5 year progression free survival. The considerable anatomical and functional development of the brain, including skill acquisition and cognitive development, that occurs during infancy has resulted in an increased significance being given to long-term neurological, physical, behavioural and psychological sequelae. This involves monitoring for aberrant or delayed development in social, gross and fine motor and speech and language, including physical and sensory deficits, and the impact that these can have on the quality of life (QoL) of the child. It is essential to consider that long term morbidity dose not arise solely from the initial disease process and oncogenesis, but to a significant degree from treatment, whether surgical, chemotherapy or radiotherapy, as discussed. Increasingly, measures are being developed to consider long term outcomes, not only to identify the health needs of NBT survivors, but as part of the ongoing risk-benefit considerations that are part of all medical/surgical interventions, but also in comparing the efficacy of different treatment modalities in terms of long-term outcomes.

51.11 Low Grade Glioma (LGG) and High Grade Glioma (HGG)

Low Grade Gliomas include pilocytic, pilomyxoid, diffuse and pleomorphic astrocytoma (of which pilocytic astrocytoma is the most common). Individually, astrocytomas and are the most commonly identified group of tumours in infancy accounting for approximately 30% brain tumours, and are a significant in the neonatal period [26]. LGG can arise anywhere in the neuronal axis, but

are most commonly supratentorial and midline tumours, involving the hypothalamic area and optic pathway [26]. In the neonatal period the mesencephalon and pons are also common primary sites [3]. While low-grade tumours classically demonstrate a more benign, indolent course in comparison to more aggressive, malignant high-grade tumours, infant astrocytomas represent a highly heterogeneous population of tumours in terms of their gross anatomy, histology and clinical behaviour [3]. Some display more aggressive pathological characteristics, with poorer outcomes and significantly reduced treatment responses than might be expected [26].

The treatment of choice is gross total resection for most low grade gliomas that are readily accessible, e.g. hemispheric, cerebellar, focal and dorsal exophytic brainstem and cervico-medullary tumors with the extent of resection has been reported as an important predictor of clinical outcome. Thus the usual post-operative recommendation for many patients with low grade glioma is serial imaging and clinical follow-up to detect disease progression. Repeat surgeries can be performed in the event of detected tumour progression or recurrence before the addition of adjuvant therapy.

The proximity of the common anatomical sites in which astrocytomas develop to fundamental structures such the optic pathway and the hypothalamus increases the risk of significant post-surgical complications and morbidity, and almost precludes gross total resection as a viable surgical strategy [26].

51.12 High Grade Glioma (HGG)

High Grade Gliomas are either anaplastic astrocytoma or glioblastoma multiforme, both rare in the neonatal age bracket. Infants with chemosensitive, histologically confirmed HGG in infancy have been described [26] with evidence to suggest that infants diagnosed below 6 months may have the best prognosis of all [26]. Figure 51.3 shows pre and post-operative images a high grade glioma in a 2 weeks old child who remains well at 2 years of age, following surgery and chemotherapy, with residual but static disease.

This is reflected in the results from baby brain protocols that suggest a much better prognosis for very young children with HGG than those in older children and adults, despite the avoidance of radiotherapy pointing to fundamental difference in the biology of these tumours at different ages. Of the patients with HGG, SEER data suggested that patients who underwent GTR had increased survival in patients <12 months [27], though previous studies have identified no such relationship between extent of surgery and survival [28].

51.13 Medulloblastoma

Medulloblastoma represent a group of highly malignant embryonal tumours [18]. On radiological imaging, medulloblastoma appear as solidly enhancing, homogenous masses, with or without cystic changes or calcification [18]. Presentation with obstructive hydrocephalus is common and leptomeningeal and cerebrospinal seeding occurs in a significant proportion of cases [3].

Neonatal medulloblastoma is associated with increased difficulty in performing gross total excision. Risk stratification considers tumours characteristics such as the degree of surgical excision, presence of disseminated/metastatic disease and histological subtype. A variety of chemotherapeutic options are used. Prognosis is generally very poor, although patients with desmosplastic histology have a better outcome.

51.14 Central Nervous System Primitive Neuroectodermal Tumours (CNS-PNET)

CNS-PNETs are embryonal tumours composed of poorly undifferentiated neuroepithelial cells, and represent a rare but highly malignant group of small cell tumours [3] and represent around 7.7% of IBT [29].

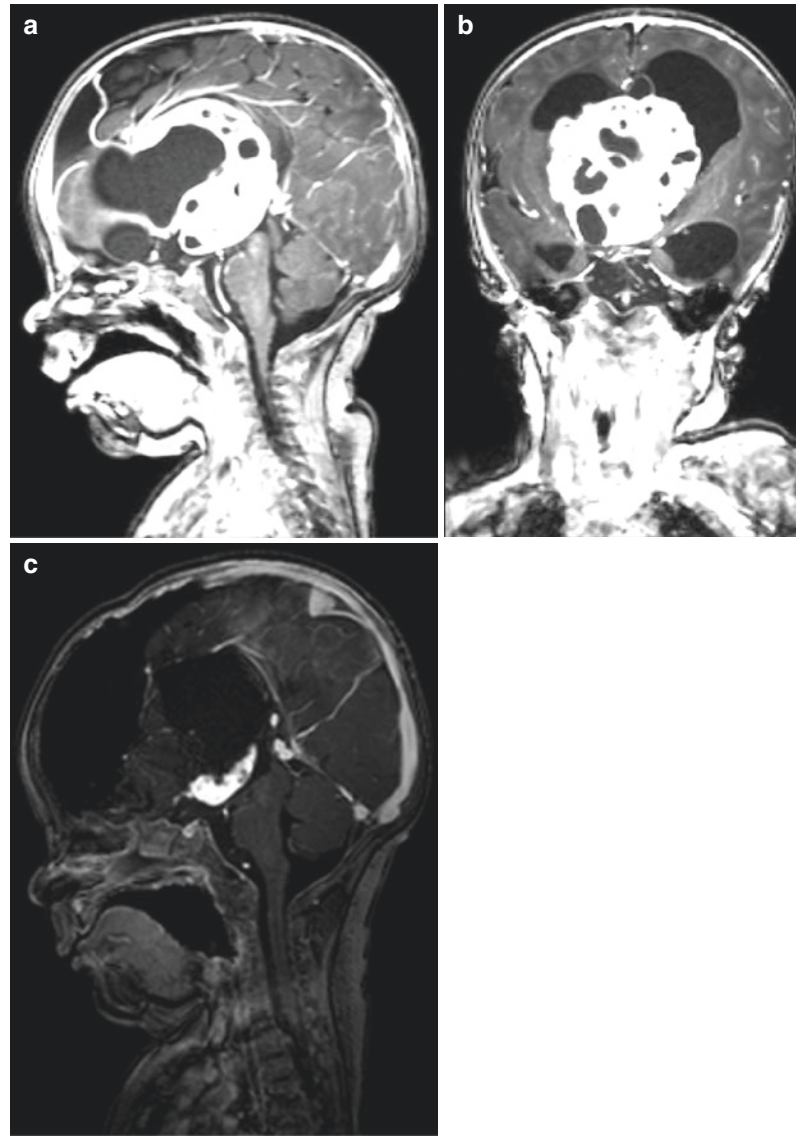

Fig. 51.3 (**a**) Sagittal and (**b**) coronal T1 images (with gadolinium) showing a large tumour in a 2 week old baby. The infant presented with a rapidly enlarging head circumference typical of acute hydrocephalus, but was clinically well otherwise. The tumour was diagnosed as a glioblastoma multiforme (WHO Grade 4) after biopsy. (**c**) Sagittal T weighted imaging (with gadolinium) following major resection, with a small amount of residual tumour left in the hypothalamic area. The child experienced no neurological deficits post operatively, but developed diabetes iInsipidus and required a ventriculoperitoneal shunt 2 weeks later

As a group of tumours, CNS-PNET can occur at several sites within the supratentorial brain including the pineal gland (pineoblastoma) [3]. Like medulloblastoma they demonstrate a propensity for dissemination through the CSF [3].

Prognosis in the neonatal and infant period is poor, with recommended treatment being maximal tumour resection and intensive chemotherapy [29]. Neonatally presenting StPNET tends to be more advanced, with larger tumours and more progressed disease, often meaning surgery is more complicated, if possible at all [3].

51.15 Atypical Teratoid/Rhabdoid Tumour (AT/RT)

Atypical teratoid/rhabdoid tumours (AT/RT) represent a group of tumours that have previously been misclassified as malignant entities such as medulloblastoma or choroid plexus

teratomas. They are foremost a tumour of infants and young children and arise predominantly within the posterior fossa, but with the potential to manifest anywhere in the CNS often with disseminated disease [30]. ATRT is associated with the tumour suppressor gene hSNF5/INI1 and diagnosed is aided by the absence of the immunohistochemical expression of INI1 expression.

Response to chemotherapy alone is generally poor, with Rorke reporting only 14% showing chemosensitivity [29]. Gross total resection is probably beneficial [30] but the prognosis in infancy is very poor, especially in the presence of disseminated disease, and in early infancy treatment is usually palliative [26].

51.16 Teratoma

Teratomas account for approximately 25–55% of NBT, [1]. Larouche describes significant variation in the prevalence of teratomas between case series, attributing this in part to the increasing accuracy that with which other tumours, such as Desmoplastic Infantile Gliomas, are now being correctly identified [26]. Teratomas characteristically demonstrate endodermal, ectodermal and mesodermal elements, commonly with immature neuroglial cells. Tumours can erode though bony and cartilaginous anatomic relations, and often directly replacing brain tissue. Isaacs reports the difficulty that lies in identifying the anatomic origin of teratomas in approximately one third of patients, though common sites include the pineal gland, the hypothalamus, suprasellar region and cerebral hemispheres [3].

51.17 Ependymoma

Ependymoma represents 11% of NBT [3] and develop from ependymal cells; cliliated epithelial cells lining the ventricles involved with the production and circulation of CSF. Presentation is often with large tumours, with a higher risk of dissemination through the CSF in infancy [26]. In infancy most arise within the fourth ventricle.

The difficulty of treating ependymoma without radiation is well acknowledged [26]. The degree of resection is the major prognostic factor [26].

Accordingly, infratentorial tumours, especially those in the posterior fossa with involvement of the lateral recess, are traditionally accepted as having a poorer outcome. Surgery is complicated by the proximity of the brain stem, cranial nerves and the great vessels. Postoperative chemotherapy is usually administering following one of the so-called prolonged baby brain chemotherapy regimens mentioned previously.

51.18 Choroid Plexus Tumours (CPT)

Choroid plexus tumours include a spectrum of neoplasms including Choroid Plexus Papillomas (CPP) accounting for approximately 5% of NBT [31], so-called ‘atypical’ CPPs and the highly malignant Choroid Plexus Carcinomas (CPC). As a group they are highly vascular tumours that display significantly increased secretion of cerebrospinal fluid. Inadequate compensatory drainage results in ventricular dilation and rapidly progressive hydrocephalus, with associated manifestations such as increasing head circumference [31]. Choroid plexus tumours predominately present in the lateral ventricle, but can also develop in the third or fourth ventricles [31]. CPC can also disseminate through the cerebrospinal fluid [31].

Complete surgical resection when possible should be performed and is usually curative for CPP and is prognostically significant for CPC. Surgery may be complicated by the risk of significant haemorrhage from tumours that commonly have well-established vascular beds [31]. Adjuvant chemotherapy is given for CPC but despite this, the prognosis remains very poor [31].

51.19 Desmoplastic Infantile Astroglial Tumours

Desmoplastic Astrocytoma (DAI) and Ganglioma of Infancy (DIG) present as exclusively supratentorial tumours, and are frequently cystic on imaging [26, 32]. Complete resection may be limited because of large tumour size at presentation, widespread intracranial infiltration, a high degree of vascularity and commonly, multilobar involvement [26]. Staged operations and pre-operative angiography/embolisation have been advocated. The differentiation between the DAI and DIG is the presence of neuronal cells histologically in DIG, but otherwise they are morphologically and radiologically very similar. The main area for discussion with these tumours is the sometimes aggressive appearance on histology suggesting a more malignant tumour. However, the tumour is generally felt to be curable with surgery alone and adjuvant therapy is not usually recommended if complete resection can be effected, with a good prognosis if this can be achieved [32].

51.20 Discussion

Future work will continue to find the balance between aggressive tumour treatment and management and the long-term morbidity that survivors face. Advances continue to be made in our understanding of tumour biology and molecular biology, with risk stratification allowing the identification of those tumour types that demand more aggressive management compared with those in which less intensive therapy will not compromise cure or survival. Alongside this, biological and clinical work must continue to develop novel therapeutic approaches such as anti-angiogenesis and pro-apoptosis agents, and differentiation-promoting agents, all of which may improve the survival and quality of life of future paediatric brain tumour patients. Fundamental to this will be continued collaboration between multi-institutional groups, to develop and validate future therapeutic approaches in clinical trials.

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Part VIII

Oncology

Epidemiology and Genetics of Neonatal Tumours

52

Charles Stiller

Abstract

Neoplasms are rare in neonates, although somewhat more frequent than in older children. In Great Britain, for birth years 1988–2007, the National Registry of Childhood Tumours recorded 394 cases of cancer (including non-malignant CNS tumours) in live-born infants less than 28 days of age. The risk of neonatal cancer was 27.6 per million live births or 1 in 36,170, equivalent to an incidence of 361 per million person-years and double the rate over the remainder of the first year of life. The most frequent cancers were germ-cell tumours (24%), neuroblastoma (23%), leukaemia (18%) and CNS tumours (13%). Cancers probably account for a minority of neonatal neoplasms, so that the total risk of benign and malignant tumours exceeds 1 in 18,000. While the short-term prognosis of neonatal cancer is rather poor, the probability of survival conditional on surviving one year from diagnosis is much higher than in older children. Survival from leukaemia, embryonal CNS tumours and rhabdomyosarcoma is especially poor for neonates, whereas neonates with neuroblastoma have much higher survival than children aged 1 year and over. The proportion of neonatal cancers associated with pathogenic germline mutations seems unlikely to be much lower than 10%; in addition, a substantial proportion are associated with chromosomal abnormalities. Exogenous risk factors are probably only relevant if exposure is prenatal. The most plausible from among the many that have been investigated are exposure to ionizing radiation and some pollutants during pregnancy and some dietary factors.

Keywords

Neonatal cancer • Epidemiology • Survival statistics • Outcomes

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52.1 Incidence

Neoplasms are rare in neonates, although they occur somewhat more frequently than in older children. The most reliable incidence data are for

P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_52

cancers, defined according to the International Classification of Childhood Cancer, Third Edition (ICCC-3) [1] as malignant neoplasms together with non-malignant intracranial and intraspinal tumours, since these diseases are ascertained by population-based cancer registries. In Great Britain, for birth years 1988–2007, the National Registry of Childhood Tumours recorded 394 cases of cancer in live-born infants less than 28 days of age. There were 183 boys and 211 girls affected, a male:female ratio of 0.9:1. The risk of neonatal malignancy was 27.6 per million live births or 1 in 36,170. This is equivalent to an incidence of 361 per million person-years, double the rate of 177 per million person-years over the remainder of the first year of life. A similarly raised incidence in the first month has been observed in the United States [2]. As will be described below, the risk of cancer in the neonate would be considerably lower if a more restrictive definition of malignancy were applied. But even with the relatively inclusive definition in the International Classification of Diseases for Oncology (ICD-O-3), on which ICCC-3 is based, it seems likely that cancers account for a minority of neonatal neoplasms and that the total risk of benign and malignant tumours in the first 28 days of life exceeds 1 in 18,000.

Childhood cancer is a diverse collection of diseases. The distribution of tumour types varies markedly with age, not only through the years of childhood but even between the neonatal period and the rest of the first year. Table 52.1 gives details of the 394 neonatal cancers registered among neonates born in Britain in 1988–2007, together with those among older infants for comparison. Figure 52.1 shows the relative frequencies of the 12 main diagnostic groups of ICCC-3 in neonates, older infants, and children aged 1–4 years at diagnosis. Among neonates, the most frequent categories were germ-cell tumours (24%), neuroblastoma (23%), leukaemia (18%) and intracranial and intraspinal (central nervous system:CNS) tumours (13%). By contrast, while leukaemia, neuroblastoma and CNS tumours had fairly similar relative frequencies among older infants, germ cell and gonadal tumours accounted for only 4% and were outnumbered by retinoblastoma, renal tumours and soft-tissue tumours. As can been seen from Table 52.1, however, the higher total incidence among neonates meant that only lymphomas and renal cancers had a markedly higher incidence after the first 4 weeks.

Of the 71 cases of neonatal leukaemia, 36 (50%) were acute myeloid, 15 (21%) were acute lymphoblastic, 5 (7%) were JMML/CMML, 1 (1%) was myelodysplasia and 14 (20%) were of unspecified type. No lymphomas were registered in this age group.

Among the 50 CNS tumours, unspecified tumours accounted for 38%, reflecting the low biopsy rate for neonatal brain tumours. Of the 11 astrocytomas, 1 was pilocytic, 5 were high-grade and 5 were of unspecified grade. The 10 embryonal tumours comprised 3 medulloblastomas, 4 primitive neuroectodermal tumours and 3 atypical teratoid/rhabdoid tumours (ATRT). Of the 5 choroid plexus tumours, 4 were papillomas and 1 was a carcinoma. No ependymomas were registered. The "other glioma" category comprised one astroblastoma and three unspecified gliomas. The single mixed glial-neuronal tumour was a desmoplastic infantile ganglioglioma.

Neuroblastoma was the second most frequent malignant solid tumour of neonates. The similar numbers of boys and girls contrast with the male excess among older children [3]. In the present series, 38 cases (42%) had Stage 4S disease according to the International Neuroblastoma Staging system [4], 11 (12%) were Stage 4, 34 (37%) had localised disease and there was no record of tumour stage for the remaining 8 (9%). A series of 134 cases of neonatal neuroblastoma in the Italian Neuroblastoma Registry contained a similarly high proportion of Stage 4S but only a single case of Stage 4 [5]. Among the tumours tested, only 2% had amplification of the MYCN oncogene which is more frequent in older children and is associated with poor prognosis [5]. In the Quebec Neuroblastoma Screening Project, nearly all cases diagnosed by screening at age 3 weeks or detected clinically before then had favourable biological features and none had MYCN amplification [6]. Neuroblastoma may

Table 52.1 Incidence of cancer among live-born neonates born 1988–2007 in Great Britain

	Neonates aged 0–27 days				Infants aged 28–364 days		
ICCC-3	*N*	Risk/10^6 live births	Rate/10^6 py	M/F	*N*	Risk/10^6 live births	Rate/10^6 py
I. Leukaemias	71	5.0	65.0	0.9	498	34.9	37.8
(a) ALL	15	1.1					
(b) AML	36	2.5					
(d) JMML/CMML and MDS	6	0.4					
(e) Other and unspecified	14	1.0					
II. Lymphomas	0	0.0	0.0	—	11	0.8	0.8
III. CNS tumours	50	3.5	45.8	1.3	448	31.4	34.0
(a) (2) Choroid plexus tumours	5	0.4					
(b) Astrocytoma	11	0.8					
(c) Embryonal	10	0.7					
(d) Other gliomas	4	0.3					
(e) (4) Mixed glial neuromal	1	0.1					
(f) Unspecified	19	1.3					
IV. Neuroblastoma etc.	91	6.4	83.3	1.0	474	33.3	36.0
(a) Neuroblastoma	91	6.4					
V. Retinoblastoma	32	2.2	29.3	1.0	306	21.5	23.3
VI. Renal tumours	5	0.4	4.6	1.5	218	15.3	16.6
(a) (1) Wilms tumour	4	0.3					
(4) pPNET	1	0.1					
VII. Hepatic tumours	7	0.5	6.4	2.5	91	6.4	6.9
(a) Hepatoblastoma	7	0.5					
VIII. Bone tumours	1	0.1	0.9	0.0	5	0.4	0.4
(d) (2) Chordoma	1	0.1					
IX. Soft tissue sarcoma	38	2.7	34.8	1.1	150	10.5	11.4
(a) Rhabdomyosarcoma	13	0.9					
(b) (1) Fibrosarcoma	10	0.7					
(3) Mal haemangiopericytoma	1	0.1					
(d) (2) pPNET	2	0.1					
(3) Extra renal rhabdoid	5	0.4					
(6) Leiomyosaroma	1	0.1					
(8) Blood vessel tumours	1	0.1					
(9) Extra osseous osteosarcoma and chondrosarcoma	1	0.1					
(e) Unspecified	4	0.3					
X. Germ-cell and gonadal	93	6.5	85.1	0.5	97	6.8	7.4
(a) CNS germ cell tumours	13	0.9					
(b) Other non-gonadal germ-cell	78	5.5					
(c) Gonadal germ cell	2	0.1					
XI. Melanoma and carcinoma	3	0.2	2.7	0.0	9	0.6	0.7
(d) Malignant melanoma	3	0.2					

(continued)

Table 52.1 (continued)

ICCC-3	Neonates aged 0–27 days				Infants aged 28–364 days		
	N	Risk/10^6 live births	Rate/10^6 py	M/F	*N*	Risk/10^6 live births	Rate/10^6 py
XII. Other and unspecified	3	0.2	2.7	2.0	16	1.1	1.2
(a) Gastrointestinal stromal tumour	1	0.1					
(b) Unspecified	2	0.1					
Total	394	27.6	360.6	0.9	2325	163.1	176.7

Numbers of cases (*N*), risk per million live births, incidence per million person-years (py) and male/female ratio (M/F). Incidence rates ignore mortality from other causes and assume zero international migration. Numbers and rates among older infants given for comparison

Source: National Registry of Childhood Tumours

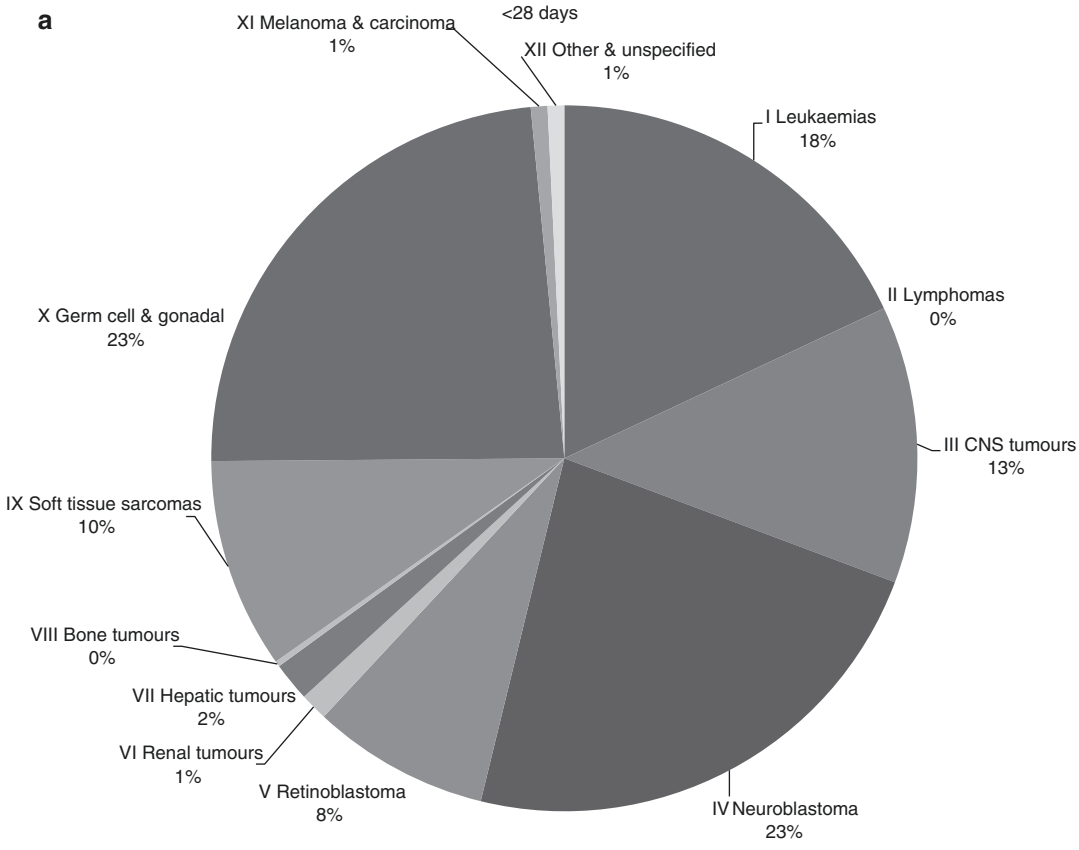

Fig. 52.1 Relative contributions of the 12 IICC-3 diagnostic groups to cancer incidence among young children in Britain by age group: (**a**) neonates aged 0–27 days, (**b**) infants aged 28–364 days, (**c**) children aged 1–4 years. *Source*: (**a**, **b**), Table 52.1; (**c**) National Registry of Childhood Tumours, unpublished data, 1988–2007

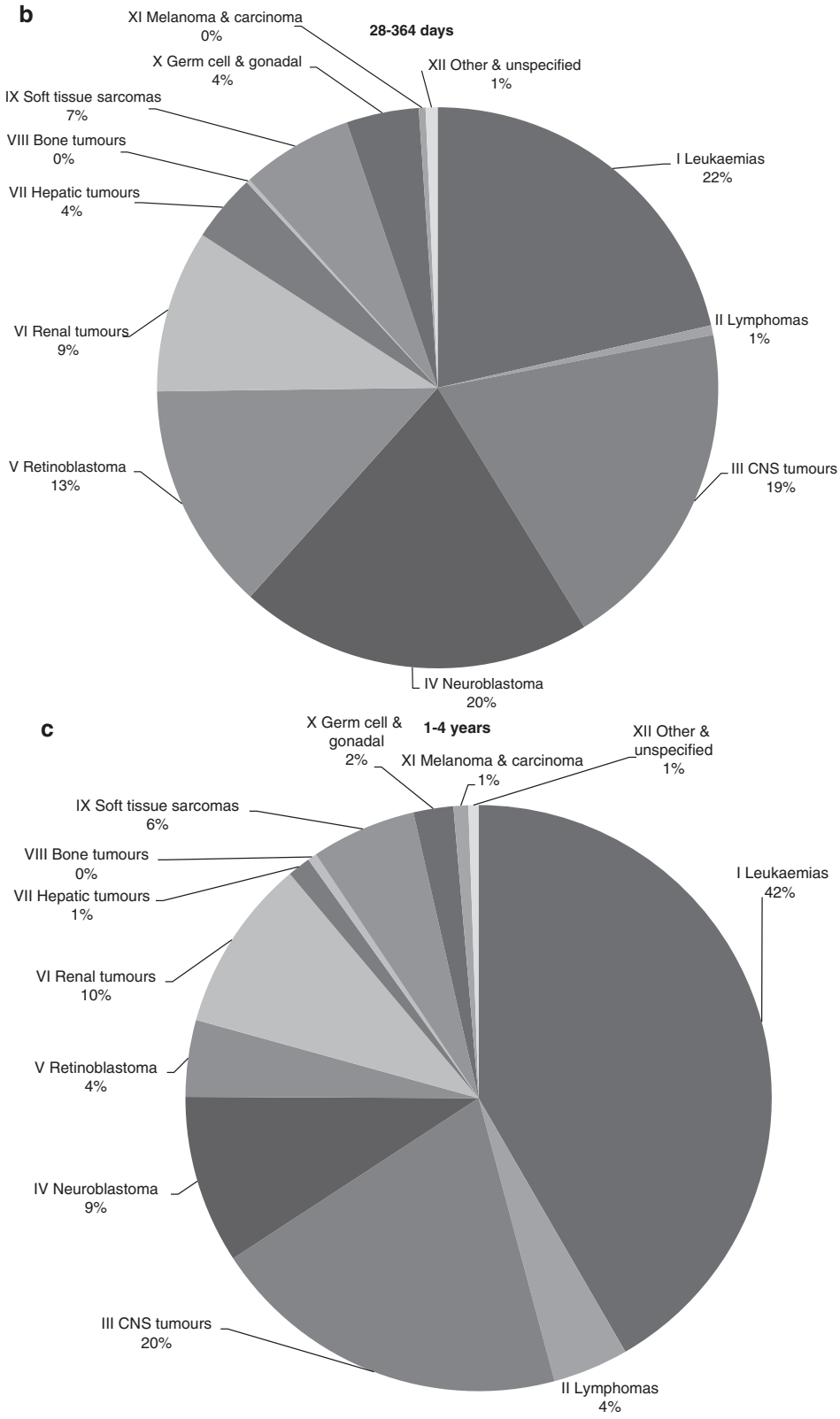

Fig. 52.1 (continued)

be detected prenatally by ultrasonography. Among 32 live-born cases of neonatal neuroblastoma diagnosed at paediatric oncology centres in Britain during 1986–94, 5 (16%) had a prenatal maternal ultrasound scan suggestive of neuroblastoma and another two had abnormal scans which could, with hindsight, be attributed to the tumour [7]. In the Italian Neuroblastoma Registry, 20% of neonatal cases diagnosed in 1980–2006 were detected prenatally, with little variation in the prenatal detection rate over the 27 year study period [5].

Of the 32 patients with retinoblastoma, 6 (19%) had unilateral and 25 (78%) had bilateral tumours.

Of the four cases of Wilms tumour, three were unilateral and one was bilateral. Although rhabdoid tumour of the kidney has its highest incidence in the first year of life, no cases were recorded among neonates. Hepatic cancer was more frequent than renal cancer; all seven cases were hepatoblastomas. A single case of chordoma was the only neonatal malignant bone tumour.

The 13 rhabdomyosarcomas were evenly divided between embryonal and alveolar subtypes, with six cases of each; the remaining case was of unknown subtype. An unusually high proportion of neonatal alveolar rhabdomyosarcoma may be of the fusion-negative variant which accounts for only 20% of cases in older patients [8, 9]. The primary sites were head and neck (3 cases), upper limb (1), lower limb (2), connective tissue of trunk (5) and bladder/prostate (2). All ten fibrosarcomas were of the infantile subtype. Primary site was known in nine cases: head and neck (2), upper limb (3), lower limb (2), and connective tissue of trunk (2). The single case of leiomyosarcoma was in the small bowel and might well be reclassified as gastro-intestinal stromal tumour if it were diagnosed today.

Germ-cell tumours were the most frequent group of tumours observed in this series. They were twice as frequent among girls as among boys. The 13 CNS tumours in this group were all teratomas, of which three were specified as malignant and three as benign. The 78 other non-gonadal germ cell tumours comprised 64 teratomas, 9 yolk-sac tumours, 4 mixed germ cell tumours, and 1 choriocarcinoma. The incidence of non-gonadal, non-CNS malignant germ cell tumours calculated here will be an over-estimate according to some definitions of malignancy. This is because immature teratoma is regarded as malignant in ICD-O-3. The present series included 38 cases described as immature teratoma with no malignant features, and if they were to be excluded, the incidence would fall from 5.5 per million live births to 2.8 per million. In a thirty-year population-based study with pathology review in the West Midlands region of England, all 49 extracranial germ cell tumours diagnosed in the first 4 months of life were classified as benign mature teratoma, although four recurred as malignant tumours [10]. The majority of the non-gonadal, non-CNS germ cell tumours in the present series (50/78, 64%)were in the sacrococcygeal region. Other primary sites were head and neck (12, 15%), mediastinum (6, 8%), intraabdominal (6, 8%) and unknown (4, 5%). The two gonadal germ-cell tumours were a testicular yolk-sac tumour and an ovarian teratoma.

It should be emphasised that the series described here does not provide an exhaustive catalogue of malignancies that can arise in neonates. For example, in the years before or after the study period, the NRCT has included neonatal cases of ocular medulloepithelioma, pancreatoblastoma [11] and pleuropulmonary blastoma. There are numerous reports of other very rare neonatal cancers in the literature.

The NRCT, like nearly all cancer registries, did not aim for complete ascertainment of benign tumours. It nevertheless contained a sizeable number of registrations for non-malignant tumours diagnosed in neonates over the same period as the malignant neoplasms discussed above. These registrations are enumerated in Table 52.2. Ascertainment was undoubtedly incomplete and biased towards (1) diagnoses most often referred to paediatric oncologists and (2) fatal tumours. The data can nevertheless provide minimum estimates of incidence for certain non-malignant neonatal tumours, also given in Table 52.2, and the proportion of tumours that are benign in some diagnostic groups.

Table 52.2 Incidence of non-malignant neoplasms among live-born neonates born 1988–2007 in Great Britain

Diagnostic group	*N*	Minimum risk/10^6 live births	M/F
Langerhans cell histiocytosis	5	0.4	0.7
Renal tumours	45	3.2	1.0
Mesoblastic nephroma	41	2.9	
Cystic nephroma	1	0.1	
Unspecified	3	0.2	
Hepatic tumours	12	0.8	0.7
Haemangioendothelioma/haemangioma	10	0.7	
Unspecified	2	0.1	
Fibromatous tumours	13	0.8	1.4
Fibromatosis	5	0.4	
Myofibromatosis	3	0.2	
Haemangiopericytoma	4	0.3	
Fibroma	1	0.1	
Extrahepatic blood vessel tumours	30	2.1	1.3
Haemangioma	14	1.0	
Lymphangioma	16	1.1	
Other soft tissue tumours	5	0.4	0.5
Rhabdomyoma	3	0.2	
Leiomyoma	2	0.1	
Germ-cell tumours	203	14.2	0.4
Extragonadal teratoma	201	14.1	
Gonadal germ-cell tumours	2	0.1	
Other gonadal tumours	8	0.6	7.0
Juvenile granulosa cell tumour	6	0.4	
Leydig cell tumour	1	0.1	
Unspecified	1	0.1	
Melanoma	4	0.3	3.0
Other and unspecified	33	2.3	0.6
Gastrointestinal stromal tumour	1	0.1	
Sialoblastoma	1	0.1	
Unspecified	31	2.2	
Total	358	25.1	0.7

Numbers of registered cases (*N*), minimum estimate of risk per million live births, and male/female ratio (M/F). Note that ascertainment is incomplete and varies between diagnostic groups
Source: National Registry of Childhood Tumours

The risk of 0.4 per million live births for Langerhans cell histiocytosis (LCH) is almost certainly too low. In the German Childhood Cancer Registry the estimated incidence in the first month of life was between 1 and 2 per million live births [12]. In a series of over 1000 children from the Austrian/German/Swiss/Netherlands subcentre of the international LCH clinical trials, the disease manifested in the neonatal period in 61 cases but was only diagnosed within the first 4 weeks in 20 of them [12], which suggests that LCH may be present in 3–6 per million neonates.

Mesoblastic nephroma seems likely to be more completely registered than most benign neoplasms of infancy because of its eligibility for clinical trials of treatment for childhood renal tumours. The minimum risk estimate of 2.9 per million live births is very close to the 3.0 per million, based on 7 cases, in the West Midlands study where ascertainment was thought to be

virtually complete [10]. The presence of 41 cases in the present series compared with four cases of Wilms tumour indicates that mesoblastic nephroma is at least ten times as frequent as Wilms tumour among neonates. By the age of 3 months, however, Wilms tumour is much more frequent than mesoblastic nephroma [13]. Among 47 cases of mesoblastic nephroma included in UK Wilms tumour trials, the median age at diagnosis was 1 month, an antenatal diagnosis of renal mass was made in 14 (30%) and a further 8 (17%) presented with an abdominal mass on routine postnatal examination [13]. This suggests that the great majority of neonatal mesoblastic nephromas are detected prenatally or diagnosed incidentally.

There are no population data on hepatic haemangioendothelioma and haemangioma but the fact that the NRCT series included ten cases, as against seven cases of hepatoblastoma, suggests that this is the most common neonatal liver tumour.

Because of its interest to oncologists, it seems likely that ascertainment of fibromatosis, including myofibromatosis, was relatively high. The data presented here suggest that these conditions are diagnosed in the neonatal period with a frequency similar to infantile fibrosarcoma.

By far the largest group of non-malignant tumours was the extragonadal teratomas which, even if ascertainment were complete, were almost three times as frequent as malignant germ-cell tumours. The excess of girls over boys was similar to that for malignant germ-cell tumours. The most frequent site was the sacrococcygeal region (144/201, 72%), followed by head and neck (33/201, 16%), intraabdominal (6/201, 3%) and intrathoracic (3/201, 1%); site was not specified in 15 cases (7%). Combining the numbers of malignant and non-malignant cases, the recorded incidence of neonatally diagnosed sacrococcygeal teratoma was 12.8 per million live births, or 1 in 78,000. This is somewhat lower that the rate of 1 in 58,700 live births for sacrococcygeal, sacral and pre-sacral teratomas in the West Midlands study, the great majority of which were diagnosed neonatally [10]. In a more recent population-based study in northern England the birth prevalence was 1 in 27,000 live births overall and 1 in 37,700 for tumours diagnosed neonatally [14]. This suggests that nationally only half of all sacrococcygeal teratomas, and 40% of non-malignant cases, were registered. In the northern England study, 50% of live born neonatal cases had been detected on prenatal ultrasound.

52.2 Genetic and Familial Associations

A substantial proportion of childhood cancers occur in association with genetic syndromes. In a large series of children and adolescents with cancer, 8.5% had germline mutations that were deemed to be definitely or probably pathogenic [15]. It seems very unlikely that the percentage is lower among neonates with cancer. In addition, a substantial proportion are associated with chromosomal abnormalities. Among young children with Down syndrome, the relative risk of leukaemia is about 50 and it is especially high for AML [16]. In the present series, 15/71 (21%) neonates with leukaemia had Down syndrome. These included 9 of the 36 with AML, 5 of the 14 with unspecified leukaemia and the single case of myelodysplasia; there were no cases of Down syndrome with ALL. These data do not include cases of transient abnormal myelopoiesis (TAM), a benign condition found in 10% of Down syndrome babies [17]. AML later develops in 20–30% of infants with Down syndrome and TAM, but virtually always beyond the neonatal period [18].

In the majority of acute leukaemia in infants, both ALL and AML, the malignant clone has a rearrangement involving the MLL gene on chromosome 11q23 [19]. Studies of neonatal blood spots have confirmed that the MLL rearrangement originates *in utero* [20]. A large number of studies has found associations between polymorphisms of several genes and the risk of childhood leukaemia but they have mostly related to types of leukaemia more often found in older children. There is some evidence that carriers of the inactivating polymorphism C609T in the NAD(P)H:quinine oxidoreductase 1 gene (NQ01) have an

increased risk of ALL or of MLL+ leukaemia [21–23]. One recent study found that slow-acetylation phenotypes of N-Acetyl transferase 2 (NAT2) were associated with MLL+ and MLL- infant leukaemia [24]. The Brazilian Collaborative Study Group of Infant Acute Leukemia has found that polymorphisms of several other genes affect the risk of leukaemia in the first 2 years of life [25, 26]. In a cohort of 641 children with Noonan syndrome who were verified as carrying a germline PTPN11 mutation, 16 (2.5%) had JMML and 8 (1.2%) had other JMML-like myeloproliferative disorders (MPD) with onset in the neonatal period, and there were a further four cases of JMML and eight of MPD with onset later in childhood [27].

Genome-wide association studies have identified several genomic loci associated with predisposition to sporadic neuroblastoma [28]. Some of these are associated with high-risk disease [28], and thus of limited relevance to neonatal neuroblastoma which is predominantly low-risk. Four predisposition loci for low-risk neuroblastoma have also been identified [29], although with no proposed mechanism as yet [28]. Three further loci have been associated with predisposition to neuroblastoma of both high-risk and low-risk forms [28].

Only 1–2% of neuroblastoma is familial and the majority of pedigrees are associated with germline mutations of the anaplastic lymphoma kinase (ALK) gene [28]. Most of the remaining familial cases result from germline mutations of the paired-like homeobox 2B(PHOX2B) gene, and affected children also have a high risk of Hirschsprung disease and congenital central hypoventilation syndrome [28]. About 10% of familial neuroblastoma is not associated with either of these genes and their aetiology remains unknown. Genetic testing for germline ALK and PHOX2B mutations is recommended for infants with a family history of neuroblastoma [28].

Retinoblastoma is caused by mutation or, rarely, deletion of both copies of the tumour suppressor gene RB1on chromosome 13q14. In heritable cases the first mutation is in the germline, while in non-heritable cases both mutations are somatic [30]. The majority of children with heritable retinoblastoma have bilateral disease whereas non-heritable cases are invariably unilateral. Among the 32 cases of retinoblastoma in Table 52.1, there was a past family history of the disease in 24/25 bilateral and all six unilateral cases and this would undoubtedly have increased the likelihood of diagnosis during the neonatal period. Based on the criterion of having bilateral tumours or past family history, at least 31/32 (97%) of the cases of neonatal retinoblastoma were of the heritable form.

Germline mutations of the tumour suppressor gene TP53 confer increased risk of a wide range of childhood cancers including soft-tissue sarcomas and adrenocortical carcinoma, and are responsible for most occurrences of the Li-Fraumeni familial cancer syndrome [31]. In a study of children with sporadic rhabdomyosarcoma, 3/13 patients aged under 3 years at diagnosis harboured a constitutional TP53 mutation, compared with none of the 20 children over 3 years of age [32]. Two of the affected children had embryonal rhabdomyosarcoma and one had alveolar rhabdomyosarcoma. The youngest child with a TP53 mutation was diagnosed at 18 months and the youngest in the series was 5 months of age. Nevertheless, it is plausible that some cases of neonatal rhabdomyosarcoma are caused by germline TP53 mutations. A very high proportion of young children with adrenocortical carcinoma carry a germline mutation of TP53 [33, 34]. Adrenocortical carcinoma does occur in infancy, although there were no cases in the 20-year series of Table 52.1. In a study of mass screening of neonates in southern Brazil, where adrenocortical tumours are strongly associated with the germline TP53 mutation R337H, the mutation was carried by 0.27% of those were screened, and adrenocortical tumours were diagnosed in 2.4% of carriers compared with 0.0012% of non-carriers [35].

While nearly all sporadic chordomas occur in adults, 9 of the 11 published cases in patients with tuberous sclerosis complex (TSC) have been diagnosed in children under 5 years of age [36]. They include four cases arising in the sacrum, a rare site for sporadic chordoma, all of them diagnosed in the first week of life [37]. TSC is caused by inactivating germline mutations of either of the tumour suppressor genes TSC1 and TSC2, and

chordoma has been found in both groups. Chordoma of the skull base, a much more frequent primary site for sporadic chordoma, has also been reported in association with TSC but the youngest infant so far recorded was diagnosed at 4 months of age [36]. Cardiac rhabdomyomas, usually diagnosed prenatally or in the neonatal period, are a major feature of TSC [38]. Subependymal giant cell astrocytoma, a low-grade glioma, occurs in 10% of patients with TSC [39] but is rarely diagnosed in neonates [38].

Rhabdoid tumour predisposition syndrome is associated with germline mutation or deletion of SMARCB1 (also known as INI1, hSNF5 or BAF47) on chromosome 22q and results in increased risk of rhabdoid tumour of the kidney, ATRT of the CNS, and extra-renal rhabdoid tumours of other sites [40].

Beckwith-Wiedemann syndrome is associated with increased risk of several childhood cancers including Wilms tumour, hepatoblastoma, adrenocortical carcinoma, rhabdomyosarcoma, neuroblastoma and pancreatoblastoma [41]. The cancers are nearly always diagnosed later than the first month of life but a few cases have been reported in neonates [11, 42, 43].

A wide range of other genetic syndromes is associated with increased risk of various childhood cancers but as they generally only manifest after the first month of life they are not discussed further here [44, 45].

There is little evidence that family members of children with germ cell tumours have a changed risk of cancer overall. In a North American case-control study of 274 children with malignant germ-cell tumours, family history of cancer before age 40 years or of ovarian or uterine cancers was associated with reduced risk of germ cell tumours in girls, whereas family history of cancer before age 40 or of melanoma was associated with increased risk in boys [46]. Nearly all neonatal germ cell tumours are extragonadal but results were not presented separately for extragonadal tumours, which accounted for less than half the cases in the study.

Several studies have found a higher relative risk of cancer in infancy than later in childhood among children with congenital abnormalities compared with children without abnormalities [47–50].

There is little evidence for any association between infant leukaemia and congenital abnormalities other than Down syndrome [51].

An excess risk of neuroblastoma in children with congenital abnormalities has been found repeatedly, but with limited consistency regarding the type of abnormality [52–55]. The association appears to be strongest for neuroblastoma diagnosed in infancy [54, 55], but it may also be more pronounced for tumours with MYCN amplification [54].

There have been numerous reports of associations between congenital abnormalities and childhood germ-cell tumours [48, 56–62]. In the largest case-control study the association was more pronounced for extragonadal tumours [63]. It also appeared to be limited to boys but this was largely accounted for by the highly significant association between cryptorchidism and testicular tumours [63]. There was little indication of association with any other specific abnormalities [63]. Sacrococcygeal teratomas are, however, frequent in infants with Currarino syndrome [64].

52.3 Other Birth Characteristics

High birth weight is associated with an increased risk of many childhood cancers. In parallel analyses of very large case-control data sets from the UK and USA, there were consistently raised risks of leukaemia, CNS tumours, renal tumours and soft-tissue sarcomas [65]. The results for leukaemia and CNS tumours were broadly similar to those in meta-analyses of previous studies [66, 67]. At least three studies have found an association with MLL+ leukaemia [68–70]. An increased risk of AML with low birth weight has also been found in some studies [65, 66], though this may be due to the fact that low birth weight is also associated with Down syndrome [65].

A meta-analysis of ten studies found that birth weight above 4000 g or below 2500 g was associated with increased risk of neuroblastoma [71], and a similarly U-shaped relationship was found in the recent UK/US study [65]. There is no consistent evidence for the increased risk being confined to a particular age group at diagnosis [52].

Low birth weight is an established risk factor for hepatoblastoma [65, 72], but it is nearly always

diagnosed beyond the neonatal period and it is unclear how many cases are truly congenital [73].

There was a particularly marked trend towards higher risk of extragonadal, non-CNS germ-cell tumours with increasing birth weight in the UK/US study [65]. In the largest previous case-control study of children with malignant germ-cell tumours, there was a significantly increased risk with parentally reported birth weight above 3500 g but the increase was much smaller and non-significant in the subset of children whose medical records could be reviewed [74]. An earlier study which had also found an association with higher birth weight speculated that this might be due to higher levels of maternal oestrogen during pregnancy [75] but the more recent study failed to provide evidence that exposure to exogenous female hormones in pregnancy increased the risk of germ-cell tumours [74]. Results were not presented specifically for infants but some neonatal teratomas constitute an appreciable proportion of body weight and a high proportion of premature births among infants with sacrococcygeal teratoma is a consequence of the tumour [14, 76].

There appears to be no association of infant leukaemia with prior fetal loss, infertility or its treatment [68, 77]. There has been little consistency in findings for neuroblastoma in relation to reproductive history [52, 54, 55, 78–80], whether or not the data were subdivided according to age at diagnosis or MYCN status. One study of rhabdomyosarcoma found a highly significant association with neonatal prior history of stillbirth [81] but a more recent, larger study found no difference in history of fetal loss between case and control mothers [82].

The two largest cohort studies of cancer in children born following assisted reproduction technology found no significant overall increase in cancer risk [83, 84]. In the Netherlands an increased risk of retinoblastoma was reported among children born after in vitro fertilisation, based on five cases diagnosed during 2000–2002 [85]. Over the next five years, however, no significantly elevated risk was found [86]. There was also no evidence for increased risk of retinoblastoma in three other large cohort studies [83, 84, 87].

52.4 Exogenous Risk Factors

The very early age at diagnosis for neonatal cancer means that exogenous risk factors that have been investigated for childhood cancer in general are only at all likely to be relevant if exposure was prenatal.

While 15–20% of childhood leukaemia may be attributable to exposure to natural background ionising radiation, the proportion among neonates is negligible because of their low total exposure by that age [88, 89].

Therapy-related AML in patients who have received chemotherapy that inhibits DNA topisomerase II (topo-II) often has the same MLL abnormalities that are found in infant leukaemia, leading to the hypothesis that maternal exposure to topo-II inhibitors in diet or medications might result in MLL+ leukaemia in the infant [90]. The hypothesis gains limited support from associations of infant AML with maternal consumption of foods containing topo-II inhibitors [90, 91] but no effect has been found for other topo-II inhibitors or for MLL+ ALL. Maternal consumption of fresh fruit and vegetables during pregnancy has been associated with decreased risk of MLL+ infant leukaemia [91]. Exposure to petroleum products during pregnancy has been associated with MLL- infant leukaemia in one study [92]. In the Air Pollution and Childhood Cancers Study in California, there was a raised risk of neuroblastoma with prenatal exposure to several pollutants; the effect was more marked for infants under 6 months of age, but there was no information on stage or MYCN status [93]. In the same study, there was a raised risk of bilateral retinoblastoma with prenatal exposure to traffic-related pollution [94]. Maternal cigarette smoking during pregnancy is not associated with infant leukaemia but the evidence on alcohol and illicit drug use is inconsistent [95].

There are numerous case reports of various neonatal tumours in infants whose mother took a wide range of drugs during pregnancy but very few of these associations have been confirmed by epidemiological studies [96]. Following the appearance of reports of neuroblastoma associ-

ated with fetal alcohol syndrome, several case-control studies found increased risk of neuroblastoma with maternal alcohol consumption during pregnancy [52]. The proportion of case mothers who drank in pregnancy was generally low, however, and no consistent association was found in the study which was based on by far the largest number of cases [97]. Several studies reported an excess risk of neuroblastoma with intake of diuretics in pregnancy [52] but the numbers of exposed cases were very small. Excess risks associated with maternal use of analgesics and other nervous system drugs have also been reported but the results were not broken down by age at diagnosis [52, 98].

Two studies have found a reduction in risk of neuroblastoma with maternal vitamin intake in pregnancy, which did not vary with age at diagnosis [99, 100]. Only the more recent study analysed the data in relation to MYCN status, and the effect was more pronounced for MYCN non-amplified disease [100]. Incidence of neuroblastoma among infants in Ontario declined by 60% since the start of folic acid fortification of flour [101] but in Hungary the risk of neuroblastoma did not decrease during the first four years of a national policy of folic acid supplementation in pregnancy [102].

The largest case-control study of sporadic bilateral retinoblastoma arising from a new germline RB1 mutation found significant associations with gonadal radiation exposure to either parent before conception [103]. While the mutations may have been radiation-induced, the results could also be due to bias, confounding or chance.

Radiation exposure during pregnancy has been associated with rhabdomyosarcoma in the child, with the association being strongest for children diagnosed before 5 years of age and perhaps limited to embryonal rhabdomyosarcoma [82].

52.5 Survival

Table 52.3 shows survival rates for infants born in 1988–2007 who had cancer diagnosed in the neonatal period. Results are presented for all ICCC-3 groups, subgroups and divisions with at least five cases. Overall survival was 64% at 1 year from diagnosis and 62% at 3 years, considerably lower than the 88% 1-year and 78% 3-year survival rates for all childhood cancer diagnosed during 1991–2000 [13]. Thus, while the short-term prognosis of neonatal cancer is rather poor, the probability of survival conditional on surviving 1 year from diagnosis is very much higher than in older children. Survival from leukaemia, embryonal CNS tumours, renal tumours and rhabdomyosarcoma was especially poor for neonates compared with older children. By contrast, neonates with retinoblastoma had 100% 3-year survival. The 79% 3-year survival rate of neonates with neuroblastoma was slightly

Table 52.3 Survival from cancer among live-born neonates born 1988–2007 in Great Britain

ICCC-3	*N*	1-year survival	3-year survival
I. Leukaemias	71	34	30
(a) ALL	15	33	13
(b) AML	36	36	36
(d) JMML/CMML and MDS	6	67	67
(e) Other and unspecified	14	14	14
III. CNS tumours	50	42	42
(a) (2) Choroid plexus tumours	5	80	80
(b) Astrocytoma	11	64	64
(c) Embryonal	10	0	0
(f) Unspecified	19	37	37
IV. (a) Neuroblastoma	91	80	79
V. Retinoblastoma	32	100	100
VI. (a) Wilms tumour and renal pPNET	5	40	40
VII. (a) Hepatoblastoma	7	71	71
IX. Soft tissue sarcoma	38	45	37
(a) Rhabdomyosarcoma	13	54	38
(b) (1) Fibrosarcoma	10	70	70
(d) (3) Extra renal rhabdoid	5	20	0
X. Germ-cell and gonadal	93	76	76
(a) CNS germ cell tumours	13	31	31
(b) Other non-gonadal germ-cell	78	83	83
Total	395	64	62

Numbers of cases (*N*), 1-year and 3-year survival rates (%)

lower than the 84% 3-year survival of all infants under 1 year of age who were diagnosed with neuroblastoma in 1991–2000 but much higher than that for children aged 1 year and over at diagnosis [13].

Most survivors of childhood cancer go on to lead normal lives. They are, however, at increased risk of second cancers and a range of other late effects depending on the type of cancer and its treatment [104–108]. There is little information on these risks specifically as they relate to survivors of neonatal cancer. There is some evidence that the risk of second cancer following heritable retinoblastoma treated with radiotherapy is especially high when the retinoblastoma is diagnosed in the first month of life [109].

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Vascular Anomalies

53

R. Dawn Fevurly and Steven J. Fishman

Abstract

Vascular anomalies have long confused patients and physicians alike. Historically, it was believed that a mother's emotions or diet could imprint upon her unborn child, resulting in a vascular birthmark. This use of the terms "cherry", "strawberry", or "port wine stain" reflect this doctrine of maternal impressions. Virchow was likely the first to attempt to categorize vascular anomalies based upon histological features. Despite his attempts, overlapping vernacular and histopathologic terms continued to contribute to confusion, resulting in misdiagnosis, inappropriate treatment, and misdirected research. In 1983, Mulliken and Glowacki presented a reliable classification system for vascular anomalies, dividing the field into two major categories: hemangiomas and malformations. Following modification to tumors and malformations, this system was formally accepted by the International Society for the Study of Vascular Anomalies in 1996 and remains in use today.

Keywords

Arteriovenous malformation • Hemangioma • Lymphatic malformation • Kaposiformhemangioendothelioma • Vascular anomaly • Vascular malformation • Venous malformation

53.1 Introduction

Vascular anomalies have long confused patients and physicians alike. Historically, it was believed that a mother's emotions or diet could imprint upon her unborn child, resulting in a vascular birthmark [1]. This use of the terms "cherry", "strawberry", or "port wine stain" reflect this doctrine of maternal impressions [2]. Virchow was likely the first to attempt to categorize vascular anomalies based upon histological features [3]. Despite his attempts, overlapping vernacular and histopathologic terms continued to contribute to confusion, resulting in misdiagnosis, inap-

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_53

propriate treatment, and misdirected research. In 1983, Mulliken and Glowacki presented a reliable classification system for vascular anomalies, dividing the field into two major categories: hemangiomas and malformations [1]. Following modification to tumors and malformations, this system was formally accepted by the International Society for the Study of Vascular Anomalies in 1996 and remains in use today [4].

The division of vascular anomalies into tumors and malformation is based upon cellular and clinical behavior, as well as unique radiographic and immunohistochemical differences. Vascular tumors are characterized by endothelial hyperplasia and include both hemangiomas and less common pediatric vascular tumors. Vascular malformations arise by vascular dysmorphogenesis and exhibit normal endothelial cell turnover [5]. Use of this bipartite system provides the framework for diagnosis, prognosis and a guide for therapy. Familiarly with the field, its classification system, and the correct nomenclature will aid clinicians in diagnosis and treatment and improve outcomes for patients affect by these lesions.

53.2 Vascular Tumors

53.2.1 Infantile Hemangioma

Infantile hemangioma (IH) is a benign tumor of endothelial cells. As the most common tumor of infancy, it affects approximately 4% of all Caucasian infants [6]. In dark-skinned babies, the incidence is lower. There is a female-to-male preponderance of 3:1–5:1 [5]. Extremely low birth weight infants (<1000 g) bear an increased risk for hemangioma with an overall incidence of 23%, with every 500 g decrease in birth weight increasing the risk by 40% [7, 8]. Additional risk factors of advanced maternal age, placental abnormalities, and multiple gestations are observed [9].

IH most commonly presents as a focal cutaneous lesion (72%), displaying a predilection for the head or neck (60%) [10, 11]. They also occur on the trunk (25%) and extremities (15%) [11]. Multiple tumors occur in 20% of cases, signaling potential involvement of extracutaneous organs such as the gastrointestinal tract or liver [5]. In infants displaying more than five hemangiomas, the risk for hepatic hemangiomas is greatly increased [12]. Hemangiomas typically present around one to 2 weeks of life. Nearly half of infants display a promontory mark, such as a pale spot or faint macular stain [5]. The superficial form develops into a raised, bosselated, crimson lesion, while deeper hemangiomas may present as raised bluish lesions with indistinct borders.

The predictable life cycle of the IH is its hallmark (Fig. 53.1). The *proliferative phase* last until 10–12 months of age and is characterized by rapid growth. A second stage of growth in proportion to the child then occurs, followed by the *involuting phase*, which spans the next 1–7 years. During this final phase, the endothelial matrix is replaced by loose fibrous or fibro-fatty tissue. By

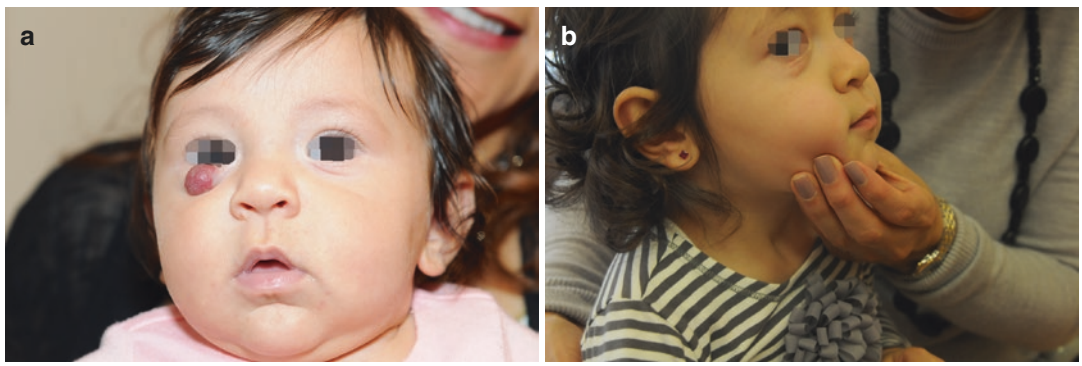

Fig. 53.1 Infantile hemangioma (IH). (**a**) Proliferating phase IH at 5 months of age. (**b**) Involuted IH at 4 years of age

age 5, 50% of tumors have completed involution. This increases to 70% by age 7, with the remainder involuted by ages 10–12 [13]. While half of patients display normal skin in the area of the hemangioma, larger tumors sometimes leave redundant skin and a fibrofatty residuum. In addition, ulcerated hemangiomas often leave scars or a yellowish discoloration [5].

While dangerous complications are rare, several situations are cause for added scrutiny [13]. Hemangiomas of the subglottis or cervicofacial region can lead to life-threatening airway obstruction [5]. Hoarseness and biphasic stridor beginning at 6–12 weeks of age provides clues to a subglottic IH. Ulcerating IH of the eyelid, nasal tip, lip, or ear can lead to disfigurement. IH located in the periorbital region can block the visual axis and lead to amblyopia. In such cases, a pediatric ophthalmologist should be involved. Through recognition of the anatomic distribution of IH, many complications may be averted with proper care and treatment. Intestinal hemangiomas can manifest as infantile bleeding and anemia, while hepatic hemangiomas can result in high-output cardiac failure, hypothyroidism, and abdominal compartment syndrome.

53.2.1.1 Etiology and Pathogenesis

Despite the prevalence of IH, insight into its etiology and pathogenesis remains limited. Several theories propose the endothelial stem/progenitor cell as the cellular source of hemangioma [14–16]. The source of these endothelial progenitors, however, remains elusive. Some studies suggest resident angioblasts, arrested in a stage of early development, give rise to these cells. A second theory proposes these cells are of placental origin, given their co-expression of several distinct markers: GLUT1, merosin, Lewis Y antigen, Fcγ-RIIb, indoleamine 2,3-deoxygenase, IGF-2 and type III iodothyronine deiodinase (DI03) [17–22]. Disruption of the maternal-fetal barrier may permit placental endothelial cells to reach fetal tissues, possibly accounting for the increased incidence of hemangioma observed with chorionic villus sampling due to local placental injury [23]. A third theory promotes IH formation stemming from angiogenesis dysregulation, as expression of vascular endothelial growth factor receptors (VEGFR) 1 and 2 are altered [24]. Activation of VEGFR2, which promotes endothelial cell proliferation, is upregulated in IH, while VEGFR1 levels, a decoy receptor that limits activation of VEGFR2 by binding ligands, are downregulated [25–28]. This may promote overgrowth of endothelial cells leading to disorganized blood vessels and studies in mice support this idea [27].

The clinical observation of growth and involution in IH are mirrored in the cellular activity of the tumor. During proliferation, overexpression of proangiogenic markers predominates with the presence of basic fibroblast growth factor, vascular endothelial growth factor, and matrix metalloproteinases [24, 29]. During involution, the majority of these markers are down regulated and angiogenesis decreases as endothelial cells undergo apoptosis [30]. Subsequently, angiogenesis inhibitors such as inteferon-β and tissue inhibitor of metalloproteinase are up regulated at this time, while proapoptotic markers mitochondrial cytochrome b and homer-2a also appear [30–32]. However, other key elements towards understanding hemangiomas, including triggers for involution, female proponderance, and trophism, remain unexplained.

53.2.1.2 Associated Structural Abnormalities

True hemangiomas are occasionally associated with other malformations.

A subgroup of patients typically with cervicofacial hemangioma exhibit associated structural anomalies of the brain (e.g. posterior fossa abnormality), cerebral vasculature (e.g. aneurysms, hypoplasia or absence of carotid or vertebral vessels), eye (e.g. cataracts, optic nerve hypoplasia), aorta (e.g. coarctation), and chest wall defects (e.g. sternal clefts) in the PHACES association [33–35]. Tumors overlying the lumbosacral region may signal spinal dysmorphism (e.g. lipomenigocele, tethered spinal cord) and affected infants less than 4 months of age should undergo screening ultrasound. Investigation at later ages generally requires MRI [36]. In addition, anorectal and genital anomalies may occur with IH of the pelvis or perineum.

53.2.1.3 Radiologic Features

Most hemangiomas can be readily diagnosed by history and physical examination. Radiographic imaging can play an important role in evaluating deep or atypical lesions. Under ultrasonographic evaluation, proliferating IH appear as fast-flow tissue masses with increased vessel density [37, 38]. MRI evaluation is reserved for cases of uncertainty and confirmation of tissue orientation. Like ultrasound, MRI of IH reveals a vascular solid mass with dilated feeding and draining vessels. Tissue is of indeterminate intensity on T1-weighted images and bright on T2-weighted images with flow voids present [38]. Involuted IH resembles an avascular fatty mass on MRI [39].

53.2.1.4 Treatment

Most IH regress without intervention, requiring only guidance, education, and support from a pediatrician or consultant. Care should be taken to recognize the emotional impact of the tumor, particularly in cases of disfiguring IH. In cases of equivocal diagnosis, dangerous location, large size, rapidity of growth, or potential for other complications, referral to a specialist is indicated.

Ulceration

Spontaneous epithelial breakdown, crusting, ulceration, and necrosis are the most common complications of IH, occurring in approximately 5% of cases. The most vulnerable areas include the lips, parotid, or perineum [40, 41]. Ulceration frequently takes place during the proliferation phase, perhaps due to overgrowth of the blood supply or growth in excess of the skin's elastic capabilities [42, 43]. Initial treatment involves cleansing of the wound, application of an antibiotic salve and use of viscous lidocaine for pain control. Superficial ulcerations heal within days to weeks, while deeper wounds may take several weeks [5]. Eschar should be sharply debrided, followed by wet-to-dry dressing changes in order to stimulate granulation tissue. Resection should be considered if the remaining scar would be similar to removal of the involuted area later.

Pharmacotherapy

For many years, corticosteroids were the mainstay of treatment for IH. Recently, a number of studies and reports have pointed to propranolol, a nonselective beta-blocker, as an effect pharmacologic agent in the treatment of IH [44–47]. Within 1–3 days of therapy, a softening and change in color of IH is noted, possibly due to inhibition of vasodilation [44, 47]. Blockage of proangiogenic signals VEGF, bFGF, and MMP 2/9 likely accounts for the halt of growth of the tumor [48]. Finally, the observation that beta-blockers can induce apoptosis in proliferating endothelial cells may account for the accelerated regression of the tumor [49, 50]. A prospective randomized trial is currently underway, the results of which will hopefully guide future therapy with this exciting treatment. Current treatment regimens recommend dosing of 0.5–0.7 mg/kg/dose tid (total daily dose of 2–3 mg/kg/day, divided tid), following a cardiology consultation [47, 51]. Potential side effects include bradycardia, hypotension, hypoglycemia, gastrointestinal complaints, and bronchospasm [46, 51–54]. A role for topical beta-blockers, such as timolol maleate, has also shown modest results [55].

Systemic corticosteroid therapy has been the most widely used treatment of endangering, ulcerating, problematic, or life-threatening IH. Oral prednisolone (2–3 mg/kg/day for 2–3 weeks) is generally favored, but in a life-threatening situation, such as airway constriction, an equivalent dose in intravenous form is recommended. Response is often evident in 1–2 weeks, which includes fading of color, a diminished rate of growth, and palpable softening. Upon stabilization, the dosage is tapered every 2–4 weeks to minimize steroid associated complications, with a goal of discontinuation by 10 months of age. Overall response rates are 80–90%. Potential side effects include Cushingoid facies (71%), growth delay (35%), personality changes (29%), gastric irritation (21%), hirsutism (13%), and hypertension [56–59]. The mechanism of action is thought to be secondary to corticosteroid suppression of vascular endothelial growth factor A, effectively limiting the vasculogenic potential of IH [60].

Intralesionalinjection of corticosteroid for small, well-localized cutaneous IH, particularly of the lip, cheek, nasal tip or eyelid, may be considered. Triamcinolone (25 mg/ml) is injected slowly at low pressure with a 3 mL syringe and 25 gauge needle, which minimizes the risk of embolization through draining veins. Dosage is typically 3–5 mg/kg per injection. This may be repeated at 6–8 weeks intervals, typically amounting to 3–5 sessions [61].

Recombinant interferon alpha (IFNα-2a or 2b) had previously been second-line therapy for IH, but has been avoided more recently due to reports of associated spastic diplegia [59]. This is a particular risk in infants less than 6 months age, occurring in 5–20% of treated patients [62]. Better second line therapy involves anti-angiogenic chemotherapy drugs, such as vincristine, which has been effective in some children unresponsive to corticosteroids [63, 64].

Embolic Therapy

Embolization is rarely indicated for instances of drug refractory IH causing severe congestive heart failure. The most common lesions necessitating embolization are hepatic hemangiomas. Arteriovenous collaterals and portohepatic shunts, not the proximal hepatic artery branches, in the tumor should be targeted. Pharmacologic therapy is continued even after successful embolization in these patients.

Laser Therapy

Flashlamp pulsed dye laser is ineffective in treating proliferating IH. Due to its superficial penetration of IH, it serves only to lighten the lesion, leaving proliferation unaffected. Small, flat lesions that do respond are typically those that would regress naturally with little to no scarring. Moreover, side effects of laser use include ulceration, partial-thickness skin loss, scarring, and hypopigmentation. Accepted indications for laser therapy include removal of persistenttelangiectasias in involuted IH or excision of a unilateral subglottic IH with continuous-wave carbon dioxide laser [65].

Surgical Therapy

Indications for surgical resection differ according to patient age and hemangioma state. Proliferating IH (during infancy) may be removed when exhibiting ulceration, obstruction, or recurrent bleeding. An upper eyelid IH unresponsive to medical management and causing visual obstruction is an example of this.

IH of the stomach, small intestine, or colon may cause recurrent GI bleeding. Endoscopy and/or laparoscopy may aid in localization of these lesions [66]. Supportive care with medical management and blood transfusions is all that is often necessary. Unresponsive tumors may benefit from endoscopic band ligation or segmental bowel or wedge resections. Unfortunately, most GI IH demonstrates patchy involvement, making surgical or endoscopic intervention difficult [67]. Surgical excision of hepatic hemangioma should almost never be necessary.

Removal of involuting IH may be beneficial in instances of large, protuberant IH. Indications for removal include inevitable excision, need for staged excision, ability to hide the scar, and desire to avoid an altered self-image [5]. Postponing resection until involution is best, as some IH involute without scarring and others leave behind excess skin and a fibrofatty residuum. In the latter instance, resection may minimize distortion and improve cosmetic appearance.

Minimizing the scar, regardless of the indication or timing of surgery, is of top priority [68]. The most common approach involves a lenticular excision with linear closure. The length of the excision must extend beyond the lesion in order to avoid permanent dog-ears. In convex areas, such as the face or forehead, central flattening often results with lenticular excision. Circular excision with intradermal purse-string closure is often more amenable to these cases. Radial folds resulting from this technique tend to smooth out within a few weeks of surgery [68].

53.2.2 Congenital Hemangioma

In contrast to IH, congenital hemangiomas evolve in utero and do not exhibit postnatal growth [69]. These tumors may be detected via prenatal screening as early as the 12th week of gestation [69–71]. Congenital hemangiomas are divided into two

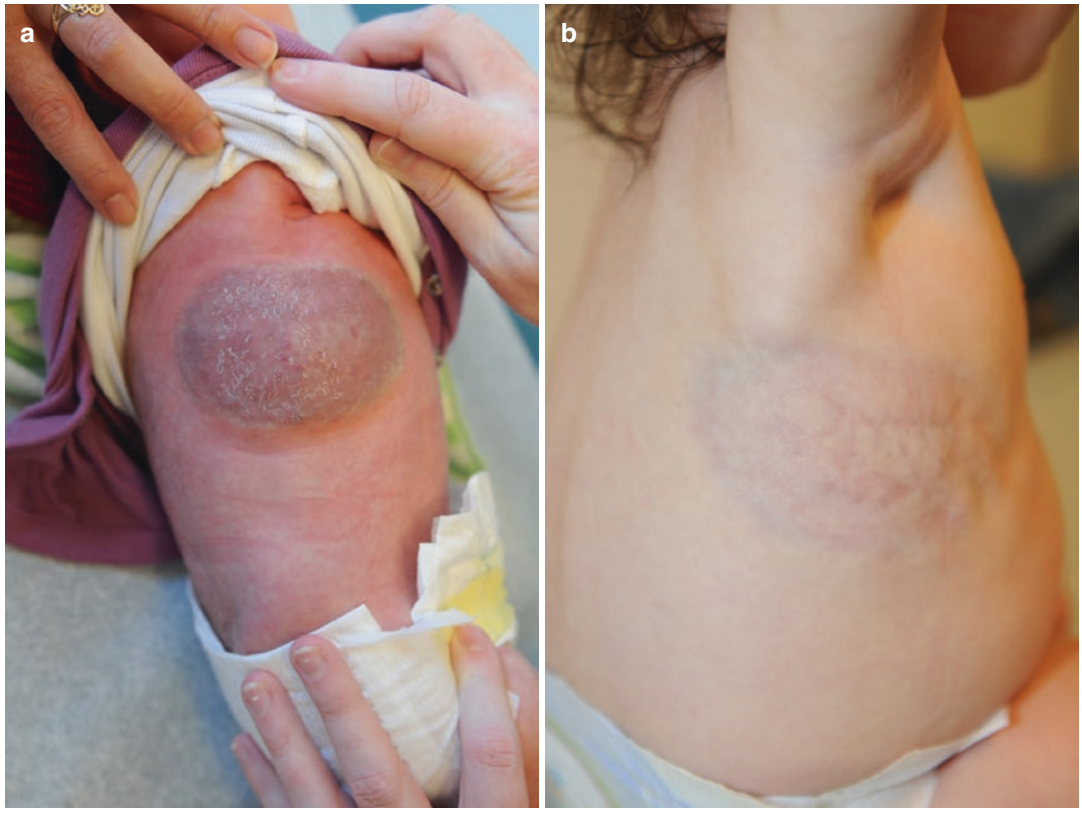

Fig. 53.2 Congenital hemangioma. (**a**) Rapidly Involuting Congenital Hemangioma (RICH) of chest at 10 days after birth. (**b**) Same child with involuting RICH at 1 year old

classes: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH) (Fig. 53.2). Both lesions tend to be solitary and lack a gender bias. In addition, these lesions stain negatively for GLUT-1, unlike IH.

In RICH lesions, regression begins early and is complete by 9–14 months of age [69]. On examination, RICH lesions present as raised, grey to violaceous in color with a depression or central area of necrosis, often surrounded by a pale halo. Telangiectasias or ectatic veins may be present. They are commonly located on the head, neck or extremities [69, 72]. Following involution, the area appears flattened, lacking the usual fatty residuum of IH [72].

NICH lesions take on a more bossed, round-to-ovoid shape with shades of pink to purple. Like RICH, they may display coarse telangectasias. Commonly affected areas include the head/neck, followed by the limbs and trunk. NICH does not undergo involution and grows with the child [73].

Both RICH and NICH are fast-flow lesions under ultrasound evaluation. Large, superficial flow voids and areas of inhomogeneous contrast are characteristic of RICH lesions on MRI. Under angiography, arterial aneurysms and direct arteriovenous shunts are identified [72]. NICH resembles IH radiologically. Because infantile fibrosarcoma may appear similar to congenital hemangiomas, biopsy may be necessary in cases of uncertain diagnosis [74].

53.2.3 Hepatic Hemangioma

Hepatic hemangiomas (HH) in infants differ from so-called "hepatic hemangiomas" of adulthood. "Hepatic hemangiomas", also known as

"cavernous hemangiomas", in adults are actually venous malformations. In contrast, HH of infancy are true vascular tumors. Three patterns are seen: focal, multifocal, and diffuse [75] (Fig. 53.3). Despite popular belief, the vast majority of these lesions are non-threatening.

Focal HH are akin to RICH lesions in that they stain negative for GLUT-1 and present fully formed at birth. In addition, involution tends to be more rapid than their IH counterparts. Infants with focal HH often possess no cutaneous hemangiomas and lesions demonstrate no gender bias. Antenatal detection is common with larger lesions [76]. Intralesional thrombosis occasionally causes transient thrombocytopenia and anemia. The vast majority of lesions require no treatment, however a small number of infants suffer from high-output cardiac failure secondary to macrovascular high-flow shunts (arteriovenous or portovenous). As the lesion involutes, these shunts typically close. While pharmacotherapy has been attempted, it is unclear what role it may play, as these lesions tend to undergo involution rapidly. Symptomatic shunts may be embolized by pediatric interventional radiologists, however, to improve heart failure. Rupture is very rare. Resection is rarely if ever indicated.

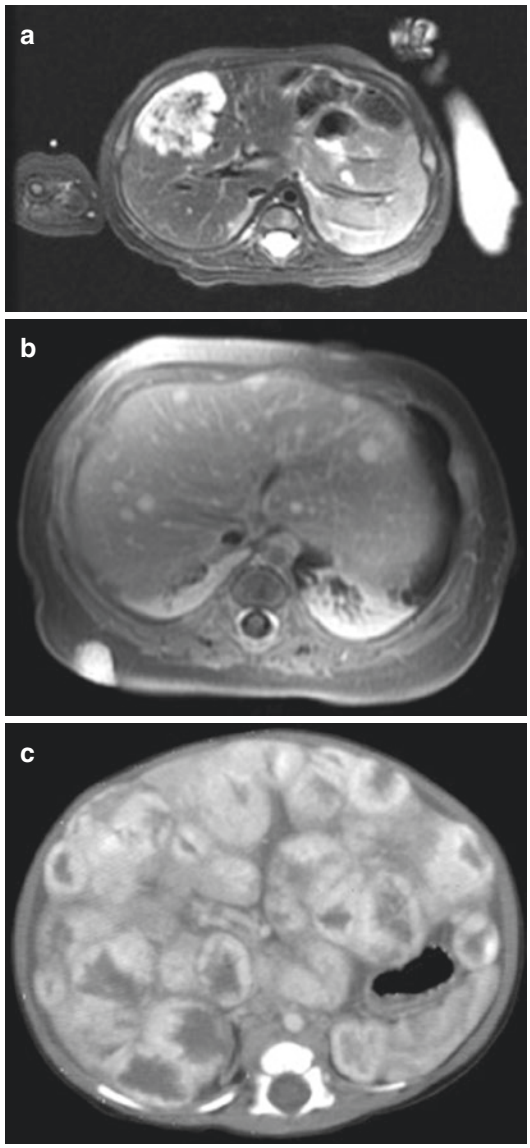

Fig. 53.3 Axial MRI images of hepatic hemangioma. (**a**) Focal hepatic hemangioma with typical heterogenous appearance. (**b**) Multifocal hepatic hemangiomas dispersed throughout liver. (**c**) Diffuse hepatic hemangioma with near complete replacement of liver parenchyma

Radiographic evaluation of focal HH reveals consistent patterns. On computed tomography (CT), focal HH are heterogeneous with centripetal enhancement. An area of central sparing is noted due to necrosis or thrombosis. Calcification is common, increasing as the lesion involutes [77]. MRI depicts focal HH as shows a well-defined, solitary, spherical tumor and appears hypointense on T1 and hyperintense on T2. Centripedal enhancement is seen on gadolinium sequences. Once again, central sparing is noted due to necrosis, thrombosis, or intralesional hemorrhage.

Multifocal HH are true infantile hemangiomas. They stain positive for GLUT-1 and possess a female preponderance. Discovery often occurs following a screening ultrasound due to multiple cutaneous lesions. Most multifocal HH are asymptomatic but a small subset may cause high-output cardiac failure due to macrovascular shunting. Traditionally, pharmacotherapy has centered around corticosteroids, but a role for propranolol is now emerging. Embolization of shunts can ameliorate the high-output state in medically unresponsive cases.

Diffuse HH warrant the greatest cause for concern. Once again, a female bias is noted. These lesions are typical IH but almost completely replace the liver parenchyma with innumerable,

compact nodule tumors. The subsequent hepatomegaly can result in compression of the vena cava or thoracic cavity, effectively resulting in abdominal compartment syndrome, respiratory distress, or multiorgan failure. IH express type 3 iodothyronine deiodinase which converts thyroid hormone to its inactive forms [20]. Due to the sheer number of tumors in diffuse HH, there is an accelerated breakdown of thyroid hormone to its inactive form in these infants, resulting in sometimes dramatic acquired hypothyroidism. Levels of type 3 iodothyronine deiodinase correlate proportionally to tumor burden. In order to prevent mental retardation and cardiac failure, exogenous hormone replacement therapy, often in large quantities, is critical. All infants with diffuse and multifocal HH should undergo TSH screening. As the tumor involutes, hypothyroidism improves and hormone replacement therapy should be titrated. Additional pharmacotherapy may involve corticosteroids or propranolol. In extreme instances in which the detection and therapy are delayed, hepatic transplantation may be necessary [75].

Multifocal and diffuse HH appear similar on imaging. On CT, multiple well-defined, spherical lesions are evident. While multifocal HH demonstrates intervening normal liver parenchyma, diffuse HH often completely replaces this parenchyma. Contrast allows for centripedal enhancement of lesions. Shunting is indicated by enlarged vessels, often with flow voids in and around the lesion. On MRI, lesions enhance homogenously and are hypointense relative to liver on T1 and hyperintense on T2 [78].

Clinical and radiographic follow up is critical in infants with HH, as deterioration is possible. Differential diagnosis includes arteriovenous malformation, arterioportal fistula, mesenchymal hamartoma, hepatoblastoma, angiosarcoma, and metastatic neuroblastoma. Percutaneous biopsy is indicated in cases of uncertain diagnosis.

53.2.4 Pyogenic Granuloma

Pyogenic granuloma is a benign, acquired vascular lesion that is often confused with IH [79]. In contrast to IH, these lesions rarely present prior to 6 months of age (average age 6.7 years) and are associated with port wine stains. Growth is rapid, erupting through the skin on a pedicle or stalk. Common locations include the head and neck. Lesions tend to bleed easily [80]. Treatment includes curettage or full-thickness excision, shave excision with cautery, cautery alone, or laser phototherapy [81]. Failure of complete excision leads to a high recurrence rate (45%) [79].

53.2.5 Kaposiform Hemangioendothelioma and Kasabach-Merritt Phenomenon

Based upon the description of a child with profound thrombocytopenia, petechiae, and bleeding in the presence of a "giant hemangioma" in 1940, the Kasabach-Merritt phenomenon (KMP) was described [82]. Seventy years later, it is now clear that KMP is never associated with IH. Instead, KMP occurs with more invasive and aggressive vascular tumors known as *kaposiformhemangioendothelioma* (KHE) or *tufted angioma* (TA) [83–85]. Both tumors are generally present at birth, unifocal, and have a propensity for the trunk, shoulder, thigh, or retroperitoneum. On examination, TA resembles erythematous macules, while KHE is more extensive and can rapidly expand. The overlying skin in KHE appears deep red-purple in color with surrounding ecchymosis (Fig. 53.4). Generalized petechiae may accom-

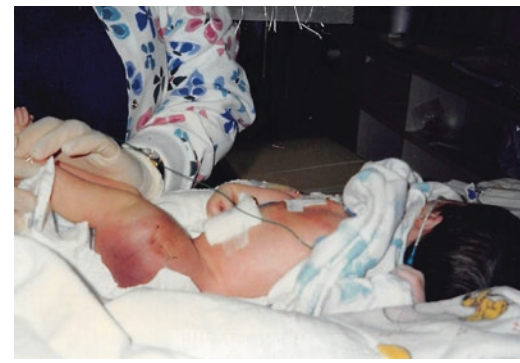

Fig. 53.4 KaposiformHemangioendothelioma (KHE) of thigh

pany the lesion in cases of profound thrombocytopenia (less than 10,000 cells/μL). Affected infants carry the additional risks of intracranial, pleural, pulmonary, peritoneal, and gastrointestinal hemorrhage with associated mortality hovering around 20–30% [86]. Thrombocytopenia results from intralesional trapping of platelets, and subsequent platelet transfusion leads to rapid expansion of the lesion [87–89]. Laboratory values reveal a normal to mildly elevated prothrombin time and activated partial thromboplastin time, an elevated D-dimer level, and a decreased fibrinogen value. Small areas of KHE (less than 8 cm in size) are less likely to suffer from KMP [90].

Histopathologic analysis of KHE reveals aggressive infiltration of normal tissues by sheets or nodules of slender epithelial cells and vascular spaces consisting of hemosiderin deposits and erythrocyte fragments [84]. TA consists of small tufts of capillaries (cannonballs) in the middle to lower dermis [85].

Radiographic evaluation of KHE and TA are similar. Both demonstrate poor tumor margin with extension into tissues across tissue planes. Like other vascular tumors, feeding and draining vessels are enlarged and enhanced signal on T2-weighted images is displayed. These vessels are small relative to tumor size, however. In addition, standing of the subcutaneous fat secondary to lymphatic invasion may occur [84].

Treatment of KHE or TA with KMP involves primarily medical care. Typical pharmacotherapeutic choices include corticosteroids, vincristine, or interferon. Vincristine has been associated with increased platelet counts and fibrinogen levels and may induce apoptosis in tumor endothelial cells, thus contributing to tumor necrosis [63, 91, 92]. Interferon-α possesses anti-angiogenic properties, but neurologic side effects such as spastic diplegia complicate its use [93, 94]. Recently, sirolimus had shown promising results for KHE with KMP and a clinical trial is now in progress [95, 96]. Heparin should be avoided as it may aggravate platelet trapping and stimulate tumor growth. In cases of KHE without KMP, treatment may be useful to diminish tumor size and long-term complications (such as joint contracture or myofascial pain syndromes) [90, 97].

53.3 Vascular Malformations

Vascular malformations are localized or diffuse errors of development affecting any segment of the vascular tree, including arterial, venous, capillary, and/or lymphatic vessels. They are typically divided in to two categories based upon channel type and flow characteristics. Slow flow anomalies include capillary malformations, lymphatic malformations, and venous malformations, while fast flow anomalies include arteriovenous malformations and arteriovenous fistulae. Complex, combined vascular malformations also exist. Congenital malformations have a prevalence of approximately 1.2–1.5% [98]. While most are sporadic, some inherited forms have been observed, often in an autosomal dominant pattern [99, 100]. Despite recent discoveries into the pathogenesis of such diseases, much still remains unclear.

53.3.1 Embryology and Development of the Vascular and Lymphatic Systems

The development of the vascular system during embryogenesis occurs by two separate but related processes: vasculogenesis and angiogenesis. Vasculogenesis involves the initial formation of blood vessels, while angiogenesis describes the formation of new vessels from existing vessels. Around the third week of development, mesodermally derived hemangioblasts congregate into blood islands. Cells in the center of these islands become hematopoietic stem cells, while those at the periphery differentiate into angioblasts, the precursors to blood vessels. These angioblasts subsequently proliferate into a capillary like network of tubes to establish a primary vascular bed. Reorganization of this plexus into a functional vascular system is achieved through angiogenesis, with the formation of new vessels and capillaries through sprouting [101].

The fate of endothelial precursors into their differentiated channel types is imprinted early in embryogenesis by distinct cell-surface markers

[102]. Arterial endothelial cells express ephrin-B2, while venous endothelial cells express its receptor, Eph-B4 [103]. Recruitment of periendothelial cells to the vessel wall promotes stabilization via inhibition of proliferation and migration. This effect is further aided by stimulation of the production of extracellular matrix and subsequent deposition of a basement membrane. This interaction is regulated by vascular endothelial growth factor, platelet derived growth factor-β, angiopoietins and their receptors, and transforming growth factor-β1 [104].

Development of the lymphatic system begins at the end of the sixth week of embryogenesis, only after the establishment of functional blood vessels [105]. Existing veins give rise to lymphatic sacs, which then reorganize to form the lymphatic vasculature [106, 107]. This process begins with the expression of lymphatic vessel endothelial hyaluronan receptor (LYVE-1) along the anterior cardinal vein [108]. Polarized expression of the transcription factor prospero-related homeobox 1 (PROX-1) then follows in a subpopulation of these cells. PROX-1 effectively serves as the master regulator of lymphatic endothelial cell development [109]. As lymphatic endothelial cells express the vascular endothelial growth factor receptor-3, they are drawn to its ligand, vascular endothelial growth factor-C, which directs budding and migration [110]. Lymphatic endothelial cells bud from the lymph sacs, undergo remodeling, and form the peripheral lymphatic system [105]. Malformations of the lymphatic system result in slow-flow anomalies and are described separately in this textbook.

53.3.2 Capillary Malformations

Capillary malformation (CM), more commonly known as port-wine stains, are dermal vascular anomalies occurring in around 0.3% of newborns [111]. They must be differentiated from the more common *nevus flammeusneonatorum* ("angel kiss" on the forehead or "stork bite" on the nuchal area), which are transient dilations of normal dermal vessels that fade over time. The latter are the most common vascular birthmark, affecting 50% of Caucasian neonates. CMs are present as birth and appear as flat, pink-red, cutaneous patches. Occurring anywhere on the body, they can be localized or extensive. CMs are composed of dilated, ectatic capillary-to-venule sized vessels in the superficial dermis. Histopathologic analysis reveals a paucity of surrounding nerves. Over time, these vessels tend to dilate due to lack of innervation, accounting for their observed darkening and nodular expansion [112]. Associated hypertrophy of the subcutaneous tissue, muscle, and bone underlying a CM is common. In cases of CM located on the extremity, leg length discrepancy may be observed. While the majority of CMs are sporadic, a familial pattern of autosomal dominant inheritance with incomplete penetration has been reported. Linkage analysis identified a locus on chromosome 5q13–15 termed CMC1, with the causative gene a negative regulator of ras termed RASA1 [113, 114].

CM may signal an underlying structural abnormality. A CM overlying the cervical or lumbar spine may be associated with an occult spinal dysraphism or tethered cord. An encephaloceleor ectopic meninges may underlie a midline occipital CM. Children with a CM along the ophthalmic and maxillary branches of the trigeminal nerve distribution should be evaluated for Sturge-Weber syndrome, an associated vascular anomaly of the ipsilateral choroid and leptomeninges. Clinical manifestations may include seizures, contralateral hemiplegia, and variable developmental motor and cognitive delay. CM may also be observed in complex-combined vascular malformations.

Treatment of CM is primarily aimed at cosmesis. Vascular-selective pulsed dye lasers are currently the treatment of choice, resulting in significant lightening in approximately 70% of patients. Early, thin CMs and those located on the face have the best outcomes [115]. The timing of therapy remains controversial, but beginning treatment by 6 months of age has shown promising early results [116, 117]. Surgical intervention may be required for associated soft tissue hypertrophy and limb length discrepancy.

53.3.2.1 Cutis Marmorata Telangiectasia Congenita

Cutis marmorata telangiectasia congenita (CMTC) is a rare congenital disorder in which affected newborns demonstrate a blue to deep purple discoloration with a characteristic reticular vascular pattern [118]. CMTC may occupy a localized, segmental, or generalized distribution, usually involving the trunk and extremities [119]. Histopathology reveals dilated capillaries in the papillary dermis and proliferation of blood vessels in the reticular dermis [120]. Occurrence is sporadic and without gender bias. Ulceration and bleeding of depressed areas or hypoplasia of the affected limb may occur. Associate stenosis of the common iliac and femoral arteries has also been observed [121]. Nearly all affected infants demonstrate steady improvement within the first year of life and into adolescence. Atrophy, pigmentation, and prominent veins often persist into adulthood.

53.3.2.2 Telangiectasia

Tiny acquired capillary vascular marks, commonly known as spider nevi or spider telangiectasias, can appear on preschool and school-aged children. No gender bias exists and epidemiological studies suggest they may be present in nearly half of children [98]. Spontaneous resolution is possible, but pulsed dye laser can remove the lesion.

Hereditary hemorrhagic telangiectasia (HHT; Osler-Weber-Rendu syndrome) is an autosomal dominant disorder affecting 1–2 per 100,000 of the Caucasian population (Fig. 53.5). HHT results from mutations in endoglin, activin receptor-like kinase 1, or Smad4. The genes encode proteins that control transforming growth factor-β signaling in vascular endothelial cells [122–124]. Diagnosis is made in the presence of at least three separate manifestations: mucocutaneous telangiectasia (such as on the fingertip, lips, oral mucosa, or tongue), spontaneous recurrent nosebleeds, visceral involvement (GI tract, pulmonary, hepatic, cerebral, or spinal AVM), and family history [125]. Spontaneous, recurrent nosebleeds often begin before school age. One third of affected individuals develop chronic anemia secondary to GI bleeding [125, 126].

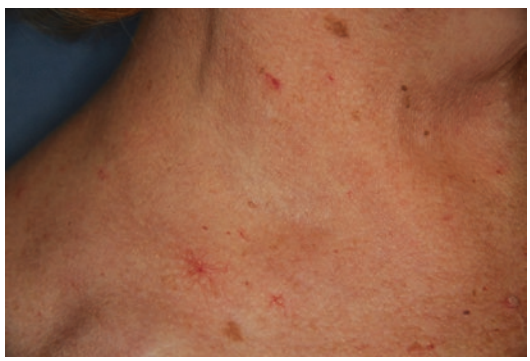

Fig. 53.5 Hereditary hemorrhagic telangiectasia (HHT)

Ataxia-telangiectasia (Louis-Bar syndrome) is an autosomal recessive neurovascular disorder appearing around 3–6 years of life. Affected children initially develop bright-red telangiectasias on the nasal and temporal area of the bulbar conjunctiva, which then progress to the face, neck, upper chest, and flexor surfaces of the forearms. Cerebellar ataxia develops synonymously, followed by progressive motor neuron dysfunction. Endocrine and immunologic deficiencies develop, with death usually occurring in the second decade of life from recurrent infections or malignancy. The defective gene, ATM, is believed to alter DNA repair mechanisms of double-stranded breaks [127].

53.3.3 Venous Malformation

Venous malformations (VMs), the most common of the vascular anomalies, are slow flow lesions often mislabeled as "cavernous hemangiomas." While present at birth, they are often not immediately evident. Common locations include the skin and soft tissues, but VMs may present anywhere in the body. Classically, a VM appears as a soft, blue, compressible, spongy mass, but presentation may range from simple varicosities to networks of channels within an organ (Fig. 53.6). VMs grow proportionally with a child and expand over time. Phlebothrombosis is common and may be painful. Histologically, VMs consist of thin-walled, dilated abnormal channels with surrounding smooth muscle deposited in clumps. This

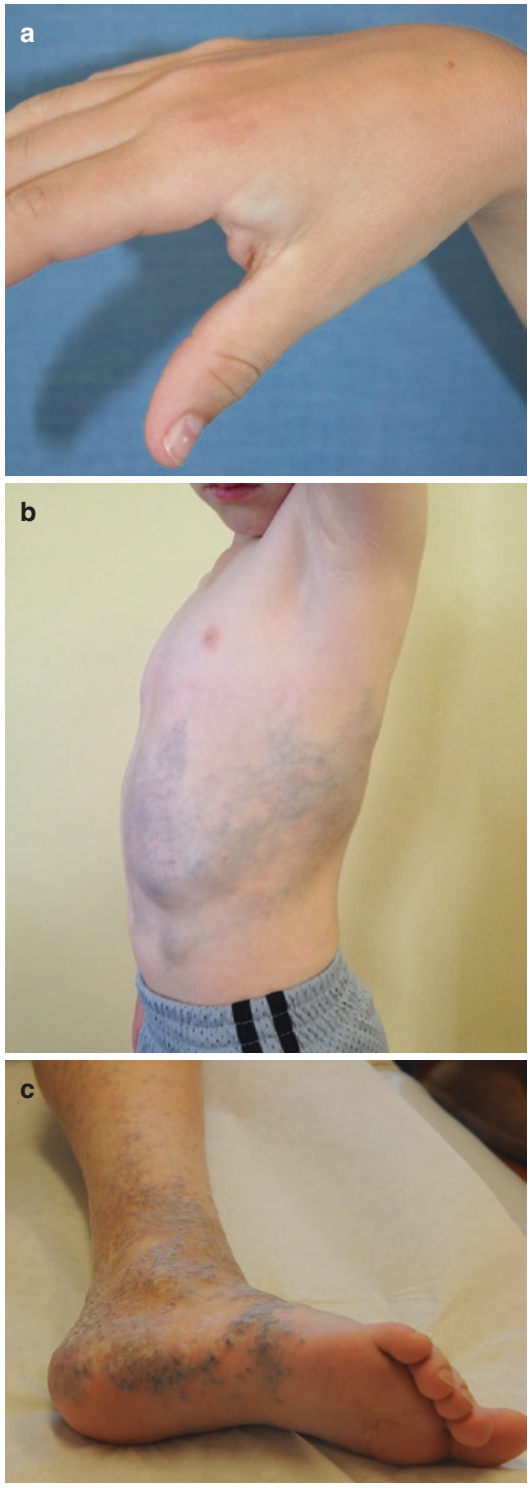

Fig. 53.6 Venous malformation (VM). (**a**) Localized VM involving thenar space of the hand. (*Middle*) Truncal VM. (**b**) Glomovenous malformation (GVM) of foot displaying cobblestone-like appearance

muscle abnormality attributes to the tendency of VMs to expand over time. There is often evidence of clot formation, fibrovascular ingrowth and phleboliths on microscopy.

Complications vary according to location of the VM. Head and neck VMs distort facial features and may cause exophthalmia, dental malalignment, and obstructive sleep apnea. Extremity VM can cause limb length discrepancies, painful hemarthrosis, and degenerative arthritis. Intraosseous VM may lead to structural weakening and pathologic fractures. GI tract lesions may be dispersed throughout the bowel, but are most commonly localized to the left colon, rectum, and surrounding pelvic and retroperitoneal structures [5, 67, 128]. Chronic bleeding and anemia may result [129]. Rectal VMs associated with ectasia of mesenteric veins are a risk factor for portomesenteric venous thrombosis [130].

The vast majority of VMs are sporadic. Half of sporadic lesions may be traced to mutations in Tie2, a receptor tyrosine kinase involved in vascular remodeling [131, 132]. Inherited VMs include *familial cutaneous mucosal VM*, an autosomal dominant condition occurring in 1–2% of the population. Affected individuals develop dome shaped lesions of the skin and GI mucosa ranging from tiny to several centimeters in size [100]. Deregulation of Tie2 is likely the cause [133, 134]. Histologically, lesions demonstrate a lack of an inner elastic membrane, possibly due to uncoupling of endothelial and smooth muscle cell signaling [135, 136]. *Glomovenous malformations* (GVMs) are another inherited condition that accounts for 5% of all lesions. GVMs appear as multiple blue nodular dermal lesions, giving a cobblestone-like appearance (Fig. 53.6). They localize on the extremities, are poorly compressible, and are often painful [137]. Histologically, dilated vessels are surrounded by epithelioid-like glomus cells expressing smooth muscle actin and vimentin [138]. A loss-of-function mutation in glomulin is to blame, resulting in defects in vascular smooth muscle differentiation [139].

Blue rubber bleb nevus syndrome (BRBNS) is a rare, sporadic disorder involving cutaneous and gastrointestinal VMs. Cutaneous lesions are gen-

erally blue to purple in color, often numerous, and have a predilection for the trunk, palms, and soles of the feet [140] (Fig. 53.7). A large, dominant VM is often present. Over time, lesions become progressively larger. Lesions of the GI tract are frequently situated in the small bowel, with chronic bleeding and anemia often the result. Lesions may also serve as a lead point for intussusception or volvulus. Capsule endoscopy is an effective tool in visualizing these lesions [141].

Imaging of VMs is best served by MRI. On T2 sequences, VMs demonstrate hyperintensity, an important contrast to that seen with lymphatic malformations, another slow flow lesion. Phleboliths are often seen as signal voids. High flow vessels are not seen within or around VMs. MRI is particularly helpful delineating deep venous anatomy of the extremity [39].

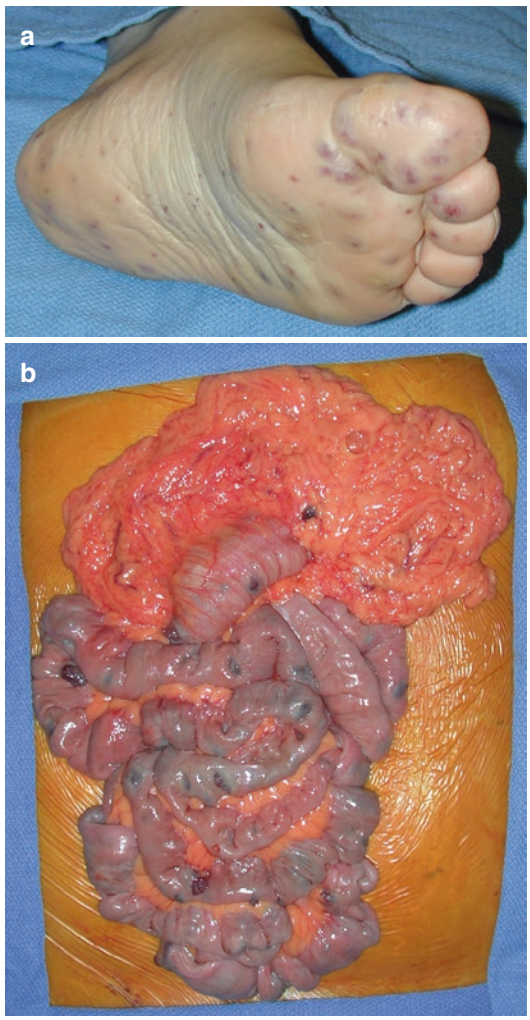

Fig. 53.7 Blue rubber bleb nevus syndrome (BRBNS). (**a**) Characteristic blue shaded cutaneous lesions of the foot. (**b**) Serosal lesions involving the bowel

53.3.3.1 Treatment

Indications for treatment of VMs include functional deficits, poor cosmetic appearance, bleeding and pain. Elastic compression stockings play an important role in management of extremity VMs. Low dose aspirin (81 mg per day) may also aid in prevention of phlebothromboses. The mainstay of treatment for VM, however, lies in sclerotherapy and surgical resection. Sclerosants act to induce endothelial damage, thrombosis, and, ultimately, scarring of the lumen. A multitude of agents have been introduced, with varying results [142]. Unfortunately, recannalization often occurs, requiring multiple treatments [143]. Local complications include blistering, full-thickness necrosis, and nerve injury, while systemic effects may include hemolysis, pulmonary hypertension, and cardiac and renal toxicities [144].

Surgical excision of a VM is often successful in instances of small, well-localized lesions. GVMs, in particular, benefit from excision due to their localized presentation and poor response to compression [137]. Larger lesions often undergo sclerotherapy in an attempt to shrink the VM prior to resection. Often, staged procedures may be required. Removal of bleeding GI lesions is indicated in cases of refractory anemia requiring frequent transfusion. Resection of GI lesions, particularly those of BRBNS, involves numerous wedge excisions and polypectomy by intussusception of successive lengths of intestine [66, 145]. Intraoperative enteroscopy aids with identification of lesions. Diffuse colorectal VMs causing significant bleeding may be treated with colectomy, anorectal mucosectomy, and coloanal pull-through [146].

53.3.4 Arteriovenous Malformations

Arteriovenous malformations (AVMs) are fast flow malformations consisting of disorganized arteries and veins that directly communicate

Table 53.1 Schobinger staging system of ateriovenous malformations (AVMs)

Stage	Clinical findings
I (Quiescence)	Pink-blue warm stain, shunting on Doppler examination
II (Expansion)	Enlargement, pulsation, thrill, bruit, tense veins
III (Destruction)	Dystrophic skin changes, ulceration, bleeding, pain, or tissue necrosis
IV (Decompensation)	Cardiac failure

(shunts), bypassing the high-resistance capillary bed. The shunts comprise the epicenter, or nidus, of the AVM. While AVMs may present at birth with life-threatening high-output cardiac failure, the majority are latent during infancy and childhood. During adolescence, they tend to expand, possibly as a result of hormonal changes [147]. Clinically, AVMs appear as a pink patch in the skin with an underlying thrill or bruit. Over time, ischemic changes, ulceration, pain, and intermittent bleeding may provide complications. A clinical staging system introduced by Schobinger helps document the natural history of the AVM Table 53.1.

The majority of AVMs are sporadic. Heritable forms have been identified, however. A capillary malformation-arteriovenous malformation (CM-AVM) is an autosomal disorder involving the presence of a randomly distributed CM along with a fast flow lesion. CM-AVM is caused by mutations in *RASA1*. Conditions that fall under this spectrum include intracranial or extracranial AVM, Parkes Weber Syndrome, and a vein of Galen aneurysmal malformation [148].

The fast flow of the AVM may be detected on ultrasonography and Doppler imaging. Dilated feeding arteries and draining veins appear as areas of contrast enhancement on CT, signal flow voids (black tubular structures) on MRI, and signal enhancement (white tubular structures) on MRA. The ability to discern the nidus may be complicated, but superselective angiography may improve detection [5] (Fig. 53.8). Muscle hypertrophy, bony changes, and increased fat may also be present on imaging.

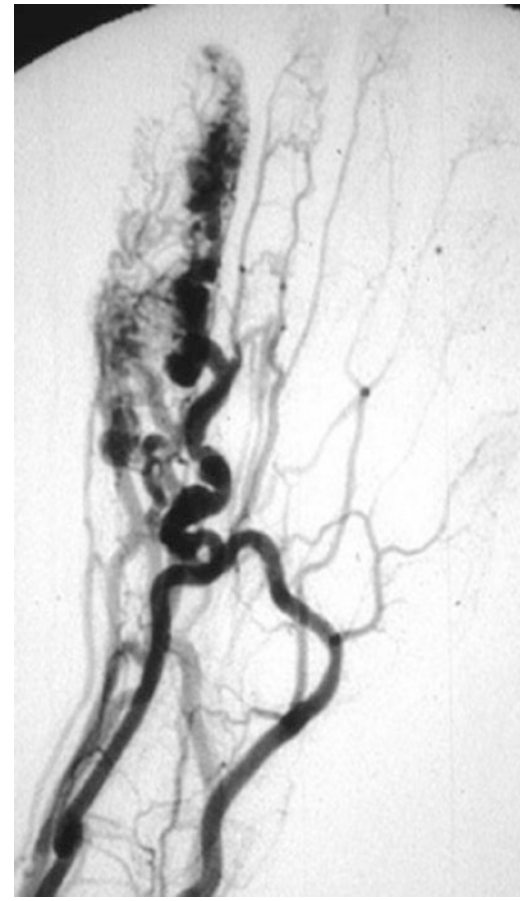

Fig. 53.8 Angiography of finger AVM displaying torturous vessels

53.3.4.1 Treatment

Due to their life-long expansion, many AVMs require treatment. The mainstay of treatment involves intravascular embolization with or without surgical excision. While infants suffering from AVM related postnatal congestive heart failure require early intervention, timing for therapy with the majority of patients is controversial. By convention, most therapy has been delayed until the presence of symptoms or endangering signs (e.g. persistent pain, bleeding, recurrent ulceration, or progression to Schobinger Stage III–IV). Attempted resection of early, poorly defined AVMs may result in incomplete resection, leading to recurrence and complicating future procedures. Alternatively, early AVMs may be more amenable to resection

and complete removal. Children should undergo a complete diagnostic evaluation and be followed annually, taking care to evaluate for signs of limb length discrepancy or expansion. Often, Stage I and II AVMs are observed until progression to Stage III.

Regardless of stage, treatment should be directed towards the nidus. Ligation or embolization of proximal feeding arteries should be avoided, as this elicits rapid recruitment of flow from nearby arteries to supply the malformation and may preclude future embolization [143]. Instead, the preferred strategy involves arterial embolization of the nidus followed by surgical resection 2–3 days later. This often aids in decreasing intraoperative blood loss. Complete removal of the nidus and surrounding tissue is attempted in order to deter recurrence. The best results are seen with well-localized AVMs, while larger and more diffuse lesions may require staged procedures, skin grafting, or possible amputation. Unfortunately, many AVMs permeate deep into the soft tissue and skeletal system, allowing for only palliative embolization. Pharmacologic agents targeting angiogenesis and extracellular matrix remodeling are currently being explored for treatment in these dire situations [149].

53.3.5 Complex-Combined Vascular Malformations

Like single-channel-type malformation, complex-combined vascular malformations are divided into slow-flow and fast-flow categories. They are often associated with soft tissue hypertrophy and skeletal overgrowth.

53.3.5.1 Capillary-Lymphaticovenous Malformation

Capillary-lymphaticovenous malformation is commonly known as Klippel-Trenaunay syndrome. Affected individuals typically present at birth with an enlarged extremity, multiple capillary malformations arranged in a geographic pattern along the lateral side of the body, lymphatic vesicles, and visible varicosities [5] (Fig. 53.9). Newborns often display a macular CM, which undergoes progressive studding with lymphatic vesicles over time. CLVM most commonly involves the lower extremity (88%), but can involve the upper extremity (29%) and trunk (23%) [150]. Soft tissue and skeletal hypertrophy of the affected limb predominate. Lymphatic anomalies include lymphatic cysts (micro- or macro-), and lymphedema. Lymphatic vesicles often erupt through the CM, causing bleeding and/or lymphatic drainage. Lymphatic malformations (LM) are common and frequently involve the pelvis, perineum, and buttock. Pelvic masses may lead to constipation, recurrent infection, or bladder outlet obstruction. Venous abnormalities include the presence of persistent embryologic veins, most commonly the marginal vein of Servelle. Incompetent valves within these veins makes these more prominent, while a deep venous system may be entirely absent. VMs in the lower extremities may extend into the pelvis and connect with femoral veins, iliac veins, or the inferior vena cava. Pulmonary embolism results in 4–25% of cases [130].

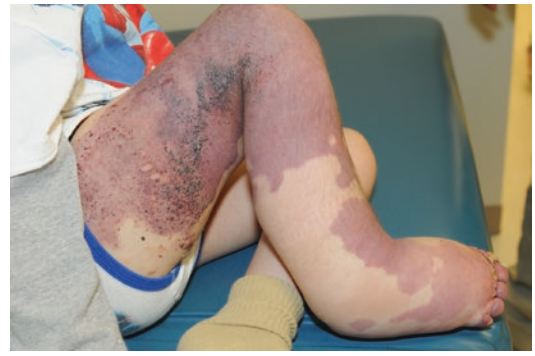

Fig. 53.9 Capillary-lymphaticovenous malformation (CLVM), also known as Klippel-Trenaunay Syndrome

MRI and MR venography (MRV) serve the most use in description of the vascular malformation of CLVM. MRV reliably maps the venous system, including the anomalous venous channels present. Often, a large lateral vein of Servelle is evident. Macrocystic, microcystic, or a combination of LM is typically present. Plain radiographs allow for identification and evaluation of leg-length discrepancies. Venography may also be utilized for planning of surgical intervention or sclerotherapy.

Treatment

Management of CLVM is typically conservative. Compression therapy, initiated following ambulation, is important to control swelling. Limb length discrepancies should be identified and followed by serial radiographs. Shoe-lifts are beneficial for discrepancies between 0.5–2 cm. For differences greater than 2 cm, epiphysiodesis of the distal femoral growth plate may be performed around 12 years of age. Grotesque enlargement of the foot may be treated with selective ablative procedures (i.e. ray, midfoot, or Syme amputation) [151]. Sclerotherapy targeting focal VMs, superficial veins, or lymphatic cysts may be of benefit. Leaking or bleeding lymphatic vesicles are also treated with sclerotherapy or laser ablation. Persistent embryonic veins are candidates for endovenous laser ablation or resection, particularly in instances of direct communication with femoral or iliac veins or the inferior vena cava in order to prevent pulmonary emboli.

Debulking procedures offer physical and psychological benefits to patients with CLVM. Evaluation of the location of soft tissue overgrowth is critical in preoperative planning. While extrafascial involvement is amenable to surgery, debulking of intrafascial overgrowth should be avoided due to risk of injury to major neurovascular structures or immobility. Staged repair may be necessary, particularly with thoracic or trunk involvement. Postoperative healing can be problematic due to involvement of abnormal tissue with poor lymphatic drainage and altered circulation. Prolonged suction drainage is used. Placement of an inferior vena cava filter and preoperative anticoagulation are used to decrease the risk of pulmonary embolism and deep venous thrombosis [151].

53.3.5.2 CLOVES Syndrome

CLOVES syndrome is characterized by congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies [152, 153] (Fig. 53.10). Its key feature is a truncal lipomatous mass, typically present at birth. These masses are hypervascular and often infiltrative, extending into the retroperitoneum, mediastinum, and pleural cavity. Involvement of the spinal canal and epidural space may lead to compression of the cord, thecal sac, or nerve root. Slow-flow vascular lesions, CMs, and LMs have been identified. Large, phlebectatic VMs may pose a risk of pulmonary embolus. Parasapinal or intraspinal AVMs can result in paresis and spasticity. MRI with venous and arterial sequences aids in evaluation. Acral deformities include wide, delta-shaped hands and feet, macrodactyly, and a sandal gap appearance of the toes. Scoliosis is present in 50% of cases.

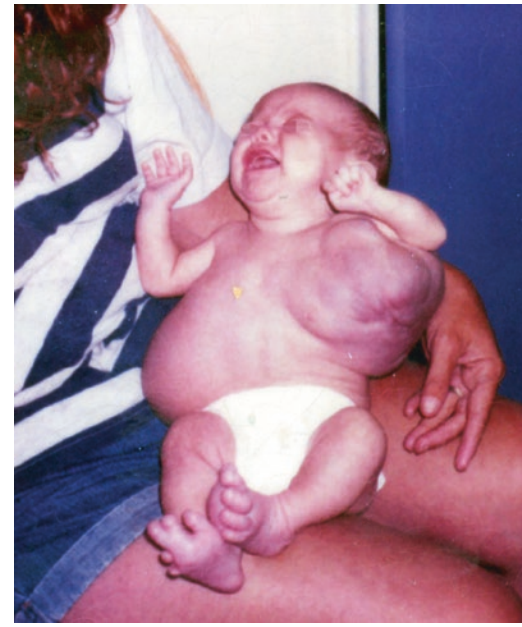

Fig. 53.10 CLOVES syndrome. Infant displaying truncal lipomatous mass, truncal capillary staining, macrodactyly, and wide, delta-shaped feet

53.3.5.3 Parkes Weber Syndrome

Parkes Weber syndrome is characterized by the presence of a patchy or confluent capillary malformation with underlying multiple micro arteriovenous fistulas (AVFs). These malformations are typically located in a lower extremity and associated with soft tissue and skeletal hypertrophy [154]. Lymphatic anomalies are often present as well. Length discrepancy can result. The stained areas are warm to palpation and thrill may be detected. Doppler examination often reveals increased flow. On imaging, the involved area dis-

plays subcutaneous, muscular, and bony overgrowth with diffuse microfistulae. Angiography and venography reveal generalized venous and arterial dilation with a soft tissue blush involving muscles and subcutaneous fat.

Treatment is reserved for symptomatic patients. While up to 30% of patients with Parkes Weber syndrome may exhibit signs of cardiac volume overload, this is typically well tolerated [154]. Rarely, cardiac failure due to shunting through the AVFs may develop. Children should be seen annually and monitored for axial overgrowth, signs of cardiac failure, and cutaneous problems related to ischemia. Repetitive superselective embolization may be employed to reduce flow and improve heart failure [5]. Limb amputation may be required for severe disease.

53.3.5.4 PTEN Hamartoma-Tumor Syndrome

PTEN hamartoma-tumor syndrome results from mutation of *PTEN* (phosphatase tensin homolog on chromosome 10), which encodes for a tumor suppressor protein involved in cell-cycle regulation. Two autosomal dominant disorders with a predisposition for cancer result: Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Cowden syndrome (CS) [155]. BRRS is characterized by macrosomia at birth, macrocephaly, penile freckling, lipomas, hamartomatous intestinal polyposis, proximal myopathy, and variable degrees of developmental delay. CS consists of multiple hamartomas and neoplasias of ectodermal, mesodermal, and endodermal origin (particularly the breast, thyroid, and endometrium). Vascular anomalies are present in approximately 50% of patient with PTEN mutations and tend to be characterized as fast-flow radiographically [154]. Histopathologically, disordered growths of blood vessels, adipose, fibrous tissue is noted. Due to the increased risk for cancer, patients with fast-flows lesions should be evaluated for *PTEN* mutations.

Conclusions

The last three decades have witnessed remarkable advances into understanding the pathogenesis of vascular anomalies. An improved genetic-anatomic-histologic classification system has clarified the identification of vascular diseases and allowed for the development of multidisciplinary approaches toward disease management and treatment. Increased understanding of embryonic development has permitted novel therapeutic approaches. With continued strides and a combined management approach, those affected by vascular anomalies may benefit.

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Tumors of the Head and Neck

54

Tomoaki Taguchi, Toshiharu Matsuura, and Yoshiaki Kinoshita

Abstract

Tumors of the head and neck in neonate, which pediatric surgeons encounter, are limited. They can be divided into three categories based on clinical manifestations; (1) Frontonasal mass, (2) Tumor in the oral cavity, and (3) cervical mass.

Keywords

Head and neck tumours • Newborn surgery • Classification • Management

Tumors of the head and neck in neonate, which pediatric surgeons encounter, are limited. They can be divided into three categories based on clinical manifestations; (1) Frontonasal mass, (2) Tumor in the oral cavity, and (3) cervical mass.

A frontonasal mass in a newborn (congenital midline nasal mass) is rare anomaly, with an incidence of 1 in 20,000–40,000 live births [1]. The common forms are dermoid cysts, encephalocoeles, nasal gliomas, and congenital hemangioma [2]. The newborn who presents with a midline frontonasal mass often poses a diagnostic challenge to the clinician. The development of the frontonasal region or anterior neuropore is complex. Understanding the developmental anatomy of the anterior neuropore and postnatal maturation will serve the pediatric surgeon well when it comes to imaging frontonasal masses [3]. The most pressing issue is whether the mass extends intracranially. There can be also many differential diagnoses. An accurate diagnosis permits proper management and prevents potentially life-threatening intracranial complications. Other frontonasal masses in the newborn include hemangiomas, myofibromatosis, hairy or teratoid polyp, fibroma, lipoma, lipoblastoma, and rarely malignancies such as fibrosarcoma, rhabdomyosarcoma, primitive neuroectodermal tumor (PNET), and hematopoietic tumors such as granulocytic sarcoma [3].

Oral tumor of newborn is represented by congenital epuris [4]. It is important to stress that clinicians should know differential diagnoses of growths in the oral cavities of newborns, including hemangioma, lymphangioma, fibroma, granuloma, rhabdomyosarcoma, osteogenic and chondrogenic sarcomas, fore-

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_54

gut duplication cyst [5] as treatment modalities will be different for each case. The clinical presentation of congenital oral tumors can be impressive due to their size and aggressive appearance. Although in the case described the lesion was small, a considerable anxiety and apprehension by the parents could be observed. Therefore, if no spontaneous regression is observed, surgical intervention should be performed as soon as possible to benefit both infant and family well-being. Periodic review of oral soft-tissue pathology can help pediatric dentists to promptly identify common and rare abnormalities affecting infants and to plan the best recommended intervention.

A cervical mass in the newborn includes teratoma, neuroblastoma (primary or metastatic), rhabdomyosarcoma, fibromatosis colli, hemangioma, foregut duplication cyst, branchiogenic cyst, and vascular and lymphatic malformation [6]. In some cases, presenting symptoms are airway obstruction and feeding difficulty. In some cases antenatally diagnosed, the ex utero intrapartum treatment (EXIT) and the operation on placental support (OOPS) are indicated for airway management at birth [7].

54.1 Nasal Glioma (Figs. 54.1, 54.2)

54.1.1 Historical Notes and Incidence

Schmidt was the first scientist to describe the comprehensive nature of the nasal glioma in 1900 [8]. However, the term he used is a misnomer [9]. Nasal gliomas are not true neoplasms; they originate from ectopic glial tissue left extracranially following abnormal closure of the nasal and frontal bone during embryonic development [3]. Therefore, some authors recommend using the term 'glial heterotopia' instead [9]. They have a 3:1 male predominance, with no familial or hereditary predisposition and no malignant potential [10]. The tumor growth rate is consistent with the patient's body growth [10].

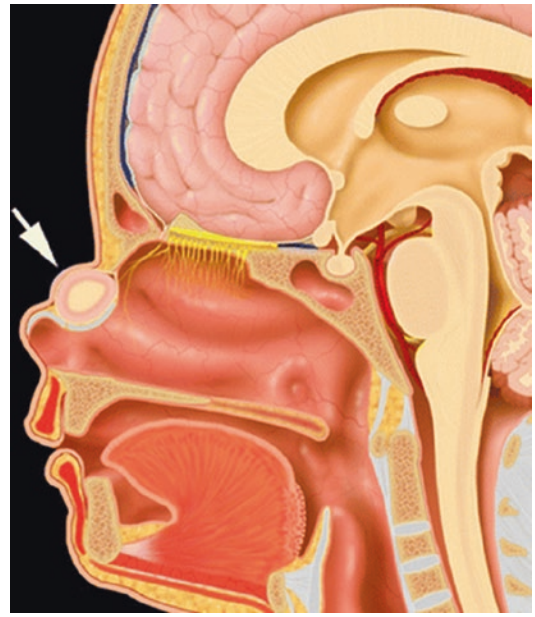

Fig. 54.1 Nasal glioma. Sagittal color plate demonstrates a nasal glioma presenting as a frontonasal mass (*arrow*). Approximately 60% of nasal gliomas are extranasal and 30% intranasal [3]

54.1.2 Pathology and Embryology

Nasal gliomas generally present at birth, rarely in adults, as a mass without associated nasal symptoms. About 60% of gliomas are extranasal, 30% are intranasal, and 10% are mixed lesions [11]. Extranasal gliomas are firm, incompressible masses that often occur along the nasomaxillary suture or near the glabella. The overlying skin may have telangiectasia, and they may easily be confused with haemangiomas. Histologically, nasal gliomas are composed of astrocytes and neuroglial cells, embedded in fibrous and vascular connective tissue [11]. They have no true capsule and mitosis is rarely noted. Multinucleated or gemistocytic astrocytes may be present but it is rare to find neurons. A fibrous stalk representing a relic of the intracranial connection can be found in 15% of cases [12]. Pathologically, these tumefactions are composed of dysplastic, neuroglial tissue and fibrovascular tissue.

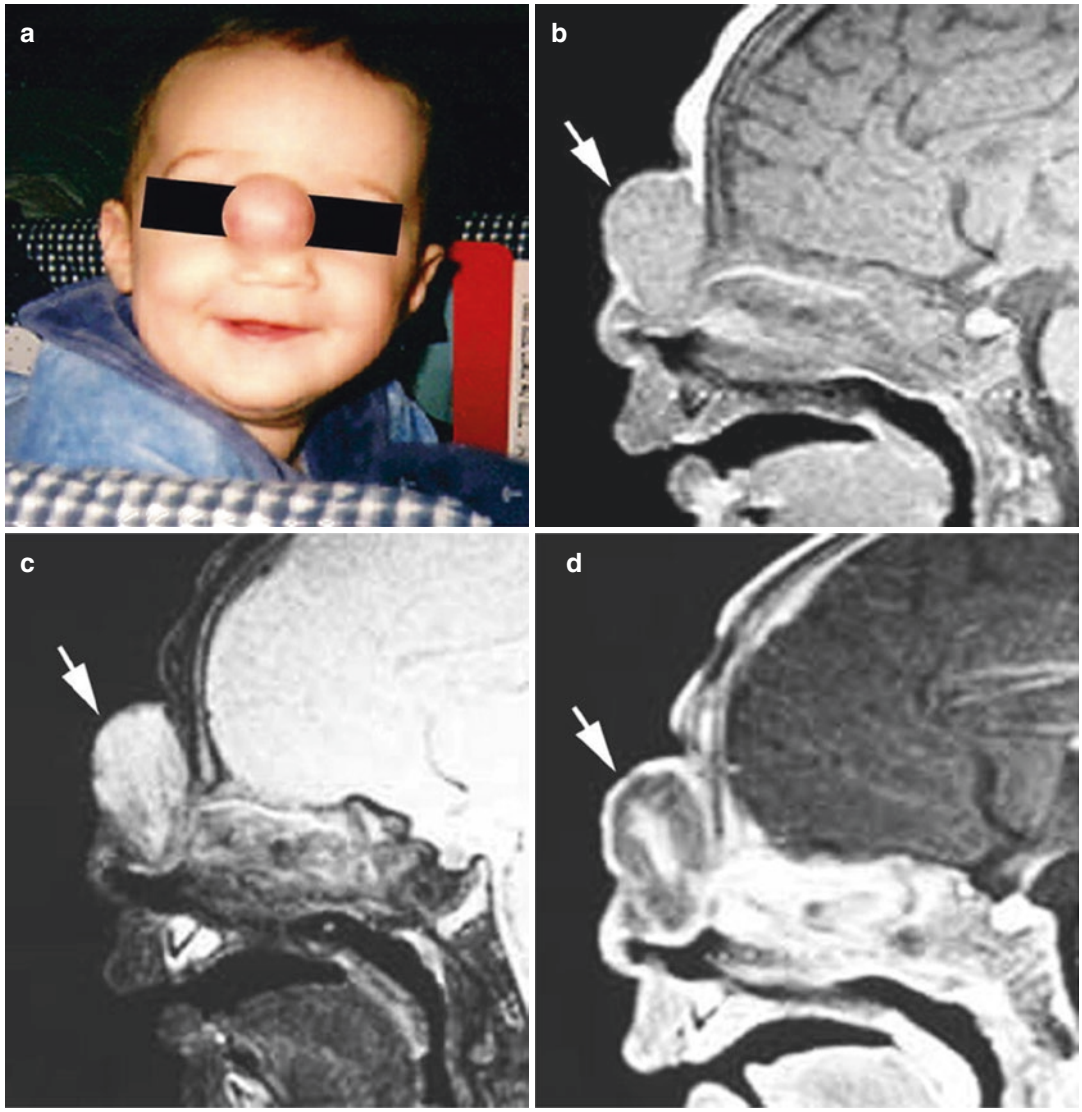

Fig. 54.2 **(a)** Extranasal glioma in a infant boy with a bulbous frontonasal mass. a Clinical photo shows a reddish frontonasal mass that enlarged with crying [3]. MRI imaging of Extranasal glioma in a infant boy with a bulbous frontonasal mass. **(b)** Sagittal T1-W image demonstrates a large frontonasal mass that is slightly hyperintense to brain (*arrow*). **(c)** Sagittal T2-W image shows hyperintensity within the extranasal glioma (*arrow*). **(d)** Sagittal T1-W image following MR contrast medium administration shows central enhancement of the nasal glioma (*arrow*) [3]

54.1.3 Clinical Picture

Nasal gliomas are one form of the congenital midline nasal masses that usually present at birth as a firm subcutaneous lump with red or bluish discoloration, lying on one side of the nasal bridge [13]. The nasal bridge may be broadened and the space between the eyes may be widened. Intranasal gliomas usually present as a pale mass with septal deviation or nasal obstruction. They often arise from the lateral nasal wall or, less often, from the nasal septum.

In all gliomas, pulsation or expansion of the lesions is absent during crying, coughing, straining or even compressing the jugular vein (Furstenberg's test). These tumors are well circumscribed, often bluish or reddish in color and often described as having a telangiectatic surface. Therefore, they are often misdiagnosed initially as capillary hemangiomas [14]. By virtue of their nasal location, they typically present with nasal airway obstruction [3].

MRI is the preferred method of evaluating all masses of the nasal dorsum, medial canthal region, and nasal cavity [3]. As mentioned, the initial clinical assessment of nasal glioma might be that of a probable hemangioma. MRI can typically distinguish these two masses.

54.1.4 Treatment

Surgical excision is the mainstay of treatment and is required for a definitive histopathological diagnosis [13]. A thorough preoperative imaging study must be performed prior to any attempt at removal of the glioma. The extent of the surgery is dictated by the exact size, location, and contents of the lesion. For pure extranasal gliomas, an external incision using either a vertical elliptical midline incision or a horizontal incision over the dorsum of the nose can yield equally good cosmetic results [11]. Some authors recommend a conservative and cosmetic incision using an external rhinoplasty approach, because nasal gliomas are benign and rarely recurrent [9]. For pure intranasal gliomas, a transnasal endoscopic approach is recommended for complete removal of the intranasal mass with no postoperative facial deformity [9]. Around 15–20% of nasal gliomas have a fibrous stalk connecting to the subarachnoid space of the brain [12]. Severe complications such as meningitis or a brain abscess can be avoided if the lesions are removed at an early stage. A neurosurgeon should be consulted whenever the tumor communicates with the brain, as a craniotomy may be necessary.

54.2 Nasal Dermal Sinus (Epidermoid or Dermoid Cyst) (Figs. 54.3, 54.4)

54.2.1 Pathology and Embryology

During fetal development of the anterior neuropore (the midline dural diverticulation that extends through the foramen cecum and protrudes through the prenasal space, terminating at the osteocartilaginous junction of the nasal bridge) typically undergoes complete regression, leaving behind the small blind foramen known as the foramen cecum. Incomplete separation of the dura (neuroectoderm) from the skin can lead to a pulling in dermal elements into the regressing dural tract. Dermal sinus and congenital inclusion cysts (epidermoid and dermoid) are possible outcomes [3].

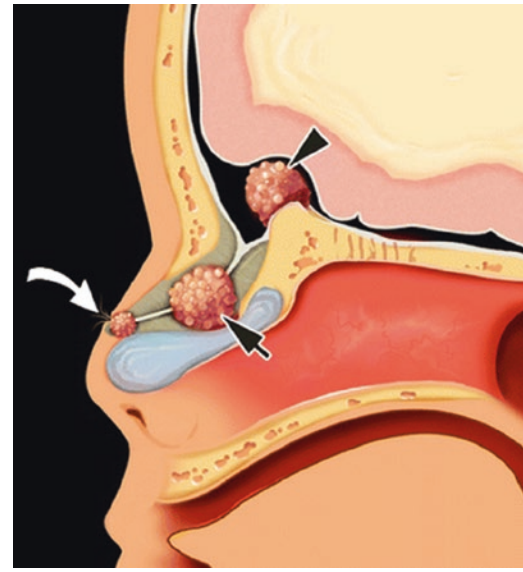

Fig. 54.3 Nasal dermal sinus. Sagittal color graphic depicts the possible spectrum of congenital cysts (epidermoid and dermoid) in a patient with nasal dermal sinus. The patient might present with a nasal dorsum pit, and underlying this might be a sinus. Epidermoid or dermoid cysts can be found anywhere from the subcutaneous nasal root region (*curved arrow*), to the deep sinus tract (*arrow*), to intracranially (*arrowhead*). The intracranial component might occur at the foramen cecum, adjacent to the crista galli, interhemispherically, or adjacent to the anterior third ventricle (courtesy AMIRSYS) [3]

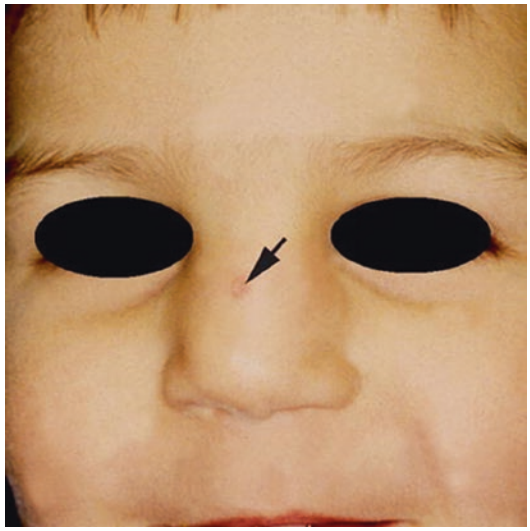

Fig. 54.4 Nasal dermal sinus and epidermoid. This infant boy presented with a draining mid-nasal pit (*arrow*). Note the broad, full nasal bridge and mild hypertelorism [3]

The epidermoid cyst represents a collection of desquamated epithelium (skin) lacking deeper dermal appendages. The dermoid cyst is composed of keratin debris and skin appendages such as sweat glands. Dermoid cysts in the frontonasal region comprise approximately 8% of all head and neck dermoids. These frontonasal inclusion cysts can occur anywhere along the course of the regressing embryologic dural tract. This includes the subcutaneous region of the nasal bridge from the glabella superiorly to the tip of the nose inferiorly, the nasal septum, and the prenasal space. Additionally, epidermoid and dermoid cysts might be found intracranially at the level of the foramen cecum and adjacent to the crista galli. There are also reports of intracranial epidermoid and dermoid cysts occurring adjacent to the anterior margin of the third ventricle.

54.2.2 Clinical Picture and Treatment

Half of the children have a dimple or pit over the nasal bridge [3]. This is usually found at the osteocartilaginous junction but can occur anywhere from the glabella to the tip of the nose. Hairs occasionally emanate from the pit, as may sebaceous discharge. A subcutaneous mass can be palpated over the nasal bridge in 30% of the patients. Approximately 50% have a broad nasal bridge and hypertelorism. The health history might be positive for meningitis caused by skin-colonizing organisms. This is strong evidence of an intracranial connection. In 80% of patients with nasal dermal sinus, the tract and associated epidermoid and/or dermoid cysts are extracranial. Craniofacial malformations have also been reported in patients with nasal dermal sinus [15]. As with any anomaly of the anterior neuropore, the most pressing clinical question is the possible connection between the clinically evident frontonasal abnormality and the intracranial compartment. In most practices, MRI has supplanted CT as the first choice and typically the only preoperative imaging study necessary in the evaluation of newborns and infants with congenital frontonasal masses and in the assessment of clinical findings suspicious for anterior neuropore anomalies without a mass. Surgical treatment is considered to be performed by pediatric neurosurgeons.

54.3 Congenital Anterior Cephaloceles (Frontonasal and Frontoethmoidal)

(Figs. 54.5, 54.6)

54.3.1 Pathology and Embryology

The pathogenesis of anterior cephaloceles is primarily based on a disturbance in the separation of neural and surface ectoderm at the site of final closure of the rostral neuropore during the final phase of neurulation in the fourth week of gestation [3]. An insufficient occurrence of apoptosis might cause this disturbance of separation [16]. Cephalocele denotes a defect in the skull and dura with an extension of intracranial contents. Categories of cephaloceles include: the herniation of meninges (meningocele); CSF,

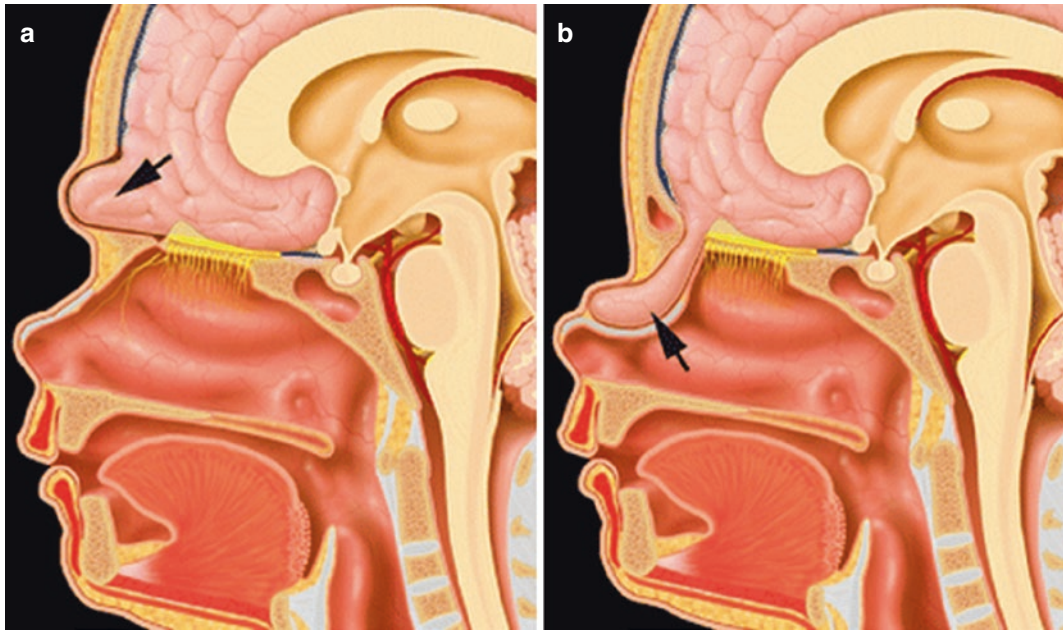

Fig. 54.5 Anterior cephaloceles, frontonasal cephalocele. **(a)** Sagittal color plate shows protrusion of meninges and brain through a frontal defect corresponding to the embryologic fonticulus frontalis (*arrow*). Frontoethmoidal cephalocele. **(b)** Sagittal color plate demonstrates protrusion of brain tissue through the foramen cecum, expanding the prenasal space and extending to the nasal bridge (*arrow*) (courtesy AMIRSYS) [3]

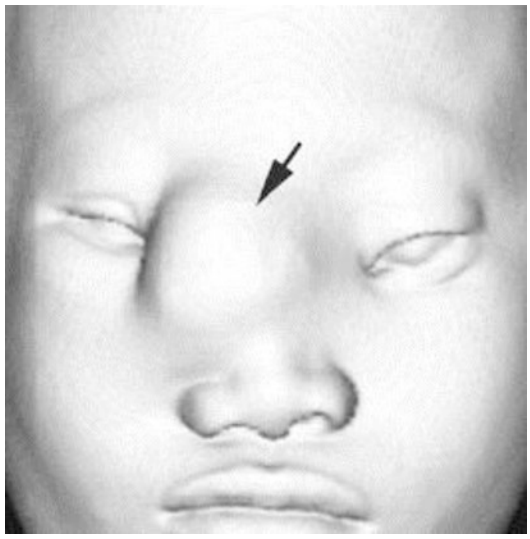

Fig. 54.6 Frontoethmoidal cephalocele in a infant boy presenting with a frontonasal mass that enlarges with crying. Surface-rendered 3-D CT demonstrates a large frontonasal mass (*arrow*). Note the associated hypertelorism [3]

meninges and brain (meningoencephalocele); atretic cephalocele, most common in the parietal-occipital area representing a form fruste of cephalocele consisting of dura, fibrous tissue, and dysplastic neural tissue; and glioceles, which consist of glial-lined cysts containing CSF [16].

54.3.2 Clinical Picture and Treatment

The frontonasal cephalocele projects through the fonticulus frontalis, and the frontoethmoidal cephalocele projects through the foramen cecum into the prenasal space. The sincipital cephalocele is usually suspected in the newborn or infant with an externally visible frontonasal mass. Frontonasal cephaloceles present with a mass at the glabella. Frontoethmoidal cephaloceles typically present with a mass at the nasal root or intranasally. Broadening of the nasal bridge and hypertelorism is often seen with anterior cephaloceles. The cephalocele commonly enlarges with crying and with jugular compression (positive Furstenberg sign). MR is the tool of choice when assessing a suspected anterior cephalocele. Frontonasal cephaloceles demon-

strate a sub-skin mass in the region of the glabella at the location of the embryonic fonticulus frontalis. The mass will show continuity with the intracranial brain. Continuity of herniated tissue and/or fluid with the brain is crucial to the diagnosis. Surgical treatment is considered to be performed by pediatric neurosurgeons.

54.4 Hemangioma (Fig. 54.7)

54.4.1 Incidence and Pathology

Infantile hemangiomas are benign tumors of vascular endothelial cells and are the most common benign tumor of infancy. They occur in up to 10%

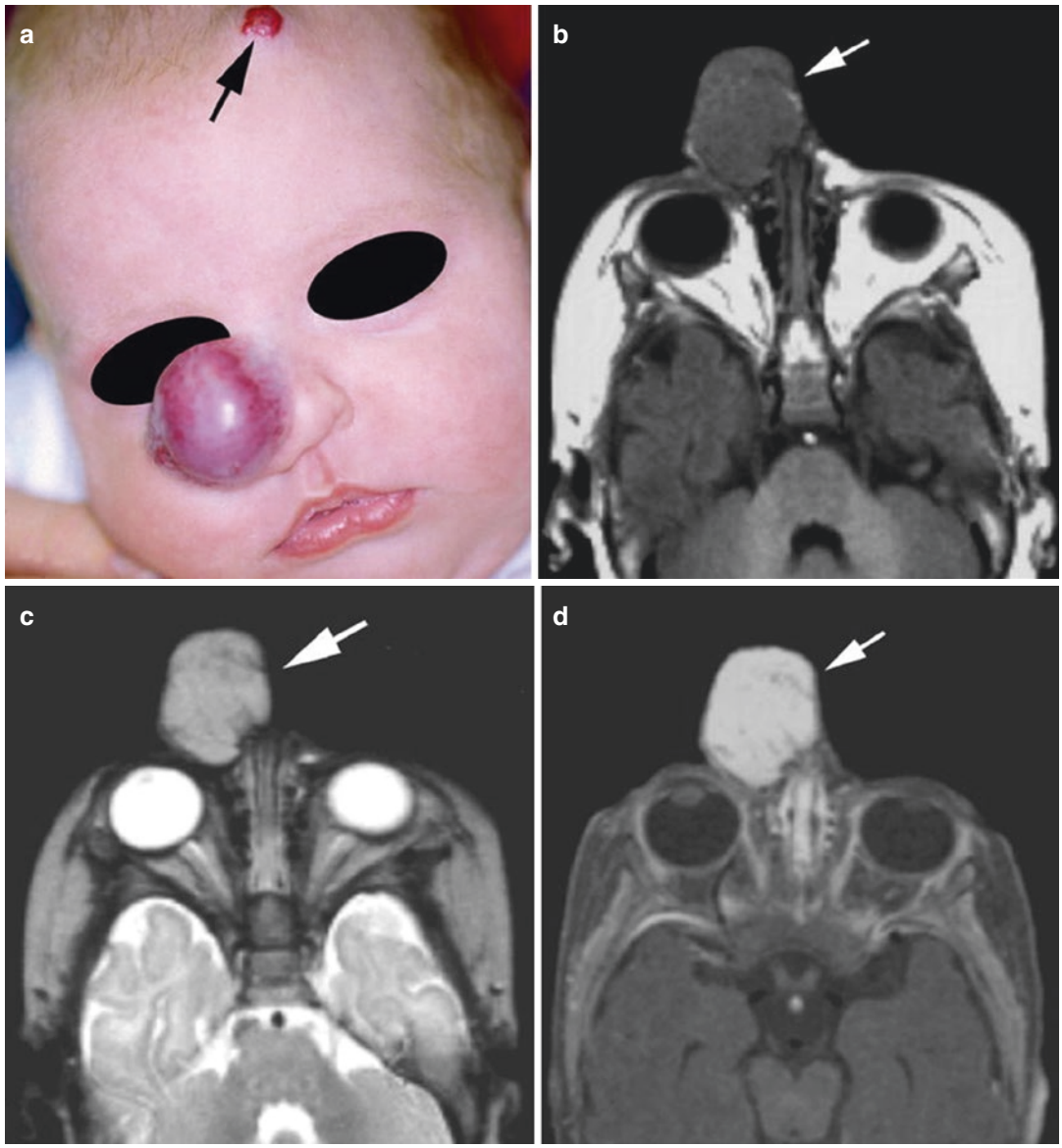

Fig. 54.7 Infantile hemangioma in a infant boy with a protuberant frontonasal mass. **(a)** Clinical photo demonstrates a large reddish-purple frontonasal mass. Note the scalp line hemangioma (*arrow*). **(b)** Axial T1-W image shows a lobulated frontonasal mass with slight T1 hyperintensity (*arrow*). **(c)** Axial T2-W image demonstrates a well-marginated hyperintense mass (*arrow*). **(d)** Axial T1-W image following MRI contrast medium administration shows robust enhancement of the hemangioma (*arrow*) [3]

of liveborn white infants with a low incidence in children of Asia and Africa descent [17, 18]. There is a 3:1 higher incidence in female infants and increased occurrence (23%) in premature, low-birth weight babies and in those whose gestation is complicated by placental abdominalities. Most hemangiomas are sporadic, solitary, and localized cutaneous lesions. However, there are reports of rare familial cases with a pattern of transmission that suggests autosomal dominant inheritance. These familial cases are often associated with other vascular anomalies. In addition, approximately 20% of the cases consist of multiple lesions. Pathologically, these unencapsulated proliferative vascular neoplasms are composed of thin-walled capillary-size vascular spaces with thin fibrous septa. These tumors have a distinct proliferative growth phase (during the first year) and an involutional phase (after the first year) [19]. Large facial hemangiomas (greater than 4 cm) can have associated central nervous system malformations.

54.4.2 Clinical Picture

Hemangiomas may differ in type, presenting as plaque-like segmental lesions or tumor-like focal lesions and deep or superficial lesions. About 80% of hemangiomas are located in the head and neck regions. Facial hemangiomas tend to occur at or close to boundaries of discrete developmental units of the face, suggesting that they may occur as a result of early craniofacial developmental events. Depending on the depth of these lesions, the overlying skin will have either a crimson, scarlet, or bluish hue. There is a clinical overlap between frontonasal capillary hemangioma and the nasal glioma. Both might present with a bluish or reddish mass.

MRI is the modality best suited to differentiate from other abnormalities.

Most hemangiomas are relatively small and pose only minor clinical problems, but approximately 20% do become clinically significant and require treatment. This may be a result of their aggressive growth and/or their location close to vital structures that they can invade, impairing function, and thus threatening the child's life. Complications include ulceration and hemorrhage, infection, and high output cardiac failure. Hemangiomas are often disfiguring and can have significant psychological/emotional impact on the affected child. This causes many parents to seek treatment rather than wait for the natural evolution to occur.

54.4.3 Treatment

Apart from the two extremes of clinical management (i.e., waiting for involution or surgical resection), complications or parental concerns may indicate treatment. Current treatment aims at inducting or accelerating the natural involution process. The most widely used option, oral/systemic or local corticosteroid treatment, has a reasonable success rate, although the reason for its efficacy is not well understood. In addition, benefits are only significant if treatment is administered in the proliferative phase. Therefore, it must be initiated early and at appropriate doses to avoid significant adverse effects. Life-threatening cases may be treated with intravenous vincristine and cyclophosphamide. Recombinant interferon alfa has also been used but is not always effective and should be avoided because of neurologic toxicity. There are reports of success in treating hemangiomas locally/intralesionally with the immune response modifier imiquimod, with becaplermin (recombinant platelet-derived growth factor) and with bleomycin. Most recently, Leaute-Labreze et al. report the treatment of severe hemangiomas associated with cardiac complications with the non-selective B-blocker propranolol [20]. A subsequent trial in children without such complications was also successful, resulting in stabilization and later regression of the lesions. Propranolol may work via vasoconstruction, decreased expression of proangiogenic factors, or by triggering apoptosis of endothelial cells. Some hemangiomas may require a combination of treatments.

In the last several years, much has been learned about molecular features of hemangioma and hemangioma-derived endothelial cells cultured

in vitro, and many pathogenetic mechanisms have been proposed. The recent findings that antibodies against VEDF prevent the activation of VEGFR2 signaling in hemangioma endothelial cells, suggest that anti-VEGF reagents may be effective in hemangioma treatment [21]. Recently, Bender et al. conducted a phase I pediatric clinical trial using the VEGF neutralizing antibody bevacizumab (BV) in children with various solid tumors to determine toxicity [22]. As a result, BV could easily be further titrated for use in children of up to 3 years of age for the treatment of aggressively growing hemangiomas.

54.5 Rhabdomyosarcoma (Fig. 54.8)

Congenital presentation of rhabdomyosarcoma is very uncommon. Out of a total of 3217 patients enrolled in the Intergroup Rhabdomyosarcoma Study (IRS) only 14 patients (0.4%) were less than 1 month old at the time of diagnosis [23]. The head, neck and trunk are the predominant sites in neonatal rhabdomyosarcoma [24]. The diagnosis of congenital rhabdomyosarcoma suggests the possible intrauterine development of this tumor. In infants aged less than 1 year, Lobe et al. noted a higher frequency of embryonal/botryoid and poorly differentiated histological types [23]. There is no direct correlation between age at diagnosis and survival. Although, age is not a prognostic indicator in disease progression, neonates with rhabdomyosarcoma have a guarded prognosis due to direct or secondary complications of chemotherapy, radiotherapy and surgery on their underdeveloped organ systems. Treatment should be risk directed and based primarily on extent of disease. Multi-drug, multicycle, dose intensive chemotherapy combined with radiotherapy and wide surgical resection when feasible has shown to improve survival of children with head and neck rhabdomyosarcoma [25]. Initial surgical resection can be considered in patients with low risk localized embryonal non-orbital non-parameningial head and neck rhabdomyosarcoma. Clinical stage of the disease is the best indicator of survival. Surgeryshould be done as the first treatment, if it causes no functional or esthetic harm, followed by systemic chemotherapy. Rdiotherapy is indaicated for the alveolar subtype of rhanbomyosarcomas or for patients with residual tumors following the first treatment.

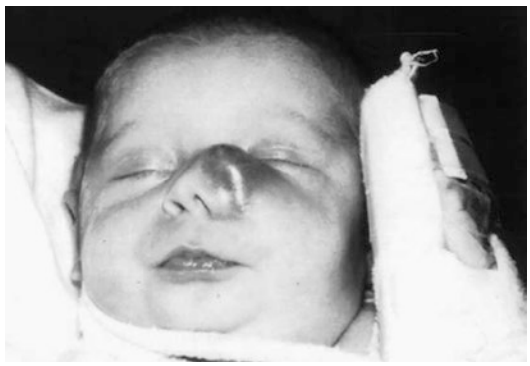

Fig. 54.8 Eighteen-day-girl infant with left paranasal rhabdomyosarcoma [25]

54.6 Myofibromatosis (Fig. 54.9)

54.6.1 Historical Notes and Incidence

Infantile myofibromatosis of the head and neck is reported as rare, but as pathologists become more familiar with histological features, this disorder may be increasingly seen by clinicians. Myofibromatosis was first described in 1954 by Stout as "congenital generalized fibromatosis", a term he chose to designate a disseminated disease of multiple nodular lesions in newborns [26]. Stout is also credited with recognizing that fibromatoses, although locally invasive, multicentric, and often aggressive, could be distinguished from fibrosarcoma, a malignant neoplasm with metastatic potential. For many years, the standard treatment of all types was aggressive, wide local resection, based on a review by Conley et al. of 40 cases of fibromatosis, including ten children younger than 15 years [27]. Subsequently, Chung and Enzinger argued for the classification of infantile myofibromatosis as a distinct lesion, based on its unique clinical and staining characteristics consistent with myofibroblastic origin [28].

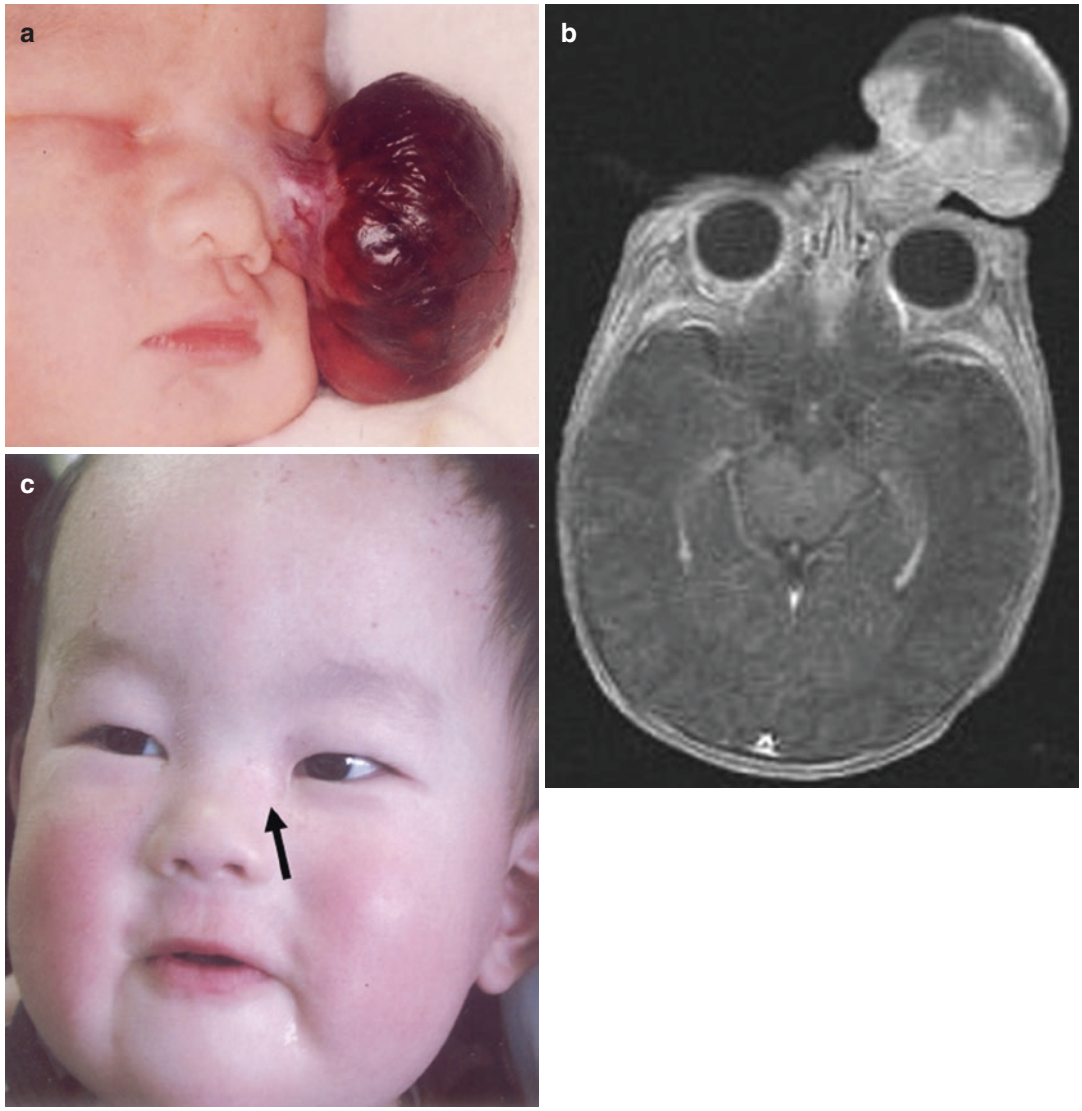

Fig. 54.9 Infantile myofibromatosis, solitary **(a)** 0-day, boy, A dark red-colored mass (5 x 4.5 x 4 cm in size) protrudes from the left alar nasal sulcus **(b)** MRI shows no invasion to the orbita. **(c)** After 1 year, cosmetic performance is satisfactory (An *arrow* shows very small scar) [29]

54.6.2 Pathology

Most nodules appeared grossly as distinct, circumscribed nodules with staining characteristics between fibroblasts and smooth muscle. Immunohistochemical stainings show the characteristic immunoprofile of myofibroma, consisting of positive immunoreactivity for vimentin and actin and negative immunoreactivity for desmin or S-100 protein. The specimens demonstrated characteristic spindle-shaped cells arranged in bundles or fascicles. There is great variability from low to high cellutarity within each specimen. A few specimens demonstrated central areas of massive cell death and necrosis, consistent with regression.

Some authors report that these lesions tend to be locally aggressive, with infiltrative growth and

a strong tendency to recur after excision, whereas other reports suggest a benign character with spontaneous regression. The overall prognosis is excellent, with the exception of generalized forms involving the viscera. The generalized form is most often seen in neonates and may be fatal due to the involvement of vital structures. Both multicentric and solitary lesions may be inherited as an autosomal recessive or autosomal dominant disorder.

54.6.3 Clinical Picture

Nearly half of patients presented with a single dermal or subcutaneous nodule. The remaining patients exhibited a mass in the aerodigestive tract, including the oral cavity, oropharynx, or nasopharynx. In general, examination revealed a nontender, well-circumscribed mass. The presence of the other symptoms correlated with the size and location of the mass. The morbidity of myofibromatosis depends chiefly on the site of the lesion. Lesions in certain locations may never be diagnosed if they regress without causing symptoms.

Myofibroma is usually a solitary lesion with relatively benign features that occasionally can become aggressive.

54.6.4 Treatment

Conservative surgical excision is recommended as primary management for tumors that affect vital functions or cause growth anomalies. Cosmetic deformities sometimes become indications for resection. Watchful waiting may be appropriate if the lesion does not affect the function or growth of neighboring vital structures. In several case reports, tumors were described that underwent complete spontaneous regression. Fukazawa et al. provided evidence for greatly increased cell apoptosis in two patients with myofibroma and proposed that spontaneous regression may be mediated by massive cell death [29]. However, factors triggering apoptosis and tumor regression are unknown.

54.7 Lipoblastoma

These are rare benign mesenchymal tumors of embryonal fat that occur in newborns, infants and children. In the review of 32 patients with head and neck lipoblastoma of children, only one case was newborn [30]. Typically, lipoblastomas present before 3 years of age [31]. Male to female ratio is 2.1:1 [30]. The most common presenting symptoms are painless enlarging neck mass and respiratory distress. MRI is the imaging modality most capable of diagnosing. CT scan was often used, but due to the similarity of lipoblastoma to lymphangioma on these images, this madality rarely leads to the correct diagnosis. Conservative complete excision with preservation of vital structures is recommended.

54.8 Foregut Duplication Cysts

54.8.1 Incidence

The estimated incidence of alimentary tract duplications is 1:4500, approximately one-thirds of which are foregut duplication cysts. Foregut duplication cysts most commonly occur in the chest and abdomen. While foregut duplication cysts may occur anywhere from the mouth to the anus, occurrence in the head and neck is uncommon, with approximately 65 reported cases by 1997. The oral cavity is the most common location in the head and neck [32].

54.8.2 Pathology and Embryology

Foregut duplication cysts are benign developmental anomalies that contain foregut derivatives. Traditionally, there are three criteria that must be met to make a diagnosis of foregut duplication cysts: they must (1) be covered by a smooth muscle layer, (2) contain epithelium derived from the foregut, and (3) be attached to a portion of the foregut. Duplication cysts are lined by one or more types of epithelium: gastric mucosa, ciliated respiratory-type epithe-

lium, stratified squamous epithelium, and simple cuboidal epithelium. All types of cysts may show squamous metaplasia, mucosal ulceration, inflammation, and necrosis, making distinction between the cysts sometimes impossible. Based on their epithelial type and other features, foregut duplication cysts may appear to closely resemble airway, esophagus, or small intestine. Therefore, the term foregut duplication cyst includes bronchogenic cyst, esophageal duplication cyst, and enteric duplication cyst.

54.8.3 Clinical Picture

The neonatal patients present with respiratory distress due to airway obstruction from the mass or feeding problems [32]. Foregut duplication cysts of the head and neck, although uncommon, should be included in the differential diagnosis of cystic head and neck lesions. Preoperative imaging is recommended to differentiate these lesions from other congenital cystic head and neck mass, namely, ranula, mucocele, piriform cyst, thyroglossal duct cyst, dermoid cyst, epidermal cyst, lymphangioma, cystic teratoma,

54.8.4 Treatment

Surgical intervention in the form of simple excision at least with complete removal of the mucosal lining is both diagnostic and therapeutic. If the cyst is left untreated, there is the potential for complications to develop. Malignant transformation has been reported to occur in long-standing foregut duplication cysts of the head and neck [33].

54.9 Congenital Epuris (Fig. 54.10)

54.9.1 Historical Notes and Incidence

Congenital epulis of the newborn is a rare tumour which is usually benign. The first description of a case is attributed to Neumann in 1871, hence it is also known as Neumann tumor [34]. Epulis is also known as a congenital gingival granular cell tumor because of its histological features. Since 1871, 216 cases have been reported. Epulis has a female predilection with 8:1 ratio with a Caucasian predisposition. Epulis is usually benign tumor and arises from the mucosa of the gingival and most frequently located on the anterior maxillary alveolar ridge and usually occurs as a single mass although 10% cases occur as multiple [4].

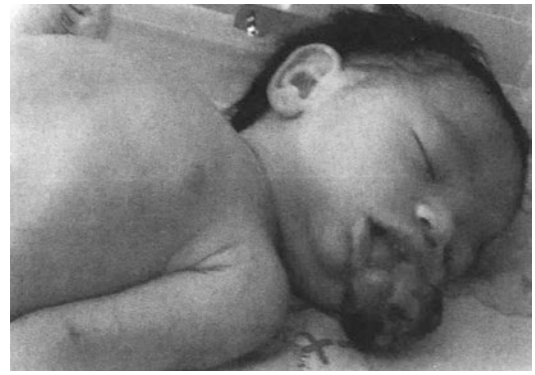

Fig. 54.10 Congenital epuris. Protruded pedunculated, pinkish red tumors in the mouse of new born [4]

54.9.2 Pathology and Embryology

Microscopic examination shows a central mass of granular cells. This mass is surrounded by a stratified squamous mucosa. The histogenesis of the tumor is unknown. The exact histiogenesis is still uncertain; it is now thought to originate from primitive mesenchymal cells of neural crest origin. Histologically, congenital epuris shows highly vascularized fibrous tissue with nests of polygonal cells with large clear and granular cytoplasm and a small nucleus, with a normal overlying epithelium. Congenital epuris shows positive staining for vimentin either either in the intercellular spaces or in the cytoplasm of granular cells, which can be explained by the abundance of collagen and its precursors. Positive reaction for desmin, a 53kd fibrillar protein, is a specific marker of muscle cells [35].

54.9.3 Clinical Picture

Epulis clinically appears as a pedunculated protuberant pink tumor with smooth or lobulated surface, sometimes protruding from the mouse. The basis of the tumor is the alveolar mucosa. The size varies from a few millimetres to 9 cm in diameter. A larger lesion may interfere with respiration or feeding. In cases with large lesions mechanical oral and nasal obstruction can impair fetal deglutition and neonatal respiratory efforts resulting in polyhydramnios prenatally or respiratory impairment postnatally. After birth, the tumor normally does not increase in size. Malignant transformation has not been reported [4].

54.9.4 Treatment

Spontaneous regression has been reported in a few cases. However, surgical excision is generally indicated due to interference with feeding or respiration. Recurrence of the tumor after surgery has not been reported yet. The recommended treatment is prompt surgical resection. A "watchful waiting" procedure can be followed because small lesion spontaneous involution can occur, although this is rare. Of the more than 200 cases of CE of the newborn reported in the English literature, there have been eight case reports that have documented spontaneous regression. It may be concluded that if a CE lesion is less than 2 cm in its largest dimensions and the lesion does not interfere with respiration or feeding, non-surgical management of the lesions ought to be considered. The advantage of conservative management of such cases is to avoid exposure of general anesthesia in a neonate for a lesion which is known to be benign and will not recur [36].

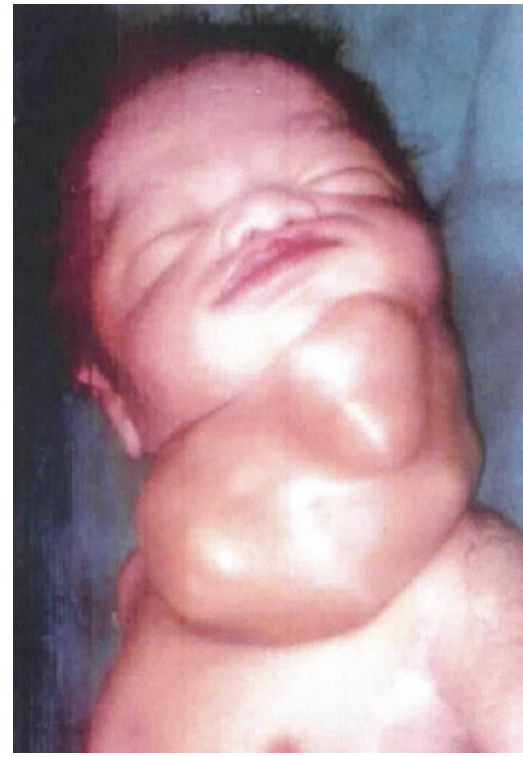

Fig. 54.11 Giant dervical teratoma in 0 day male newborn [40]

Table 54.1 Anatomical location of fetal and neonatal teratomas [37]

Anatomical location	No.	%
Sacrococcygeal teratoma	214	40
Intracranial teratoma	71	13.3
Cervical teratoma	70	13.1
Oropharygeal and nasopharyngeal teratoma	41	8
Cardiac teratoma	40	7.5
Gastric teratoma	14	2.6
Orbital teratoma	13	2.4
Mediastinal teratoma	13	2.4
Facial teratoma	8	1.5
Miscellaneous	17	3

54.10 Germ Cell Tumors (Fig. 54.11)

Germ cell tumors are relatively common in the fetus and neonate and are the leading neoplasms in some perinatal reviews. Germ cell tumors are a varied group of benign and malignant neoplasms occurring in the perinatal period. They are found in various sites, both gonadal and extragonadal, the latter in midline locations such as the sacrococcygeal area, retroperitoneum, mediastinum, neck, and intracranial region (Table 54.1) [37]. Most germ cell tumors of the fetus and neonate are histologically benign and are classified as

either mature or immature teratomas [38]. *Yolk sac tumor* (endodermal sinus tumor) is the leading malignant germ cell tumor of the perinatal period and throughout childhood [38].

54.11 Cervical Teratoma

54.11.1 Incidence and Pathology

Cervical teratomas account for approximately 13% of neonatal teratomas [37]. The histologic appearance of these masses is varied because all three germinal layers are represented. Often immature neural elements are identified, especially in the solid portion of the tumor, suggesting neuroectodermal origin [39].

54.11.2 Clinical Picture

Airway compromise is the most serious postnatal complication of giant cervical teratoma [39], and prenatal diagnosis is crucial, allowing for early recognition of neck masses that obstruct the airway. A prenatal ultrasound can identify the characteristic appearance of multiloculated cystic mass originating most commonly from the anterolateral aspect of the fetal neck. Polyhydroamnios and rarely nonimmune hydrops are associated with this condition. The other conditions that need to be considered for a mass at this site include cystic hygroma (lymphangioma), cervical goiter, cervical sarcomas and neuroblastoma.

54.11.3 Treatment and Prognosis

Polyhydramnios and prematurity were associated with a poor outcome. Fetal death in utero was attributed to an effect of the tumor. The chances of survival in live born neonates is related to pulmonary hypoplasia as the result of in utero airway obstruction, the extent of neonatal airway obstruction, and the degree of pulmonary immaturity [37]. Survival with *cervical teratoma* depends on the size of the tumor and extent of the involved tissues, with respiratory compromise being the main cause of subsequent morbidity and mortality. EXIT and OOPS are indicated for airway management at birth [7]. After delivery and stabilization, early resection is the recommended treatment of *cervical teratomas* because affected neonates may have acute airway obstruction or lose a previously secure orotracheal airway within hours or days after delivery [40]. Moreover, resection is the most effective method of achieving total control of the airway. Immediate surgical intervention has reduced the significant mortality rates in newborns with cervical teratoma from more than 80% in nonoperative cases to less than 10% in operative cases. [40]. Neonates with cervical teratomas generally have a good outcome provided that the tumor is resectable. Although yolk sac tumor components were present in only 1 of 70 (1.4%) of cervical teratomas, it also removes the risk of malignant change, which occurs at much higher rates in patients with cervical teratomas not diagnosed or treated until later childhood or beyond, a situation perhaps analogous to sacrococcygeal teratomas [40].

Currently, there are no definite chemotherapy guidelines for neonates with cervical teratomas. Azizkhan et al. [40] recommend that chemotherapy should be given only in infants with disseminated metastases (that have not differentiated) and those who have invasive tumors and residual tumor after resection. Long-term follow-up with imaging and α-fetoprotein determinations are additional recommendations.

54.12 Epignathi and Nasopharingeal Teratoma

Some *epignathi* and *nasopharngeal* teratomas are so large and extensive that they are incompatible with life and therefore inoperable, which explains the high mortality rate [38]. The most common presenting findings here were a mass, respiratory distress, polyhydramnios, and dysphagia. Surgical resection of pharyngeal teratomas results in cure but is not without serious and sometimes fatal complications [41]. Radical disfiguring surgery, which could result in impair-

ment of speech and swallowing or massive fatal hemorrhage, is contraindicated in the neonate [41]. Larger tumors may require multiple-operative procedures to obtain an optimal result. Before proceeding to surgical excision, it is imperative to rule out the existence of intracranial extension. The demonstration of hydrocephalus or an intracranial mass in fetuses and neonates with epignathi should facilitate counselling and prevent inappropriate intervention in cases in which the prognosis is very poor [42]. The neonates who were operated on did much better than fetuses who had no resections.

54.13 Facial Teratoma

Some *facial teratomas* are located superficially within the soft tissues of the face and head, whereas others are more extensive involving the underlying maxilla, orbit, or the intracranial cavity [43]. Large tumors may cause polyhydramnios and dystocia requiring cesarian section for delivery. Superficially (extracranial) located teratomas are associated with a good outcome. In the review by Isaacs, all eight of the facial teratomas, including the one fetus, were cured after surgical resection [37].

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Cystic Hygroma and Lymphatic Malformations

55

Shigeru Ono

Abstract

Lymphatic malformations (LMs) are uncommon congenital low-flow vascular anomalies previously referred to as lymphangiomas or cystic hygromas. The terminology of vascular and lymphatic lesions needs to be standardized. Vascular and lymphatic lesions, in general, have been notoriously difficult for pathologists to diagnose and classify because of the large number of entities and their variants, and their frequently overlapping clinical and histopathologic features. This problem has been compounded by imprecise terminology with various names referring to the same lesion or, conversely, a particular term denoting different entities. Recently, the International Society for the Study of Vascular Anomalies (ISSVA), an organization comprised of specialists in various disciplines interested in vascular anomalies, approved a novel classification of vascular lesions that distinguishes malformations from tumors and provides an easily understood and concise nomenclature.

Keywords

Cystic hygroma • Lymphatic malformations • Management • Sclerotherapy Outcome

Lymphatic malformations (LMs) are uncommon congenital low-flow vascular anomalies previously referred to as lymphangiomas or cystic hygromas. The terminology of vascular and lymphatic lesions needs to be standardized. Vascular and lymphatic lesions, in general, have been notoriously difficult for pathologists to diagnose and classify because of the large number of entities and their variants, and their frequently overlapping clinical and histopathologic features. This problem has been compounded by imprecise terminology with various names referring to the same lesion or, conversely, a particular term denoting different entities. Recently, the International Society for the Study of Vascular Anomalies (ISSVA), an organization comprised of specialists in various disciplines interested in vascular anomalies, approved a novel classification

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_55

Table 55.1 The International Society of the Study of Vascular Anomalies classification of lymphatic malformations

Lymphatic malformations (LMs)
Common (cystic) LMs
Macrocystic LMs
Microcystic LMs
Mixed cystic LMs
Generalized lymphatic anomaly (GLA)
LM in Gorham-Stout disease
Channel-type LM
Primary lymphedema
Others

of vascular lesions that distinguishes malformations from tumors and provides an easily understood and concise nomenclature [1]. The ISSVA Classification of Vascular Anomalies was recently updated in 2014, in which LMs has been classified into Simple Vascular Malformations, and further classified as shown in Table 55.1 [2]. According to some reports, the terms such as hemangioma or lymphangioma should be abandoned. The suffix -oma implies a tumor, including neoplasm. Indeed, LMs is a malformative lesion, sometimes with a tumor-like shape, but not a real tumor pathologically. For this reason, the classification accepted by ISSVA eliminates the term lymphangioma, and recommends instead the use of the term lymphatic malformation.

55.1 Classification of LMS

Many different classifications for LMs have been proposed in the literature, and these are sometimes confused because of overlapping clinical or histological features. Historically, lymphangioma has been classified into three groups: (1) lymphangioma simplex, composed of capillary-sized, thin-walled lymphatic channels; (2) cavernous lymphangioma; and (3) cystic lymphangioma (hygroma), composed of cysts from a few millimeters to several centimeters in diameter [3]. Although some previous investigators divided LMs into cystic, cavernous, and mixed types, the differences between these types in the literature are obscure. The most common LM classification scheme is based on the mean size of the cystic lesions. Lesions with a diameter greater than 1 cm are considered macrocystic (previously referred to as cystic lymphangioma or cystic hygroma), while lesions with a diameter less than 1 cm are considered microcystic (previously referred to as cavernous lymphangioma). Lesions containing both macroscopic and microscopic components can be referred to as mixed type [4–7]. As described above, the updated ISSVA classification of LMs has been acceptable (Table 55.1). When the size of the cervical macrocystic LMs is large, the term "cystic hygromas" is often used even now. LMs sizes are determined mainly by ultrasonography or magnetic resonance imaging (MRI). The classification of LMs is important clinically from the point of view of response to therapy (see below) [8, 9].

55.2 Embryology

LMs result from abnormal connections between the lymphatic and venous systems or from the abnormal development of lymphatic vessels [10]. The lymphatic system develops at the end of the fifth week as individual endothelial outgrowths from the venous system. Most recent reports regard lymphangioma as a lymphatic malformation that arises from sequestrations of lymphatic tissue that fail to communicate normally with the lymphatic system between 6 and 9 weeks gestation [10, 11]. Failure of the jugular lymphatic sacs to connect to and drain into the jugular veins leads to lymphatic fluid stasis and the development of single or numerous fluid-filled lesions in various locations of the neck. These abnormal remnants of anomalies may have a cavity in which to proliferate, and may accumulate vast amounts of fluid, which accounts for their cystic appearance. This hypothesis is most reasonable mechanism thus proposed for the formation of LMs, especially cervical cystic hygroma [11]. However, this theory fails to explain the often invasive character of the lesions.

55.3 Clinical Features

The approximate incidence of LMs is between 1 and 6000–16,000 live births [12]. No sexual or racial predictions have been demonstrated [4]. About 50% of LMs often manifest at birth and over 90% are diagnosed by at least the end of the second year of life. With modern advances in prenatal ultrasonography, the number of cases of prenatally diagnosed of LMs has increased [13–15]. LMs have recently been one of the most common prenatally diagnosed anomalies of the neck. It is relatively easy to detect large masses composed of macrocystic or microcystic LMs using ultrasonography or MRI. With ultrasonography single or multiple sonolucent cysts with or without several septa can typically be found. In our experience, 10 of 124 children (8%) with LMs could be diagnosed prenatally with ultrasonography or MRI. Especially in severe complicated cases with respiratory or circulatory morbidity, there would be some usefulness in perinatal management, including intubation or tracheostomy. Moreover, prenatal diagnosis of LMs could enable elective delivery and appropriate postnatal management, leading to improved prognosis of the condition [15]. Prenatal diagnosis of LMs would be also important for complicated cases with cardiac anomalies and/or chromosomal abnormalities when counseling parents.

Any part of the body served by the lymphatic system may be affected. Most of macrocystic LMs appear in the neck or axillary regions, whereas microcystic types show a predilection for the face, tongue, trunk, extremities, or retroperitoneal regions. In our experience, over 70% of macrocystic LMs were located in the neck and axillary region, and 70% of LMs in the neck and axillary region were of the macrocystic type. In contrast, microcystic LMs were more common than macrocystic LMs in the other sites, especially the face, tongue, and extremities. These correlations between site and type of LMs affect the treatment strategy for LMs.

LM masses are clinically poorly defined, and are usually soft and compressible with almost normal skin color (Fig. 55.1). LMs have the potential for rapid enlargement as a result of trauma, hemorrhage, or infection. The incidence of spontaneous infection has been reported ranged from 7 to 30% with bacteria [16]. LMs are histologically benign regardless of their type or location; however, they often expand into surrounding tissues, such as the trachea, major vessels and nerves, and can become life-threatening in some cases [17]. As mentioned above, MRI is particularly useful for the evaluation of the type and extension of LMs involving the neck, axillary, thorax, retroperitoneum, and extremities. MRI is also valuable for evaluating the involvement of surrounding tissues and the complex vascular lesions of LMs [18].

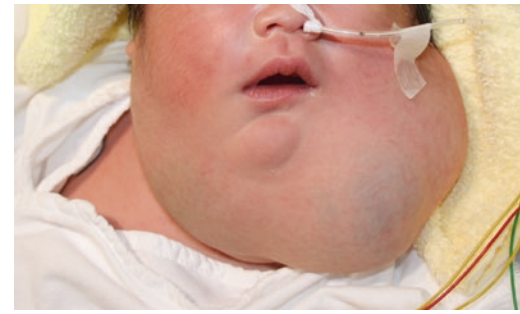

Fig. 55.1 Huge cervical microcystic lymphatic malformations (Cystic hygroma) in neonate

55.4 Treatment Strategies for LMS

All treatment strategies are based on a thorough initial assessment to detect the degree of functional impairment and/or disfigurement. Treatment options for LMs include observation, aspiration, sclerotherapy, and surgical excision. A wait-and-see strategy is recommended at least for 2 or 3 months after birth in asymptomatic patients, because there is a possibility of spontaneous regression of the lesion, reported in 12.5% of patients regardless of size and location [19].

Traditionally, surgical resection was the first-choice treatment strategy for LMs. However, complete resection of LMs is often impossible because it is technically difficult or unfeasible to

remove all involved lesions and preserve the important surrounding structures. Surgical resection of LMs can be also associated with various complications and some morbidity [20, 21]. Incomplete resection may be followed by refractory lymphorrhea, wound infection, and high incidence of lesion recurrence. With regard to lymphorrhea, a recently developed instrument incorporating a vessel sealing system may be useful to reduce or prevent the leakage of lymphatic fluid. In some cases, with LMs of the tongue or extremities, partial surgical resection of the lesion to reduce its volume may be effective and useful for improvement of quality of life as will be described in further detail below.

Sclerotherapy is a widely accepted nonsurgical treatment strategy, and with recent advances is able to shrink the size of LMs, especially those of the macrocystic type [22, 23]. Various agents have been used in sclerotherapy of LMs, such as OK-432 [24], bleomycin [25, 26], doxycycline [6], fibrin sealant [27], Ethibloc [28], alcohol [29], Pingyangmycin [30], and hypertonic saline [31].

For macrocystic LMs, sclerotherapy with the use of OK-432 seems to be a widely accepted first-line treatment because of its safety profile and dramatic efficacy in shrinking the size of LMs [4, 7, 32]. However, there are few reports that have fully clarified the sclerosing mechanism of these agents [33]. In patients with macrocystic LMs, OK-432 injection therapy resulted in statistically significant complete or marked shrinkage of the lesion in over 80% of patients without any side effects. In contrast, OK-432 therapy was not so effective in patients with microcystic LMs, with complete or marked shrinkage in only 34% of patients (Table 55.2). It is interesting to note that the average number of OK-432 injections for microcystic LMs was higher than that for the macrocystic type. This suggests that some cases of microcystic LMs required repeat injections of OK-432 to achieve a clinical response. Since microcystic LMs are composed of multiple small cysts, diffusion of injected OK-432 and the evoked chemical reactions would be limited locally. Therefore, we advocate that OK-432 injection should be performed at least several times and at several sites for patients with microcystic LMs even if a clinical response is not obtained after the initial injection.

Table 55.2 Results of OK-432 therapy for lymphatic malformations in 124 children

Types of LMs	No. of patients	Complete or marked shrinkage	Slight shrinkage or no response
Macrocystic	42	34 (81%)[a]	8 (19%)[a]
Microcystic	82	28 (34%)[a]	54 (66%)[a]

LMs lymphatic malformations
[a]$p < 0.005$

Some reports have demonstrated over 80% efficacy of sclerotherapy with bleomycin for macrocystic LMs [25, 26]. Bleomycin was initially developed as an anti-tumor agent by Umezawa in 1966 [34]. Bleomycin has antineoplastic activity in a variety of malignant tumors. In addition, bleomycin incites a mild inflammatory effect on the endothelial cells composing the LM cyst walls. Although minor transient side effects such as fever, local cellulitis or induration, and skin discoloration have been reported, the major concern with bleomycin administration is the potential risk of interstitial pneumonia and pulmonary fibrosis [25, 35].

Other sclerosants for LMs have also yielded relatively good results in the treatment for macrocystic LMs, although in small series. However, sclerosing therapies could hardly be expected to achieve a dramatic effect in most cases of diffuse microcystic LMs. The results of OK-432 injection therapy for microcystic LMs are also not satisfactory, with an efficacy rate of 34% in our experience. Nonetheless, the efficacy of the other aforementioned sclerosing agents is not as pronounced as that of OK-432 in the treatment of microcystic LMs [29]. Most studies have confirmed that results with microcystic LMs are inferior to those with macrocystic LMs [22]. Therefore, the optimal treatment strategy for LMs in children is still controversial, especially for microcystic LMs; however, these sclerotherapy with certain agents should be considered when thinking about a long-term strategy for large microcystic LMs.

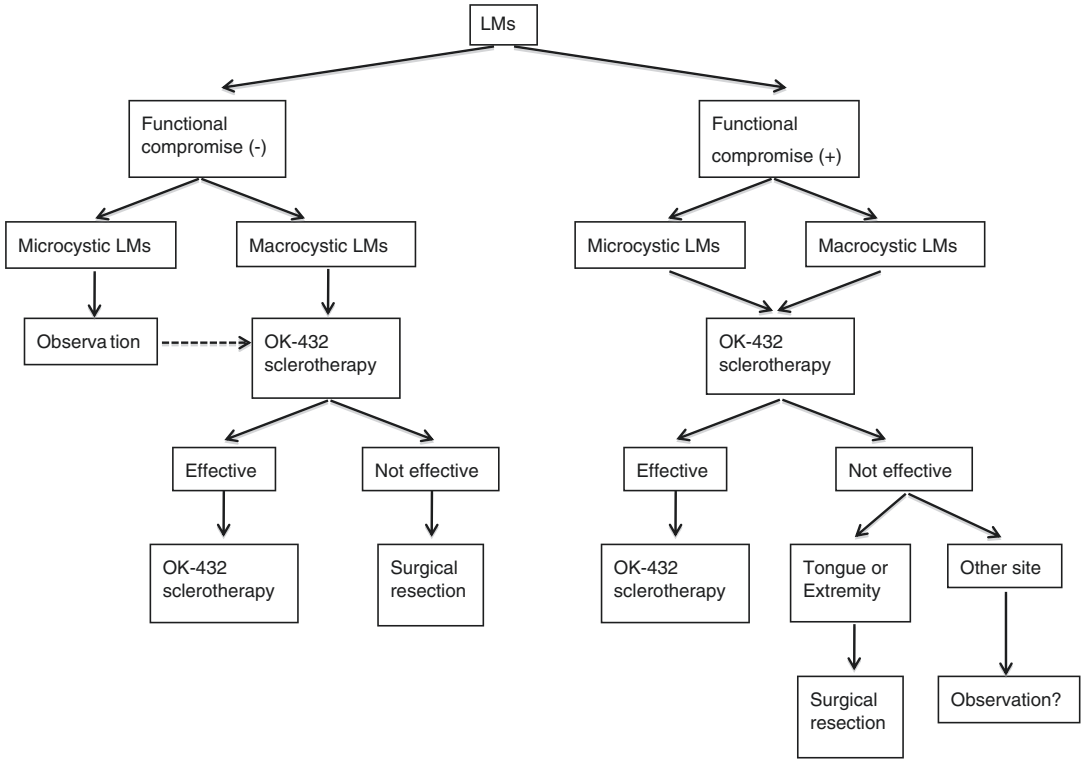

Fig. 55.2 The treatment algorithm for lymphatic malformations

Even if a wait-and-see strategy can be recommended in many cases of uneventful LMs in neonates and infants, the proliferative growth of such lesions requires an adequate treatment indication. LMs that persist lifelong require treatment in the majority of cases, especially when clinical symptoms occur. Based on individual parameters such as the diameter, location, or growth behavior, different therapeutic options as sclerotherapy and/or surgical intervention can be performed. None of those treatment concepts, however, represents the only treatment method of choice. The treatment algorithm for LMs is proposed and illustrated in Fig. 55.2.

55.5 OK-432 Injection Therapy

OK-432, an inactivated preparation of a low-virulence strain of group A *Streptococcus pyogenes* of human origin pretreated with benzylpenicillin G and heat preparation, is an effective sclerosing agent [36] (Picibanil, Chugai Pharmaceutical Co., Tokyo, Japan). With regard to the mechanism of the sclerosing action of OK-432, we speculate that OK-432 induces an inflammatory response at the site of injection that leads to sclerosis and occlusion of the sites of lymphatic leakage from LMs. Alternatively, OK-432-induced inflammation could also lead to increased resorption and/or drainage of excessive lymphatic fluid from LMs by opening new channels [37]. These two mechanisms may be mutually causing the shrinkage of LMs. Therefore, it is important that local inflammation with fever occurs after OK-432 injection to achieve clinical improvement in terms of LM size reduction. We have adopted OK-432 injection therapy for both macrocystic and microcystic LMs as an initial treatment since 1987 [24].

OK-432 injection therapy is routinely performed as the first-line treatment for all cases of macrocystic and microcystic LMs. If there is a clinical response of inflammation, repeat injections

are performed every 6–8 weeks for several months. Even if there is no evidence of clinical improvement after the initial injection, OK-432 is injected at least two times or more. The degree of response to OK-432 therapy is divided into the following four categories according to the size of the LM after treatment: complete shrinkage (almost disappeared), marked shrinkage (50% or greater shrinkage), slight shrinkage (less than 50%) and no response [38].

If there is slight or no shrinkage in response to OK-432 injection therapy, surgical resection is attempted later, especially for cases involving the tongue or extremities.

55.6 Protocol of OK-432 Therapy for LMS

OK-432 is usually injected under general anesthesia in neonates and infants and in cases where the LM is located on the tongue or face. In patients aged more than 10 years, OK-432 is injected under local anesthesia. OK-432 is prepared by diluting 0.1 mg of OK-432 stock solution in 10 mL of normal saline with contrast medium. The cystic fluid is aspirated, and should be examined to confirm the diagnosis of LM. The fluid should be thin and tan in color. An equal volume of diluted OK-432 is then injected through the same lesion. The maximum volume of OK-432 solution injected at one time is 20 mL (0.2 mg), regardless of the volume of fluid aspirated from the lesion. For patients in which aspiration of intralesional fluid is difficult, e.g. those with microcystic LMs, the OK-432 solution is injected into the lesion at several sites. Extension of OK-432 within the lesion and microscopic communication between the components of multicystic LMs are confirmed under X-ray fluoroscope. Repeat injections of OK-432 are performed every 6–8 weeks for several cycles when there is evidence of clinical improvement. Even with no clinical response, it is recommended that OK-432 be injected at least two or three times in each patient [39].

55.7 Outcomes of Nonsurgical Treatment (OK-432 Sclerotherapy)

It has been demonstrated that OK-432 sclerotherapy would be safe and effective as the choice of treatment of LMs with significance in macrocystic type [4, 5, 7, 8, 32, 39–42]. In the literature, the number of OK-432 injections per patient ranged from 1 to 18, with an average of 2.0–4.3 [8, 41, 42]. The average number of OK-432 injections was 1.8 for macrocystic LMs and 6.2 for microcystic LMs [7]. This suggests that some cases of microcystic LMs required repeated injections of OK-432 to achieve a clinical response. Since microcystic LMs are composed of multiple small cysts, diffusion of injected OK-432 and chemical reactions evoked would be limited locally. Therefore, for patients with microcystic LMs, OK-432 injection should be performed at least several times and at several sites even if a clinical response is not obtained after the initial injection. The overall outcomes of OK-432 therapy are shown in Table 55.2. Complete or marked shrinkage of the lesions was found in 81% (34/42) of patients with macrocystic LMs. In contrast, only 34% (28/82) of patients with microcystic LMs showed complete or marked shrinkage following OK-432 injection therapy. OK-432 injection therapy was significantly more effective for macrocystic LMs than microcystic LMs ($p < 0.001$).

The relationship between LM locations, types and resection after OK-432 injection is shown in Table 55.3. Surgical resection of LMs following OK-432 injection therapy, including either complete or partial resection but not incisional biopsies, was performed in 22% (27/124) of patients. Lesions requiring surgical resection were most commonly located in the extremities (43%, 6/14) or the tongue (38%, 6/16). Surgical resection following OK-432 therapy was required least frequently for LMs in the neck and axillary region (2%, 1/41) and the retroperitoneum (0%, 0/6). Moreover, most of the patients (89%, 24/27) who underwent surgical LM resection had microcystic LMs. Microcystic LMs were significantly

Table 55.3 Relationship between location and type of lymphatic malformations and resection after OK-432 injection in 124 children

Locations of LMs	No. of patients	No. of cases with resection after OK-432 injection (%)	Types of LMs	
			Macrocystic	Microcystic
Face	26	7 (27)	1	6
Tongue	16	6 (38)	0	6
Neck & Axilla	41	1 (2)	0	1
Trunk	21	7 (33)	1	6
Retroperitoneum	6	0 (0)	0	0
Extremities	14	6 (43)	1	5
Total	124	27 (22)	3[a]	24[a]

It means that Microcystic LMs were significantly more likely to require surgical resection after OK-432 therapy when compared to macrocystic LMs (Macrocystic were 3/42 and Microcystic were 24/82, respectively)($p < 0.005$)
LMs lymphatic malformations
[a]$p < 0.005$

more likely to require surgical resection after OK-432 therapy when compared to macrocystic LMs ($p < 0.005$).

55.8 Surgical Treatment

Surgical treatment, including complete resection of LMs, may still be one of the treatments of choice for macrocystic LMs. The incidence of postoperative complications, including seromas, hematomas, wound infection or abscess, and nerve damage, is over 30% [20, 43]. Since advancement in sclerotherapy with OK-432 or bleomycin in macroscopic LMs has demonstrated significant efficacy, the role of surgical resection is more limited. However, if a poor response to OK-432 injection is recognized, surgical excision might be considered next. Based on the size, site, and type of LM, surgical excision should be considered following sclerotherapy for patients with LMs. In particular, when the LM occurs in the extremities, tongue, or trunk, we have tended to resect following an unsuccessful trial of OK-432 injection therapy [39].

Total surgical resection may be incomplete in most cases of microcystic LMs because they commonly extend into the surrounding tissues. Some severe complications, such as refractory lymphatic leakage, lymphatic fluid retention, and infection, may occur after partial resection of LMs. Moreover, incomplete excision is frequently associated with recurrence or further growth of LMs. Therefore, it is necessary and important to consider the indications for surgical excision of LMs, based on the site and type of LM as well as the clinical response to OK-432 injection. Some studies have reported that surgical excision of microcystic LMs following OK-432 therapy achieved satisfactory volume reduction with minimal complications [9, 40]. Recently, new technological hemostatic device, the Vessel Sealing System (VSS), is used widely in general and head and neck surgery. It is an electrothermal bipolar device that can provide excellent hemostasis by denaturing the collagen and elastin in vessel walls and lymphatic lumens and reforming them into a hemostatic seal [44]. VSS is also used to perform partial resection of refractory microcystic LMs, making it easy to maneuver intraoperatively and achieve excellent postoperative results without lymphatic leakage or fluid collection [45]. Surgical treatment strategies should be based on clinical responses of initial sclerotherapy and individualized according to site and type of LMs.

Management of LMs involving the tongue is also controversial and challenging. There is no consensus regarding treatment of LM-induced macroglossia, and children with this condition may have functional issues with speech difficulties, dysphagia, and dental problems (Fig. 55.3). Airway obstruction and obstructive

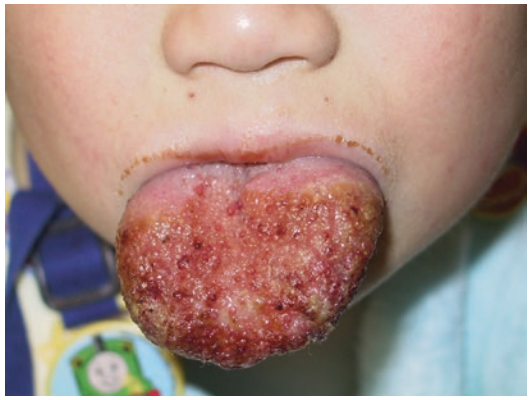

Fig. 55.3 Macroglossia induced lymphatic malformations with difficulty of mouth closure

sleep apnea followed by recurrent tongue trauma with bleeding pain or mucosal changes are the most common indications for treatment of LMs involving the tongue. Acutely enlarging LMs with tongue involvement are treated with steroids and antibiotics, and refractory bleeding from mucosal blebs would be managed with cautery, ablation, or laser therapy [46–48]. Reduction surgery for LM-induced macroglossia is used to reduce dental trauma to the tongue with associated refractory bleeding [49]. The preferred methods of tongue reduction are superficial laser ablation and surgical excision. The most commonly used procedures for surgical tongue reduction are anterior wedge and midline keyhole reduction [50].

55.9 Choice of New Therapies

New therapies as non-surgical treatment for LMs, especially diffuse microcystic or recurrent LMs, are come across occasionally in some case reports. Oral administration of sildenafil, propranolol, and sirolimus has been reported to be effective for LMs [51–53]. Sildenafil is phosphodiesterase inhibitors that have recently emerged as a potential treatment modality for lymphatic malformations [51, 54]. Although propranolol is known to have efficacy in the treatment for infantile hemangioma, recent studies have reported having a potential of treatment efficacy for some cases with LMs, especially including mixed vascular component [52]. Sirolimus is an mTOR inhibitor that reported having the efficacy in the treatment of refractory LMs. In a newborn with LMs of the neck with significant respiratory involvement and diffuse lymphangiomatosis, the treatment with sirolimus was found to be very effective, with complete resolution of the disease, good tolerability with no adverse events [53, 55]. These therapies should be estimated with prospective and randomized studies in the near future.

55.10 Massive Pleural Effusion and Ascites

The most prevalent clinical manifestation of LMs is the exertion of a mass effect on surrounding tissue, but in some cases the accumulation of large amounts of lymphatic fluid in the pleural or abdominal cavities may lead to respiratory distress. Diffuse microcystic LMs, in particular, can result in large chylous pleural effusions or chylous ascites that are often refractory to treatment. Chylous fluid collections develop when the lymphatic system becomes obstructed or disrupted, and can arise in a variety of clinical conditions, including malignancy, blunt trauma, liver cirrhosis, or surgical intervention in adults, and trauma, obstruction, or lymphatic abnormalities in children [56]. Lymphatic abnormalities in children include mainly LMs, which can give rise to physiologically compromising pleural effusions and ascites leading to respiratory distress (Figure 55.4).

Conventional conservative management of patients with LM-induced chylous pleural effusions or chylous ascites involves observation and feeding with medium-chain triglyceride-supplemented milk (MCT milk) [57]. However, MCT milk has only a minimal effect on pleural effusions or ascites associated with LMs. The thoracoscope- or laparoscope-guided direct injection of OK-432 is one of the optional treatment procedures for controlling chylous pleural effusion and chylous ascites associated with diffuse microcystic LMs. Although the role of OK-432 in the treat-

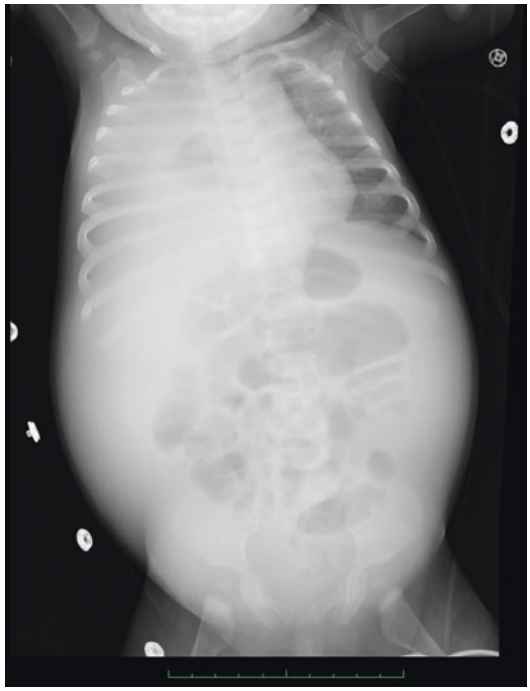

Fig. 55.4 Thoracoabdominal X-ray showing right pleural effusion and massive ascites associated with diffuse microcystic lymphatic malformations

ment of LM-induced pleural effusion or chylous ascites is unclear, the successful treatment of patients with microcystic LMs and pleural effusion or ascites using OK-432 injection therapy has been reported [58]. It is speculated that OK-432 induces an inflammatory response at the site of injection that leads to sclerosis and occlusion of the sites of lymphatic leakage. Alternatively, OK-432-induced inflammation could lead to increased resorption or drainage of lymph fluid. These two mechanisms are not mutually exclusive.

Conservative management strategies, such as dietary control, MCT milk, somatostatin, and diuretics, should be tried unless complications resulting from the fluid collections are life threatening [57, 59–62]. If these methods fail, surgical interventions such as therapeutic paracentesis and drainage should be considered. If these surgical approaches are also ineffective, the direct injection of OK-432 into the LMs under thoracoscope or laparoscope guidance is recommended. This technique should be considered for patients with refractory lymphatic fluid collections in the pleural or abdominal cavities caused by diffuse microcystic LMs.

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Liver Tumors

56

Jörg Fuchs and Steven W. Warmann

Abstract

Primary malignant liver tumours are rare and account for 1–2% of all solid tumours in childhood.

Hepatoblastoma (HB) is a rare solid tumor in infancy and toddlers that accounts for approximately 55% of all malignant liver tumours. The incidence is approximately 1 case per 1,000,000 children. The description of morphological and histological differences between HB and hepatocellular carcinoma (HCC) was a major discovery under the aspects of treatment efficiency and outcome for the children. The observation of an increased HB incidence in children born before 28 weeks gestation (birth weight below 1500 g) compared to children born at term is difficult to explain. The exposure of endogenous metabolites, hormones, as well as exogenous toxic substances e.g. drugs could influence the tumour development of dividing hepatoblasts.

Keywords

Liver tumors • Newborns • Classification • Staging • Surgery • Outcomes.

56.1 Malignant Liver Tumours

56.1.1 Malignant Epithelial Tumors: Hepatoblastoma and Hepatocellular Carcinoma

56.1.1.1 Pathology

Primary malignant liver tumours are rare and account for 1–2% of all solid tumours in childhood [1].

Hepatoblastoma (HB) is a rare solid tumor in infancy and toddlers that accounts for approximately 55% of all malignant liver tumours. The

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_56

incidence is approximately 1 case per 1,000,000 children. The description of morphological and histological differences between HB and hepatocellular carcinoma (HCC) was a major discovery under the aspects of treatment efficiency and outcome for the children. The observation of an increased HB incidence in children born before 28 weeks gestation (birth weight below 1500 g) compared to children born at term is difficult to explain. The exposure of endogenous metabolites, hormones, as well as exogenous toxic substances e.g. drugs could influence the tumour development of dividing hepatoblasts [2–4].

Different histological classifications have been proposed over the last decades. Currently HB are commonly subdivided into three subgroups according to the SIOPEL Liver Tumor Study Group classification (Table 56.1) [5].

The growth pattern of HB is unifocal in 85%; 15% of all tumors show a multifocal growth pattern. Characteristics of the epithelial tumor compounds range from anaplastic to embryonal and further on to well differentiated fetal cells. Therefore, the group of epithelial HB comprises purely fetal, embryonal, mixed embryonal/fetal, macrotrabecular, and small cell undifferentiated (SCUD) subtypes. The macrotrabecular subtype is a transition form to HCC and is commonly found in older children.

The subgroup of mixed epithelial/mesenchymal HB can be further subdivided into tumors with or without teratoid features. Mixed HB may contain osteoid, fully developed bones, muscle cells, and other tissues. In teratoid HB structures resembling germ cell tumours have been observed.

In contrast to fetal and embryonal HB exist so called highly malignant transitional liver cell tumours (TLCT). Most of these tumors are very aggressive and occur in older children or young adolescents. In the literature this entity is discussed controversly. These tumors are considered as being compositions of immature blastemal cells in combination with the classical features of all other liver tumors cells. Additionally, other new tumor entities of the liver such as desmoplastic nested spindle cell tumours have been described in few case reports [6].

Table 56.1 Classification of HB according to the SIOPEL Study Group

Wholly epithelial type
Fetal/pure fetal subtype
Embryonal/mixed fetal and embryonal subtype
Macrotrabecular subtype
Small cell undifferentiated subtype
Mixed epithelial and mesenchymal type
Without teratoid features
With teratoid features
HB, not otherwise specified

Hepatocellullar carcinomas (HCC) show a slightly decreased incidence over the last 20 years. The incidence is approximately 0.5 per 1,000,000 children above the age of 10 years, with a somewhat higher occurrence in the Asian population. One reason might be the immunization of infants against perinatal transmission of hepatitis B virus infection. From the epidemiological point of view we can distinguish between two groups of HCC: those developing in the context of advanced chronic liver diseases (α[alpha]-1-antitrypsin deficiency, hereditary tyrosinemia, chronic cholestatic disease and long term use of TPN) and children who develop sporadic tumors. The histological features of HCC are similar in children and adults. HCC cells are larger and more polymorphic than HB cells and include bile pigment as typical pattern. The most common genetic alteration is mutation of p53. Nearly 25% of all pediatric HCC belong to the fibrolamellar subtype (polygonal cells nested in a dense fibrous stoma). Pediatric HCC are characterized by low levels of cyclin D1 and a higher frequency of LOH 13q [7].

56.1.1.2 Clinical Presentation

Liver tumours in children most commonly present with a right upper quadrant mass as leading symptom. Unfortunately, by the time of detection, most of these lesions have grown to an enormous size. Approximately 20% of the children with HB and up to 40% with HCC have lung metastases at diagnosis. Further typical clinical signs of malignant epithelial liver tumors in children are abdominal distension, sometimes abdominal pain including vomiting or nausea, and loss of body weight. Anaemia is often present. Sometimes the patients present with paraneoplastic symptoms such as pubertas precox [8]. HB is the most common tumor in the age group below 5 years with an incidence peak between 2 and 3 years.

In contrast, HCC occur in patients between 5 and 20 years of age. HB is regularly found in association with several syndromes including Wiedemann-Beckwith, hemihypertrophia, or familiar adenomatous polyposis (FAP) [9].

Both tumor entities show an elevated serum α[alpha]-fetoprotein level in more than 85%. HB with an initial α[alpha]-fetoprotein level below 100 µg/L have a poor prognosis [10]. Other laboratory parameters are often normal. Especially serum bilirubin levels are physiologic, transaminases may be slightly elevated. In HB the thrombocyte count can be increased to over $500 \times 10^9/1$ [11].

56.1.1.3 Diagnostics

Availability and repeatability are the reason for the wide use of ultrasound scan. This investigation allows the description of tumour extension and also judgement of tumor response during chemotherapy. Sometimes HB are difficult to distinguish from the regular liver parenchyma because of the almost equal echogenicity [12]. The advantage of Doppler studies lies in the excellent assessability of borders between tumour and vessels under the aspect of moveable planes and tumor involvement (e.g. portal vein or hepatic vein). This applies in particular to the visualization of flow irregularities as well as small and localized portal or cava vein thrombi. Results from this investigation are especially helpful for the surgeon to estimate the type of liver resection [8].

Multislice CT scan and/or MRI are gold standard of the diagnostic in HB and HCC. These investigations are a roadmap for staging with a special focus on the PRETEXT- system (Fig. 56.1) and also an essential part for risk

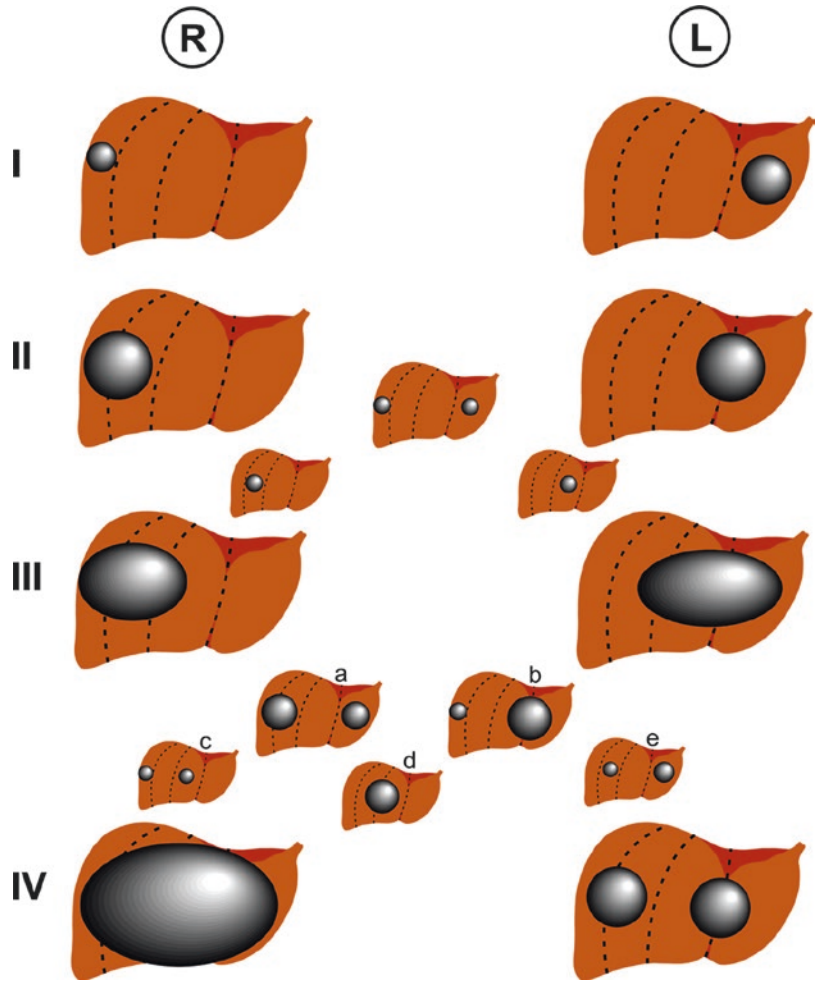

Fig. 56.1 PRETEXT staging system according to the SIOPEL Liver Study Group

stratification. The advantage of MRI is the absence of ionizing radiation. Furthermore, Angio-MRI is an excellent tool for reconstruction of the venous and arterial anatomy.

However, there exists also the possibility of computer-aided evaluation of imaging data using software assistants (for example MeVis LiverAnalyzer and MeVis Liver Explorer). These tools allow three-dimensional visualisation of liver tumors including all liver segments together with virtual simulation of liver resections. Further advantages of this system are establishment of detailed virtual risk analyses according to the liver segments, vessels, and biliary structures together with assessment of functional aspects based on the volume estimation of the liver remnant (Fig. 56.2) [13].

Thoracic CT scan is indicated in every pediatric epithelial malignant liver tumor in order to exclude lung metastases and as part of correct staging.

Conventional angiography is usually not necessary and plays a role only for interventional treatment options such as chemoembolisation or intra-arterial application of chemotherapy in selected unresectable cases after chemotherapy.

The possible role of PET-CT or PET-MRI scan in the primary diagnostic workup of liver tumors or in the diagnostic of metastases or relapses has not yet been clarified. These modern tools should be analyzed in further studies [14].

56.1.1.4 Staging and Risk Stratification

Currently there exist three different staging systems for liver tumors in childhood. The well-known TNM classification system plays a historical role and is used in several national and international trials for HCC [15]. Meanwhile, we distinguish between the pre-operative

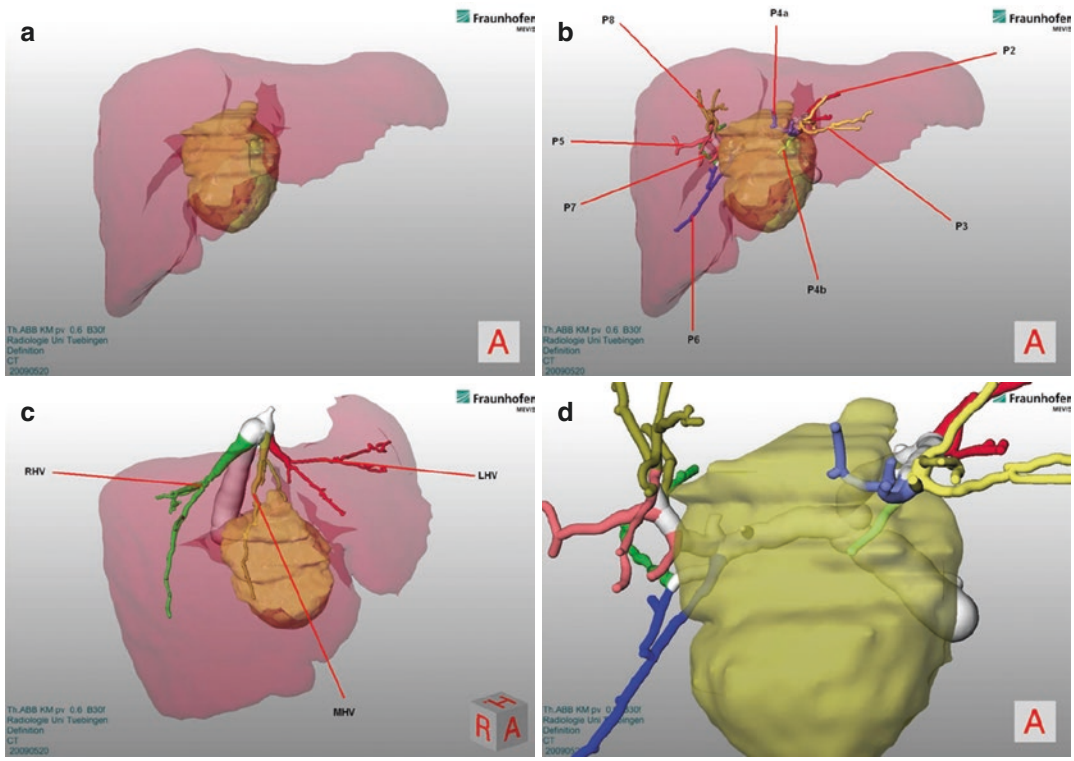

Fig. 56.2 3D reconstruction of a central liver tumor in a 4 year-old boy with central HB before mesohepatectomy. (**a**) Liver and tumor. (**b**) Anatomy of portal venous branches. (**c**) Hepatic veins. (**d**) Detailed view on tumor and portal veins

PRETEXT-system introduced by the SIOPEL group and the postoperative staging system according the Children's Cancer Study Group:

Stage I: Completely resected tumor
Stage II: Microscopic residual tumor
Stage III: Macroscopic residual tumor
Stage IV: Distant metastases

The main advantage of the PRETEXT (Pre Treatment Extent of Disease)-system is the standardized preoperative judgement of the tumor extension including risk stratification with a prognostic impact. The PRETEXT staging is based on Couinaud's system of liver segments which are grouped into four sections. In the original system, the caudate lobe or segment one was ignored. Additionally, the PRETEXT system describes the extension of disease beyond the liver, defining status v as affection of the inferior cava vein or hepatic veins, p as portal vein involvement, e as extrahepatic disease, and m as presence of metastases [16]. In 2007 Roebuck et al. added new relevant factors for risk stratification to the PRETEXT-system [17]. New parameters are caudate lobe involvement (C), tumor focality (F), and tumor rupture with different subdivisions [17]. The disadvantage of this system is the possibility of over-staging the liver tumor, probably as a result of the difficulty to distinguish between displacement and infiltration of liver parenchyma by the tumour. Another relevant issue is the weakness of standardisation of the radiological technique. This is relevant for unilocular tumors staged as PRETEXT III and IV with regard to the subsequent decision between tumor resection and liver transplantation [18].

In contrast, the postoperative staging system is exact and based on histological examination of the completeness of the liver tumor resection. Meanwhile both systems are used in different international trials under the aspects of evidence based comparison of treatment results.

Until recently, HB have been divided into two risk groups: the low (standard) risk group and the high risk group. The differences of characterisation of the risk groups within the treatment protocols are marginal. There is an agreement that high risk HB fulfil one or more of the following criteria:

- Mutifocality of the tumor
- Invasion of large vessels
- Distant metastases
- Lymph node involvement or extrahepatic disease
- Serum α[alpha]-fetoprotein level below 100 μg/1

All other tumors have been regarded as low or standard risk HB [19, 20]. This system has also been used for HCC in children. Based on the risk stratification children with liver tumors receive different regimens of chemotherapy. All children with high risk liver tumors receive delayed surgery after primary chemotherapy.

Until now, the prognostic significance of molecular findings, histology, or logarithmic α[alpha]-fetoprotein decline is still controversial. Neither the age of the children, sex and histological subtype, nor molecular genetic parameters such as LOH 11p15, DNA ploidy, and β[beta]-catein expression are significant prognostic factors for survival [21–24].

As a novel initiative the CHIC (Childhood Hepatic malignancies International Collaboration) Group has recently created a global approach to risk stratification in children with HB based on a data acquisition and interpretation combining the experiences with over 1600 patients from several international multicentre trials. Based on their analyses the authors proposed four risk groups: very low, low, intermediate, and high. This new stratification will be used as basis for adapted treatment protocols as well as for the prospective international cooperative study "Pediatric Hepatic International Tumor Trial (PHITT)". [25, 26].

56.1.1.5 Treatment

Chemotherapy. 40–60% of all liver tumors are unresectable at the time point of diagnosis and 10–20% of the children present with primary lung

Table 56.2 Relevance of preoperative chemotherapy for the resectability of liver tumors [31, 35, 86]

Entity	Response (%)	Resectabilitiy
Low risk HB	90	>90
High risk HB	74–84	64–70
HCC	46–49	36–47

metastases. The efficiency of chemotherapy in HB and HCC is proven and plays a key role for a successful treatment (Table 56.2) [27–29]. Different chemoherapy regimens are applied in HB depending on the respective stratification. Various cytotoxic drugs are used within the different international trials including cisplatin, doxorubicin, vincristin, 5-fluorouracil, irinotecan, cyclophosphamid, and carboplatin. In a randomized study the SIOPEL group could demonstrate that cisplatin monotherapy achieves similar results (complete resection rates and survival) in children with standard risk HB compared to those receiving combined doxorubicin/cisplatin treatment. This important analysis is an example for the success of reducing toxicity in standard tumors and thus preventing late effects (secondary malignancies, cardiomyopathy) [28, 30–32].

The treatment of high risk HB and relapsed HB is a challenge and requires an international collaboration in order to realize statistically relevant analyzes. High dose chemotherapy with stem cell rescue could not improve resection rates or treatment results.

The efficiency of chemotherapy in HCC is not yet clear. Several studies could show that these tumors respond to cisplatin and doxorubicin (PLADO) or cisplatin, 5-fluorouracil, and vincristin regimens. The response rate is approximately 50% in pediatric HCC treated with chemotherapy. In contrast, the response rate observed in adults is 0–33% [33]. Currently, an international study analyses the efficiency of cisplatin and doxorubicin together with the multikinase inhibitor sorafenib on HCC based on observations in adults. First results show a better response rate in comparison to conventional chemotherapy resulting in a higher rate of complete tumor resection. However, for the final judgment of response and survival rates the data are preliminary.

Surgery. Surgical procedures in pediatric liver tumors range from biopsy to extended liver resection and liver transplantation.

In the SIOPEL protocols ***tumor biopsy*** is recommended for risk stratification and biological reasons [34]. According to the German Liver Tumor Study Protocol tumor biopsy is not necessary in the age group between 6 months and 3 years as well as in cases presenting with the combination of typical radiological findings and elevated α[alpha]-fetoprotein level. In the CCSG-group primary surgery of low risk liver tumors is allowed [34–36].

Complete ***tumor resection*** is the main prognostic factor for survival in pediatric malignant liver tumors. The anatomical liver resection should be realized whenever possible because of a lower local recurrence rate [37, 38]. There exist different types of anatomical and non- anatomi-

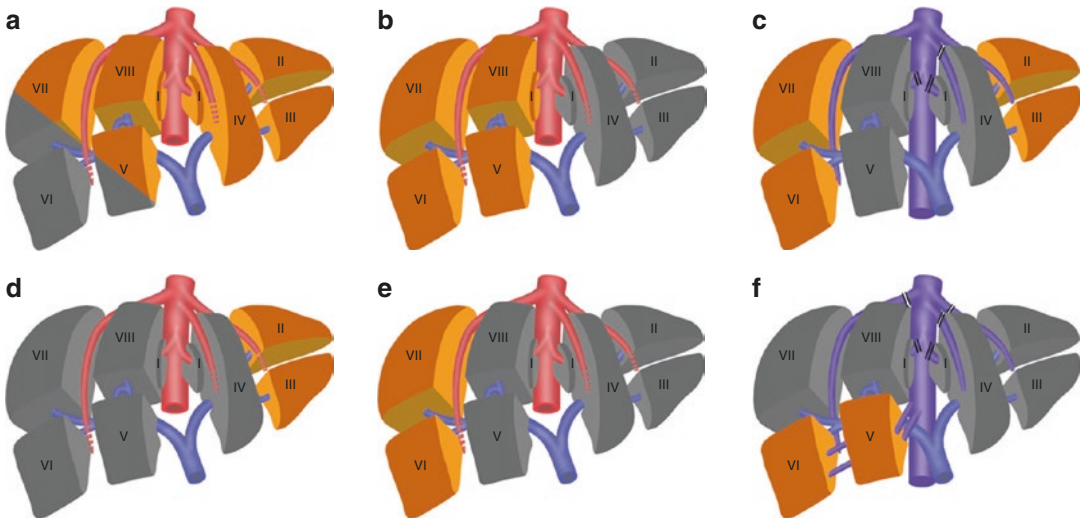

Fig. 56.3 Types of liver resections (resected portion in grey). (**a**) "Wedge resection". (**b**) Left hemihepatectomy. (**c**) Central hepatectomy ("mesohepatectomy"). (**d**) Right trisectionectomy. (**e**) Left trisectionectomy. (**f**) Atypical extended hepatectomy

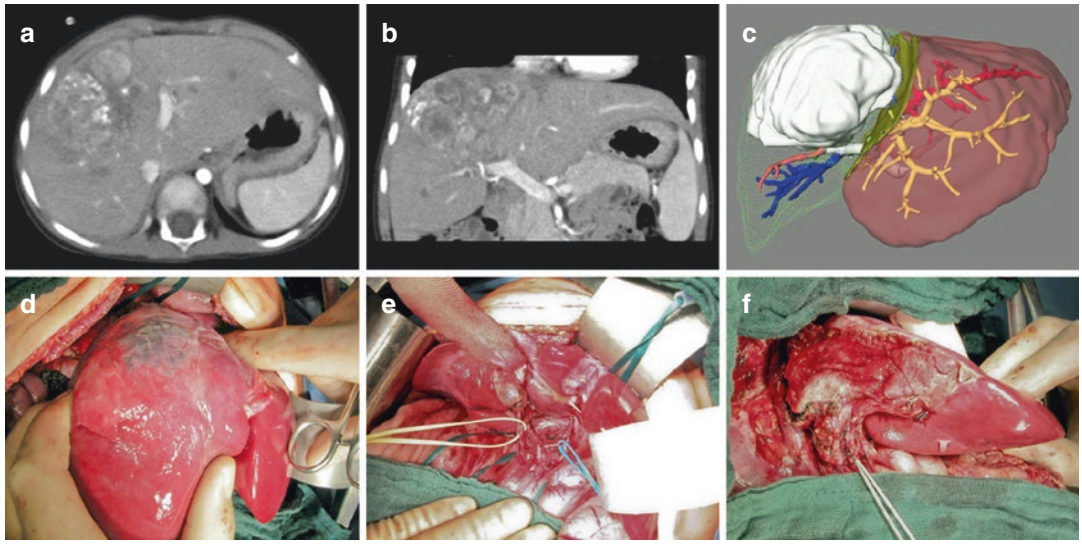

Fig. 56.4 Right TSE in a 2 year-old boy with stage I HB, NED after 6 years. (**a, b**) Tumor after chemotherapy (CT scan). (**c**) 3D reconstruction with simulation of virtual resection. (**d**) Intraoperative situs. (**e**) Dissection of porta hepatis. (**f**) Status after right TSE

cal liver resections (Fig. 56.3). In contrast to the adult population liver cirrhosis is an uncommon coexisting disease in children, also in those with HCC. Therefore, it is possible to remove up to over 80% (extended liver resection or trisegmentectomy) of the liver parenchyma without relevant liver dysfunction (Fig. 56.4) [39].

The standard approach for liver resection is the transverse laparotomy or a three-cornered, star-shaped incision when wider access is needed. The first step is the complete mobilisation of the liver. This is a precondition for achieving a free operative field and for the control of possible bleeding complications. Some surgeons prefer the preparation of vascular exclusion using loops or clamps in order to reduce the blood loss during the parenchymal phase of liver resection. Total vascular isolation is realized using the Pringle Manoeuvre; clamping of the supra- and intrahepatic cava vein is necessary in selected cases such as tumor involvement of the cava vein or hepatic veins, or in extended liver resections [40].

Usually, the Pringle manoeuvre is sufficient for reducing the blood loss during liver surgery by temporarily clamping the vascular structures within the hepatoduodenal ligament. Clamping is well tolerated for 30 min without postoperative liver dysfunctions. Vascular exclusion is possible for up to 60 min in selected cases; however, most surgeons recommend an "intermittent" form of Pringle's manoeuvre with short phases of reperfusion [41].

There exist several tools for the transsection or division of the liver parenchyma such as CUSA, harmonic knife, water-Jet, Laser devices or the conventional finger fracture technique. However, a precise knowledge of liver anatomy and tumor conditions rather is most important for the management of liver parenchyma and complete tumor resection.

Hemihepatectomies are indicated in children with PRETEXT I and II tumors. In unilocular tumors staged as PRETEXT III and IV, there is a controversial discussion between extended tumor resection versus ***liver transplantations***. Several authors could show, that children with such constellations have a good outcome (5 year overall survival above 80%) after extended right or left hepatectomies, mesohepatectomies, and extended atypical left hepatectomies [42, 43]. Otherwise, the results of primary liver transplantation are remarkable in unifocal and multifocal PRETEXT III and IV tumors (5 year overall survival above 75%) (Fig. 56.5) [42–44].

Further challenges in the surgical treatment of liver tumors are vascular involvement of hepatic,

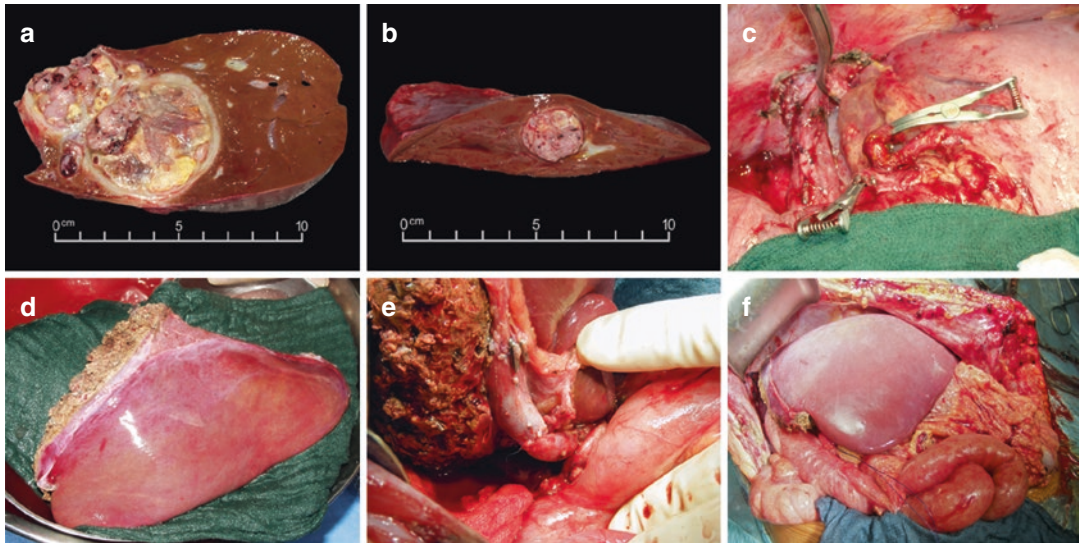

Fig. 56.5 Liver transplantation in a 6 year-old boy with multifocal Transsitional Cell Tumor, stage IV. (**a**, **b**) Macroscopic view of multiple tumor lesions within resected specimen. (**c**) Status after hepatectomy. (**d**) Donor liver (segments II/III). (**e**) Portal vein anastomosis during liver transplantation. (**f**) Status after transplantation showing a well perfused organ

cava, or portal vein and pre-existing extrahepatic disease. In these cases radical surgical procedures are indicated and include liver resection under cardiopulmonary bypass in selected cases. The number of cases is very limited and a clear treatment recommendation is difficult [45]. The German Liver Tumor Study Group HB99 analyzed the data of high risk HB with and without involvement of major hepatic vessels. On one hand there was a difference in overall and event free 3-year survival in both groups, on the other hand the data showed that radical surgery with reconstruction of large vessels can lead to an improved survival in selected cases.

The SIOPEL III study demonstrated the positive impact of liver transplantation in children with multifocal HB. Although there is a controversial discussion about the detailed indication of liver transplantation in HB and HCC, this procedure is recommended in all multifocal liver tumors without extrahepatic disease [46]. Pre-existing lung metastases are not a contraindication for liver transplantation in HB; however, they should be cleared after chemotherapy or be surgically removed prior to transplantation. The results of primary liver transplantations are significantly better than results of rescue transplantations [44, 47]. However, all relevant data in this field are based on retrospective analyses. Meanwhile a world wide database for these highly complex tumors has been established for prospectively judging the long term outcome (PLUTO—Pediatric Liver Unresectable Tumor Observatory) [48].

The Milan criteria (single tumor below 5 cm in diameter; or less than three lesions below 3 cm in diameter, absence of macrovascular invasion and extrahepatic disease) were developed for adult HCC. These criteria have been expanded to come closer to the "up-to-seven" recommendation, where the summary of the largest tumor size and the numbers of tumor nodules should not exceed seven. Nevertheless, the relevance of these criteria has not yet been clarified for children. Some authors report on survival of children with more than three nodules and larger tumors after liver transplantation. Accordingly, some oncologists recommend liver transplantation in children showing response to neoadjuvant chemotherapy regardless of macrovascular invasion and extrahepatic disease. In the end, these constellations are often controversially discussed without clear concept.

56.1.1.6 Treatment of Lung Metastases

Primary lung metastases occur in almost 20% of children with ***hepatoblastoma***. These children

are regarded as high risk patients and are usually treated with an intensified chemotherapy regimen [49]. Primary hepatoblastoma lung metastases generally respond sufficiently to chemotherapy and often disappear completely. All relevant international trails recommend surgical treatment of lung metastases persisting after initial chemotherapy as well as an aggressive surgical management of lung relapses. In some situations, patients benefit from a simultaneous resection of lung metastases together with the hepatic resection of the liver tumor in a single stage approach [50]. Because of the possible need for a liver transplantation [51, 52], metastasectomy should especially be performed in cases of PRETEXT III tumors with involvement of hepatic/portal vein or in children with PRETEXT IV tumors and persistent nodules after several cycles of chemotherapy. However, the number of respective patients is low and in contrast to other embryonal tumors the determination of independent prognostic factors with statistical power is difficult in this subgroup. Otherwise serum α[alpha]-fetoprotein level is an available tumor marker in hepatoblastoma patients for the judgment of follow up and detection of relapses. This also applies in lung metastases. Serum α[alpha]-fetoprotein levels can be used for distinguishing between benign and malignant lesions. Metastatic disease in hepatoblastoma is combined with a poorer outcome. Most reports on the relevance of lung metastases surgery in hepatoblastoma have an anecdotal character. The SIOPEL Study group could significantly improve their treatment results over three study periods. In the SIOPEL-3 HR study the 3 year event free survival was 56% and the overall survival was 62% (71 study patients with metastases) [32].The SIOPEL experiences underline the relevance of radical surgery in combination with intensified chemotherapy in cases of metastatic disease.

56.1.1.7 Chemoembolization, Radiofrequency Ablation, and Cryoablation

The experiences with hepatic artery chemoembolization (HACE) for children with liver tumors are limited. After a temporary occlusion of the tumor supplying artery, different cytotoxic drugs are applied (cisplatin, doxorubicin, mitomycin) every 2–4 weeks until tumor become surgically resectable. In approximately 30–40% of all cases the tumor resection was reported feasible. A tolerable toxicity has been described. However, this method is an experimental treatment option and only indicated in selected cases with an unresectable status after chemotherapy and when there is a contraindication for liver transplantation [53–55].

Radiofrequency ablation is used effectively in adults with recurrent HCC or other metastatic lesions in the liver below 3 cm in diameter. There exist no series in pediatric populations; this technique may be useful for ablation in cases of local recurrences. The technique can be used percutaneously, laparoscopically, or as open approach under ultrasound guidance. Another option is the cryoablation with liquid nitrogen or argon gas units (temperature below 160 °C). Both techniques are a reasonable alternative for selected patients [56].

56.1.1.8 Prognosis

The prognosis of children with HB has been significantly improved over last two decades due to a better risk stratification with selective treatment concepts. Meanwhile the 5 year overall survival of children with standard or low risk HB is nearly 90% in all international trials [57]. Microscopic tumor rests do not influence the prognosis significantly [30, 35, 58]. High risk tumors are a major challenge. The 5-year overall survival of patients with lung metastases is 65–70% and the event free survival is 55–63% including all treatment options such as liver transplantation and intensified chemotherapy. Only 33% of the children with an initial AFP below 100 µg/1 survive after 3 years [32]. The introduction of liver transplantation improved the outcome of children with high risk tumors [59]. It is remarkable that the 5-year overall survival in children with primary liver transplantation is 85% whereas it is 40% in patients undergoing rescue liver transplantation for incomplete tumor resection or tumor recurrence [60].

Children with initially completely resectable HCC have a good prognosis and benefit from adjuvant chemotherapy. The 5-year overall survival ranges between 70 and 80%. In contrast, children

with advanced HCC (stage III or/and PRETEXT III) have a poor outcome with a 5-year overall survival of 15–20% [33, 61]. There are almost no survivors in the group of children with stage IV HCC. For the last two subgroups new therapeutic strategies are needed. In contrast to earlier studies the fibrocellular variant does not seem to have a better prognosis than the other HCC [62]. Presence of lung metastases and macrovascular invasion are among the strongest predictors for tumor recurrence within the transplanted liver. Therefore, the indications for liver transplantation in children with HCC have to be analyzed in a world wide data bank such as PLUTO for better definition of indications for liver transplantation. Finally, due to the preliminary data the effect of sorafenib on the outcome of children with HCC cannot yet be definitely judged [63].

56.1.2 Liver Sarcoma

Undifferentiated embryonal sarcomas of the liver (UESL) account for 5–10% of malignant liver tumors in children. The histological appearance is mesenchymal but can at the same time be characterized by a morphological diversity. Tumor cells often are spindle-shaped with an ill-defined outline. By now there is no specific immunohistochemical expression marker [64, 65]. A link between this entity and mesenchymal hamartoma of the liver is currently being controversially discussed [66].

Clinical presentation combines abdominal pain and a mass of the upper right abdomen. Diagnostic workup regularly reveals a discrepancy of internal architecture between Ultrasound and CT scan [67].

Chemosensitivity has been observed in some tumors, but complete surgical resection represents the central prognostic factor of treatment for children with UESL. However, this might be difficult to accomplish in some cases because of complex tumor extension or possible vascular invasion.

Despite the introduction of multimodal treatment approaches the outcome of patients is still unfavorable. Overall survival rates (approximately 20% after 5 years) are impaired by the occurrence of local relapses or secondary distant metastases.

Angiosarcoma of the liver usually affects adults and is rarely seen in children. The rarity of this tumor in the pediatric population makes the diagnosis of angiosarcoma in patients younger than 21 years a difficult proposition. As part of the group of vascular hepatic tumors, this entity presents predominantly with an abdominal mass. However the whole spectrum of clinical appearances of hepatic vascular tumors might be observed including high-output cardiac failure and Kasabach-Merritt-Syndrome. Histologically, tumors display hyperchromatic epitheloid or spindle-shaped cells which contain mitotic activity. Cells are commonly positive for the endothelial marker CD31.

Distinguishing hepatic angiosarcoma from other hepatic vascular tumors might be difficult and requires open biopsy in cases of uncertainty. Because of the aggressive behavior, a radical surgical approach including liver transplantation is justified in this entity [68].

56.1.3 Malignant Rhabdoid Tumor of the Liver

Malignant rhabdoid tumors (MRT) of the liver are rare and associated with a poor prognosis. Histologically they show an epitheloid differentiation and express cytokeratin and vimentin. Recent reports suggest that germ line and acquired mutations of the INI1 gene are present in MRTs and this is associated with absence of immunostaining for INI1 in the tumor tissue. The prognosis of this tumor is poor, however, successful treatment results with combined chemotherapy (ICE and VDC) together with secondary complete resection have been reported [69].

56.1.4 Infantile Choriocarcinoma

This rare but highly aggressive malignancy arises from the trophoblastic cells of the placenta. It is regularly associated with anemia and hepatomegaly. Serum β[beta]-HCG levels are usually elevated and can be used for diagnostic workup as well as for follow up. Tumors are highly vascularized. Mortality is high because of a rapid tumor progression. Several cases of successful

treatment approaches have been reported, usually combining multimodal neoadjuvant chemotherapy and secondary complete resection [70, 71].

56.2 Benign Liver Tumors

56.2.1 Hemangioma

Hemangioma is the most common benign liver tumor of infancy and childhood; in over 80% of cases the diagnosis is made within the first 6 months of live. It occurs slightly more often in girls than in boys [72]. The exact incidence of liver hemangioma is difficult to judge since many tumors don't cause symptoms and are therefore not diagnosed. Also, many lesions do not require surgery or non-surgical treatment.

56.2.1.1 Pathology

Hemangioma may occur unifocally or multifocally within the liver. In accordance with the current classification of pediatric vascular tumors, liver hemangioma are sub-divided into lesions with or without spontaneous regression. The expression of Glucose Transporter Protein 1 (GLUT-1) allows differentiating between the two subgroups. The term "hemangioendothelioma of the liver" should not be longer used.

56.2.1.2 Clinical Presentation and Diagnostic Workup

In some cases the diagnosis is established prenatally. It is sometimes associated with a fetal hydrops. Liver hemangiomas are possibly associated with cutaneous hemangiomas. The leading post-natal symptom is a distended abdomen. A possibly life-threatening high output cardiac failure is present in up to 15% of cases. Without treatment this can lead to death in approximately 80% of cases. In 15–60% of cases hemangioma are detectable on other parts of the body, namely skin, pancreas, bones, and others (Fig. 56.6). Children are at risk of developing critical clinical conditions such as Kasabach-Merritt-Syndrome.

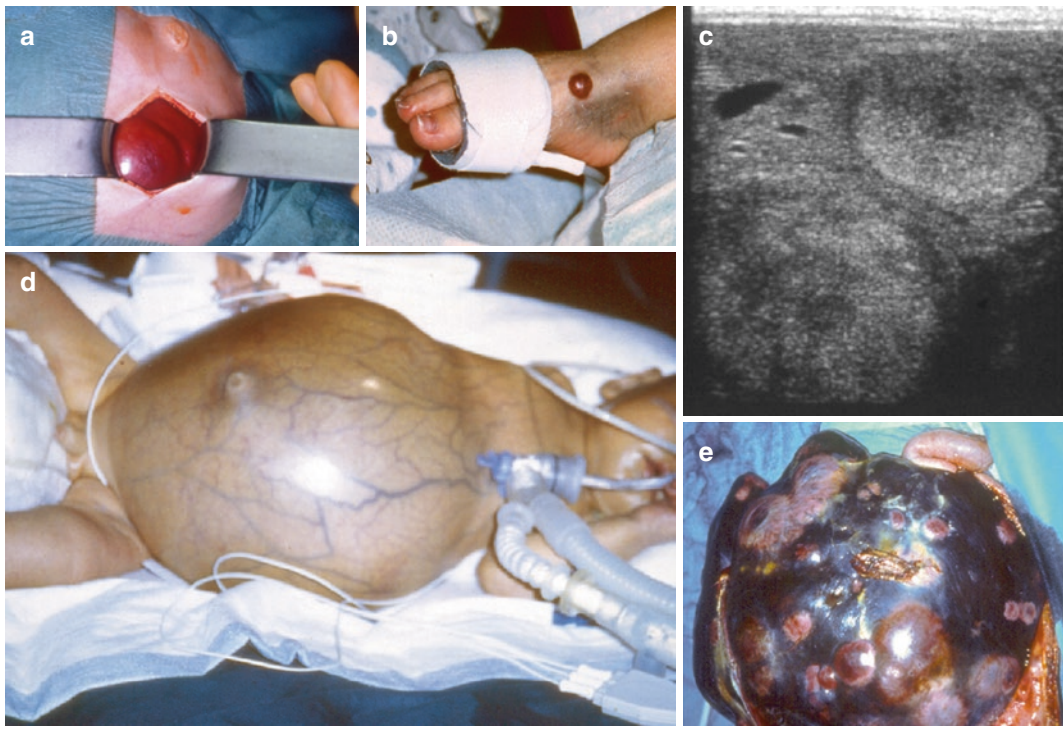

Fig. 56.6 Hemangiomatosis in a 6 month-old boy with multifocal involvement of liver segments. (**a**) Primary biopsy of a solid area. (**b**–**d**) Subsequent rapid tumor progress despite conservative treatment. (**e**) Intraoperative aspect during hepatectomy and liver transplantation (The child survived without evidence of disease)

Anaemia is present in over 50% of patients, approximately 20% develop hyperbilirubinaemia; elevation of serum transaminases can also occur. Furthermore, serum α[alpha]-fetoprotein can be increased making delineation of malignant epithelial liver tumors difficult.

Doppler sonography is the determining diagnostic tool regularly displaying hyperechogenic and increasingly perfused areas, an increased velocity within the hepatic artery (up to 100–200 cm/s), and a calibre change of the abdominal aorta at the celiac trunk-level [73]. Occasionally, the appearance might resemble solid nodules which should be clarified histologically. Regression is a regularly observed development in liver hemangioma. Indicators are size reduction, reduction of perfusion parameters, or calcification.

Computed tomography (CT) scan or Angio-Magnet Resonance Imaging (MRI) are important additional tools which have their relevance in the context of differential diagnoses. Angiography is mainly reserved for interventional treatment approaches.

56.2.1.3 Therapy

Depending on the clinical presentation, therapeutic options display a wide variation ranging from simple observation to liver transplantation.

Typical small asymptomatic nodules within the parenchyma can be observed since they are associated with a high probability for spontaneous regression. In contrast, symptomatic children require prompt treatment which often includes intensive care measures. Management of cardiac failure is hereby the initial therapeutic aim.

Medical treatment approaches for hepatic hemangioma include administration of high dose steroids (for example Prednisolon 2–5 mg/kg/day for 4 weeks), α[alpha]-interferon (1–33 mU/m^2/day), or β[beta]-blocker [74]. However, experiences concerning treatment of liver hemangioma in children using the latter are thus far limited. Success rates of steroids have been reported as being up to 25%; interferon therapy seems more successful (success rates 50–80%) [75].

Supra-selective embolization of liver hemangioma represents an alternative to surgery which can successfully be applied in bilobar processes as well. It has already been used in newborns or infants; experienced specialists use the approach via femoral vein, oval foramen, and descending aorta to the hepatic artery [76].

Surgery is indicated in unilobar lesions and preferably consists of anatomical resection. Ligation of the right or left hepatic artery represents an alternative to interventional approaches although there is no supra-selectivity and a higher risk for liver necrosis. Liver transplantation serves as ultima ratio in cases of multifocal hamangiomas with critical and/or progressive clinical course.

Today, a staged approach is commonly used as basis for the treatment of hepatic hemangioma; Fig. 56.7 displays a proposed system. The relevance of chemotherapy as well as irradiation is currently regarded as low since there are several other treatment options.

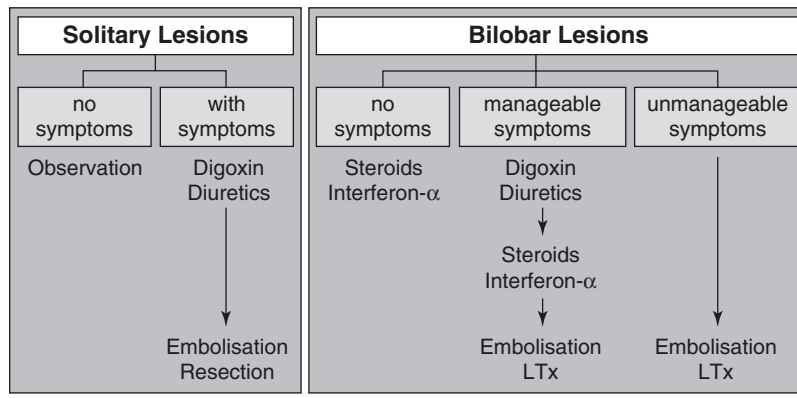

Fig. 56.7 Management of liver hemangioma

56.2.2 Hamartoma

Mesenchymal Hamartomas of the liver are the second most common benign liver tumor. In 85% of cases they are diagnosed in children below of 2 years of age; boys are more often affected than girls [77].

56.2.2.1 Pathology

The lesions are mostly cystic, might however also appear peduncular within the parenchyma. The cysts are lined with epithelium as well as endothelium. Whether they represent real tumors or rather hamartuous malformations is a still ongoing debate.

56.2.2.2 Clinical Presentation and Diagnostic

Leading symptom is a distended abdomen with a palpable mass in projection of the liver. Classical unspecific symptoms include vomiting, anaemia, or loss of appetite. If affected, newborns are often in critical clinical conditions displaying respiratory distress syndrome. In some cases when hydrops is present, the diagnosis of liver hamartoma can be established antenatally.

There are no typical tumor markers or other specific serum parameters. Differentiation of hamartoma from hemangioma or malignant epithelial tumors is possible using imaging analyses (Ultrasound, CT scan, MRI). Echogenic nodules and multicystic fluid-filled septated lesions are typical radiological findings in hepatic hamartoma [78].

56.2.2.3 Therapy

Surgical resection is the treatment of choice in hepatic hamartoma. Liver transplantation has to be considered in cases of bilobar affection because marsupilation and debulking are both associated with high rates of tumor recurrence.

Furthermore, there is a relevant risk of malignant transformation into undifferentiated embryonal sarcoma. In rare cases spontaneous regression has been observed following biopsy of the lesions [79].

56.2.2.4 Prognosis

Prognosis of hepatic hamartoma is excellent after complete resection. However, relevant intra- and postoperative complications have been described which must not be neglected [78].

56.2.3 Adenoma

Hepatic adenomas in children are rare. Associations with maternal intake of contraceptives or corticoids, but also with diabetes mellitus and disorders of glycogen metabolism have been observed. Cytologically, adenomas are hardly distinguishable from normal hepatocytes. The microscopic lobular architecture is lacking in adenomas.

These tumors sometimes cause upper abdominal pain and subsequent diagnostic workup reveals the mass within the liver. At ultrasound, adenomas are commonly isodens with sporadic inhomogeneous areas caused by haemorrhage. Definite diagnostic workup should be performed using CT scan and/or MRI. In some cases differentiation from focal nodular hyperplasia or highly differentiated hepatocellular carcinoma (HCC) is impossible and biopsy becomes necessary in order to achieve a definite diagnosis [80]. Because of relevant associated risks (intratumoral or intraabdominal haemorrhage, malignant transformation) complete resection of the tumor is recommended.

56.2.4 Focal Nodular Hyperplasia (FNH)

This tumor occurs in up to 3% of the adult population which makes it a quite common liver lesion. Only a small number of cases have been reported in children. The age maximum lies between 7 and 14 years. A correlation with intake of contraceptives has been discussed. However, the exact aetiology of these tumors is still unclear. FNH occur increasingly as secondary tumor after various malignant diseases [81, 82]. Diagnosis is often made by chance in the workup of other

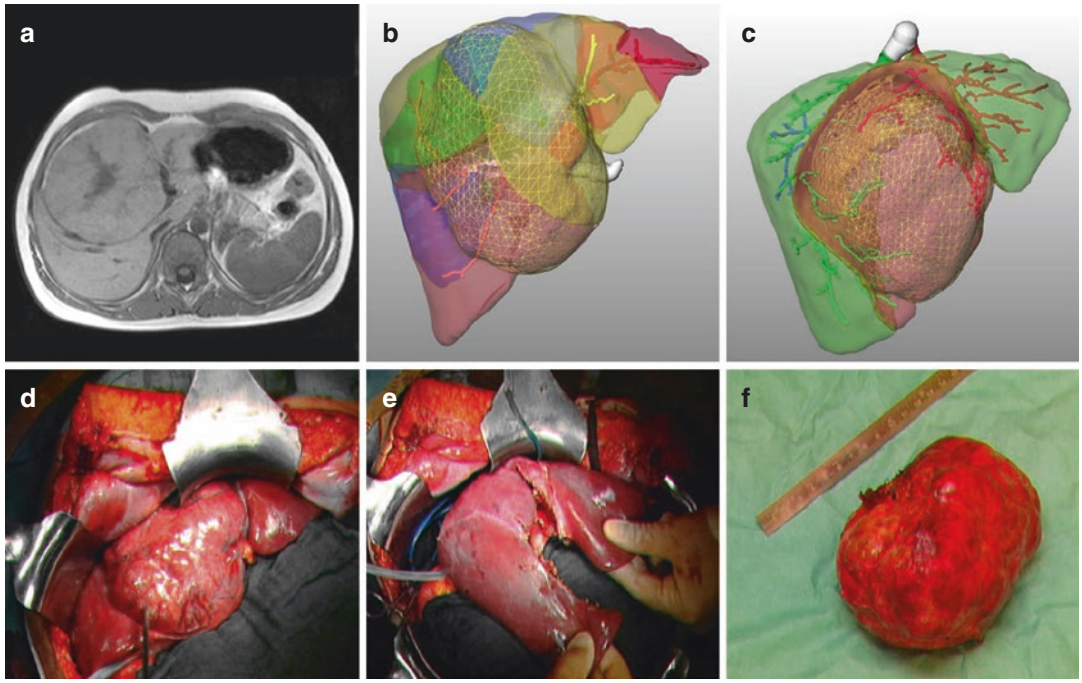

Fig. 56.8 Focal nodular hyperplasia (FNH) in a 12 year-old girl. (**a**) MRI scan showing the centrally located tumor. (**b**) 3D reconstruction of liver with portal venous segmentation and tumor. (**c**) Virtual simulation of central hepatectomy. (**d**) Intraoperative situs. (**e**) Intraoperative view after mesohepatectomy. (**f**) Resected specimen

pathologies. Morphologically, there is a central region of fibrosis, usually with vessels of increased diameter. Hepatocytes are cytologically unsuspicious; however, they don't display the typical lobular architecture of the liver.

Ultrasound plays a prominent role within the diagnostic workup. Hepatic scintigraphy (HIDA-scan) and MRI are important especially for excluding differential diagnoses. Most authors suggest the surgical resection of the lesions since simultaneous existence of HB/HCC has been described [83, 84] (Fig. 56.8). However, a wait-and-see-strategy has also been described [85].

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Neuroblastoma

57

Joshua N. Honeyman and Michael P. La Quaglia

Abstract

Neuroblastoma is a common solid tumor of infancy and childhood. It is uniquely characterized by a distinct natural history and prognosis in infants compared with older children. Whereas older children often experience rapidly progressive disease with a poor prognosis, many infants have indolent tumors that may exhibit only minimal progression over time or may even regress entirely. While the prognosis for infants with neuroblastoma is typically optimistic, patients still require multimodal therapy, ideally provided by institutions with expertise in the treatment of pediatric cancers.

Keywords

Neuroblastoma • Newborn • Staging • Surgical management • Outcomes

57.1 Introduction

Neuroblastoma is a common solid tumor of infancy and childhood. It is uniquely characterized by a distinct natural history and prognosis in infants compared with older children. Whereas older children often experience rapidly progressive disease with a poor prognosis, many infants have indolent tumors that may exhibit only minimal progression over time or may even regress entirely. While the prognosis for infants with neuroblastoma is typically optimistic, patients still require multimodal therapy, ideally provided by institutions with expertise in the treatment of pediatric cancers.

57.2 History

In 1864, Rudolf Virchow published a description of a patient with an abdominal glioma, providing the first account of what would eventually be known as neuroblastoma [1]. It was not until 1901, when William Pepper described a series of infants with large abdominal tumors that spread to the liver but spared bone [2], that the infantile phenotype of neuroblastoma was first identified; years later, these same patients would be defined as having stage 4S disease [3]. In 1907, Sir Robert

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_57

Hutchinson described a very different metastatic pattern for the same primary tumor—specifically, to the skull and orbits [4]. Three years later, James Homer Wright was the first to recognize the tumor as being of primitive neural cell origin, to describe the classic bone marrow involvement, and to use the term "neuroblastoma" [5]. The phenomenon of tumor maturation and differentiation, another significant component of the infantile presentation of neuroblastoma, was reported by Cushing and Wolbach in 1927 [6].

More recently, molecular aspects of neuroblastoma have been elucidated and correlated with clinical risk stratification of patients. In the 1950s, catecholamine metabolites were first identified as potential tumor markers [7]. Starting in the 1970s [8], a series of papers described the genetic and genomic aspects of neuroblastoma. In 1983, the N-*myc* oncogene was implicated in the pathogenesis of neuroblastoma [9], and since then, the amplification of N-*myc* has been found to be of significant prognostic importance. Therapeutically, the treatment of patients with neuroblastoma has been enhanced by molecular targeted treatments [10] and immunotherapy [11], which have been developed based on a greater understanding of the biochemical characteristics of neuroblastoma.

57.3 Epidemiology

Neuroblastoma is the most common pediatric extracranial solid tumor, accounting for 5% of all childhood cancers [12, 13]. While the median age at diagnosis is 2 years, 40% of cases occur in infants (age <12 months). In this age group, it is the single most common tumor overall, representing 25% of all cancers diagnosed in the first year of life [13, 14].

In the United States, the age-adjusted incidence of neuroblastoma in infants is 54.1 per million, compared with 7.3 cases per million children under age 20 [13]. During the period from 1974 to 1991, infants experienced a 3.1% average annual increase in incidence. The increase was higher in boys (4.1%) than in girls (2%).

The incidence of neuroblastoma in Europe is comparable, where 52.6 cases occur per million infants [15]. In addition, the incidence of neuroblastoma in infants increased from 35.4 cases per million in 1978 to 57.8 cases per million in 1997. The European data also demonstrate a slightly higher incidence in male infants than in female infants (54.6 vs. 50.5 cases per million).

A review of international registries suggests that the overall incidence of neuroblastoma is highest in affluent regions with predominantly white Caucasian populations, including the United States, Canada, Europe, Israel, Australia, and New Zealand. In the first year of life, the incidence ranges from 25 to 50 cases per million, representing 30% of all cases of neuroblastoma [16, 17]. A Japanese review of neuroblastoma occurring within the first month of life found an average incidence of 1 case per 210,000 live births [18].

Multiple studies have been undertaken to identify population risk factors for development of neuroblastoma, but there have been no clear causative or correlative factors identified. Areas of particular interest have included parental exposure to occupational and environmental toxins [19–24], but to date, no definitive associations have been determined. Patterns of community infections have also not correlated with neuroblastoma incidence [25].

In infants, several maternal factors have been identified that are associated with neuroblastoma in infancy, including intrapartum maternal anemia, neonatal respiratory distress, and 1-min Apgar score less than 7 [26]. Another review of birth records and cancer registries identified maternal hypertension and an age younger than 20 years to be associated with infant neuroblastoma [27]. In infants 6 months of age and younger, neuroblastoma was correlated with high birth weight, heavier maternal gestational weight gain, maternal hypertension, advanced maternal age, ultrasound, and respiratory distress. In contrast, risk of neuroblastoma in older infants correlated with low birth weight, but heavier maternal gestational weight was protective [28].

57.4 Molecular and Genetic Pathogenesis

The elucidation of genetic factors associated with neuroblastoma began with the identification of neuroblastoma pedigrees and the validation of inherited patterns of disease. A family history of the disease is present in about 1–2% of new cases [29–31], and siblings of index cases have a standardized incidence ratio of 9.7 [32]. While few pedigrees have been reported in the literature, the identification of these patient clusters first implicated a potentially heritable genetic component to the pathogenesis of neuroblastoma [29].

Additional observational data that demonstrate a genetic component of neuroblastoma include its occasional association with other congenital anomalies, both inherited and sporadic. A predisposition to neuroblastoma has been found with disorders of neural crest development, including congenital central hypoventilation syndrome [33], Hirschsprung disease [34, 35], and neurofibromatosis type 1 [36], as well as overgrowth syndromes such as Beckwith-Wiedemann [37]. Other associations have been described, including tuberous sclerosis, Friedrich ataxia, dermatomyositis, Soto syndrome, and cystic fibrosis.

In the 1970s, observations of genetic susceptibility led Knudson and Strong to propose a mutational model for neuroblastoma [31, 38] that expanded upon their previous work developing a two-hit model of tumorigenesis in retinoblastoma [39].

The molecular biology of neuroblastoma has been explored from many perspectives, from cytogenetics to genomics, genetics, and proteomics. Cytogenetic studies in particular have provided an early window into the underlying abnormalities in the function and organization of the neuroblastoma cell. DNA ploidy status of neuroblastic tumors is a significant predictor of outcome [40], particularly in infants [41]. Most aggressive, unfavorable tumors, as well as most neuroblastoma cell lines, are near-diploid or tetraploid, with genetic alterations in the form of amplifications, deletions, and translocations. In contrast, favorable tumors are typically hyperdiploid or tetraploid, with chromosomal duplications.

The most common genetic abnormality in primary neuroblastoma is a gain of genetic material from chromosome 17q [42–44], occurring in over half of tumors. This can occur via unbalanced 1;17 translocations, translocations involving other chromosomes, or the gain of a whole chromosome. While the gain of chromosome 17q in hyperdiploid tumors is associated with better overall prognosis, 17q gain has been associated with worse outcome [45, 46].

Another frequent genetic abnormality in neuroblastoma is deletion in chromosome 1p [8, 47]. Loss of heterozygosity (LOH) at 1p has been seen in over 25% of tumors, and the consistently deleted portion maps to 1p36.2–36.3 [48–50]. Although LOH at 1p has been found to correlate with features of high-risk disease [48, 51, 52], its independent prognostic utility is more relevant to event-free survival than to mortality.

Chromosomal abnormalities at 11q and 14q also occur in neuroblastoma. LOH at chromosome 11q is frequent, occurring in 30% of primary tumors [53, 54]. This chromosomal abnormality is associated with lower rates of N-*myc* amplification and may correlate with worse outcome in patients with non-N-*myc*–amplified tumors. Alterations of chromosome 14q are less common, occurring in approximately 25% of primary tumors [55]. Deletions in 14q have been correlated with LOH at 11q. LOH at 11q and 1p are independently associated with worse outcome [56], as are single-nucleotide polymorphisms at chromosome band 6p22 [57].

Neuroblastoma is closely associated with the amplification of the N-*myc* oncogene, which is normally expressed in the developing nervous system and other tissues. It encodes a nuclear phosphoprotein that acts as a transcriptional regulator. N-*myc*, which is located on the short arm of chromosome 2 (2p24.1), was first cloned in 1983 from a neuroblastoma cell line [9]. Amplification can reach levels of 50–400 copies [58], and involves a region of approximately 130 kilobases [59].

The consequences of N-*myc* amplification have been demonstrated in both cell lines [60, 61]

and animal models [62], where the overexpression of *myc* is sufficient for malignant transformation. However, in tumors without N-*myc* amplification, the role of this oncogene has not been fully characterized.

The clinical significance of N-*myc* amplification in neuroblastoma has been clarified over the past three decades. First associated with advanced stage in untreated primary tumors [63], N-*myc* amplification was subsequently associated with rapid disease progression and worse overall prognosis [64]. As a result of its prognostic significance, N-*myc* amplification is included in all risk stratification schemes for neuroblastoma patients.

Neurotrophin signaling pathways, which play a role in the neuronal development, have also been implicated in the pathogenesis of neuroblastoma. The *TRK* gene family encodes receptors for neurotrophin, or nerve growth factor. Three specific high-affinity neurotrophin receptor genes have been identified (*TRKA*, *TRKB*, and *TRKC*), each with its own pattern of association. TrkA is the high-affinity receptor for nerve growth factor, which drives the differentiation of neural cells. *TRKA* expression is inversely related to disease stage and N-*myc* amplification status. Thus, high *TRKA* expression is associated with favorable neuroblastomas [65, 66]. TrkB binds brain-derived neurotrophic factor and neurotrophin-4, promoting cell growth and survival. In contrast to *TRKA*, *TRKB* expression is correlated with advanced disease stage and N-*myc* amplification status [67]. TrkC binds neurotrophin-3. *TRKC* expression is strongly correlated with *TRKA* expression [68] and, thus, is also associated with a favorable prognosis [69, 70].

57.5 Histopathology

Neuroblastic tumors originate from the neural crest–derived sympathetic nervous system and adrenal gland. Anatomically, they can arise anywhere along the sympathetic ganglia or in the adrenal medulla. The two predominant cell types identified in neuroblastic tumors are neuroblasts, which are primitive neural cells that are typically precursors to neurons and glia, and Schwann cells, which form the neuronal stroma. In the characteristic "rosette" structure, clearly visible tumor nuclei surround the fibrillary cytoplasm. (Fig. 57.1) The relative distribution of these cells within a single tumor is of significant prognostic importance and is a component of the classification systems described below.

Neuroblastoma is one of a spectrum of peripheral neuroblastic tumors that also includes ganglioneuroma and ganglioneuroblastoma, and multiple histopathologic classification schemes have been developed to differentiate these tumors. In 1984, Shimada and colleagues proposed an age-based tumor classification system for neuroblastoma [71]. The five features evaluated in the Shimada classification system were the degree of

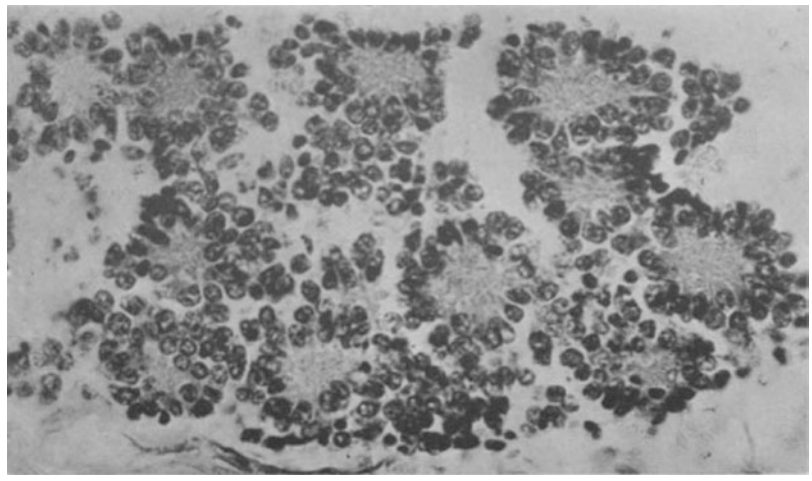

Fig. 57.1 Neuroblastoma histology featuring classic 'rosettes' from James Homer Wright's 1910 review [5]. Image ©1910 Rockefeller University Press. Originally published in J Exp Med. 12:556–561. Used with permission

neuroblast differentiation, the extent of Schwannian stromal development, the mitosis-karyorrhexis index (MKI), the presence or absence of a nodular pattern, and the patient's age at diagnosis. The MKI is determined by counting the number of cells in mitosis and in karyorrhexis. The latter cells demonstrate condensed and fragmented nuclear material with condensed and eosinophilic cytoplasm.

Since 1994, the International Neuroblastoma Pathology Committee (INPC) has standardized the terminology and diagnostic criteria for peripheral neuroblastic tumors, adopting a modified Shimada classification system [72, 73]. The INPC system for neuroblastic tumors includes four pathologic categories: neuroblastoma; ganglioneuroblastoma, intermixed; ganglioneuroma; and ganglioneuroblastoma, nodular. Tumors are then subclassified as either favorable or unfavorable.

Neuroblastoma is defined as Schwannian stroma-poor and is categorized under three specific subtypes: differentiating, poorly differentiated, and undifferentiated. Differentiating neuroblastoma contains neuroblasts with abundant neutrophil and 5% or more of the cells exhibiting differentiation. Poorly differentiated neuroblastoma contains neuroblastic cells with a background of neutrophils. Undifferentiated neuroblastoma is a rare subtype containing undifferentiated neuroblastic cells; these tumors often require additional testing beyond histopathologic analysis to confirm the diagnosis.

Ganglioneuroblastoma is classified as intermixed or nodular. The intermixed tumors are Schwannian stroma-rich and feature incomplete neuronal maturation with foci of neuroblastic cells in varying degrees of differentiation. Nodular tumors contain macroscopic, hemorrhagic neuroblastomatous nodules that coincide with a background of ganglioneuroma or ganglioneuroblastoma, intermixed.

Ganglioneuroma is a Schwannian stroma-dominant tumor with two subtypes: maturing and mature. These subtypes are distinguished based on the degree of differentiation of the ganglion cells present within the tumor.

Beyond defining clinically significant pathologic groupings, the purpose of the INPC system is to determine prognostically meaningful groups. Table 57.1 shows the favorable and unfavorable prognostic groups for neuroblastoma, as described by both the original Shimada system and the INPC classification. Ganglioneuroblastoma, intermixed, as well as ganglioneuroma are considered favorable histologies, regardless of the patient's age. Ganglioneuroblastoma, nodular, is stratified based on the classification of the tumor's nodular component.

The significance of age group in both the original Shimada classification and the INPC system underscores the fundamentally different biology observed in infants with neuroblastoma compared with older children.

Table 57.1 Prognosis based on histopathologic grouping [72]

Prognostic group	Age group (years)	INPC	Shimada (original)
Favorable	<1.5	Poorly differentiated or differentiating and low or intermediate MKI tumor	Stroma-poor; favorable
	1.5–5	Differentiating and low MKI tumor	Stroma-poor; favorable
Unfavorable	<1.5	Undifferentiated tumor	Unfavorable
		High MKI tumor	Unfavorable
	1.5–5	Undifferentiated or poorly differentiated tumor	Unfavorable
		Intermediate or high MKI tumor	Unfavorable
	≥5	All tumors	Unfavorable

From Shimada H, Ambros IM, Dehner LP, et al. The International Neuroblastoma Pathology Classification (the Shimada system). *Cancer* 1999; 86(3):364–372. Used with permission
MKI mitosis-karyorrhexis index

57.6 Staging and Risk Grouping

Since the mid-twentieth century, multiple staging systems have been developed to provide a means of clinically grouping and stratifying neuroblastoma patients based on their overall risk. These systems have been used to guide treatment and to monitor patients enrolled in clinical trials. The effort to consolidate the disparate staging systems into an internationally accepted prognostic staging system resulted in the development of the International Neuroblastoma Staging System (INSS) in 1988 [74].

The INSS was most recently revised in 1993. The major revisions included a redefinition of the midline (the vertebral column), a clarification of inclusion criteria for stage 4S disease (upper limit of 10% bone marrow involvement and age <1 year), and a general recommendation for the use of metaiodobenzylguanidine (MIBG) scintigraphy scanning to evaluate the extent of disease [75] (Table 57.2).

A commonly cited limitation of the INSS classification system is its reliance on intraoperative findings. During the initial evaluation of a patient, particularly in the setting of clinical trials, it became clear that a new staging system that relied on preoperative findings was needed. The International Neuroblastoma Risk Group (INRG) developed its own pretreatment risk classification system based on a series of image-defined risk factors [76] (Table 57.3).

Table 57.2 International Neuroblastoma Staging System [75]

Stage	Description
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumor infiltrating across the midline,[b] with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow[a] (limited to infants <1 year of age)

From Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the International Criteria for Neuroblastoma Diagnosis, Staging, and Response to Treatment. J Clin Oncol. 1993; 11(8): 1466–1477. Used with permission

[a]Marrow involvement in stage 4S should be minimal, ie, <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The MIBG scan (if performed) should be negative in the marrow

[b]The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column

Table 57.3 International Neuroblastoma Risk Group Staging System [76]

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

From Monclair T. Brodeur GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. J Clin Oncol. 2009; 27(2):298–303. Used with permission

As an adjunct to staging systems, risk groupings provide additional guidance for treatment planning. Different risk stratification systems take into account not only the INSS stage, but also the underlying biology and histopathologic characteristics of the tumor.

The Children's Oncology Group has established the most widely accepted risk groupings in North America. It stratifies patients into high-, intermediate-, and low-risk groups based on INSS stage, age, N-*myc* amplification status, INPC category, and DNA ploidy. This risk stratification system is used for Children's Oncology Group trials [77] (Table 57.4).

In 2009, the INRG also developed and published a risk stratification system based on their preoperative staging system [78] (Table 57.5).

Neuroblastoma in infants has two distinct personalities. The first, which is frequently associated with stages 3 and 4 and exhibits N-*myc* amplification, closely resembles the disease in older children and is characterized by aggressive growth and metastatic spread. The other, classified as stage 4S, has a more indolent biology and is characterized by spontaneous regression and optimistic prognosis with even minimal therapy [16]. Infants with disseminated disease who do not meet all the criteria for stage 4S disease are necessarily classified as having stage 4 disease.

The metastatic distribution for stage 4S disease includes the liver, bone marrow, skin, and lymph nodes. Aspirates of the bone marrow must have <10% malignant cells. The natural history of 4S disease includes complete maturation and regression, even in the setting of advanced disease [16, 79, 80]. Factors associated with spontaneous regression in stage 4S disease include triploidy, lack of N-*myc* amplification, and no LOH. Patients with N-*myc*–amplified tumors were found to have worse event-free survival than patients with non–N-*myc*-amplified tumors [81]. Moreover, patients with non–N-*myc*-amplified tumors have been shown to have a favorable prognosis, even in the setting of reduced systemic treatment [82, 83].

However, there is also a subgroup of patients with stage 4S disease who have rapidly progressive intra-abdominal disease. Such infants are at an increased risk of respiratory compromise and disseminated intravascular coagulation, so a more

Table 57.4 Children's Oncology Group Neuroblastoma Risk Grouping [77]

INSS stage	Age (years)	N-*myc* status	INPC category	DNA ploidy	Risk group
1	0–21	Any	Any	Any	Low
2a/b	<1 year	Any	Any	Any	Low
	1–21	Nonamplified	Any	—	Low
	1–21	Amplified	Favorable	—	Low
	1–21	Amplified	Unfavorable	—	Low
3	<1	Nonamplified	Any	Any	Intermediate
	<1	Amplified	Any	Any	High
	1–21	Nonamplified	Favorable	—	Intermediate
	1–21	Nonamplified	Unfavorable	—	High
	1–21	Amplified	Any	—	High
4	<1.5	Nonamplified	Any	Any	Intermediate
	<1	Amplified	Any	Any	High
	1.5–21	Any	Any	—	High
4S	<1	Nonamplified	Favorable	>1	Low
	<1	Nonamplified	Any	1	Intermediate
	<1	Nonamplified	Unfavorable	Any	Intermediate
	<1	Amplified	Any	Any	High

From *Neuroblastoma treatment (PDQ)*. Bethesda, MD: National Cancer Institute; National Institutes of Health. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/Page3#Section_14. Accessed February 20, 2012

Table 57.5 International Neuroblastoma Risk Group (INRG) Consensus Pretreatment Classification Schema [78]

INRG stage	Age (months)	Histologic category	Grade of tumor differentiation	N-*myc* status	11q aberration	DNA ploidy	Pretreatment risk group
L1/L2		GN maturing; GNB intermixed					(A) Very low
L1		Any except above		NA			(B) Very low
				Amp			(K) High
L2	<18	Any except above		NA	No		(D) Low
					Yes		(G) Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No		(E) Low
					Yes		(H) Intermediate
			Poorly differentiated or undifferentiated				
				Amp			(N) High
M	<18					Hyperdiploid	(F) Low
	<12					Diploid	(I) Intermediate
	12–18					Diploid	(J) Intermediate
	<18						(O) High
	≥18						(P) High
MS	<18			NA	No		(C) Very low
					Yes		(Q) High
				Amp			(R) High

From Cohn SL, Pearson ADJ, London WB, et al. The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report. J Clin Oncol. 2009;27(2):289–297

GN ganglioneuroma, *GNB* ganglioneuroblastoma, *Amp* amplified, *NA* not amplified

aggressive chemotherapeutic treatment strategy may be necessary to ameliorate this risk [16].

Neonates diagnosed with neuroblastoma generally have the same favorable prognosis as older infants [79, 84]. However, there is some evidence that patients younger than 2 months may have a worse prognosis and that patients older than 6 months may require more aggressive therapy [85].

57.7 Fetal Neuroblastoma

Due to the increased use of prenatal ultrasound, more infants with neuroblastoma are receiving the diagnosis prenatally. In one series from the United Kingdom Children's Cancer Study Group, 15% of patients (5/33) were diagnosed based on prenatal ultrasound [79]. In a study of the Italian Neuroblastoma Registry, 20% of newborns (27/134) were diagnosed prenatally [84].

A multi-institutional series of fetal neuroblastoma suggested expectant management with serial ultrasounds for uncomplicated pregnancies [86]. These infants typically have a favorable prognosis based on early-stage and low-risk molecular classification [87]. Surgery is typically curative, although many investigators propose a trial of observation alone in carefully selected patients [87–89].

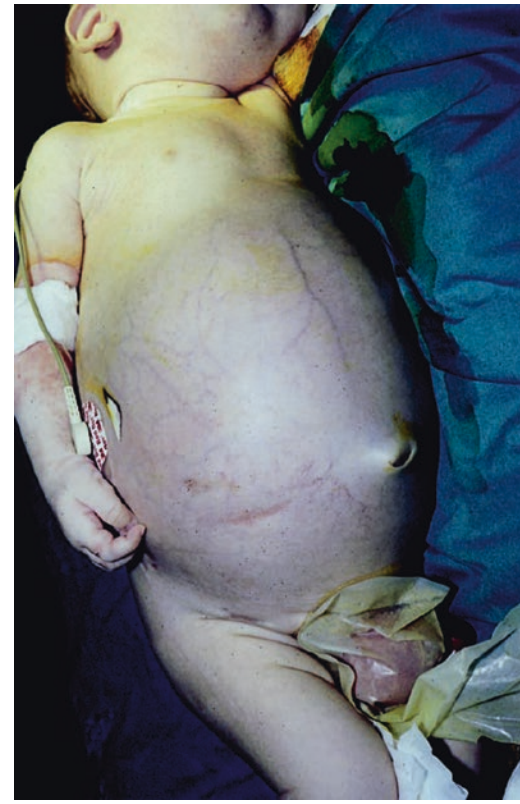

Fig. 57.2 Infant with massive liver involvement from stage 4S neuroblastoma [122]. Image courtesy of Brian H. Kushner, MD, Memorial Sloan-Kettering Cancer Center, New York, NY. ©2004 Society of Nuclear Medicine. Originally published in J Nucl Med. 2004 Jul;45(7):1172–88

57.8 Clinical Presentation

The clinical presentation of neuroblastoma is dictated by a series of factors, including the location of the primary tumor, the burden of metastatic disease, the age of the patient, and the metabolic activity of the tumor. A neuroblastic tumor can arise from anywhere within the sympathetic nervous system and the adrenal medulla. The specific location of the tumor may influence the timing of presentation and the local symptoms present at diagnosis. The metastatic burden, the age of the patient, and the metabolic activity of the tumor can also affect the clinical appearance.

The most common site for primary neuroblastoma is the abdomen. Three-quarters of neuroblastomas occur in the abdomen, the vast majority of which arise from within the adrenal gland. Of all tumors diagnosed within the first month of life, 90% are adrenal in origin [89]. Patients with these tumors can present with abdominal pain, abdominal distention, and bowel or urinary dysfunction. A large abdominal mass in infants more often represents extensive hepatic metastatic disease than a large primary tumor. These large masses can cause compressive symptoms, leading to respiratory distress and requiring emergency surgical resection. (Fig. 57.2).

After the abdomen, the posterior mediastinum is the second most common site of primary neuroblastoma. Infants with these tumors can be symptomatic at presentation, or in some infants, these tumors are found incidentally on chest radiographs

[90]. Upper mediastinal and cervical tumors can arise in patients with Horner's syndrome. Because of their low risk of metastasis, cervical tumors are associated with favorable prognosis [91]. However, given their location, complete surgical resection of locoregional disease may be difficult. Symptoms associated with these tumors may include Horner's syndrome.

Neuroblastoma can also arise in the pelvis, most commonly from the organ of Zuckerkandl. Infants with these tumors may present with a lower midline mass or a mass on rectal examination. Symptoms may include bowel or bladder dysfunction, pain, or weakness [92].

Metastatic tumors in infants are often found in the liver, bone, and subcutaneous tissue. Characteristically, subcutaneous metastases often have a blue color, leading to their description as "blueberry muffin" lesions. Bony orbital metastases can present with periorbital ecchymoses and proptosis. Bone marrow involvement can result in anemia. Because of the growth pattern of neuroblastic tumors along radicular nerves, tumors can invade the epidural space. Spinal disease may present with lower-extremity weakness and pain, as well as cord compression.

Infants may also present with paraneoplastic syndromes. Neuroblastomas often secrete catecholamines, but these are typically precursor molecules that are not adrenergically active. Catecholamine release can, however, cause hypertension and tachycardia. Neuroblastomas have also been reported to secrete vasoactive intestinal peptide, which can trigger chronic watery diarrhea.

Another paraneoplastic disorder associated with neuroblastoma is opsomyoclonus ("dancing eyes, dancing feet"). Symptoms of opsomyoclonus include truncal ataxia and rapid irregular eye movements.

57.9 Diagnosis and Initial Evaluation

A detailed history and physical examination are essential in the preliminary assessment of a patient with neuroblastoma. The history can provide information about the extent of disease, potential paraneoplastic disorders, and comorbid conditions. The physical examination should include a thorough assessment of the primary tumor site, whether abdominopelvic, mediastinal, or cervical. Evaluation of palpable lymph node basins, liver, orbits, and skull is essential when examining a patient who may have neuroblastoma. In addition, a complete neurologic examination should be performed to rule out any tumor involvement of the spine.

The initial evaluation of neuroblastoma should also include a complete laboratory and radiologic workup. The necessary studies will vary based on the individual patient, but certain studies are necessary for all patients to ensure proper clinical staging and risk stratification. Furthermore, since some patients will undergo aggressive chemotherapeutic and surgical interventions, it is important to obtain baseline metabolic data.

In addition to basic laboratory investigations, including complete blood count, metabolic panel, and coagulation studies, blood tests for lactate dehydrogenase, ferritin, neuron-specific enolase, and ganglioside GD2 should also be performed because of the potential prognostic significance of these serum markers.

Since most neuroblastomas maintain the necessary enzymes for catecholamine synthesis, metabolites of this pathway are excreted in the urine, and they can be readily detected. Urinary levels of homovanillic acid and vanillylmandelic acid are elevated in the majority of neuroblastoma cases. Thus, these levels can assist in the initial diagnosis of neuroblastic tumors, as well as provide information about the metabolic activity of the tumor. Urinary homovanillic acid and vanillylmandelic acid levels have also been correlated with the degree of tumor differentiation and may be used to assess treatment response and monitor patients for recurrence.

Radiologic assessment of neuroblastoma serves three purposes: confirmation of diagnosis, establishment of primary disease site, and evaluation of metastatic disease. Although the basic imaging evaluation typically includes obtaining plain radiographs of the chest and abdomen, cross-sectional imaging is the most important modality for surgical planning.

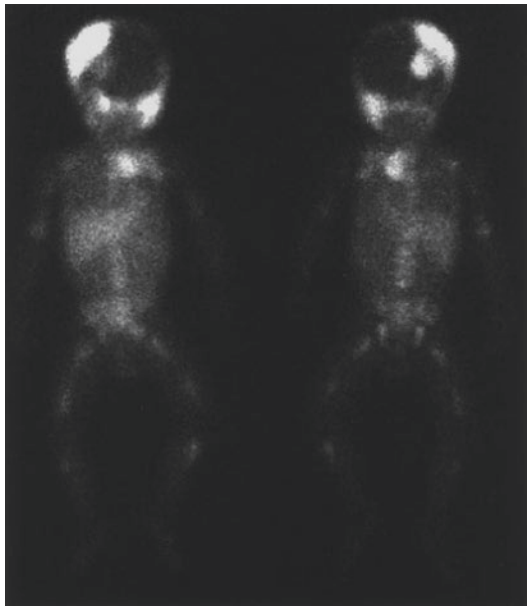

Fig. 57.3 MIBG scan of an infant with neuroblastoma involving the posterior mediastinum, bone marrow, right parietal skull, and left sphenoid [122]. Image courtesy of Brian H. Kushner, MD, Memorial Sloan-Kettering Cancer Center, New York, NY. ©2004 Society of Nuclear Medicine. Originally published in J Nucl Med. 2004 Jul;45(7):1172–88

Metaiodobenzylguanidine (MIBG) scintigraphy is an increasingly important component of the radiologic evaluation of neuroblastic tumors. MIBG is a radiolabeled structural homolog of noradrenaline that shows preferential uptake in adrenergic tumors such as neuroblastomas and pheochromocytomas. Iodine-123–labeled MIBG (^{123}I-MIBG) is currently the most sensitive and specific scintigraphic method for evaluating metastatic disease, so its routine use in the evaluation of new patients with neuroblastoma is recommended. In patients with MIBG-negative neuroblastic tumors, who represent approximately 10% of new patients, a bone scan using technetium-99m (^{99m}Tc)-diphosphonate can be used to evaluate for osteolytic lesions. (Fig. 57.3).

Bilateral bone marrow aspiration is another important component of the initial staging of neuroblastoma. While standard histologic assessment is essential, the addition of immunohistochemical and cytologic techniques provides greater sensitivity and can offer additional molecular insights that will aid in the initial evaluation of the patient. Histologic evaluation may reveal either classic rosettes, composed of clumps of tumor cells, or individual tumor cells.

Multiple immunohistochemical markers are useful in the diagnosis of neuroblastoma [73]. Markers that are typically positive in neuroblastoma include neuron-specific enolase, chromogranin A, synaptophysin, tyrosine hydroxylase, protein gene product 9.5, ganglioside GD2, and NB84. Markers that are typically negative in neuroblastoma include actin, desmin, low-molecular-weight cytokeratin, leukocyte common antigen, and vimentin.

57.10 Surgical Management

Surgery plays an essential role in the diagnosis, staging, and therapy of neuroblastoma. For patients with suspected neuroblastoma, initial tissue diagnosis is crucial for accurate tumor classification and molecular risk stratification. Except in those patients in whom the primary tumor is small and more easily resected, an incisional biopsy is usually the first step in the surgical management of neuroblastoma.

The primary goal of the initial biopsy is to obtain an adequate amount of high-quality tissue for histopathologic, molecular, and genetic analysis. Minimizing the invasiveness of this procedure is essential to shorten the time to chemotherapy initiation. To facilitate future surgery, the incision should be oriented along the planned incision for the definitive resection. Also, in anticipation of systemic therapy, vascular access for chemotherapy can be placed at the time of initial biopsy.

Subsequent surgical management of infants with neuroblastoma depends on clinical presentation. The most significant factor for achieving local tumor control is resection of the primary tumor along with removal of any involved regional lymph nodes. Patients with low-risk, localized neuroblastoma can be treated effectively with surgery alone [93], achieving survival rates as high as 94–98% [94, 95].

Although gross total resection has been correlated with outcome in neuroblastoma [96–98], prognosis is most dependent on the underlying biology of the tumor, not the extent of resection [99]. Resection of the primary tumor in patients with metastatic disease may improve outcome if the metastases can also be controlled [100], although, again, the underlying biology of the metastatic tumors is more important to overall survival than resection status [101]. In low risk infants, complete resection is not always necessary [102], and patients with stage 4S tumors may not require resection at all [103].

Patients with high risk neuroblastoma may benefit from neoadjuvant chemotherapy, since resection of the primary tumor prior to chemotherapy is associated with increased rates of treatment-related complications [104], and neoadjuvant chemotherapy increases resection rates for the primary tumor [105].

Indicators of resectability in abdominal disease include tumors that do not cross the midline and tumors that cross the midline without vessel encasement. Aggressive surgical intervention in patients without these indicators has not been shown to improve outcomes. These patients warrant adjuvant therapies prior to resection, which may allow for downstaging of the primary tumor.

As mentioned above, the INRG staging system uses image-defined surgical risk factors to classify patients [76]. While vessel encasement is commonly encountered during attempted resection, and the INRG considers vessel encasement to be a risk factor for worse outcome, some series have demonstrated that visceral vessel encasement does not preclude gross total resection [106].

57.11 Chemotherapy

Chemotherapy plays a significant role in the management of disseminated neuroblastoma, as well as of high- and intermediate-risk disease. Multiagent therapy is the mainstay of treatment. In the neoadjuvant setting, chemotherapy is particularly useful to decrease the total tumor burden. For patients with disease that is initially deemed unresectable, preoperative chemotherapy can increase the possibility of gross total resection.

In patients with high-risk neuroblastoma, systemic treatment has trended toward the use of higher dose intensities. In these patients, myeloablative chemotherapy has been shown to improve outcomes [107, 108]. However, even in these patients, efforts have been made to reduce the total exposure to chemotherapy [109]. Infants with advanced-stage disease have also been found to benefit from a reduction or elimination of chemotherapy [110].

In patients with intermediate- and low-risk neuroblastoma, efforts have been made to reduce total exposure to chemotherapy, because these patients generally have good overall survival and because of the increased awareness of the long-term toxicities of chemotherapy. Many of these patients can be cured with surgery alone. Reduced doses and duration of chemotherapy did not have a detrimental effect in patients with intermediate-risk neuroblastoma without N-*myc* amplification [111].

The most common chemotherapeutic regimen for patients with intermediate-risk disease is a combination of cisplatin, cyclophosphamide, doxorubicin, and etoposide. In patients with high-risk disease, systemic treatment usually requires a different set of chemotherapeutic agents, including cyclophosphamide, ifosfamide, cisplatin, vincristine, doxorubicin, melphalan, etoposide, teniposide, and topotecan.

57.12 Radiation Therapy

Neuroblastoma is a radiosensitive tumor, and while external-beam radiation therapy is not curative, it can help control local disease. In patients with high-risk neuroblastoma, radiation therapy has been shown to reduce the risk of local relapse with doses ranging from 15 to 30 Gy, delivered in 1.5- to 3.0-Gy fractions, depending on tumor size, patient age, and tumor location.

Radiation therapy also has applications in the acute setting, such as in infants with massive hepatic disease. While usually not indicated in stage 4S neuroblastoma, radiation therapy may be used on an emergency basis for patients suffering

respiratory distress from large hepatic metastases who did not respond to initial chemotherapy. In the emergency setting, radiation therapy may also play a role in controlling tumors that extend into the spinal canal. While it may provide rapid control of expanding tumors when combined with laminectomy, radiation therapy also increases the risk of vertebral damage and growth arrest.

In appropriately equipped centers, intraoperative radiation therapy is an important treatment option in patients with high-risk, locally recurrent, or persistent neuroblastoma [112–114]. This technique allows for the delivery of higher doses of radiation to the tumor bed while sparing the surrounding normal tissues.

External-beam radiation therapy is also a powerful tool in the palliation of end-stage disease, particularly in providing relief from painful bone metastases.

57.13 Other Therapies

Immunomodulatory agents and immunotherapeutics have promising roles in the future of neuroblastoma therapy. The tumor-associated disialoganglioside GD2 is found on the surface of most neuroblastoma cells, and monoclonal antibodies against GD2 have shown promise in the treatment of neuroblastoma. Targeted monoclonal antibody therapies can exploit the intrinsic pathways of antibody-dependent cellular cytotoxicity, or they can be conjugated to toxins or to diagnostic markers, such as radionuclides (e.g., ^{131}I). Treatment of high-risk neuroblastoma with a combination of granulocyte macrophage–colony stimulating factor, interleukin-2, and an anti-GD2 antibody has been shown to be effective in early clinical trials [115].

MIBG provides another means for the targeted delivery of beta-emitting radionuclides to neuroblastoma cells. The tissue specificity of MIBG increases tumor exposure while reducing overall systemic toxicity. ^{131}I-MIBG has been used as an adjuvant treatment in combination with chemotherapy and bone marrow transplantation for high-risk neuroblastoma.

Retinoic acid derivatives, specifically 13-*cis*-retinoic acid, have been shown to slow the growth of high-risk neuroblastoma, induce differentiation, and improve survival when used in combination with myeloablative chemotherapy and radiation [107, 108].

57.14 Screening

The observation that mortality varies inversely with patient age, combined with the diagnostic utility and noninvasive nature of urine metanephrine testing, prompted the introduction of population-wide infant screening protocols for neuroblastoma. However, population screening for neuroblastoma in infants remains a controversial issue.

In Japan, a nationwide screening protocol for neuroblastoma was introduced in 1984, which required the testing of urinary vanillylmandelic acid levels in all 5-month-old infants. While screening did have a marginally positive effect on survival, there was a concomitant increase in the overall incidence of neuroblastoma [116]. The additional cases that were detected included a number of low-grade tumors that would not otherwise have become clinically apparent. Consequently, the inclusion of these additional low-grade tumors improved the calculated survival rates. The Japanese screening program was halted in 2003 pending further review of the data.

An aggressive screening protocol in Quebec, Canada, in which all children born during a 5-year period were offered screening for urine metanephrines at 3 weeks and 6 months of age, did not result in a reduction of mortality due to neuroblastoma [117]. A similar screening protocol in Germany offered urine screening to children at 1 year of age. Again, there was no demonstrable mortality benefit [118].

Currently, there are no widely accepted methods of population-based screening of infants for neuroblastoma. For such a screening protocol to be successful, it must yield increases in overall survival while avoiding the overdiagnosis of tumors that are not clinically significant. Advances

in our understanding of the molecular biology of neuroblastoma may provide insights that lead to better screening methods.

57.15 Survival and Late Effects

Survival trends in infant populations with neuroblastoma are typically positive. In Europe, 5-year overall survival increased from 37% between 1978 and 1982 to 66% for the period between 1993 to 1997 [15]. This far outpaced the rates of survival in older children, who experienced an increase from 21 to 45% during the same period.

In results published by the Childhood Cancer Survivor Study [119], the cumulative incidence of chronic health conditions in survivors of neuroblastoma was 41.4% at 20-year follow-up. Neurologic symptoms were most common and included weakness, sensory deficits, and pain. In the same study population, the cumulative incidence of secondary malignancies was 7% at 30 years after the original neuroblastoma diagnosis [119].

While patients with stage 4S disease typically have good oncologic outcomes, they remain at an increased risk of long-term sequelae. In a single-center study, 20% of patients had long-term disease- or treatment-related effects [120].

In patients with advanced-stage neuroblastoma (stages 3 and 4), late complications have been found in up to 95% of childhood survivors [121]. Complications ranged from hearing loss, primary hypothyroidism, ovarian failure, musculoskeletal abnormalities, and pulmonary abnormalities.

Because of these health-related late complications of neuroblastoma and its treatment, survivors may also be at risk for social and economic sequelae. Long-term follow-up of patients with neuroblastoma is essential to ensure good oncologic outcomes, as well as to address any long-term complications.

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Neonatal Soft Tissue Sarcomas

58

Timothy N. Rogers and Helen L. Rees

Abstract

Soft tissue lesions in neonates are relatively common. They cause concern for parents and can also present diagnostic difficulties for health professionals. Fortunately most are benign and usually vascular or developmental in origin. However, a small number of these lesions are found to be malignant and can present significant challenges in terms of management and may carry a poor prognosis. Therefore it is important to develop an approach to the diagnosis and management of all soft tissue lesions that will allow such tumours to be distinguished from the more common benign lesions.

Keywords

Neonatal soft tissue sarcoma • Classification • Surgical management • Outcomes

58.1 Introduction

Soft tissue lesions in neonates are relatively common. They cause concern for parents and can also present diagnostic difficulties for health professionals. Fortunately most are benign and usually vascular or developmental in origin [1]. However, a small number of these lesions are found to be malignant and can present significant challenges in terms of management and may carry a poor prognosis. Therefore it is important to develop an approach to the diagnosis and management of all soft tissue lesions that will allow such tumours to be distinguished from the more common benign lesions.

Soft tissue sarcomas are a heterogeneous group of tumours showing different pathways of differentiation depending on the putative cell of origin. They mainly derive from muscle, connective and supportive tissues, vascular and adipose tissues and can therefore arise at almost any anatomical site including superficial and deep soft tissues and within internal organs

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_58

such as kidney and liver. By far the commonest subtype in children is rhabdomyosarcoma (RMS) with the remaining subtypes being grouped together as "non-rhabdomyosarcoma" (non-RMS) tumours, more commonly presenting in the adult population. RMS are generally categorised according to prognosis and site whilst the non-RMS tumours are classified by tissue of origin.

There are a number of issues which must be considered when a diagnosis of soft tissue sarcoma is made in a neonate. Firstly some malignant soft tissue tumours will behave differently in the neonate compared with their natural history in older children or adults, despite being histologically identical. In addition, delivery of multimodality therapies to neonates offers unique challenges and therefore it is important to consider the management of these tumours in the context of the age of the patient rather than just the histological diagnosis.

In this chapter we will include discussion around the epidemiology, histopathology, biology and clinical aspects of neonatal soft tissue sarcomas as well as appropriate management of this rare group of tumours. As well as those tumours historically described within the soft tissue sarcoma family we will also discuss malignant peripheral nerve sheath tumours, malignant rhabdoid tumours and the locally aggressive group of myofibroblastic lesions derived from mesenchymal tissue [2, 3].

58.2 Epidemiology

The incidence of malignancy occurring during the neonatal period (first 28 days of extra-uterine life) is over three times that of other paediatric age groups [4]. However, neonatal malignancy remains rare. In the United States, 130 neonates/year or 36.5 per 1 million live births over the neonatal period are diagnosed with cancer [5, 6]. It is worth noting that the definition of a congenital neoplasm is not consistent. Some describe neoplasms diagnosed up to 3 months after birth as being congenital. These congenital neoplasms account for 0.5–2% of all childhood neoplasms with a prevalence of 1.7–13.5 per 100,000 live births [7]. Others define congenital tumours as those recorded at birth or observed during the first week of life [8].

The commonest malignancy to present in the neonatal period is neuroblastoma. Other tumours presenting during this period include germ cell tumours, renal tumours, intracranial tumours, hepatic tumours and soft tissue sarcomas. Soft tissue sarcomas make-up 11% of malignancies diagnosed in the neonatal period [9]. Fifty percent of neonatal soft tissue sarcomas are diagnosed at birth with the remainder presenting during the first 4 weeks of life [9]. Rarely these tumours are identified on antenatal ultrasound.

Over the past 40 years, collaborative groups have studied some of these rare paediatric malignancies in the context of clinical trials where continued improved outcomes have been achieved. The Intergroup Rhabdomyosarcoma Study Group (IRSG) studies 1–4 showed that out of 3217 paediatric RMS treated in these trials only 14 (0.4%) were diagnosed in the neonatal period [10]. Overall soft tissue sarcomas represent about 8% of all childhood malignancies and by far the commonest histological subtype across all age ranges is rhabdomyosarcoma. However, only 2% of soft tissue sarcomas present in the neonatal period.

Neonatal soft tissue sarcomas can be broadly divided into three histologically distinct subgroups; rhabdomyosarcoma represents over a third of patients with the heterogeneous group of "other" non-rhabdomyosarcoma soft tissue sarcomas and congenital infantile fibrosarcoma making up the rest [9]. The United Kingdom National Registry of Childhood Tumours for infants born 1988–2007 and diagnosed in the first 4 weeks of life reflects this distribution (Table 58.1, see Table 52.1 in Chap. 52). In this National Registry the incidence of neonatal sarcoma was 2.6 per million live births.

Table 58.1 Epidemiology of neonatal tumours (see Table 52.1 in Chap. 52)

	Male	Female	Total
Rhabdomyosarcoma	9	4	13
Fibrosarcoma	3	7	10
Malignant haemangiopericytoma	1	0	1
Mesenchymal chondrosarcoma	1	0	1
Extrarenal rhabdoid	0	5	5
Peripheral PNET	2	0	2
Malignant haemangioendothelioma	1	0	1
Epithelioid sarcoma	1	0	1
Soft tissue sarcoma NOS (not otherwise specified)	1	2	3
Total sarcomas	19	18	37
Total cancers	183	211	394

Data from National Registry of Childhood Tumours for infants born 1988–2007 and diagnosed in the first 4 weeks of life

Table 58.2 Histological subtypes of soft tissue sarcomas described in the neonatal period

Frequency	Histological subtype
Most commonly occurring	Rhabdomyosarcoma Infantile fibrosarcoma
Others	Malignant peripheral nerve sheath tumour (2) Alveolar soft part sarcoma Malignant rhabdoid tumour of soft tissues Malignant ectomesenchymoma (13) Epithelioid hemangioendothelioma Malignant haemangioendothelioma Leiomyosarcoma (2) Epithelioid sarcoma Clear cell sarcoma of soft tissue (2) Malignant mesenchymal sarcoma (9) Angiosarcoma (9) Chondrosarcoma (9) Primitive sarcoma (9) Peripheral neuroectodermal tumour Malignant haemangiopericytoma

Sarcomas accounted for 9.4% of all cancers in neonates.

58.3 Histopathology

Soft tissue sarcomas constitute a heterogeneous group of tumours with over 70 histological sub types of sarcoma recognised. It is very important to make an accurate histological diagnosis as the management and outcomes vary considerably between subtypes. Table 58.2 shows a list of soft tissue sarcomas documented in the literature as arising in the neonatal period [3, 11, 12]. RMS, the most common sarcoma seen in childhood, is further subdivided into a number of histological subtypes based on prognosis. The more common subtypes include embryonal rhabdomyosarcoma (ERMS) and alveolar rhabdomyosarcoma (ARMS). RMS will be discussed in more detail later. There are a few sarcomas where there are no documented cases arising in neonates to be found following a thorough review of the literature. These subtypes include synovial sarcoma, desmoplastic small round cell tumour, undifferentiated sarcoma of the liver and low-grade fibromyxoid sarcoma.

58.4 Genetics and Biology

Advancing knowledge and understanding about the biological features of tumours has allowed us to begin to characterise the behaviour of soft tissue sarcomas as well as many other types of tumours. Increasingly this knowledge is contributing not only to making the diagnosis but also towards planning the treatment of that patient. Recent molecular studies have provided us with a battery of cytogenetic abnormalities that can be detected almost routinely when a tumour is investigated by the pathologist. In many tumours there are a variety of abnormalities including chromosomal translocations, inversions, gene amplification and gene rearrangements. Several childhood sarcomas bear reciprocal chromosomal translocations which correlate with specific tumour

Table 58.3 Common cytogenetic abnormalities found in soft tissue sarcomas

Histology	Translocation/cytogenetic abnormalities	Fusion Gene
Alveolar rhabdomyosarcoma (ARMS)	t(2;12)(q35;q14) t(1;12)(q36;q14)	PAX3/FOXO1A PAX7/FOXO1A
Embryonal rhabdomyosarcoma (ERMS)	Gain of chromosomes: 2,8,11,12,13, 20 LOH at 11p25	
Congenital infantile fibrosarcoma (CIF)	t(12;15)(q13;q25) Trisomy: 8,11,17 and 20	NTRK3/ETVG (TEL)
Ewings/PNET	t(11;22)(q24;q12) t(11;22)(q22;q12) t(17;22)(q12;q12) t(7;22)(p22;q12)	EWS/FLI1 EWS/ERG EWS/E1AF EWS/ETV1
Desmoplastic small round cell tumours (DSRCT)	t(11;22)(q13;q12)	EWS/WT1
Clear cell sarcoma (CCS)	t(12;22)(q13;q12)	EWS/ATS1
Inflammatory myofibroblastic tumours	t(1;2)(q25;p23) t(2;19)(p23;q23)	TPM3/ALK TPM4/ALK
Alveolar soft part sarcoma	t(X;17)(p11;q25)	TEL/ASPL
Synovial sarcoma (SS)	t(X;18)(p11;q11)	SYT/SSX1 SYT/SSX2 SYT/SSX4
Malignant rhabdoid tumours (MRT)	Loss of INI1 on q22	

types. Table 58.3 shows some of the more common cytogenetic abnormalities which can be identified in a variety of soft tissue sarcomas. This list includes some tumours which have not been reported in the neonatal age group. In order to continue our pursuit of knowledge around the biological behaviour of all solid tumours, it is essential that we continue to collect fresh tissue at biopsy or resection for cytogenetic analysis which can be performed using both FISH (fluorescent in situ hybridisation) and RT-PCR (reverse transcription polymerase chain reaction). In many cases, the significance of the genetic abnormality is not clear. However, in other instances, such as for ARMS bearing the fusion gene PAX3-FOX01A, we have known for a number of years that these tumours carry a worse prognosis [13].

58.5 Specific Tumour Types

58.5.1 Rhabdomyosarcoma

ERMS does not have structural chromosomal rearrangements but rather has frequent chromosome gains. The most notable gains in ERMS are to chromosomes 2, 8, 11, 12, 13, and 20 [14–16]. Loss of heterozygosity (LOH) at 11p15 (the Beckwith—Wiedemann region) is a frequent abnormality in ERMS [17]. This is also the location for the IGF-2 gene. LOH leads to an overexpression of the IGF-2 gene and this event is proposed to play a part in the pathogenesis of ERMS [18]. Approximately 85% of ARMS carry the characteristic reciprocal translocation t(2;13)(q35;q14) resulting in the formation of *PAX3-FOX01A which codes for a chimeric transcription factor. A variant translocation* t(1;13)(p36;q14) which occurs in approximately 10% of ARMS, gives rise to *PAX7-FOX01A fusion protein and is thought to carry a better prognosis* [13]. The molecular disruptions caused by these translocations are well characterised and involve three developmentally important transcription factors, PAX3, PAX7 and FOX01A (formerly FKHR). These translocations rearrange the transcription factors PAX3 and PAX7, and juxtapose these genes with FOX01A (formerly FKHR), a member of the fork head transcription factor family. The juxtaposition of

PAX3/7 and FOX01A causes transcriptional upregulation.

Recently there has been some interesting work investigating the difference between fusion positive and fusion negative ARMS. Williamson et al. performed gene expression analysis on over 200 histologically verified RMS. The tumours were divided into ERMS, fusion positive ARMS and fusion negative ARMS. They were able to show convincingly that ERMS and ARMS fusion-negative are one and the same; that is, they arise in the same locations and have a comparable frequency of metastases—distinct from ARMS fusion-positive. Most importantly, they have indistinguishable outcomes with therapies that were not stratified for histological subtype. This piece of work may allow us already to consider how we stratify treatment based on molecular investigations [19].

58.5.2 Infantile Fibrosarcoma

The majority of congenital infantile fibrosarcomas (CIF) carry the characteristic t(12;15)(p13;q26) translocation which gives rise to an ETV6-NTRK3 fusion gene [20]. The t(12;15)(p13;q25) fuses the *ETV6 (TEL)* gene from chromosome 12q13 with the 15q25 neurotrophin-3 receptor gene, *NTRK3 (TRKC)*. Fusion transcripts are expressed in tumour cells and encode for the ETV6-NTRK3 fusion protein. This protein has a role in activation of the P13-Akt pathway which is involved in cell survival. This translocation is identical to that seen in cellular mesoblastic nephroma, with a similar histology [21]. This fusion has not been described in adult fibrosarcoma. In addition, trisomies of chromosomes 8, 11, 17 and 20 are consistently found in infantile fibrosarcomas, and again are also described in the cellular form of CMN [21].

58.5.3 Malignant Rhabdoid Tumour

In malignant rhabdoid tumours the INI1 (SMARCB1) gene on chromosome 22q functions as a classic tumour suppressor gene. SMARCB1 acts as an epigenetic tumour suppressor which functions as a "gatekeeper" within the cell cycle. The presence of germline mutations (in up to 30% of patients) are correlated with manifestations at a very early age, synchronous and metachronous tumours at different locations, and poor prognosis [22].

58.5.4 Ewing's Sarcoma Family of Tumours

Ewing's sarcoma/soft tissue Primitive Neuro-Ectodermal Tumours (PNET) are characterised by translocations involving the EWS gene on chromosome 22. Amongst paediatric sarcomas, Ewing's sarcoma appears to have the greatest variety of fusion partners, resulting in considerable complexity in analysis and interpretation. T(11;22) involving the EWS gene on chromosome 22 and the FLI1 gene on chromosome is the most common translocation, present in 85–90% of Ewing's tumours. Approximately 5–10% of Ewing's sarcomas carry an alternate translocation (see Table 58.3) [21].

58.5.5 Desmoplastic Small Round Cell Tumour (DSRCT)

The molecular hallmark of DSCRT is a unique chromosomal translocation (t11;22)(p13:q12) resulting in a transcript EWS-WT1, which is diagnostic of this tumour. EWS is located on chromosome 22 at 22q12 whilst the Wilms tumour suppressor gene (WT1) is located on chromosome 11, at 11p13. This transcript encodes for a protein which acts as a transcriptional activator that fails to suppress tumour growth. Variant forms resulting from alternative splices are recognised and are more common in tumours arising in unusual sites [21].

58.5.6 Clear Cell Sarcoma of Soft Tissue

Clear cell sarcoma (CCS) of soft tissue is another example of a tumour bearing a translo-

cation involving the EWS gene [21]. The t(12;22)(q13;q12) fuses EWS with the ATF1 gene on chromosome 12. However fusions associated with CCS are not specific and have also been associated with angiomatoid fibrous histiocytoma, which has a much more favourable prognosis [21].

58.5.7 Synovial Sarcoma

Synovial sarcomas (SS) are characterised as a group by the presence of a specific translocation t(X;18)(p11.2;q11.2). This translocation is considered the "gold standard" for the diagnosis of synovial sarcoma and is present in >95% of cases. The t(X;18)(p11.2;q11.2) translocation fuses the SSXT(SYT) gene from chromosome 18 with SSX1 (about 2/3 of cases), SSX2 (about 1/3 of cases) or SSX4 (rare cases) genes from the X chromosome. Cases with both SYT/SSX1 and SYT/SSX2 fusion transcripts have been described and the SYT/SSX1 transcript is reported to be significantly associated with biphasic Synovial sarcoma.

58.6 Genetic Predisposition Syndromes

A number of recognised genetic predisposition syndromes are associated with the development of soft tissue sarcomas. These include Beckwith-Weidemann syndrome, Li Fraumeni syndrome, retinoblastoma, neurofibromatosis type 1, Costello syndrome, Rubinstein-Taybi syndrome and Gorlin basal cell naevus syndrome. However, sarcomas developing in these clinical situations seldom present in the perinatal period. Nevertheless, it is important to recognise any potential genetic predisposition to cancer so that genetic counselling, screening, surveillance and timely treatment can be offered [23].

58.7 Clinical Presentation and Differential Diagnosis

Initial signs and symptoms depend on the site of the tumour, extension into surrounding tissue and the presence or not of metastases. Identification of neonatal soft tissue tumours may be made in the foetal period [24–27], at birth or within the first month of life. Routine antenatal ultrasound may identify a mass. Polyhydramnios, hydrops foetalis, obstructive uropathy or growth restriction can be associated with intra-uterine tumours [22, 23, 28]. Pre-natal MRI with planned post-natal MRI is the radiological investigation of choice to further characterise these tumours and inform decisions about obstetric and post-natal care [27]. If a mass is small at the time of routine obstetric ultra-

Table 58.4 Commonest presenting signs and symptoms by primary site

Primary site	Symptoms and signs
Skin and subcutaneous tissue	Asymptomatic mass Discoloured subcutaneous nodule Solid or semicystic swelling
Head and neck (including orbital, paranasal, nasopharyngeal and sinuses)	Painless or painful swelling Proptosis Ptosis Ophthalmoplegia Facial nerve palsy Other cranial nerve palsies Nasal discharge Trismus
Limbs	Painless swelling
CNS	Irritability Seizures Hydrocephalus
Abdomen/genito-urinary tract	Painless scrotal lesions Haematuria Vulval nodule Polypoid vaginal lesions Antenatal diagnosis of abdominal mass Postnatal diagnosis of abdominal mass Intestinal obstruction
Metastatic disease	Otherwise unexplained: Poor feeding Seizures Pain Irritability Pancytopenia

sound scanning or develops later in gestation, it may remain undetected until presenting as dystocia during natural delivery [27]. Presentation at delivery with obstructed labour has been described in congenital infantile fibrosarcoma [29].

Soft tissue sarcomas may be clinically and ultrasonographically mistaken for haemangiomas or vascular malformations which are the commonest soft tissue tumours diagnosed in early life [8, 30–32]. There are a few reports of angiosarcomas presenting in pre-existing complex vascular malformations [33]. It is important to recognise this possibility if a pre-existing lesion changes characteristics. (Table 58.4).

Cutaneous and subcutaneous sarcomas of the neonate can present as asymptomatic masses. They may be solid to semicystic, solitary or multiple, skin coloured or erythematous, blue or yellow, fungating or ulcerating.

Intra-Abdominal masses or retroperitoneal masses may be identified on antenatal scanning or on post-natal examination. Haemoperitoneum from an extensive intra-abdominal rhabdoid tumour has presented in an ex-premature corrected to term neonate with sudden abdominal distention, fall in haematocrit and irritability [22].

Neonatal surgeons need to be aware of the possibility that intestinal obstruction can in rare instances, be caused by intestinal tumours as this in turn may require a different surgical approach [34, 35]. When faced with this intra-operative finding, the surgeon should try to achieve a complete resection.

Non-neoplastic conditions of the scrotum are usually diagnosed clinically. However if a tumour is suspected then appropriate investigations must be undertaken as the correct oncological approach differs from the approach to commoner benign pathologies. If a tumour is not suspected and a direct scrotal approach made, then the risk will be that of contaminating the surgical field with tumour cells resulting in the need for re-resection.

Table 58.5 Differential diagnosis of lesions by primary site

Site	Benign	Malignant
Head and neck	Branchial cyst/ remnant	Teratoma
	Thyroglossal cyst	Neuroblastoma
	Lymphangioma	Leukaemia
	Haemangioma	Retinoblastoma
	Abscess	
	Dermoid cyst	
	Encephalocoele	
	Epulis	
	Congenital goitre	
	Sternomastoid tumour	
	Ectopic thyroid	
	Thymic cyst	
Skin and subcutaneous lesions	Haemangioma	Neuroblastoma
	Xanthoma	Leukaemia
	Other vascular anomaly	
Abdominal/ pelvic masses	Hydronephrosis	Neuroblastoma
	Ovarian cyst	Mesoblastic nephroma
	Vitello-intestinal remnant	Teratoma
	Urachal remnant	Nephroblastoma
	Lymphangioma	Hepatoblastoma
	Hepatic vascular	
	Renal cystic disease	
Scrotal masses	Hydrocoele	Germ cell tumour
	Hernia	Sarcoma
	Testicular torsion	
Vaginal/vulval lesions	Prolapsing ureterocoele	Sarcoma
	Condylomata	

58.8 Making the Diagnosis

58.8.1 Principles

When there is suspicion that a neonatal soft tissue lesion may be malignant then tissue diagnosis is essential. In this situation, consultation with a wider experienced team may be helpful. An experienced paediatric dermatologist can help to distinguish the commoner benign

lesions from the rare atypical malignant ones and your local paediatric oncologists may be helpful to plan appropriate investigations such as imaging and tumour markers ahead of a biopsy. (Table 58.5).

58.8.2 Tumour Markers

Whilst there are no tumour markers specific for soft tissue sarcoma, exclusion of other tumours is always helpful. Therefore a single timepoint collection of urine for catecholamines will exclude neuroblastoma in the majority of cases and a normal AFP/BHCG (corrected for the age of the infant), will exclude germ cell tumours.

58.8.3 Imaging

Ultrasound of a suspicious lesion should be the first radiological investigation. Sonography can delineate whether a palpable abnormality is a mass, whether the mass is solid or cystic, and vascular characteristics of the lesion. For extensive or deep lesions, cross-sectional imaging is preferred and MRI has replaced CT in most cases. MRI will delineate the extent of the lesion, define local involvement of surrounding structures and demonstrate characteristics of the lesion. Malignant tumours often show an infiltrative growth pattern shown by encasement of neurovascular bundles and growth into surrounding structures such as joints and bone and these features can usually be identified and clearly documented on MRI. It is often appropriate to perform an MRI before biopsy so post-surgical changes do not distort the radiological appearance.

In addition to its diagnostic value, MRI is used to monitor post-operative complications as well as to evaluate response to therapy. Limitations of MRI include the inability to differentiate residual or recurrent disease from post-operative oedema, inflammation and haemorrhage. CT is superior to MRI in the evaluation of bone involvement; therefore, CT should be performed when osseous invasion is suspected. As part of a staging process once histopatholgical diagnosis is confirmed, a Technecium 99 m scan may be required to exclude bony metastases.

Distinction between different tumour subtypes is not always possible because they often have similar appearances, however there are sometimes features demonstrated on an MRI which point to a particular subtype of sarcoma. For example, rhabdomyosarcomas are usually isointense to muscle on T1-W, intermediate to high intensity on T2-W, and may have signal voids due to vessels having high flow velocity. Infantile Fibrosarcomas are similar to rhabdomyosarcomas on T1-W and T2-W imaging but their margins are usually poorly defined. Synovial sarcomas are usually also isointense on T1-W and hyperintense on T2-W imaging. Evidence of intra-tumoural haemorrhage may be present, and fluid-filled levels are seen in 20% of scans. These tumours can be predominantly cystic and therefore can be mistaken for a Baker's cyst, or a haematoma. Their appearance can also be similar to a ganglion [27, 36].

58.8.4 Biopsy

The history, examination and radiological evaluation of a soft tissue mass should provide sufficient clinical information for a differential diagnosis to be made ahead of a biopsy of the lesion. This is essential to ensure that the biopsy is taken and transported in the correct manner to the laboratory to allow the pathologist to make the diagnosis.

Incision biopsy is usually the appropriate initial surgical procedure. Excision biopsy should only be undertaken if a microscopically clear resection can be achieved without danger or mutilation. In an excisional biopsy, margins and specimen should be carefully marked to allow re-resection should the biopsy reveal a positive margin on histological assessment. Incision biopsy is also indicated if the regional lymph nodes are positive or there is metastatic disease.

In accessible sites open incisional biopsy is indicated. Longitudinal incisions are frequently better than horizontal incisions on areas such as

an extremity. A biopsy to confirm malignancy requires that the biopsy tract be excised at the time of reoperation; if the biopsy site is inappropriately placed, a much larger subsequent excision would be required. In less accessible sites, multiple core-needle biopsies under ultrasound guidance may be appropriate. Endoscopic biopsies are appropriate for pelvic or paranasal tumours if technically feasible.

It is important to obtain sufficient tissue for histology, immunohistochemistry, cytogenetics, biological studies and for frozen storage/tissue banking. Prior discussion with the pathologist and pathology laboratory is essential so the specimen is processed correctly.

Biopsy of the regional lymph nodes is recommended where possible. Current trials have adopted a more aggressive approach to evaluating lymph nodes. Previously it was thought that lymph node involvement was rare. Of the patients whose lymph nodes were clinically negative but were biopsied anyway, 17% were found to have microscopic disease [37]. The utility of sentinel-lymph node mapping is being evaluated. For extremity tumours if sentinel lymph node mapping is not available, aggressive sampling is warranted.

58.9 Specific Tumour Types

58.9.1 Rhabdomyosarcoma

RMS is the commonest subtype of soft tissue sarcoma seen in the neonatal population. Rhabdomyosarcoma arises from embryonic mesenchymal cells that have the potential to differentiate into skeletal muscle. RMS and can be further divided into the following subgroups based on prognosis:

- Superior prognosis
  - Botryoid embryonal
  - Spindle
- Intermediate prognosis
  - Embryonal
- Poor prognosis
  - ARMS including
  - Solid variant
  - Undifferentiated

The subtypes most frequently found in neonates with rhabdomyosarcoma are embryonal, botryoid variant and undifferentiated rhabdomyosarcoma [10].

Rhabdomyosarcoma is one of the "small round blue-cell tumours" of childhood. Occasionally, these types of tumours can be difficult to differentiate. Rhabdomyosarcoma cells tend to have variable differentiation along the myogenesis pathway. The various rhabdomyosarcoma subtypes often have characteristic features that allow them to be distinguished histologically. For example, botryoid are classically described macroscopically as "grape-like" in appearance. Histopathologically, it is necessary to identify a cambium layer beneath an intact epithelium in at least one microscopic field to make this diagnosis. For the diagnosis of ARMS to be made, the characteristic "alveolar" pattern needs to be present even if just in a small focal area. However, in order to confirm the diagnosis of RMS immunohistochemistry must be performed as well as cytogenetic analysis to confirm the presence or not of chromosomal aberrations. The most sensitive and specific immunohistochemical test for RMS is for myogenin. Myogenin belongs to a group of myogenic regulatory proteins whose expression determines commitment and differentiation of primitive mesenchymal cells into skeletal muscle. The expression of myogenin has been demonstrated to be extremely specific for rhabdomyoblastic differentiation, which makes it a useful marker in the differential diagnosis of rhabdomyosarcomas from other malignant small round cell tumours of childhood. The percentage of cells expressing myogenin is significantly higher in alveolar than embryonal RMS [21]. As discussed previously (Genetics and Biology section) cytogenetic analysis using FISH and/or RTPCR should be routinely performed to look for evidence of translocation or chromosomal loss. This may further help to confirm a sub-classification of RMS which in turn

will contribute to the decisions regarding treatment and prognosis.

RMS can arise anywhere in the body but the anatomical distribution does vary with patient age. The head, neck and trunk are the predominant sites in neonatal RMS [9]. In early childhood, head and neck and genito-urinary tumours predominate whereas in older children the proportion of extremity tumours with alveolar histology increases. Paratesticular RMS accounts for 12% of childhood scrotal tumours and usually presents between 4 and 5 years of age [38]. In childhood, paratesticular RMS accounts for 7% of RMS but only one paratesticular RMS has been described in the neonatal age group up to 2000.

Neonatal RMS carries a very poor prognosis unless it can be fully resected. The Children's Cancer Group reported on 11 neonates with RMS. Nine of these received chemotherapy to which they had a poor response and 2/11 were alive at the time of reporting, one with metastatic disease, and the other after total cystectomy. Two neonates received radiotherapy [39]. The results reported by the Intergroup Rhabdomyosarcoma Study Group were better with 6/14 patients surviving at 3 year follow-up. Seven died of disease and one died of chemotherapy-related toxicity [10].

Children below the age of 1 year have a poorer prognosis than older children. Whilst this may in part be due to biological factors, the difficulties in delivering multimodality treatment in this age group should not be underestimated.

58.9.2 Congenital Infantile Fibrosarcoma

Infantile fibrosarcoma is the most common soft tissue sarcoma diagnosed in infants under 1 year of age. Infantile fibrosarcomas make-up between 20 and 50% of malignant soft tissue tumours in neonates and infants. 30–50% are present at birth. Most report a male predominance. The predominant anatomic sites in neonates are the extremities (58%), trunk (25%), and head and neck (17%) [40]. They are subcutaneous lesions but can rarely occur in the mesentery, retroperitoneum or orbit [41]. Metastases are rare, occurring in less than 10% of cases with dissemination most commonly to the lungs.

Histologically these tumours are composed of spindle-cells arranged in bundles and fascicles, resulting in a characteristic "herring-bone" appearance. Unlike adult fibrosarcoma, infantile fibrosarcoma is often infiltrated by inflammatory cells, and tends to have less pleomorphism. Immunohistochemistry tends to be non-specific

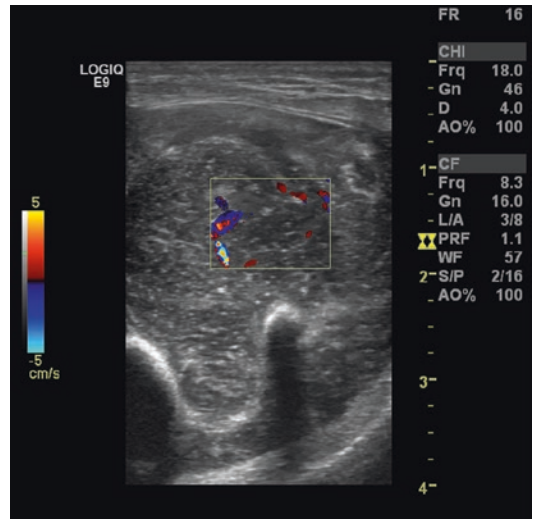

Fig. 58.1 Ultrasound at day 8 of life showing a large right calf mass

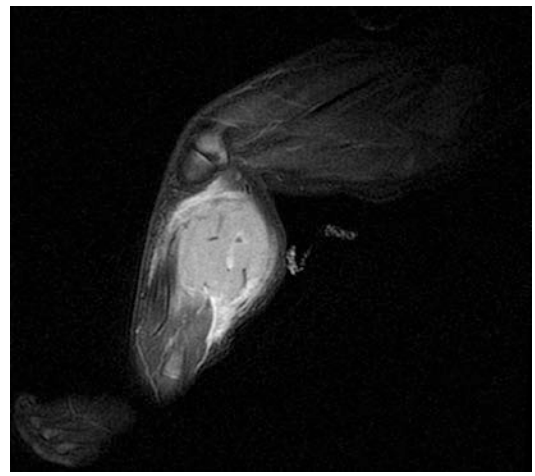

Fig. 58.2 MRI Sagittal STIR sequence at 15 days of life showing right calf mass involving neurovascular bundle and expanding between tibia and fibular bones

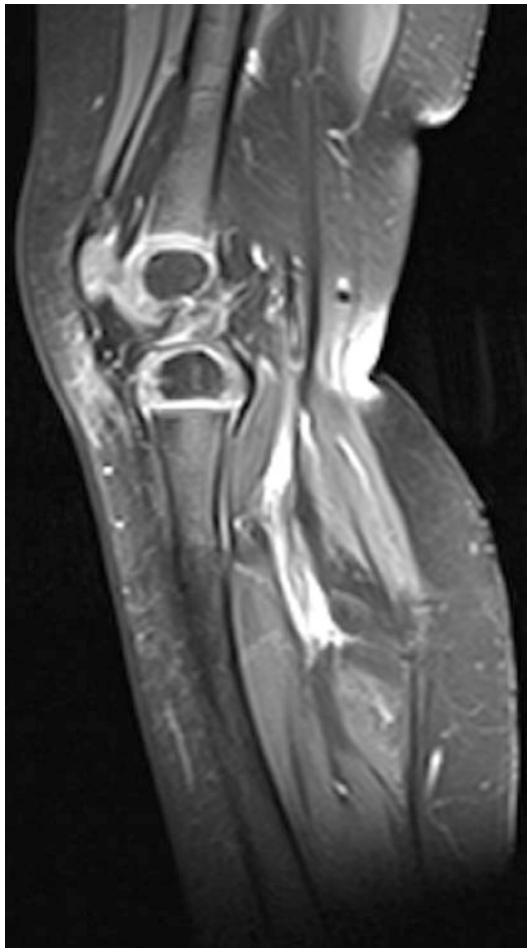

Fig. 58.3 MRI Sagittal STIR sequence 16 months after commencement of chemotherapy showing almost complete response to systemic therapy alone

[21]. The translocation t(12;15) and resulting fusion product are present in the infantile-type of fibrosarcoma but not in the adult-type.

Clinically they are violaceous firm tumours that enlarge rapidly, often within a few weeks or months. They can grow to become massive but conversely spontaneous regression has been reported.

Surgery is the mainstay of treatment if it can be achieved simply without mutilation. In those under 3 months of age a "wait and see" approach could be considered to allow for possible spontaneous regression. Infantile fibrosarcoma is chemosensitive and where a tumour is felt to be inoperable, chemotherapy can be tried to permit subsequent conservative surgery [11] (see Figs. 58.1, 58.2, and 58.3). Infantile fibrosarcoma has a much better prognosis than the adult form of fibrosarcoma with a 5 years survival estimated between 84 and 93%. The Children's Cancer Group reported that all 12 of their cases were disease free at a median follow-up of 6.6 years [9]. Local recurrence rates are high, ranging from 17 to 43% and often occur within the first few weeks after the initial excision. Even if local disease does recur, repeat surgical resection will result in cure in the majority of the cases. Therefore close follow-up is essential to allow earlier intervention in the event the disease returns locally [32].

58.9.3 Extracranial Malignant Rhabdoid Tumour (MRT)

Extracranial Rhabdoid tumours are highly aggressive malignant tumours of childhood. The tumour was given the name "rhabdoid" because microscopically it resembles a rhabdomyosarcoma although it does not show skeletal muscle markers by electron microscopy, immunoperoxidase, or cytogenetic studies. The most well-known extracranial site for rhabdoid tumours to occur is the kidney but tumours can be found elsewhere in soft tissues outside the CNS. Recently there has been recognition that rhabdoid tumours of the kidney and CNS are identical or closely related in terms of the characteristic genetic abnormalities [42]. It is less clear whether the non-renal extracranial rhabdoid tumours share the same histogenic origins as their renal and CNS counterparts. Therefore appropriate cytogenetic analysis on tumours with these histological features is essential.

Some cases of malignant rhabdoid tumours have been reported at birth and a few more in the first month of life [43]. In the perinatal period the extrarenal non-CNS site predominates. When the tumour occurs *in utero,* it is more likely to present at birth with multiple metastases and a rapidly progressive, downhill clinical course ending in early death. Rupture of the tumour *in utero* causing a severe foetal anaemia has been described. Rhabdoid tumour may present with subcutaneous nodules resembling the "blueberry muffin" lesion more commonly associated with neuroblastoma before

discovery of the primary tumour. 75% of patients have metastases at diagnosis [22, 42]. The tumour metastasizes to multiple sites such as the skin, placenta, bones, lungs, lymph nodes, brain and liver.

The histological diagnosis of rhabdoid tumour is based on identifying the characteristic rhabdoid tumour cell and the presence of a deletion or mutation of the INI1 gene located on chromosome 22q11. The INI1 gene (SMARCB1) on chromosome 22q functions as a classic tumour suppressor gene. The observation that mice, which have only one functioning copy of the INI1 gene present, are predisposed to MRT supports this premise [44]. Germline mutations of INI1 have been documented in patients with more than one primary tumour within the CNS and kidney and therefore the presence of MRT in a neonate requires the additional consideration of genetic investigation and counselling for the family.

Treatment is multimodal with surgery, chemotherapy with or without radiotherapy. Cure generally is achieved only in cases of localised disease. Chemotherapy usually results in a partial but not durable response and is often administered to simplify the tumour resection or reduce the radiation field.

Regardless of location, all rhabdoid tumours are highly aggressive and have a universally poor prognosis.

58.9.4 Desmoplastic Small Round Cell Tumour

Desmoplastic small round cell tumour (DSRCT) is a highly aggressive tumour that mainly affects young adults, and has a strong male predilection. Occasionally the histological diagnosis may be challenging if the immunohistochemistry is inconclusive or the fibrous stroma is poorly represented in a small biopsy [21]. However, the translocation t(11;22)(p13;q12) which results in the chimeric fusion transcript EWS-WT1, characterises this tumour. Therefore, once again, appropriate cytogenetic analysis, should be requested where the clinical features might suggest this diagnosis.

58.9.5 Malignant Ectomesenchymoma

Malignant ectomesenchymomas are usually diagnosed in the first 3 years of life. Surgery is the mainstay of treatment and survival correlates with resectability. These tumours are treated in a similar way to high-risk rhabdomyosarcomas [45].

58.9.6 Ewing's Sarcoma Family of Tumours

Ewing's sarcoma or soft tissue PNETs are a group of tumours that arise from pluripotential neural crest cells. Histologically they have small round blue cells and characteristically Homer-Wright rosettes. PNETs have varying degrees of neuroectodermal differentiation [21]. PNETs are highly aggressive and have a high local recurrence rate. Common sites of metastasis are lung, bone, and liver. Wide excision is performed, but if this is not feasible then amputation should be considered. Chemotherapy usually precedes definitive surgery and adjuvant radiotherapy may be useful in the presence of microscopically positive surgical margins [8].

58.9.7 Synovial Sarcoma

Synovial sarcoma (SS) is the most common non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in childhood. Despite its name it does not arise from the synovium but from the soft tissue in close proximity to it. As discussed previously over 90% of SS carry the characteristic reciprocal t(x; 18)(p11.2;q11.2).SS typically presents as a painless mass located near a joint, but can present as acute arthritis or joint contracture. Synovial sarcomas have been reported in a wide variety of anatomical sites, including visceral organs and the head and neck. They may appear as purely cystic and are the most common malignant tumour to be mistaken for a benign lesion.

58.9.8 Epithelioid Sarcoma

Epithelioid sarcoma is a rare tumour that primarily affects adolescents and young adults but does occur in neonates [31]. It most commonly presents as a superficial lesion in the distal extremities, particularly the hands, and although typically indolent in behaviour, carries a high risk of recurrence and late metastasis. A "proximal" form of epithelioid sarcoma has been described, that has a propensity to occur in the perineum, pelvis and genitourinary tract. It is more aggressive than the classic form of epithelioid sarcoma. Cytogenetically, epithelioid sarcomas have shown non-specific chromosomal gains and deletions.

58.9.9 Malignant Peripheral Nerve Sheath Tumour (MPNST)

Malignant peripheral nerve sheath tumours arise from cells differentiating towards those of the peripheral nerve sheath. They occur rarely in the neonatal period but have been described causing neonatal intestinal obstruction [34]. Complete surgical resection offers the only chance for cure as these tumours are not usually chemosensitive. Overall MPNST carries a poor prognosis but there is a suggestion that survival for patients less than 1 year may be better than in older patients [46].

58.9.10 Clear Cell Sarcoma of Soft Tissue

Clear cell sarcoma of soft tissue (CCS) almost always arises in deep soft tissues, closely related to aponeuroses and tendons of the extremities. CCS is primarily a tumour of adolescents and young adults, and is unusual in children younger than 10. CCS is the most common malignancy of the ankle and foot in adolescents with up to 75% arising in the extremity. Early diagnosis with wide local excision offers the best chance of cure with a 5-year survival ranging from 47 to 63% [47].

58.9.11 Low-Grade Fibromyxoid Sarcoma

This neoplasm displays a deceptively bland microscopic appearance, and yet carries a significant risk of metastases, with a propensity for a long latent period before metastases develop. It occurs primarily in young adults, but 19% of cases are seen in children [21].

58.9.12 Hemangioendothelioma

Hemangioendotheliomas (HE) includes a variety of neoplasms of vascular origin. Malignant Hemangioendotheliomas are considered to be angiosarcomas. Kaposiform HE, spindle cell HE and retiform HE are low-grade tumours, and should be treated by surgery alone. Epithelioid Hemangioendotheliomas (EHE) include two distinct subtypes, epithelioid hemangioendothelioma of soft-parts, and epithelioid hemangioendothelioma of bone, lung and liver. Treatment of these lesions is unclear as they do not usually respond to chemotherapy. Alpha-interferon treatment has been advocated and may work by an anti-angiogenic mechanism [48].

58.9.13 Haemangiopericytoma

Haemangiopericytomas are composed of mesenchymal cells derived from pericytes that occur in blood vessels. Haemangiopericytomas constitute 3% of pediatric soft tissue sarcomas. One neonate in Great Britain was diagnosed in the 20 year period 1988–2007. When occurring in the first year of life their behaviour is more benign and sometimes demonstrates spontaneous regression or maturation into a haemangioma. Treatment is wide local excision with chemotherapy reserved for incomplete resection [49].

58.9.14 Mesenchymal Chondrosarcoma

Mesenchymal chrondrosarcomas are rare aggressive tumours arising from soft tissues in about a

third of cases. They are thought to originate from chondroblasts that have failed to develop into mature chondrocytes and have the appearance of primitive connective tissue cells. One neonate in Great Britain was diagnosed in the 20 year period 1988–2007.

58.9.15 Myofibroblastic Lesions and Aggressive Fibromatosis/Desmoid

58.9.15.1 Myofibromatosis

These lesions are benign and are derived from contractile myoid cells around blood vessels [50]. These tumours can be divided into three different entities:

1. Infantile myofibroma (solitary)
2. Multicentric myofibromatosis and
3. Multicentric myofibromatosis with visceral involvement.

There are no specific cytogenetic changes identified in this group of tumour. Solitary or multicentric lesion are most commonly found within subcutaneous tissues of the head and neck although can also be found on the extremities. Visceral lesions can occur within any of the major organs such as liver and heart. These lesions can often grow rapidly to begin with but usually settle down and can regress spontaneously. Complete resection is curative but not always possible. Therefore when vital structures such as the heart, lungs, pleura, mesentery, liver and even the central nervous system are involved, surgical resection can be challenging if not impossible and this form of the disease carries a very poor prognosis [51–53].

58.9.15.2 Inflammatory Myofibroblastic Tumours

These tumours usually involve the abdomen or lungs and behave in a benign manner. However they can be locally invasive particularly in the abdomen and recur in about 25% of cases. Again they can be multifocal in origin and can prove fatal if they involve a large portion of the bowel mesentery. Resection with a clear histological margin is the treatment of choice. Chemotherapy, immunosuppressive therapy and radiotherapy are generally not effective.

58.9.15.3 Solitary Intestinal Fibromatosis

This is a rare cause of neonatal intestinal obstruction. This tumour is diagnosed at laparotomy and may appear as a circumferential firm white mass causing marked narrowing of the intestinal lumen. Solitary Intestinal Fibromatoses have been reported in both small and large bowel [54]. Spindle cell neoplasms originating from fibroblastic, myofibroblastic or smooth muscle cell origin have also been reported in the literature to cause intestinal obstruction in neonates [54]. These lesions are categorised as a variety of lesions including fibromatosis, fibrosarcoma, or leiomyosarcoma. Fibromatosis is a neoplastic proliferation of myofibroblasts and/or fibroblasts and therefore some of the reported cases of intestinal leiomyosarcoma may represent fibromatosis [54]. When fibromatosis is occurs as a solitary lesion the prognosis is excellent. In contrast, the generalised or multiple form of fibromatosis demonstrates a high rate of local recurrence and overall carries a worse prognosis [55].

58.9.15.4 Aggressive Fibromatosis or Desmoid Tumours

Aggressive fibromatosis (AF) are fibrous tissue proliferations that are locally aggressive, but do not metastasize. They tend to grow slowly and diffusely along fascial planes and lack a defined edge. Resection, although difficult, is the treatment of choice. When unresectable, there are a number of adjuvant therapies available to try. These range from non-cytotoxic agents such as anti-inflammatory agents/NSAIDs and Tamoxifen to chemotherapy agents such as doxorubicin or cyclophosphamide. These tumours grow slowly and therefore the treatment strategy involves prolonged exposure to therapy of between 12 and 18 months. For this reason methotrexate and vinblastine is a good low dose combination that is frequently adopted as it is effective and least toxic over

time. There is a variable response to chemotherapy with approximately a 50% response rate. Local recurrence rate is reported to occur in between 25 and 75% of resected cases. Positive microscopic margins, large initial tumours and extremity/girdle tumours have the highest chance of recurrence [45].

58.9.16 Staging

Once a diagnosis of soft tissue sarcoma is made then the patient needs to be staged fully in order to assess the extent of disease and plan treatment. There are different staging classifications depending on whether the diagnosis is RMS or Non-RMS. In addition, the staging in the USA is slightly different to that used across Europe.

Non-Rhabdomyosarcoma soft tissue sarcomas are staged according to the TNM Classification. The staging process includes radiological assessment of the primary site, the drainage nodal basins, and distant sites looking for metastatic disease. Bone marrow aspirates and trephines identify the presence of metastatic disease in the marrow whilst patients with parameningeal primary tumours require a lumbar puncture to assess for presence of disease in the cerebrospinal fluid. (Table 58.6).

After surgical resection a post-surgical pTNM Classification uses the same variables with the designation complemented by histological findings. In the case of rhabdomyosarcomas, the stage designated at diagnosis as localised or metastatic and the treatment pathway is defined according to the risk stratification (see below). In addition there is an IRS grouping classification based on primary tumour status after surgical treatment or biopsy. (Table 58.7).

Table 58.6 TNM staging classification

T1	Tumour confined to tissue of origin
T2	Tumour extends beyond tissue of origin
a	≤5 cm in maximum diameter
b	>5 cm in maximum diameter
N0	No nodal involvement
N1	Nodal involvement
M0	No distant metastases
M1	Distant metastases

Table 58.7 IRS staging classification

IRS 1	Primary tumour macroscopically and microscopically completely removed
IRS 2	Primary tumour macroscopically removed but with proven or suspected microscopic residual disease
IRS 3	Macroscopic primary residual disease
IRS 4	Metastases or malignant non-regional nodes

58.10 Risk Stratification

Patients are stratified according to a number of variables that have been shown to predict the likelihood of recurrence. These variables include:

1. Primary tumour site,
2. tumour size,
3. age at diagnosis,

Table 58.8 Risk stratification for treatment of non-metastatic Rhabdomyosarcoma in Europe

Risk Group	Subgroups	Pathology	IRS Group	Site	Nodal stage	Size and age
Low	A	Favourable	1	Any	N0	Favourable
Standard	B	Favourable	1	Any	N0	Unfavourable
	C	Favourable	2, 3	Favourable	N0	Any
	D	Favourable	2, 3	Unfavourable	N0	Favourable
High	E	Favourable	2, 3	Unfavourable	N0	Unfavourable
	F	Favourable	2, 3	Any	N1	Any
	G	Unfavourable	1, 2, 3	Any	N0	Any
Very high	H	Unfavourable	1, 2, 3	Any	N1	Any

4. IRS grouping,
5. pathology,
6. nodal involvement
7. Presence of metastases.

The European paediatric soft tissue sarcoma group (EpSSG) risk stratification designates patients according to whether they are Low risk, Standard risk, High risk, Very high risk based on the variables listed above. For example favourable pathology would include all embryonal, botryoid and spindle cell RMS whilst alveolar subtype falls into unfavourable category (see Table 58.8). The patients are then stratified into a subgroup (A–H) and a treatment strategy is decided. The Intergroup Rhabdomyosarcoma study group (IRS) uses slightly different risk stratification with subgroups separated into low, intermediate and high risk.

58.11 Multimodality Therapy

General considerations in the delivery of chemotherapy to neonates with cancer include their body composition, body water, body surface area, and body weight. Physiological differences in renal and liver function, P450 enzyme activity, and nutritional requirements need to be taken into account in order to treat neonates effectively whilst minimizing treatment related toxicity [17]. Treatment should aim to limit any compromise to normal growth and development of the neonate. Extravasation injuries can be devastating therefore chemotherapy needs to be delivered into a central vein via reliable central venous access.

58.12 Primary Site Management

58.12.1 Surgical Management

The general principles of surgical management include complete wide excision of the primary tumour and surrounding uninvolved margins while preserving function. However, the surgical strategy needs to be informed by the histological diagnosis as some tumour types can afford a more conservative surgical approach or may require upfront chemotherapy before any definitive surgical procedure [56]. There are virtually no circumstances where it would be appropriate to embark on a "debulking" procedure. The quality of resection is often crucial to local control and is graded:

– R0—microscopically clear margin,
– R1—macroscopic resection with positive microscopic margins,
– R2—macroscopic tumour left at resection margin

Primary resection should only be undertaken if an R0 resection can be achieved without danger or mutilation. Generally an incision biopsy is appropriate if the regional nodes are involved and/or there are distant metastases.

Primary Re-Excision (PRE) is performed to achieve microscopic clearance in patients with residual tumour (certain or doubtful) after primary operation, before other therapies, if this can be done without danger or mutilation. PRE should be considered, even if the margins are apparently normal, if the initial resection was not a "cancer" operation (i.e. malignancy was not suspected at initial excision).

Secondary Operation. The aim is to achieve an R0 resection of residual tumour after neoadjuvant chemotherapy. Marginal resection R1 may be acceptable depending on the histological type of soft tissue tumour, particularly infantile fibrosarcoma. If neoadjuvant chemotherapy (or chemotherapy and radiotherapy) have been unsuccessful then mutilating surgery may be indicated.

Reconstructive surgical options need to be considered before the primary tumour is treated. This is done in conjunction with a reconstructive plastic, orthopaedic or urologic surgeon as the case dictates.

58.12.2 Radiotherapy

Radiotherapy delivered to neonates carries a very high morbidity and is generally avoided if at all possible. It is destructive to normal tissues within the radiotherapy field and interferes significantly with normal growth. In addition having radiotherapy poses a significant risk for development of second malignancies in later life. In order to limit the morbidity, brachytherapy at certain sites using intracavitary or interstitial implants is being used in older children in the management of bladder/prostate and head and neck soft tissue sarcomas [57, 58].

58.12.3 Site-Specific Surgical Treatment

The surgical treatment of soft tissue sarcomas is site-specific, and will be discussed by individual site.

58.12.3.1 Head and Neck

Complete surgical resection is difficult but may be appropriate after neoadjuvant chemotherapy. Histological diagnosis will influence the need for a radical local therapy approach. For example, infantile fibrosarcoma may respond to chemotherapy alone and not require complete resection. Conversely, treatment of rhabdomyosarcoma requires complete resection to offer the best chance of cure. Parameningeal sites pose the greatest difficulty. Radiotherapy is initially withheld in neonates because of the high associated morbidity. The planning of reconstructive surgery needs to be done ahead of resection.

58.12.3.2 Orbital Rhabdomyosarcoma

Biopsy is usually the only local therapy required although occasionally enucleation or exenteration may be needed.

58.12.3.3 Vagina

Chemotherapy alone may be sufficient treatment. Conservative local resection may be feasible to resect the tumour. In older girls, intra-cavitory brachytherapy after ovarian transposition is often preferable.

58.12.3.4 Bladder/Prostate

Cystoscopy and biopsy should be the initial procedure. Primary resection is seldom indicated and only for small tumours in the fundus of the bladder. Neoadjuvant chemotherapy followed by conservative surgery and radiotherapy (external beam or brachytherapy) may be appropriate. If this is not feasible then exenterative surgery should be considered.

58.12.3.5 Paratesticular Rhabdomyosarcoma

Orchidectomy should be through an inguinal incision with ligation of the cord at internal ring. With very large tumours a scrotal approach may be appropriate keeping the tunica vaginalis intact.

58.12.3.6 Extremities

Wide local excision is usually indicated. Again, histological diagnosis will influence the need for a radical local therapy approach. Frozen sections of resection margins can inform intra-operative surgical decisions. Amputation may need consideration because the radiotherapy effects on growth and function may deliver a poorer result than amputation.

Conclusion

Neonatal soft tissue sarcomas are a rare heterogeneous group of tumours. A growing understanding of their differing biological characteristics in the context of multinational cooperative studies will continue to improve the treatment strategies offered. The aim to improve survival outcomes in poor prognosis tumours and minimise treatment morbidity in those with favourable tumours will continue. Early involvement of a multidisciplinary team is key to appropriate management.

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Renal Tumours

59

Robert Carachi

Abstract

Renal neoplasms are rare in the newborn and account for only 8% of neonatal tumours. Congenital mesoblastic nephroma (CMN), first described by Kastner in 1921, is the most common renal tumour in the neonate. It is also known as a fetal renal hamartoma, mesenchymal hamartoma of infancy, or lipomyomatous hamartoma.

Keywords

Newborn renal tumors • Congenital mesoblastic nephroma

59.1 History

Renal neoplasms are rare in the newborn and account for only 8% of neonatal tumours. Congenital mesoblastic nephroma (CMN) first described by Kastner in 1921 [1], is the most common renal tumour in the neonate. It is also known as a fetal renal hamartoma, mesenchymal hamartoma of infancy, or lipomyomatous hamartoma.

59.2 Incidence and Epidemiology

It has an incidence of 2.8% of all renal tumours of childhood, with a mean age of presentation of 3.4 months in contrast to an average age of 3 years in Wilms' tumours [2]. Its frequency is 22.8% of all primary tumours in children 1 year old or less [3]. The majority of renal neoplasms originating in the fetus and found during the first weeks of life, differ in structure and in biological behaviour from a nephroblastoma. In the CCG Neonatal Study there were 25 neonatal renal neoplasms of which 17 were CMN and the rest were Wilms' tumours [4]. A review of neonatal Wilms' tumours in the national Wilms' tumour register identified 15 cases out of 6832 patients with an incidence of 0.16% demonstrating how rare malignant renal neoplasms are in neonates.

59.3 Pathology

Bolande and associates, in 1967, recognised CMN as a unique lesion that could be distinguished

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_59

clinically and pathologically from true congenital Wilms' tumour by its benign clinical behaviour, a preponderance of mesenchymal derivatives and lack of the malignant epithelial components typical of Wilms' tumour [5]. A definite infiltrative tendency distinguishes CMN from hamartomas with more limited growth potential. CMN is usually solid, unilateral and can attain a very large size like a uterine fibroid.

Histological differentiation is that of a spindle cell neoplasm with interlacing bundles of fibroblasts and myofibroblasts. Tumour types have irregular interdigitating margins in the perirenal fat and wide margins of excision are desirable for complete removal. Incomplete removal results in tumour recurrence which happens within a year of resection in most instances [6].

Atypical and more aggressive mesoblastic nephromas tend to be soft, fleshy tumours with areas of gross haemorrhage and necrosis and are more cellular without recognisable normal glomeruli or tubules.

Another variant is a congenital cystic mesoblastic nephroma (cellular variant) which can present as a unilocular haemorrhagic cyst. This can be detected antenatally and mis-diagnosed as a haematoma in the kidney. The lining of the wall of this cyst shows a typical cellular rim comprising of mitotically active small round and spindle-shaped cells giving the diagnosis of CMN [7].

Gaillard and colleagues recently reported pathological and molecular characteristics of CMN in 35 cases [8]. Based on cellular criteria, 14 were classified as classical, 4 as partly cellular and 17 as cellular CMN. The mean ages were 24, 11 and 70 days, respectively. There were 13 intrarenal tumours (stage I), but 9 classical, 3 partly cellular and 5 cellular CMNs extended to the perirenal fat (stage II) and 5 cellular tumours ruptured (stage III). In order to assess cellular proliferative activity, silver staining of nucleolar organiser region (Ag-NOR) proteins was performed on 19 CMNs. The number of Ag-NOR dots per cell was significantly lower in classical and partly cellular CMN than in cellular CMN, whatever the stage.

Within the cellular CMNs, the mean number of Ag-NOR dots was statistically higher in the single case that recurred with fatal outcome. The number of Ag-NOR dots, DNA content measurements, the histological subclassification, and the presence or absence of tumour at the surgical margins, may be useful features in selecting those patients who will benefit from further treatment after nephrectomy.

59.4 Cytogenetics

A characteristic chromosomal translocation, t(12;15)(p13;q25) has been described which results in fusion of the ETV6 (TEL) gene from 12p13 with the NRTK3 neurtrophin-3 receptor gene (TRKC) from 15q25. This results in a chimeric RNA which is characteristic of both infantile fibrosarcoma and the cellular variant of congenital mesobhlastic nephroma. This suggests a close relation between these two conditions [9].

Human epidermal growth factor receptors (HER) play a critical role in the branching morphogenesis of renal tubules. In addition HER2 expression in Wilms' tumour had been assessed and its role in tumorgenesis has been established. Amplification and over expression increases the metastatic potential of a tumour and promotes chemoresistance [10].

59.5 Tumour Markers

It has been reported that abnormal renin production and hypertension are common features of CMN. Several investigators have reported distinctive patterns of immunoreactive renin staining, suggesting that mesoblastic nephromas are a source of increased renin production producing hypertension [11, 12].

The most intense staining for renin was observed within areas of recognisable cortex trapped within the tumour. Renin was localised in cells in the walls of vessels running up to the glomeruli.

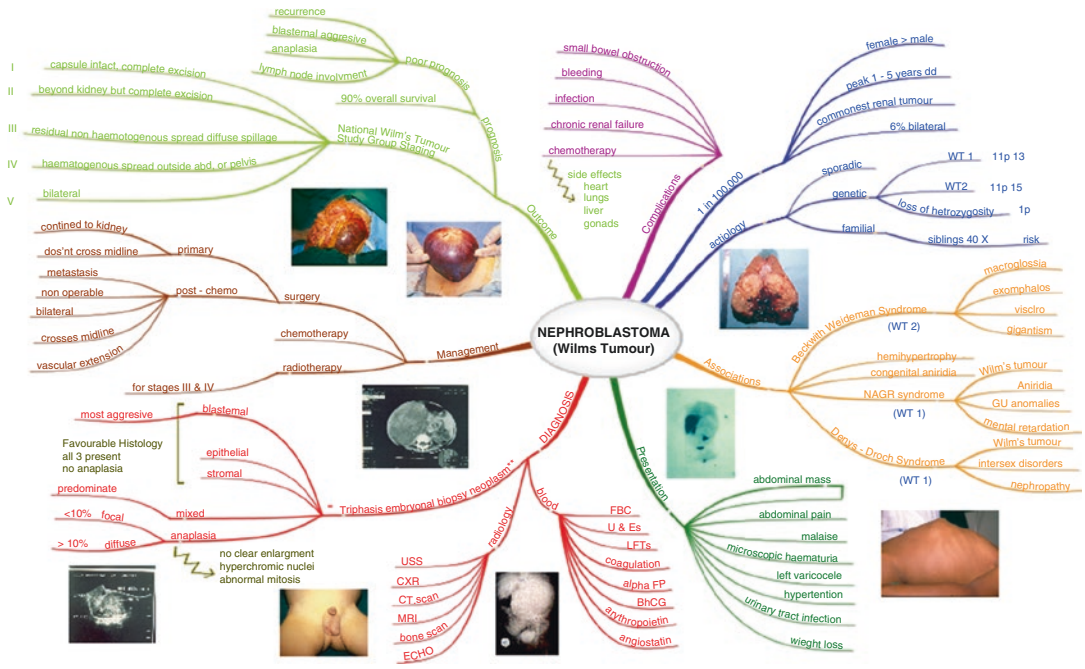

Fig. 59.1 Mind map. Practical Problems in Pediatric Surgery—An Atlas and Mind Maps. Eds. R. Keilani, R. Carachi, D. Gupta, E. Broadis, S. Sharma. Jaypee Brothers, ISBN 978 81 8448 723 7

59.6 Clinical Features

Although prenatal ultrasound is capable of detecting renal neoplasms in utero, there is no specific sonographic characteristics that can differentiate a CMN from a Wilms' tumour. Both tumours present as a palpable abdominal mass in the neonate. Males outnumber females by 2 to 1 with CMN and both sexes are equally affected by Wilms' tumours.

The newborn usually presents with a large, non-tender abdominal mass. Maternal polyhydramnios and prematurity are frequently seen although the reason for this is unclear. Male to female ratio ranges from 1.8:1 to 3:1 [6, 12] Hypertension has been recognised as a presenting feature, and there is an association between preoperative hypertension and cardiac arrest during surgery [6]. Some patients present with haematuria. In the congenital cystic mesoblastic nephroma variant the patient may present with a haemorrhagic problem. Recently mind maps have been introduced to explain in a didactic fashion the clinical features, investigations, differential diagnosis and management of CMN and Wilms' tumour (Fig. 59.1).

Detailed antenatal ultrasound scans may pick up a solid tumour of the kidney. Plain films of the abdomen show a large, soft-tissue abdominal mass that is rarely calcified. Sonography demonstrates the solid nature and renal origin of the mass and most commonly shows a mixed echogenic intrarenal mass.

CMN should easily be distinguished from more common renal masses in the newborn [13]—hydronephrosis or multicystic kidney—which are sonolucent. MRI scans give detailed imaging of the renal tumour and its surrounding structures.

59.7 Treatment

Nephrectomy of this benign tumour is curative without the need for supplementary radiation or adjuvant chemotherapy. Even when there has been intraoperative rupture, excisional surgery

is curative, and local recurrence is rare. Distant metastasis has been reported but is extremely uncommon [14]. In a review of 38 patients with the cellular variant of mesoblastic nephroma showed that seven children had recurrence and three died. Pathologically positive surgical margins were the only statistically significant predictor of recurrent disease. Frozen section may help in obtaining tumour-free margins during surgery. Recent studies on molecular biology may shed further light on tumour behaviour and add criteria for further therapy after surgery.

59.7.1 Preoperative Preparation

Blood samples are obtained for a full blood count, group and crossmatch. Tumour markers renin, active renin, and inactive renin should also be assayed because these tumours have been documented as producing high levels of these hormones [12]. Erythropoietin levels should also be assayed. Careful monitoring and control of blood pressure is required to prevent dangerous perioperative fluctuations. A central venous cannula for intravenous infusion is inserted into the neck vein or subclavian vein as well as an arterial cannula to monitor blood pressure.

59.7.2 Operative Technique

59.7.2.1 Position

The patient is placed supine with a roll under the lumbar spine to create a lordosis.

59.7.2.2 Incision

An upper transverse muscle-cutting incision from the flank across the midline provides adequate exposure. *Laparotomy and exposure of the renal pedicle.*

The abdomen is entered, taking care not to cut into the tumour while incising the abdominal wall muscles. The small intestine is displaced towards the opposite side and covered with moist packs. The liver and the opposite kidney are inspected for the presence of any other disease. This is very rare in this condition. Free fluid is sampled and sent for cytology.

The colon overlying the tumour is retracted medially and the posterior peritoneum lateral to the colon is incised and reflected forward to the midline. Tumour handling should be minimised in hypertensive patients to prevent excessive release of renin. The inferior vena cava and renal veins are both palpated for the presence of tumour. The ureter is identified and a tape is passed around it. It is traced as far down as possible into the pelvis, ligated with 3–0 chromic catgut and divided. Next the gonadal vessels are ligated and divided. Before mobilisation of the tumour, abdominal packs are used to isolate the operative site from the rest of the abdominal cavity. This is to prevent any dissemination of tumour if there is spillage during the time of surgery. The renal vein is doubly ligated and divided. The renal artery is exposed and transfixed with non absorbable sutures.

The para-aortic lymph glands, together with surrounding tissue, are dissected off the aorta and inferior vena cava and labelled carefully. The tumour is removed from the posterior abdominal wall using finger dissection. The excised specimen should contain kidney, Gerota's fascia, fat from the lumbar fossa and para-aortic lymph glands.

After removal of the tumour, haemostasis is obtained with diathermy coagulation or suture ligatures. No drain is required.

59.7.2.3 Postoperative Care

Postoperative recovery following resection of mesoblastic nephroma is rapid. Nephrectomy of this benign tumour is curative. If on histology the tumour is found to be Wilms', it should be treated in accordance with the degree of involvement as outlined in the National Wilms' Tumour Study Programs.

59.7.2.4 Complications

The main complication of CMN is rupture of the tumour during surgery. Howell and colleagues reported intra-operative rupture in 20% of their cases [6]. In practice this is extremely rare despite intra-operative rupture, excellent subsequent relapse-free survival has been reported within tumour.

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Ovarian and Genital Tract Neoplasms

60

Carmen Capito, Daniel Orbach, and Sabine Sarnacki

Abstract

Neonatal tumors occur every 12,500–27,500 live births and ovarian and female genital tract tumors are reported as rare cases in the literature.

Ovarian tumor is an exceptional condition in neonates and, in contrast to older children, sex-cord-stromal tumors are the most frequently reported symptomatic neoplasms.

Considering gynecological neoplasms, a vaginal bleeding in a female neonate should always alert on the risk of vaginal malignant neoplasm with rhabdomyosarcoma and malignant germ cell tumors as the first tumoral types encountered.

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Considering gynecological neoplasms, a vaginal bleeding in a female neonate should always alert on the risk of vaginal malignant neoplasm with rhabdomyosarcoma and malignant germ cell tumors as the first tumoral types encountered

Keywords

Neonatal ovarian tumors • Gynaecological tract neoplasms • Vaginal tumors • Surgical management • Outcomes

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60.1 Neonatal Ovarian Tumors

60.1.1 Introduction

Ovarian lesions encountered in prenatal and early postnatal period are predominantly benign and mainly represented by functional ovarian cysts

P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_60

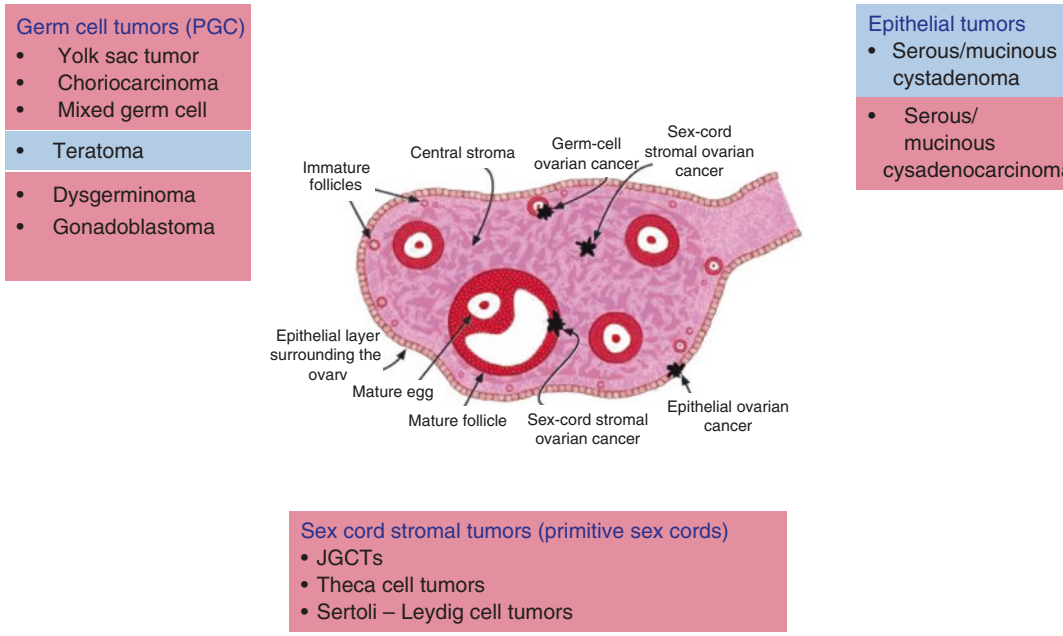

Fig. 60.1 Classification of ovarian tumors

(Fig. 60.1). Considering the entire pediatric age group, ovarian tumors represent nearly 50% of all ovarian masses [1]. Among them, 90% are benign [2]. Three major histopathological groups are recognized [3]. The most frequent is represented by germ cell tumors (60–70%) with teratoma as the major entity and a median age of occurrence of 9 years [4]. This type can be seen in neonates and particularly in its cystic form. A second group is composed by epithelial cell tumors (10–20%) such as cystadenoma and cystadenocarcinoma. These tumors have never been reported in neonates and are mostly seen in adolescence and adulthood. The last group is sex-cord-stromal tumors (10%), very heterogeneous and includes fibro-thecoma, juvenile granulosa cell tumors (JGCT), Sertoli and/or Leydig cell tumors (SLCT) and unclassified sex-cord-stromal tumors [5, 6]. Whereas SLCT and thecomas predominate during adolescence, JGCT predominantly develop during infancy and childhood at a median age of 7 years [7].

Neonatal presentations of ovarian neoplasms have been rarely reported and as in older children, germ cells tumors are expected to be the most frequent type encountered. But these neoplasms and specifically teratomas will rarely be symptomatic in the neonatal period because of their small size explaining why sex-cord-stromal tumors are the symptomatic type the most frequently reported [8–11].

60.1.2 Pathological Entities Encountered in Neonates

Sex-cord-stromal ovarian tumors (SCST) are developed from the peri-ovocytic follicular and stromal cells [1, 5, 12, 13]. Three major histological entities are classically described. Granulosa cell tumor is the most frequent subtype in this group and originates from the granulosa cells of the ovarian follicle. In this subtype, the main steroid secretion is estradiol [7, 14–17] which induces isosexual precocious puberty in girls. In the literature, up to 70% of juvenile granulosa cell tumor of prepubertal occurrence display an estradiol secretion leading to precocious puberty [16–18]. Fibro-thecoma originates from the stromal cells of the ovary that will give rise to the future theca. This type, very rare in the pediatric age group, rarely displays hormonal secretion with almost exclusively androgen secretion and rarely estrogen secretion, as it derivates from stromal cells. The last subtype is Sertoli-Leydig

cell tumor (SLCT). One third of these SLCT induce virilization, but more than 50% have no endocrine manifestations [19]. In case of pure Sertoli tumor, isosexual precocious puberty is a frequent condition [20]. Considering the similarities between Leydig and theca cells in one hand and Sertoli and granulosa cells in the other hand, it is hypothesized that SLCT originate from an ovarian-testicular "trans-differentiation" of unknown mechanism [13]. The physiopathology of those three subtypes is not clear [5, 13, 17, 19, 20] but this illustrates well the peculiar framework of neonatal ovarian tumors and the tight relations between development anomalies and tumorigenesis [21]. Recently, SCST and particularly SLCT were reported to be associated to germline-inactivating DICER1 mutations (mapped to chromosome 14q) as a part of the tumor spectrum of the DICER1 pleuropulmonary blastoma familial tumor predisposition syndrome. This implies that constitutional genetic screening for DICER1 mutations is now mandatory when an ovarian neoplasm is found to be a SLCT as it could be the initial clinical presentation of DICER1 mutations within a family [22].

Germ cell tumors (GCT) comprise highly malignant GCT (yolk sac tumors, choriocarcinoma, embryonal carcinoma, mixed GCT and dysgerminoma), moderately malignant lesions (immature teratoma) and benign lesions (gonadoblastoma and mature teratoma). Their aetiology is unknown and the cell of origin is believed to be the totipotent germ cells [23, 24] These cells develop among the endodermal cells of the yolk sac near the origin of the allantois and migrate to the gonadal ridges during the first month of development. It is thus hypothesized that GCT are developmental tumors arising from a pathological undifferentiated cell that remains within the gonad since the end of ovarian embryogenesis and proliferate slowly, until tumoral lesion becomes evident for diagnosis. The same hypothesis is done for extragonadic locations of GCTs. Curiously the incidence of the different histological subtypes varies according to the anatomical initial location and also the age at diagnosis. In the neonatal period, mature teratoma is mostly encountered in the sacrococcygeal sites (which concern mostly female) [23, 24]. Malignant subtypes and particularly yolk sac tumors are generally encountered in older children after 1 year of age, except for the genital tract location.

60.1.3 Presentation and Differential Diagnosis

Three major modes of revelation can be seen:

- Clinical signs of abnormal hormonal secretion
- Radiological lesions diagnosed fortuitously or during follow up of prenatal pelvic cystic lesion
- Palpable abdominal mass or other rare situations

60.1.3.1 Clinical Signs of Atypical Hormonal Secretion

In case of sex cord stromal tumors, almost 70% produce steroids. Specific signs of abnormal hormonal impregnation at this age can thus reveal them: premature pubarche (Fig. 60.2), breast enlargement, vaginal bleeding or virilization at birth. Prenatal presentation of this type of tumor has been rarely reported [8, 9] and virilized genitalia at birth was reported in one case [9].

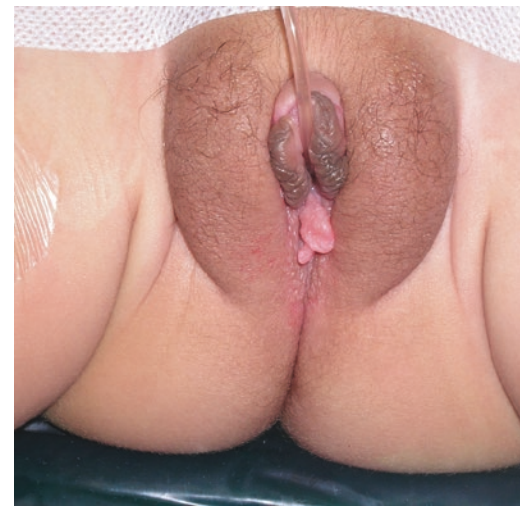

Fig. 60.2 Premature pubarche at birth associated with a prenatal ovarian sex cord stromal tumor

Differential diagnosis of isosexual precocious puberty in neonates is the so called "mini-puberty" occurring during the first 3–4 months of the child development. This mini-puberty state is generally associated with mild signs of hormonal impregnation such as small breast enlargement, acne eruption and possible vaginal bleeding. A pelvic ultrasound evaluation will easily allow this differential diagnosis.

60.1.3.2 Radiological Lesions Diagnosed Fortuitously or During Follow Up of Prenatal Pelvic Cystic Lesion

All these tumors can present as abdominal solid and/or cystic masses. If solid or mixed solid cystic masses are easily attributed to organic lesions needing surgical management, difficulties are essentially encountered with exclusive cystic lesions during neonatal period. Indeed, ovarian cyst is a frequent situation encountered during prenatal diagnosis. Functional cysts are due to foetal impregnation by maternal steroid secretion. These cysts are mainly simple but maybe sometimes complicated (associated ovarian torsion, haemorrhage). Nevertheless, they require precise postnatal follow up until normalization of ovarian images is achieved. This is supported by few series of prenatal ovarian cysts where cases of mature teratomas [25, 26] were identified after surgical removal of a persisting prenatal cyst. This suggests that an ovarian cyst diagnosed prenatally and persisting after breastfeeding weaning or more generally after 6 months should be considered as a potential ovarian tumor [27].

60.1.3.3 Palpable Abdominal Mass or Other Rare Presentations

Diagnosis of an ovarian tumor in the neonatal period as an abdominal mass is exceptional. One case of neonatal Meig's syndrome has been reported associated with a mature teratoma [11].

60.1.4 Management and Prognosis

60.1.4.1 Preoperative Management

The major issue challenging the surgeon is to be able to perform conservative surgery for benign lesions but also to strictly follow the rules of carcinologic surgery for malignant lesions. The intrinsic contradiction between both approaches underlines the need for a diagnosis of the malignant or benign nature of the lesion before surgery. Because of the problem of potential peritoneal spreading of malignant cells, percutaneous cytopunction or fine needle biopsy is not recommended. Diagnosis relies on two main features at this age: imaging and biological markers evolution (AFP, HCG). Interpretation of normal values of AFP in neonatal period is sometimes difficult due to physiological high levels until the age of 1 year. Absence of spontaneous decrease during follow-up must be a sign of alert.

60.1.4.2 Radiological Features

Whereas ultrasound exam is the best way to detect the lesion, pelvic CT or ideally MRI allows a reliable location of the lesion in the gonad (Fig. 60.3). It also permits an accurate description of the components of the lesion orienting on the histological subtype. Indeed, MRI disclosing heterogeneous tumors with different tissue component such as adipose tissue or calcifications will be very specific of germ cell tumors and particularly mature teratoma. Regarding the most frequent malignant lesion encountered in the neonatal period, i.e. SCST, it is usually a solid or mixed lesion but pure cystic lesions have been described in oldest girls [28].

Metastatic spreading is rare in the pediatric age group and has never been reported in neonates. Nevertheless, pretherapeutic work up should include

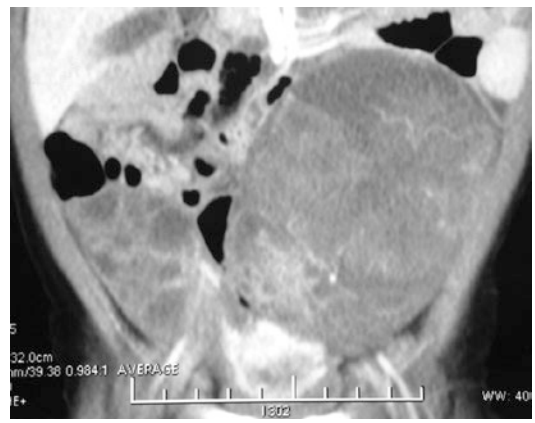

Fig. 60.3 CT image of a bilateral ovarian sex cord stromal tumor in a neonate

thoraco-abdominal CT if a malignant histology is suspected looking for retroperitoneal lymph nodes enlargement and lung or liver metastasis.

60.1.4.3 Biological Markers

The biological markers according to the histological subtype are listed below.

- Sex cord stromal tumors
- Juvenile granulosa cell tumors: antimullerian hormone (AMH), inhibin B, estradiol (70%), rarely testosterone
- Sertoli Leydig tumors: testosterone, estrogen and in some cases a moderate production of AFP is possible [6, 29]
- Germ cell tumors
- Yolk sac or endodermal sinus tumor: alpha-foetoprotein (AFP). The interpretation of this marker is difficult in the neonatal period regarding the elevated level of this marker at birth, with a slow decrease during the first year of life. Interpretation relies thus on kinetic more than absolute level (normal level < 10 ng/mL after 1 year of life) (Table 60.1).
- Choriocarcinoma or GCT with a choriocarcinoma component: β-HCG, total HCG
- Embryonal carcinoma: non secreting tumors even if in some cases AFP may be slowly elevated especially in case of mixed tumour,
- Dysgerminoma: non secreting even if low level of β(beta) HCG may be observed
- Mature and immature teratoma: markers are by definition normal

Table 60.1 AFP level until normalization

	AFP level (ng/mL)	Standard deviation
Premature	134,734	41,444
Newborn	48,406	34,718
2 weeks	33,113	32,503
1 month	9452	12,610
2 months	323	278
3 months	88	87
4 months	74	56
5 months	46,5	19
6 months	12,5	9,8
7 months	9,7	7,1
8 months	8,5	5,5

60.1.4.4 Surgical Procedure

In case of SCST or suspected malignant GCT, total ovariectomy is recommended with adnexectomy if the fallopian tube is involved. Considering mature teratoma, the estimated risk of metachronous contralateral teratoma is around 10%. Thus partial surgery, when possible, is recommended if this subtype is radiologically suspected. If post operative pathological analysis reveals a part of malignant contingent, a second procedure will be performed in order to complete the ovariectomy. A strict follow-up is recommended to detect early metachronous lesion. In all cases, the rule is to avoid any tumor effraction during surgery because the sanction will be adjuvant chemotherapy with high risks for these young patients. Thus, it is mandatory to avoid a laparoscopic approach to remove the lesion in these paediatric ovarian tumors since even apparent mature teratoma can have a small content of malignant subtypes with undetectable levels of biological markers. The surgical treatment of ovarian lesions in girls is performed by a supra-pubic approach, which allows the exteriorization and treatment of the lesion. Before this step, a laparoscopic exploration is mandatory in order to perform the staging of the tumor including: obtain a sample of ascitis or peritoneal washing (in the absence of ascitis) for cytology and inspect the peritoneal surfaces (including diaphragmatic domes), the abdominal organs, with special attention to the contralateral ovary, pelvic and retroperitoneal lymph node and liver. Biopsy of any suspicious areas should be performed and omentectomy if the omentum (or parts of it) is abnormal. Adjuvant chemotherapy is exceptionally necessary in this age group as complete surgical resection is generally obtained.

60.1.4.5 Prognosis

Prognosis in this specific age group is unknown as the onset of malignant tumor of the ovary in the neonatal period is an exceptional condition. However, providing a non metastatic disease at diagnosis and a complete resection of the lesion without tumor effraction, long term prognosis should be as good as their older counterpart, meaning around 88% and more than 90% long

term survival rates for respectively sex cord stromal tumors [7, 13] and malignant germ cell tumors [30].

60.2 Neonatal Genital Tract Tumors

60.2.1 Introduction

Tumors of the genital tract are very rare but classically diagnosed in infants. Different entities are encountered with by frequency: rhabdomyosarcoma, malignant germ cell tumors and other rare entities such as clear cell adenocarcinoma; this last subtype being diagnosed later in life [31]. Their primitive location can be the vulva, the vagina or the uterus cervix. Prognosis of these tumors relies on the local tumor control obtained nowadays with less radical surgical management than in past decades [32, 33]. Recent therapeutic regimens combine chemotherapy, conservative surgery and in some cases local radiation therapy (essentially brachytherapy).

60.2.2 Pathological Entities Encountered in Neonates and Their Molecular Characteristics

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in childhood and also the most frequent tumor of the paediatric female genital tract [31–35]. The tumor arises from mesenchymal derivated cells and histologically resembles normal fetal muscle. Vagina is the most frequent localization encountered in the neonatal period. RMS are classified in two main subtypes in the pediatric population: embryonal and alveolar. The recent improvement in cytogenetic characterization of these two subtypes has improved the differential diagnosis [36] which is of great importance as alveolar RMS is associated with a more aggressive disease pattern and a higher mortality.

Embryonal RMS neoplasms are typically comprised of spindle shaped cells, with a stromal rich appearance [36]. Botryoid tumors, which are a particular form of embryonal RMS with a grape-like aspect, occur almost exclusively in the bladder or vagina of infants and young children. These embryonal RMS are characterized by a loss of maternal imprinting (loss of heterozygosity) at the 11p15 locus, a region harbouring the insulin-like growth factor 2 (IGF2) gene, H19 and P57, the latter being two tumor suppressor genes [36]. These tumor types tend to occur in the younger age group and account for almost two third of all RMS. Recent analysis have found a new recurrent VGLL2-related fusion transcript in “infantile RMS” that encourage to search all rare transcripts in addition to classical ones at this age to help diagnosis [37].

Alveolar RMS is typically comprised of small round densely packed cells, arranged around spaces resembling pulmonary alveoli. These subtypes of RMS tumors harbour distinguishing chromosomal translocation marker, with typically t(2;13)(q35;q14, 36). This translocation creates a fusion protein (PAX3-FOX01) that is thought to be responsible at least in part for its malignant phenotype [38, 39]. A variant translocation t(1;13) leading to the fusion protein PAX7-FOX01, can also be seen with a slightly better prognosis [36]. Alveolar RMS is more frequently diagnosed in older children considering the urogenital tract.

Although mostly sporadic, some syndromes can predispose to development of RMS in childhood such as Neurofibromatosis type 1, Li-Fraumeni, Costello and Beckwith-Wiedemann syndromes.

Malignant germ cell tumor (GCT). Vagina remains a rare primary location of GCT (3–8% of all GCT) and in contrast to the ovary, germ cells tumors encountered in genital tract location are mainly malignant ones, with yolk sac tumors accounting for almost all the cases [31, 36, 40, 41]. They are supposed to derive from an aberrant migration of totipotent germ cells, like other extra gonadal germ cells tumors. Most of these tumors will be secreting ones (AFP).

Clear cell carcinoma of the vagina was related to prenatal exposure to diethylstilboestrol during the first trimester of pregnancy. Since this treatment is no longer used, this tumor type has disappeared in the diagnosis algorithm of young girls vaginal tumors. Anyway, some recent studies seem to advocate a transgenerational effect of this treatment via epigenetic transmission [42]. This should then be kept in mind even extremely rare.

60.2.3 Presentation and Differential Diagnosis

60.2.3.1 Presentation

Recent large review by Fernandez Pineda et al. [31] has highlighted the frequency of the symptoms in vaginal tumors as follow:

- Bleeding or blood tinged discharge from the vagina (61%)
- Protruding mass (39%) (Fig. 60.4)

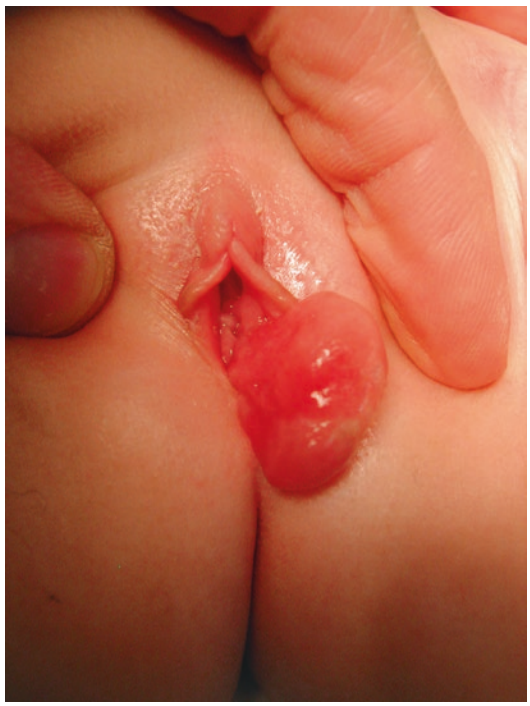

Fig. 60.4 Embryonal bifocal tumor (vaginal and bladder) revealed by a protruding mass in a 5 months old baby

Considering vulvar tumor, the diagnosis is suspected by local examination with the discovery of a mass bulging in the perineum.

Uterus tumors are generally diagnosed in older children because of delayed symptoms before diagnosis. This may partially explain their worst prognosis. In a large series by Martelli et al. [32], median age at diagnosis for vulvovaginal rhabdomyosarcoma was 21 months (range, 9 months to 15.6 years) whereas for uterus RMS, it was 15 years (range, 10 months to 16.6 years). Bleeding remains the most reliable sign in this location.

Neonatal rhabdomyosarcomas have generally aggressive biologic behaviour as 50% of the patients reported in some large series [43, 44] had widespread disease at the time of diagnosis. Metastatic disease can appear in the lungs, lymph nodes, liver, bone marrow, bone, and brain. However this seems not to be the case in the specific urogenital tract location [32, 35].

60.2.3.2 Differential Diagnosis

Differential diagnosis of vaginal blood discharge in neonatal period remains hormonally induced genital bleeding that can occur during the so called "mini-puberty" of the first 3–4 months of the child development or in case of secreting sex cord stromal tumors. The absence of associated signs of hormonal impregnation will point on genital tract neoplasm and ultrasound, pelvic MRI and/or vaginoscopy will confirm the diagnosis.

60.2.4 Management and Prognosis

60.2.4.1 Imaging and Histological Studies

As most of vaginal GCT are secreting Yolk Sac tumors (YST), the first exam must be blood analysis of biological markers (AFP, β-HCG, total HCG). Normal physiological level in the neonatal period of these markers should also be taken into account. Initial management of these tumors should then include histological diagnosis and evaluation of the disease extension. Surgical

biopsies remain the gold standard in order to obtain enough materials for immunohistochemical and molecular biology studies especially if blood markers are negative. This will be performed under general anaesthesia and the procedure will include a vaginoscopy and a cystoscopy. Both explorations are mandatory as extension to the adjacent tract can occur and rare cases of true double locations have been observed (personal observation). As one part of the tissue harvested must be rapidly frozen for molecular studies it is important to carefully prepare this surgical procedure. If a complete resection can be achieved without large mutilation, this should be attempted. Otherwise a central catheter should be placed at the end of the procedure in order to rapidly start chemotherapy treatment.

Complementary investigations include abdominal ultrasound, thoraco-abdominal CT or MRI (Figs. 60.5 and 60.6), bone scintigraphy and bone marrow aspirate if bone metastases are suspected.

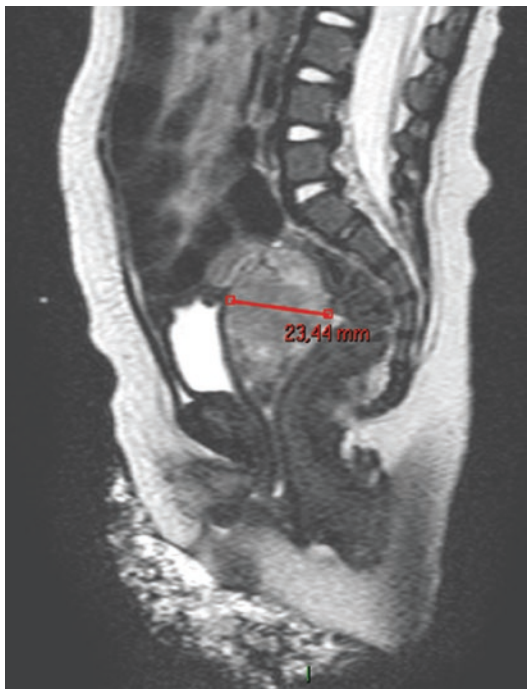

Fig. 60.5 Secreting vaginal yolk sac tumor in a 8 months girl, AFP 3268 UI/mL – Pelvic MRI, T2 weighted sequence

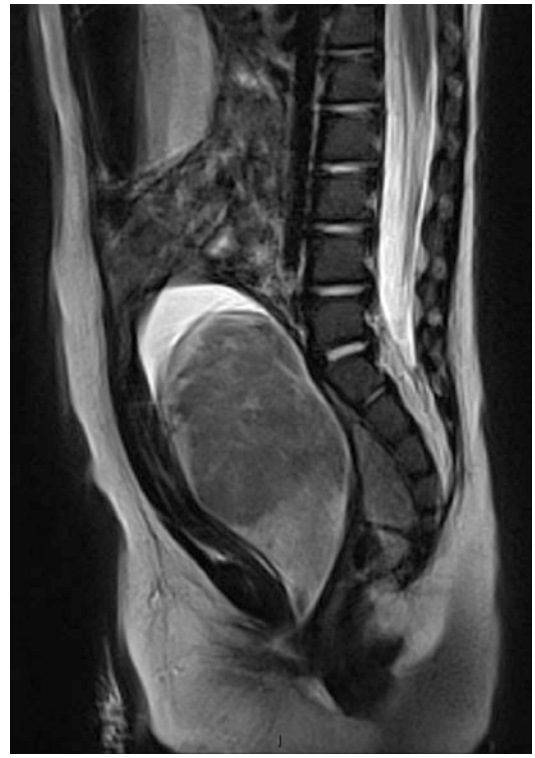

Fig. 60.6 Pelvic MRI of a vaginal rhabdomyosarcoma—T2 weighted sequence

60.2.4.2 Therapeutic Strategies

The treatment regimen proposed should take into account the particularities of the young age of the patient. Indeed, immaturity of enzymatic processes for drug metabolism, and risks of unacceptable long-term morbidity should always be kept in mind. Thus, in contrast to older children, external radiation therapy will never be proposed in neonates. A local radiation therapy (brachytherapy) will be reserved to infants with residual disease or after relapse.

First line treatment combines chemotherapy and surgery and their chronology will be dictate by the stage at presentation, the location of the primary tumor, the resectability at each step of treatment, the expected morbidity of the operative procedure and the histological characteristics of the lesion. The most effective and less deleterious chemotherapy regimen in neonatal rhabdomyosarcoma associates vincristine and actinomycin D. Cyclophophamide is reserved to

advanced disease [32, 35, 45, 46]. For neonatal malignant germ cell tumors, the regimen associates carboplatine and etoposide.

Regarding the surgical treatment, the strategy is different between vaginal GCT and urogenital RMS. In both cases, iterative urogenital endoscopies are performed along the treatment protocol to better plan the modalities of the surgical resection. It is important to explore both the urinary and genital tract to appreciate the extension of the disease but also because potential double location (vagina and bladder) of RMS is possible (personal observation). Whereas treatment could be achieved without surgery in urogenital RMS when complete imaging defined remission is obtained after chemotherapy, surgical resection of the primary location is always mandatory in vaginal GCT. In this latter case, efficiency of neoadjuvant chemotherapy usually allows to avoid mutilating surgery and to propose partial colpectomy. For urogenital RMS, surgical local treatment could be completed by local brachytherapy and thus mutilating surgery is exceptional. Ovarian transposition should then be considered if brachytherapy is decided [35].

Follow up consists of periodical endoscopies under general anaesthesia and repeated MRI (every 3 months during the first 2 years of follow up and twice a year after). Relapse, if occurring, is essentially local and will benefit of extensive surgery whatever importance of mutilation rather than external radiation therapy which exposed to higher morbidity in this age group [35]. Whereas the options for reconstructive surgery (vaginoplasty, bladder reconstruction) will be exposed to parents before mutilating surgical treatment, this will be proposed after complete oncological remission.

60.2.4.3 Prognosis

Genital tract locations are known to be of better prognosis regarding the overall prognosis of rhabdomyosarcoma. This prognosis seems more or less identical to older children with a long term survival rate of 70% [32, 35]. More accurately, infants with embryonal histology and complete surgical resection have a cure rates higher than 90% [45] and those with metastatic disease at diagnosis a long-term survival rates under 25% [44, 45]. At this opposite, vaginal malignant germ cell tumors in these locations have an overall good prognosis provided that early diagnosis is made and multidisciplinary care is provided [40, 47, 48].

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Sacrococcygeal Teratoma

61

Dhanya Mullassery and Paul D. Losty

Abstract

Sacrococcygeal tumour (SCT) is the commonest neoplasm seen in the newborn. A 'teratoma' (derived from the Greek language meaning "Monster")—is best defined as a neoplasm arising from primitive tissues which originated from all three embryonic germ cell layers—endoderm. Mesoderm and ectoderm. SCT occurs in 1:30,000–40,000 births according to recent publications emerging from the UK and Europe (Ayed et al. Prenat Diagn. 35: 1037–47, 2015; Pauniaho et al. Acta Paediatr. 102:e251–6, 2013). There is often a female preponderence (3:1) except in familial cases of SCT which may have an equal gender distribution (M:F = 1).

Keywords

Sacrococcygeal teratoma • Prenatal diagnosis staging • Surgery • Outcomes

61.1 Introduction

Sacrococcygeal tumour (SCT) is the commonest neoplasm seen in the newborn. A 'teratoma' (derived from the Greek language meaning "Monster")—is best defined as a neoplasm arising from primitive tissues which originated from all three embryonic germ cell layers—endoderm. Mesoderm and ectoderm. SCT occurs in 1:30,000–40,000 births according to recent publications emerging from the UK and Europe [1, 2]. There is often a female preponderence (3:1) except in familial cases of SCT which may have an equal gender distribution (M:F = 1).

61.2 Pathology

Primordial germ cells originating in the region of the yolk sac of the developing human migrate to the genital ridge on the posterior abdominal wall at 4–5 weeks gestation [3]. Arrested or aberrant cell migration is thought to result in the development of totipotent germ cell tumours often at midline anatomical sites. Tumours may therefore contain hair, teeth, neural and gastrointestinal

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_61

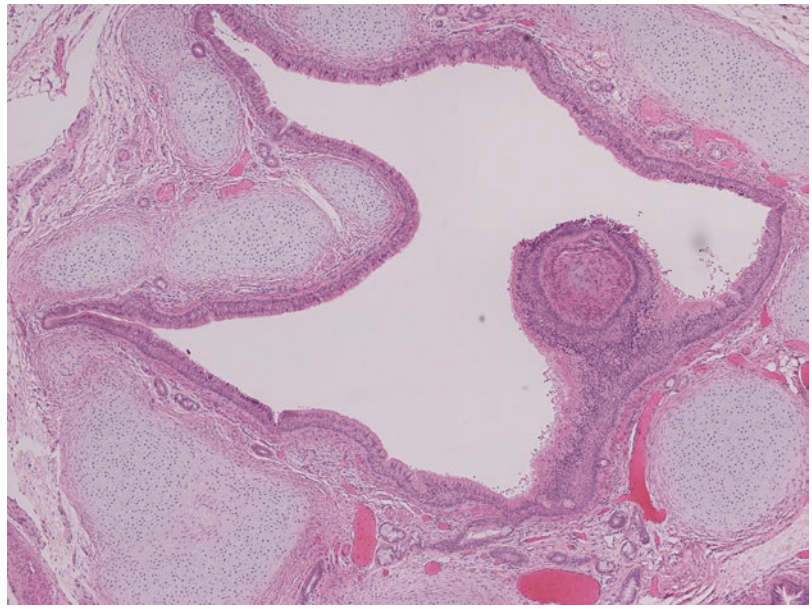

Fig. 61.1 Histology sacrococcygeal tumour specimen. Pathology shows SCT tumour with central cystic areas surrounded by respiratory type epithelium with lobules of cartilage, connective tissue including blood vessels and adipose tissue

like tissues (Fig. 61.1). Most sacrococcygeal lesions (95%) are mature 'benign' or 'immature' teratomas with 5% belonging to the malignant spectrum of endodermal sinus tumours (EST)]. A small number of patients (5%) may harbour metastastic disease at primary presentation. Risks of malignancy are reported to be significantly greater in SCT tumours which are often less apparent externally and those also encountered in older patients that may present beyond the typical neonatal period. Altman proposed that the higher malignancy rate(s) encountered in older infants is likely a reflection of delayed diagnosis with consequent histological transformation of occult lesions.

61.3 Fetus with SCT

The diagnosis of SCT is most often made in the fetal period with the routine use of obstetrical screening ultrasound [4]. Some 70–80% of SCTs are now detected by prenatal sonography. Real time ultrasound is useful in monitoring growth characteristics of SCT tumours which may have haemodynamic consequences for fetal well being. Rapidly growing lesions may contribute to a 'vascular steal' phenomenon arising in the fetus with risks of 'in utero' death from hydrops and 'maternal mirror' syndrome—a pre-eclamptic associated illness developing in mothers with severe hypertension and proteinuria. Prenatal SCT detection should always prompt a careful search for other anomalies present in up to 15–30% cases. These may include haemangioma(s), chromosomal disorders, anorectal, urologic, spinal meningocoele, orthopaedic and cardiac pathologies. Mothers should be offered amniocentesis to exclude these chromosomal disorders such as trisomy(s) 13, 18, and 21. Fetal MRI can be deployed in selected cases to view definition of anatomy with tumour extension into the pelvis or abdominal cavity(s) readily seen on magnetic resonance imaging. These fetal medicine studies may influence the site and mode of planned delivery [4, 5].

A recent publication from Finland reported a high mortality (33%) for antenatally detected SCT after excluding termination of pregnancies [2]. This emphasises the crucial need for prenatal counselling by an expert team [4]. The strongest predictors for fetal death are placentomegaly with hydrops a marker of cardiac failure in the fetus. This is related to anaemia occurring in the fetus resultant from

haemorrhage into tumour. Maternal polyhydramnios contributes to early rupture of membranes and premature birth. The histological identification of anterior pituitary gland like tissues in pathology sections of SCT lends speculation to the role of vasoactive substances released by the tumour contributing to fluid retention in the fetus and hydrops.

Although several fetal intervention procedures have been advocated for SCT ranging from simple amnioreduction to fetal tumour resection clinical experience is strictly limited to only a few centres worldwide and is associated with procedure related morbidity with risk of preterm labour [4]. Minimally invasive techniques that have been promoted include laser, radiofrequency ablation, thermocoagulation and tumour embolisation using coils or alcohol [6]. Recent work has suggested improved outcomes for 'vascular' ablation (objective here to target the tumour's feeding vessels) compared to 'interstitial' ablation (goal to directly ablate the tumour itself) in these high risk groups [6, 7].

Elective delivery with C-section hysterotomy near term (>37 weeks) is best advocated for neoplasms >5 cm in size to avoid obstructed vaginal labour with its risks of tumour rupture and fetal death. In those fetuses with impending hydrops, early C-section is advisable as soon as fetal lung maturity is established i.e. >30 weeks gestation [4, 8]. This may also be achievable in premature 'high risk' cases by maternal antenatal corticosteroid administration a practice we have occasionally employed in Liverpool with some success.

61.4 Newborn Presentation

In the newborn a "monstrous" like neoplasm is readily observed at the base of the spine within the buttock region that frequently displaces the normal external anatomy of the anal orifice (Figs. 61.2 and 61.3). Large tumours can have pelvic or abdominal cavity extension that may obstruct the urinary tract resulting in hydronephrosis. Likewise large tumours may interfere with bladder and bowel emptying from birth by compression of vital anatomy.

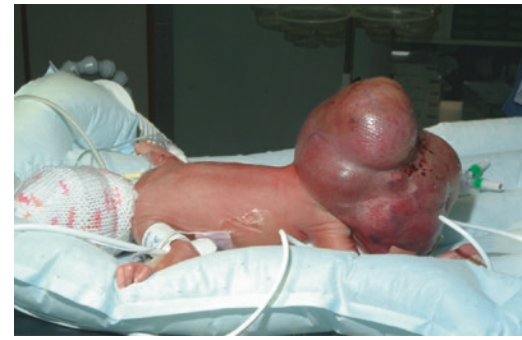

Fig. 61.2 Premature female infant with large sacrococcygeal teratoma

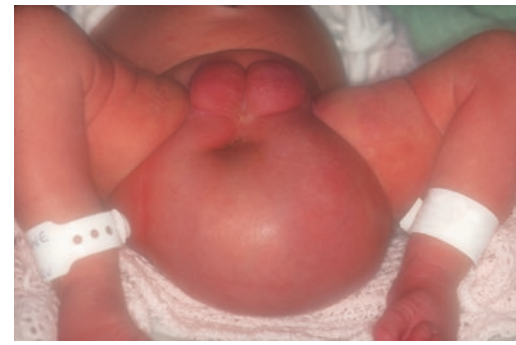

Fig. 61.3 Term newborn with large tumour displacing the normal anatomical site of the anal orifice

61.5 Associated Conditions

Associated conditions are reported in up to one third of patients most commonly involving the urogenital system including hydronephrosis and vesicoureteric reflux [9, 10]. Others mentioned earlier include anorectal malformations, myelomeningocele, hip dysplasia and sometimes lung hypoplasia. The most common and well known syndrome linked with SCT is the Currarino triad [11]. Trisomy(s)—13, 18, and 21 are excluded by offering prenatal screening. Currarino syndrome defines the co-existence of a presacral mass lesion, sacral bony defect and anal stenosis [11]. The condition is transmitted in an autosomal dominant pattern with identifiable mutations in the homeobox family of genes—MNX1 formerly HLXB9 [11, 12].

61.6 Investigations after Birth

An abdominopelvic ultrasound is the first recommended screening investigation ordered. Magnetic resonance imaging can provide very clear definition of Altman stage to plan operative strategy [13]. Serum tumour markers—alpha fetoprotein (AFP) and beta human chorionic gonadtropin (B-HCG) levels are routinely obtained and measured. AFP is greatly elevated in fetal life (100, 000 IU or higher). AFP half -life varies considerably in early postnatal life with levels reaching normal values by 12 months of age. AFP and HCG should be routinely assayed in follow up visits post resection to monitor and detect tumour recurrence.

61.7 Staging

Altman (1973) surveyed members of the Surgical Section of The American Academy of Pediatric Surgical and proposed the following staging classification (Fig. 61.4) [13].

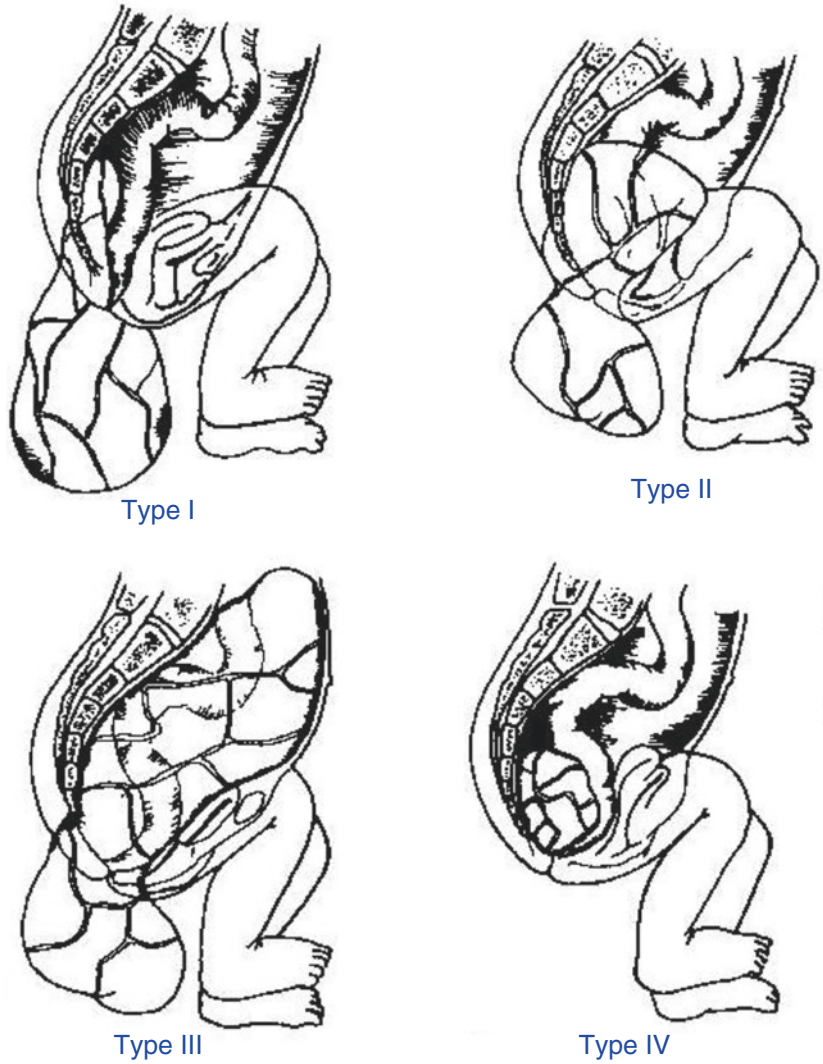

Fig. 61.4 Altman staging system (Surgical Section American Academy Pediatrics 1973). Type I lesions (46.7% of reported cases) predominantly external tumours, Type II (34.7%) external tumours with intrapelvic extension, Type III (8.8%) tumours visible externally with predominant intrapelvic and abdominal extension, Type IV (9.8%) entirely presacral lesions. Adapted from Altman RP, Randolph JG, Lilly JR. Sacrococcygeal teratoma; American Academy of Pediatric Surgery Survey 1973. J Pediatr Surg. 1974; 9: 389–398

Table 61.1 CCG/POG staging system for malignant extra gonadal germ cell tumours

Stage	Description
I	Complete resection at any site, coccygectomy for SCT, negative tumour margins, tumour markers negative or positive
II	Microscopic residual, lymph nodes negative, tumour markers negative or positive
III	Gross residual or biopsy only, retroperitoneal nodes negative or positive, tumour markers negative or positive
IV	Distant metastases including liver

Type 1: predominantly external with minimal presacral component
Type 2: presenting externally with significant intrapelvic extension
Type 3: apparent externally but predominant mass pelvic extending into abdomen
Type 4: presacral with no external presentation

The CCG/POG staging system for malignant extra gonadal germ cell tumours is shown in Table 61.1.

61.8 Postnatal Management

Following patient work up early elective resection of SCT is planned (in the absence of metastatic disease)—where complete resection is judged feasible from imaging studies. Neoadjuvant chemotherapy is administered in cases of malignancy where metastatic disease is evident or the primary tumour is deemed initially unresectable. Modern chemotherapy regimes for malignant extra gonadal germ cell tumours include platinum based therapy (carboplatin or cisplatin), etoposide and bleomycin (PEB or JEB) in association with vinblastin and ifosfamide for high risk tumours.

Operation for SCT entails gross tumour resection with coccygectomy [14, 15]. The surgeon must also pay particular attention to meticulous reconstruction of the pelvic floor to ensure preservation of bladder and bowel function along with aesthetic buttock wound closure. Blood should be cross matched, coagulation profile(s) checked, arterial line monitoring secured and a urinary catheter inserted to monitor renal function. The author routinely inserts an internal jugular central venous catheter (Broviac) before commencing tumour resection to ensure the anaesthetist has adequate circulatory access for blood, platelet products or pharmacologic agents (e.g. inotropes) if necessary. Broad spectrum antibiotics should be routinely administered. The patient is placed in a prone 'sky-diver' position with the shoulders and pelvis supported with the aid of rolls. A Chevron incision (or modified Chevron/midline PSARP in small lesions) is commenced after outlining the operative field with a skin marking pen (Fig. 61.5). Care should be taken to preserve as much skin as possible at the commencement of the operation. Excess or redundant skin can be trimmed after tumour resection. Resection aided by bipolar diathermy proceeds with great attention to avoid tumour spill or rupture with efforts to secure and ligate the middle sacral vessels and resection of the coccyx. As the resection proceeds a suitably sized Hegar dilator positioned in the rectum aids its ready identification. The tumour is then carefully freed from its lateral and inferior attachments avoiding injury to the internal and external anal sphincter complex. Reconstruction of the pelvic floor is aided with use of a muscle nerve stimulator. The thinned out levator ani are sutured to the perichondrium of the anterior surface of the sacrum which brings the displaced anus into a more normal anatomical position. The gluteal muscles are reconstructed in the midline and the overlying skin defect closed with fine interrupted absorbable sutures (Fig. 61.6). Large lesions (Altman I and II) extending into the pelvis may be adequately resected with a Chevron perineal approach. Abdominal tumour extension (Altman III) if desired may be first approached through an infraumbilical incision to isolate and secure feeding vessels. The patient may then be turned with temporary abdominal wound closure achieved with an adhesive steridrape. The Chevron perineal stage of the operation is continued with tumour resection and coccygectomy. Recent reports emphasise the importance of surgical aesthetics with avoidance of unsightly scars as many SCT patients are female. Modified elliptical posterior sagittal incisions which can then be closed in the midline can provide cosmetically superior results [10]. Principles of surgical oncology should be strictly adhered to and it must be remembered that the coccyx should always be

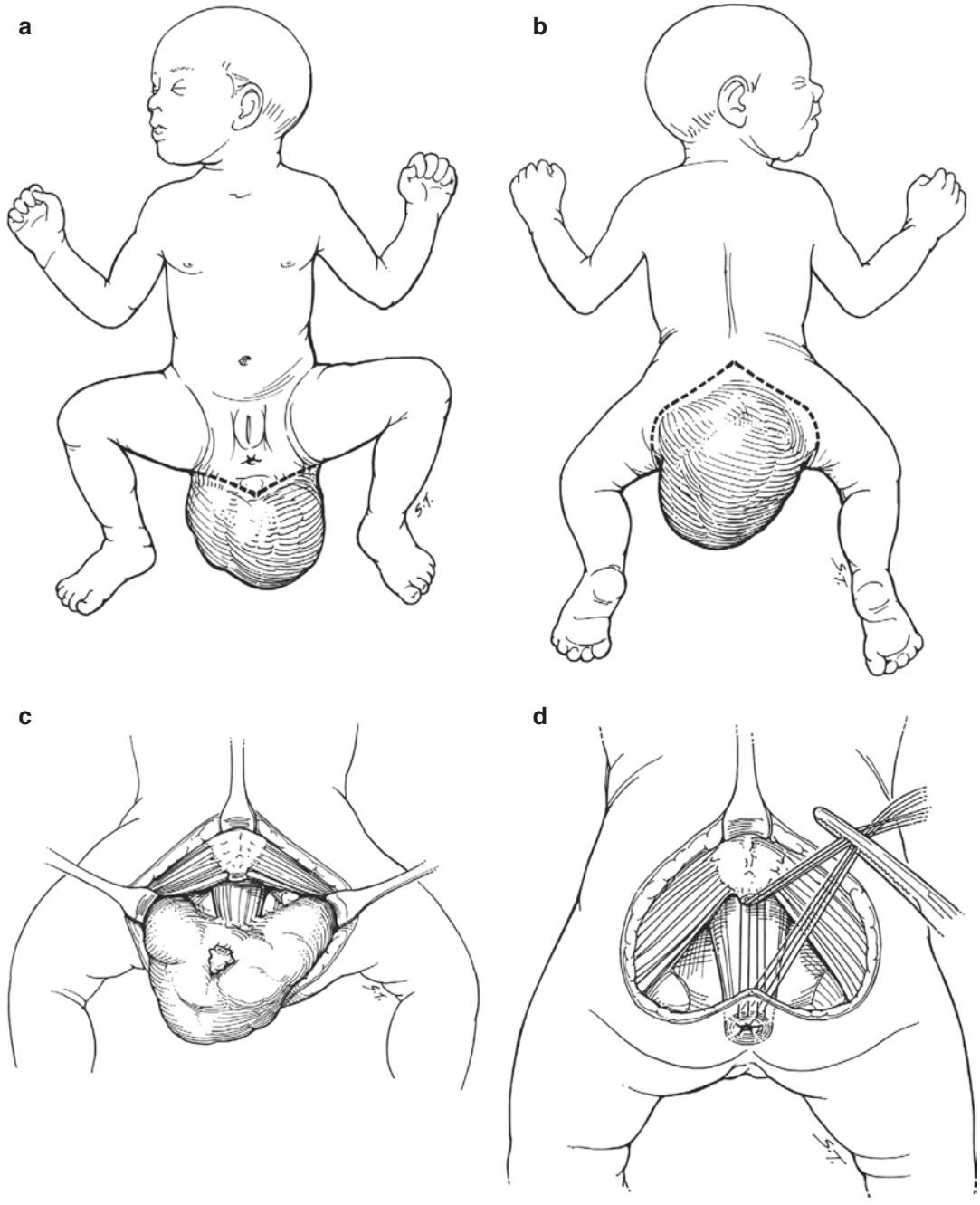

Fig. 61.5 Principle phases of surgical resection. The tumour is resected with coccyx and the pelvic floor reconstructed to aid restore normal anatomy. Adapted from Rescorla FJ. Semin Pediatr Surg 2012;21:51–60.

excised with the tumour mass to reduce risks of recurrence [10].

The major intraoperative risks for the patient and attending surgeon is exsanguinating haemorrhage usually from sacral vessels feeding the tumour. Several methods have been suggested to control or ligate the median sacral artery before mobilising the tumour. Bentley first reported ligation of the median sacral artery before attempting to resect SCT tumours [15]. Lindahl

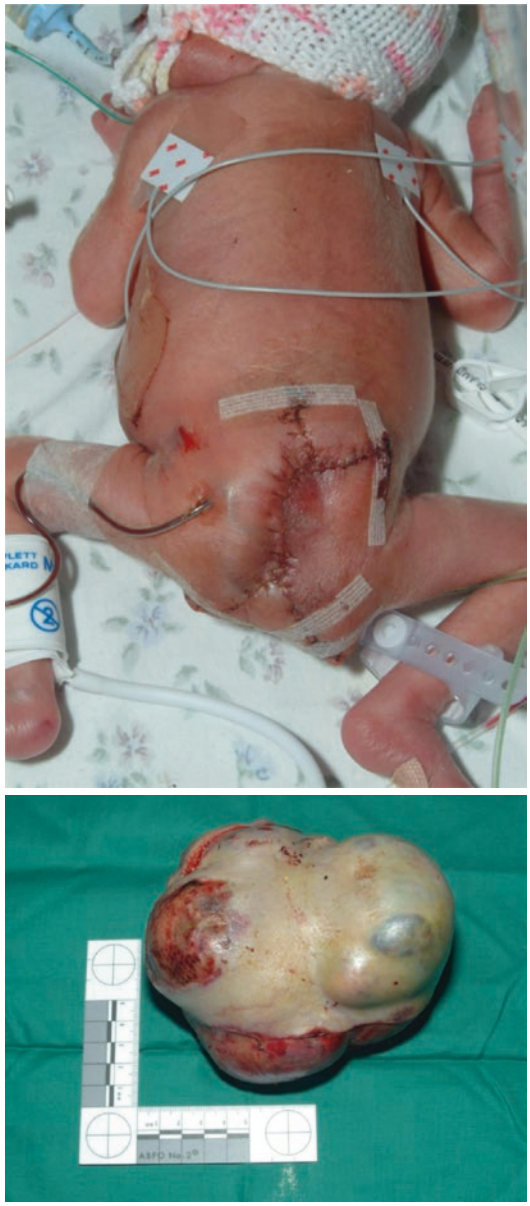

Fig. 61.6 Infant (Fig. 61.2 photo) immediately after surgery with resected tumour

also advocated use of an aortic snare to minimise risk of haemorrhage during resection of a giant lesion in a newborn [16]. Minimally invasive surgery has been deployed in a similar fashion to obtain vascular control of large Altman stage tumours. Interventional radiology with angiography and embolization has likewise been successfully utilised to occlude feeding vessels prior to resection of a large SCT [17]. Altman IV lesions (not often seen in newborns) are resected using a posterior saggital approach.

61.9 Prognosis and Outcomes

Poor prognosis for those detected antenatally will include in utero deaths, need for fetal intervention and early perinatal fatalities [4, 18]. Tumour volume to fetal weight ratio (TFR >0.12) and solid tumour volume to estimated fetal weight index (STVI >0.16) have recently been proposed as prognostic indicators for impending fetal cardiac failure, hydrops and mortality of the fetus before 32 weeks gestation [19, 20]. Benachi et al. suggested a prognostic staging classification based on SCT tumour diameter (>10 cm) with the presence of pronounced vascularity, cardiac failure and rapid growth resulting in 58% mortality in a "high risk" group [21].

The primary cause(s) for postnatal deaths in SCT patients are exsanguinating haemorrhage and malignant disease. Thirty day postoperative mortality rate(s) for SCTs are estimated at 5–6%, mainly from haemorrhage, coagulopathy and prematurity. Further scrutiny of SCT mortality figure(s)–(up to 15% in some published studies)—also shows primary tumour malignancy or disease recurrence(s) as risk factors [20–25].

An overall survival rate of 95% should be achieved for most benign lesions in the newborn period managed in experienced surgical centres [25]. In patients harbouring malignant tumours 87% survival is attainable with the new platinum based chemotherapy regimens [23, 24]. Distant metastases to multiple organ sites is a strong prognostic factor for poor survival especially so in those few infants who do not benefit from neoadjuvant chemotherapy [23, 24].

Incomplete resection of tumour is a well documented risk factor for local recurrence [24]. Recurrences in up to 11% of cases after SCT operations are detailed. Recurrent lesions may be mature or immature teratomas or endodermal sinus tumours. Malignant recurrences have been observed even after previous resection of benign tumours. These are thought to result from very small foci of malignant cells residing in a

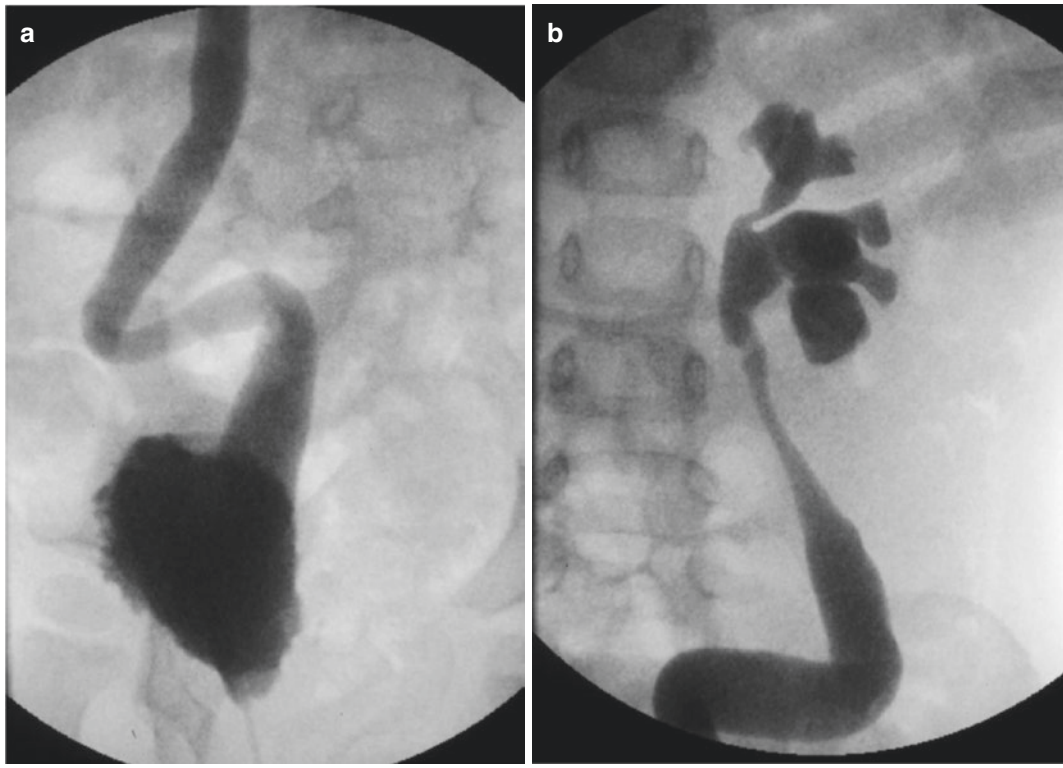

Fig. 61.7 Voiding cystogram showing neuropathic bladder with vesicoureteric reflux in a female patient some months after surgical resection of an Altman Stage III sacrococcygeal tumour

predominantly benign looking lesion. Recurrences can occur weeks, months or many years after primary resection which emphasises the need for vigilant long term follow up with monitoring tumour markers aided by surveillance ultrasound imaging [25]. Treatment for a benign recurrence is 'red-do' surgical resection. Malignant recurrences need a combination of treatment modalities—chemotherapy and 're-do' resection. Survival metrics for an SCT recurrence are of the order of 86% [24].

Data reporting functional outcome(s) after operation for SCT have become increasingly important. Bladder and bowel continence problems have been recorded in up to 30–40% of survivors [25–28]. It is not clear whether this is primarily linked to the tumour itself compressing/stretching pelvic organs and vital nerves or secondary/iatrogenic to acquired pelvic dysautonomia after surgical operation. Some published reports cite a higher prevalence of functional deficits in patients who have had large Altman type II and III tumours. Bowel and bladder disturbance require an individualized co-ordinated patient care plan. Investigations should include US imaging (pre and post micturition urine volume), urodynamics, voiding cystography (Fig. 61.7) and anorectal manometry where feasible. Clean intermittent catheterisation, rectal enemas/suppositories and in older patients (>5 years) the ACE procedure (appendicostomy stoma) may be required. Studies now also note a significant proportion of adult survivors with impaired sexual function and quality of life issues [27]. These findings serve to highlight the need for comprehensive long term follow up clinics to measure the success of selected management programmes. Publications also report a high incidence (10–40%) of cosmetically unacceptable scars of particular concern in young girls and boys with obvious psychological impact on self esteem and body image. Finally with many paediatric surgical centres in the UK, Europe and elsewhere perhaps treating no more

than one or two new cases per year a debate could be made for centralising care to improve patient outcomes [25].

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Part IX

Urology

Management of Impaired Renal Function in the Newborn

62

Henry Morgan and Caroline Ann Jones

Abstract

The neonatal kidney can adapt to the usual physiological processes occurring after birth and allow homeostatic regulation to transfer from the placenta to the kidney. However during this period of transition the neonatal kidney is vulnerable. It is less able to withstand stress such as hypotension, hypoxia or hypovolaemia which will result in a decrease in kidney function. It is therefore not unexpected that the incidence of acute renal failure in children is highest in the neonatal period, with an incidence similar to adult patients. This is more pronounced in the more immature infants. Improvements in perinatal and neonatal medicine have increased the survival chances of critically ill neonates. However mortality and morbidity rates remain significant for those newborns who have suffered from a kidney injury with a reported incidence of death in 25–50%.

Keywords

Renal function • Newborn renal physiology • Renal failure • Peritoneal dialysis • Outcomes

62.1 Introduction

The neonatal kidney can adapt to the usual physiological processes occurring after birth and allow homeostatic regulation to transfer from the placenta to the kidney. However during this period of transition the neonatal kidney is vulnerable. It is less able to withstand stress such as hypotension, hypoxia or hypovolaemia which will result in a decrease in kidney function. It is therefore not unexpected that the incidence of acute renal failure in children is highest in the neonatal period, with an incidence similar to adult patients [1]. This is more pronounced in the more immature infants. Improvements in perinatal and neonatal medicine have increased the survival chances of critically ill neonates. However mortality and morbidity rates remain significant for those newborns who have suffered from a kidney injury with a reported incidence of death in 25–50% [2, 3].

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_62

For practical purposes the term 'renal impairment' is used to describe any reduction in kidney function. This chapter will primarily address changes in the glomerular filtration rate (GFR), which occurs as a consequence of kidney injury in the neonatal surgical unit. A reduction in GFR results in acidosis, hyperkalaemia and an accumulation of waste products. These metabolic changes have an adverse effect on cellular function and post-operative recovery. Specific, isolated, disorders of neonatal renal tubular function such as Bartter's Syndrome and Neonatal Oxalosis are beyond the scope of this chapter.

Malformations of the kidneys and renal tract are the most commonly detected antenatal anomaly. These kidneys are more vulnerable to the various nephrotoxic injuries associated with surgical treatment. An understanding of neonatal renal function will aid the clinician in the appropriate management of fluid, electrolyte, nutritional and acid-base disturbances in the neonate with surgical problems. This chapter will help the clinician to identify those patients with renal impairment, which can be a particular challenge in the neonate. There is a high incidence of non-oliguric renal failure [2] which may be manifest only by a creatinine increase within the normal range for an older child. Guidance will be given on appropriate nutritional, fluid and electrolyte management, avoidance of potential complications from nephrotoxic medication in order to optimise surgical recovery. The indication for renal replacement therapy and practical consideration regarding dialysis in newborn children will be considered.

62.2 Normal Renal Function in the Newborn

Nephrogenesis starts at gestational age week five and nephrons are functional at week eight. From approximately 10 weeks gestation the foetus produces increased amounts of urine, which is the main constituent of amniotic fluid. By 36 weeks gestation nephrogenesis is complete and each kidney has approximately 1,000,000 functional nephrons [4]. No new nephrons are able to form after this period and kidney growth is a result of an increase in length and cell number of existing nephrons. In utero the kidneys do not contribute to foetal homeostasis which is performed by foetal-maternal exchange across the placenta.

62.2.1 Glomerular Filtration Rate

Glomerular filtration rate is low after birth and is closely correlated to gestational age. It is approximately 5 mL/min/1.73 m^2 in neonates of 28 weeks gestation and 10–20 mL/min/1.73 m^2 in term infants. Post natally there is a rapid increase in GFR with a two fold increase occurring in the first 2 weeks of life. The increase in GFR is a result of haemodynamic factors and renal maturation. Following birth haemodynamic factors, including an increase in cardiac output, fall in renal vascular resistance and increase in mean arterial blood pressure, lead to an increase in renal blood flow. GFR will thus increase in absolute terms, even if the proportion of renal blood flow that is filtered remains unchanged. The proportion of renal blood flow that is filtered also increases. Structural changes in the glomerular capillary bed increase the basement membrane surface area available for filtration and GFR rises. Adult values of GFR, 80–120 mL/min/1.73m^2 (a 5–10-fold increase compared newborns) are usually reached by 1–2 years [5].

Nephrogenesis is directly proportional to gestational age which may explain the lower GFR seen in the more premature infants. Plasma creatinine is usually higher in the more premature infants and does not fall steadily from birth, but rises in the first few days of life, reaching a peak and then falling to an equilibrium. This effect is more pronounced with increasing prematurity [6]. This is most likely to be due to tubular 'back leak' of creatinine across the immature tubules and may not represent true renal impairment [7].

Formal measurement of GFR, using a fully filtered, non-secreted, tracer, such as Cr^{51} EDTA, is invasive and expensive. Creatinine is usually used as a measure of GFR, but may not be accurate in the neonate. Creatinine may be falsely elevated if the patient has a high bilirubin and the

biochemical analyser does not correct for non-creatinine chromogens, including medication. The Schwartz formula can be used to estimate GFR once the plasma creatinine has stabilised [8]. Estimated GFR = body length (cm) × K/creatinine (μmol/1) The constant K is 33 for term infants and 24 for low birth weight infants [9]. Reference ranges for normal creatinine may vary between different laboratories, depending on the analyser, but are between 30 and 58 μmol/1 in infants age 0–2 weeks and 20–48 μmol/1 in infants age 2–26 weeks. As already indicated foetal kidneys do not contribute to the excretion, thus the neonate's creatinine at birth reflects maternal plasma creatinine values and is not a measure of neonatal renal function.

62.2.2 Water Homeostasis

In early postnatal life there is a reduction in total body water, extracellular water and extracellular sodium and chloride. This loss of extracellular volume is readily apparent as the postnatal weight loss, which is greater in the more immature infants where a weight loss of up to 10% can occur. This is caused by the inability of the neonatal kidney to generate concentrated urine. Maximal urine concentration in the first week of life is about 700 mosmol/kg compared with 1000–1200 mosmol/kg in an adult. The metabolic demand for urine concentrating ability is high. In utero this burden is carried out by the placenta. It takes time for postnatal adaptations to occur. Neonates consume large volumes of dilute fluid, in the form of breast milk, relative to the body size. (Breast milk contains ~10 mmol/L sodium.) This high free water intake reduces the need for a significant urine concentrating capacity. The main clinical consequence of a low urine concentrating capacity is the risk of water depletion and hypernatraemia if insufficient fluids are provided.

Conversely the ability to excrete excess water following the administration of hypotonic fluid is limited by the low neonatal glomerular filtration rate. Thus increasing the likelihood of fluid overload and hyponatraemia in these circumstances.

Insensible water loss is also greater in the neonate as a result of increased trans-epidermal water loss. Trans-epidermal water loss is inversely correlated with gestational age as a result of a large ratio of surface area to weight and is also affected by environmental factors including temperature, relative humidity and air circulation. Fluid prescriptions need to be adjusted for increased insensible water losses particularly in the premature infant exposed to phototherapy and overhead heaters. Although the range of fluid intake that can be tolerated is wide, the limits can be reached when renal function is impaired.

62.2.3 Sodium Homeostasis

At birth there is a limited capacity to excrete a sodium load or conserve sodium if there is a sodium restriction. In the first week of life fractional sodium excretion is high and this is greater in the more immature infants. This results in a fall in the plasma sodium and chloride and relatively high urinary sodium to plasma sodium. Again this may be explained by the high metabolic requirement for this active process and resulting limited sodium and chloride reabsorption in the neonatal kidney. Intravenous fluids should ensure the correct sodium content to avoid plasma sodium falling. Conversely foetal sodium excretion is usually less than 10% of the intake in premature infants. Colonic sodium reabsorption decreases with increasing gestational and postnatal age and may help to counterbalance urinary sodium loss.

Causes of hyponatraemia occurring shortly after birth include excessive hypotonic fluid given to the mother and inadequate sodium content of neonatal feed or intravenous fluid. Antidiuretic hormone is also released in response to neonatal pathology, including asphyxia, which results in excessive water reabsorption. Causes of hyponatraemia occurring later include inadequate sodium content of the neonatal feed or intravenous fluid with the more immature infant being less able to adapt. Excessive sodium losses from the gastrointestinal tract including patients with short bowel syndrome and an ileostomy or patients with upper gastrointestinal losses are also at an increased risk

of developing hyponatraemia. Excess renal tubular sodium losses may occur in patients with intrinsic renal pathology, including dysplasia but in the neonatal surgical unit may be more common in the recovery phase of acute renal failure or following the diuretic phase after treatment for an obstructive uropathy such as posterior urethral valves.

62.2.4 Potassium Homeostasis

The rate of potassium excretion in the neonate is low and the tubules are less able to respond to a potassium load than an older child. Plasma potassium in the more immature infants is greater than in term infants and is also increased by hypoxia, metabolic acidosis, catabolic state, potassium administration, oliguric renal failure and reduced potassium secretion by the immature distal nephron.

62.2.5 Tubular Function

Tubular function matures later than glomerular function and reaches maturity by 1 year of age. The increase in tubular glucose reabsorption in infancy and childhood parallels the increase in GFR. Glycosuria is commoner in neonates and is higher in the more immature infants. Likewise aminoaciduria is more common in the neonate. The degree of aminoaciduria is variable between different amino acids. These factors need to be considered when interpreting amino acid profiles for metabolic conditions [10]. Phosphate reabsorption is greater in the neonate than in older infants and children. This is to achieve a positive phosphate balance for bone accretion.

62.3 Impaired Renal Function in the Newborn

The low GFR of the neonatal kidney helps to explain why it is vulnerable to periods of stress resulting in renal impairment. It limits the newborns ability to adapt to haemodynamic changes, such as hypotension, hypovolaemia and vasoactive drugs, and more readily accumulates non-excreted waste products (elevated creatinine) and the other associated features of renal impairment. It is also less able to adapt to injury from hypoxia or nephrotoxic drugs. The neonate with an acute surgical condition is likely to be exposed to more than one of these factors and is consequently at risk of renal impairment. Table 62.1 lists some causes of renal impairment according to the timing of the renal injury. Causes may also divided into pre-renal, intrinsic-renal and post-renal (obstruction to urine flow). This aides management strategies.

Table 62.1 Causes of neonatal renal impairment

Antenatal vascular injury
• Maternal medication—ACE inhibitors, NSAIDs
• Twin-twin transfusion
• Co-twin death
Renal tract congenital abnormalities
• Obstructive uropathy—Posterior urethral valves
• Polycystic kidney disease—Autosomal recessive
• Renal hypo—Dysplasia
• Renal agenesis
• Renal tubular dysgenesis
• Diffuse mesangial sclerosis
• Congenital nephrotic syndrome (Finnish type)
Acquired postnatal renal injury
• Shock
• Dehydration
• NEC with third space losses
• Cardiac failure
• Cardiopulmonary bypass, ECMO
• DIC
• Vascular thrombosis—Umbilical artery and venous cannulation
• Perinatal asphyxia
• Infection—Pyelonephritis, congenital infections, fungal UTI +/− obstruction
• Closure of abdominal wall defects
• Nephrotoxic medication—Indomethacin (PDA), ACEi (cardiac failure), aminoglycosides, vancomycin, amphotericin

62.3.1 Pre-renal

Preterm neonates with reduced renal perfusion, from a reduced circulating volume, account for approximately one third of cases of impaired renal function [11] A true circulation volume contraction or a decrease in the effective circulating volume may be present. Renal hypoperfusion

reduces GFR, which is manifested by an increase in plasma creatinine, as there is less blood available to be filtered at the glomerulus. Adaptive mechanisms include the Renin, Angiotensin, Aldosterone system, which increases renal vascular resistance to support blood pressure and perfusion to other vital organs. GFR is maintained by alteration in glomerular afferent and efferent arteriolar tone, increasing glomerular hydrostatic pressure. In this way total renal blood flow is reduced but the proportion filtered is increased thus maintaining GFR. Urea is disproportionally reabsorbed and then recirculated in order to improve urine concentrating ability. This reduces urine output, helping to maintain circulating volume. The kidney avidly retains sodium, the main cation of the extracellular fluid, which helps to maintain ECF volume and circulating volume. These two features lead to the characteristic pattern of a low urine sodium concentration (<10 mmol/1) and concentrated urine (>plasma osmolality) observed in pre renal impairment. As a temporary measure GFR can be reduced in order to protect vital organs against the low circulating volume. Correcting the underlying disturbance in circulating volume will return renal function to normal.

62.3.2 Intrinsic-Renal

If renal hypoperfusion persists renal tubular cells suffer from a hypoxic/ischaemic injury leading to Acute Tubular Necrosis (ATN). In this setting GFR is further reduced by sloughing of tubular epithelial cells forming casts in the tubular lumen and obstructing urine flow. Local reduction of 'single nephron GFR' is activated by the macular densa registering a high solute flow in the distal nephron. This reduction prevents excessive solute loss but if widespread will reduce overall GFR. Creatinine may filter back across the damaged tubule. Inappropriately high urine sodium levels, in the presence of low circulating volume are seen as sodium can no longer be avidly reabsorbed by the injured tubular epithelial cells. Clinically ATN may be identified by a persistent elevation of creatinine despite improvement of circulating volume.

Restoration of renal perfusion will enable tubular cells to recover. The length of time before recovery is variable. Patients may require dialysis for several weeks and still eventually recover complete renal function. Acute cortical necrosis occurs following more prolonged or severe ischemia and results in long term renal impairment.

In the neonatal surgical unit necrotising enterocolitis increases the relative risk of renal impairment and is associated with more severe renal impairment [12]. Nephrotoxic injury from medication is a significant cause of intrinsic renal impairment. Other causes of intrinsic renal disease resulting in neonatal renal impairment include Renal Dysplasia, Hypoplasia and Autosomal Recessive Polycystic Kidney Disease. Neonates who do not have renal tract anomalies but do have other major anatomical or genetic abnormality have a higher incidence of renal impairment [12]. Neonates who have undergone cardiac surgery or with severe birth asphyxia are at particular risk [13].

62.3.3 Post-renal

The commonest cause of obstructive renal disease in the neonate is secondary to posterior urethral valves. Other causes include sacrcoccygeal teratoma, urethral atresia and a neuropathic bladder. Spina bifida is a well recognised cause of neuropathic bladder which may present difficulties in the neonatal period. The majority of VACTERL patients (92%) have bladder involvement that requires urological intervention [14]. Mild renal pelvis dilatation may indicate obstructive renal pathology in a patient with oliguric renal impairment because the kidney cannot 'generate' sufficient urine flow to lead to significant hydronephrosis. This situation needs careful consideration and may result in intervention such as nephrostomy.

62.4 Evaluation of the Newborn with Renal Impairment

The term renal impairment is a term used to describe any reduction in glomerular or tubular function. There has been an increased effort to standardise the definitions for renal impairment,

to improve the ability to compare studies, predict clinical course and improve outcome. Long term renal impairment is described as Chronic Kidney Disease (CKD). This has little significance in the neonatal surgical unit but does have some relevance when considering the long term outcome of the children. Acute changes in GFR, whether baseline levels are normal or not, are classified as Acute Kidney Injury (AKI), synonymous with the previous term 'acute renal failure'. The pRIFLE classification was proposed in 2007 to classify acute kidney injury in children [15]. This stratified patients according to those at **R**isk, **I**njury, **F**ailure, **L**oss & **E**nd stage renal disease. This followed the RIFLE classification initially introduced for the recognition of AKI in adults in 2004 [16]. These scoring systems use two clinical parameters to stratify patients in severity of their kidney injury. Firstly the change in serum creatinine, both absolute and relative changes, and secondly urine output. Table 62.2 shows an abbreviated comparison between these systems indicating the scale of changes. The value of these systems is significant, They have shown that AKI has a negative impact upon survival. It is pertinent to note that patients not only die from AKI but suffer from functional changes in other organs as a consequence of reduced renal function.

Unfortunately this classification has not been validated in the neonates. Currently the diagnosis of acute kidney injury is dependent on a change in serum creatinine as a marker of GFR and the presence of oliguria. A change in serum creatinine may not occur until 25–50% of the kidney function is lost and may overestimate renal function at a lower GFR because of the tubular secretion of creatinine. Conversely serum creatinine will underestimate GFR if the analyser does not correct for non-creatinine chromogens, including bilirubin. This is particularly relevant for neonates who are jaundiced. There is a wide distribution of normal serum creatinine in the neonate, which as previously discussed is dependent on prematurity and age. The presence of oliguria will not identify those infants with polyuric renal failure. In neonates, there is up to a 40% incidence of non-oliguric renal impairment. Oliguric renal failure is associated with a higher mortality rate than non-oliguric renal failure [2]. Despite these difficulties the underlying principles remain valid for newborn children, and can be used to identify patients at risk of, or who have developed, renal impairment.

Urinary biomarkers of AKI, including neutrophil gelatinase-associated lipocalin (NGAL) kidney injury molecule (KIM-1) and urinary interleukin-18 are currently being explored for their ability to diagnose AKI early in the disease process [17]. These biomarkers are currently being validated as a useful clinical tool in neonates, who are at risk of AKI from cardiopulmonary bypass surgery [13]. Genetic risk factors for renal impairment from various nephrotoxic insults have been investigated [18, 19]. but these are not yet clinically useful.

Antenatal sonography may detect structural renal tract abnormalities and raise the concern that the child will be born with a degree of renal impairment. At present there is no readily available way to estimate renal function prior to birth. The classic example of this is the baby with oligohydramnios and abnormal kidneys (e.g. Autosomal Recessive Polycystic Kidney Disease). They may not have sufficient urine output and amniotic fluid for adequate lung development but still have a urine output adequate to avoid renal replacement therapy for a considerable period [20].

62.5 Management

Following the diagnosis of renal impairment, understanding the pathogenesis will enable the infant to receive the appropriate treatment. A careful physical examination should be undertaken with close attention to hydration status and circulating volume. An accurate weight is the best guide to changes in overall hydration status. The urine should be collected and analysed for urinalysis, microscopy and microbial culture and electrolytes. Urinary electrolyte concentrations can be used to help differentiate pre-renal and intrinsic-renal impairment. Meaningful interpretation can be made on random, spot urine specimens. A low

Table 62.2 Classification of Acute Kidney Injury (AKI) in children in comparison to adult.

	Adult				Children		
AKIN staging		AKIN/RIFLE	RIFLE		pRIFLE		
Stage	Serum creatinine	Urine output (common to both)	Class	SCR or GFR	Class	eGFR	Urine output
I	↑SCr by >0.3 mg/dL or ↑SCr by >150–200%	<0.5 mL/kg/l/h x > 6 h	Risk	↑SCr by 150% or ↓GFR by 25%	Risk	↓eGFR by 25%	<0.5 mL/kg/h × 8 h
II	↑SCr by >200–300%	<0.5 mL/kg/L/h x > 12	Injury	↑SCr by 200% or ↓GFR by 50%	Injury	↓eGFR by 50%	<0.5 mi/kg/h × 16 h
III	↑SCr by >300% or SCr > 4.0 mg/dL with acute rise of at least 0.5 mg/dL	<0.3 mL/kg/L/h >24 or anuria × 12 h	Failure	↑SCr by 300% or SCr > 4.0 mg/dL with acute rise of 0.5 mg/dL or↓GFR by 75%	Failure	↓eGFR by 75% or <35 mL/min per 1.73 m^2	<0.3 mL/kg/h × 24 h or anuric × 12 h
			Loss	Failure × > weeks 4	Loss	Failure × > 4 weeks	
			ESRD	Failure × > 3 months	ESRD	Failure × > 3 months	

AKIN, Acute Kidney Injury Network, For AKIN classification: an acute (within 48 h) reduction in kidney function is required.
(p)RIFLE (pediatric) risk injury failure loss ESRD, *ESRD* end-stage renal disease, *SCr* serum creatinine, *GFR* glomerular filtration rate, *eGFR* estimated glomerular filtration rate

urinary sodium concentration (<10 mmol/1) and low fractional excretion of sodium ((Urine sodium × serum creatinine)/(serum sodium × urine creatinine) <1%) suggests pre-renal impairment. Blood should be sent for sodium, potassium, chloride, bicarbonate, urea, creatinine, calcium, phosphate, magnesium, albumin and total protein. A renal ultrasound scan should always be performed.

The management of renal impairment requires attention to, fluid balance and electrolyte homeostasis. Low urine output renal impairment is not frequently present in neonates, which greatly facilitates conservative treatment. Conversely if urine output is restricted there is a very significant challenge, particularly to provide sufficient calories for growth.

62.5.1 Fluid Management

Standard neonatal fluid guidelines (for infants with normal renal function) provide an acceptable starting point from which to modify according to clinical circumstance [11, 21]. In the presence of renal impairment the guiding principle is that intake and output must be balanced. Each fluid prescription must be individualised. Fluid administration must be directed by fluid losses including insensible water losses (evaporative) of 30 mL/kg/day (or 20 mL/kg/day if ventilated) [22] Urine output, gastrointestinal losses and surgical drain losses should be replaced with equal volumes. Strict recording of fluid balance and daily weighing is required.

If pre-renal impairment is suspected a fluid challenge of 10–20 mL/kg over 1–2 h of isotonic saline solution should be given. Another fluid challenge can be given followed by furosemide 1–2 mg/kg. This should result in an improvement in urine output if the diagnosis of pre-renal failure is correct. If there is no improvement following two fluid boluses and the infant is no longer considered to be hypovolaemic further fluid volumes must be carefully considered to avoid fluid overload, cardiac failure and pulmonary oedema.

Management is greatly facilitated if urine output is maintained. It is reasonable to try and promote this with the cautious use of diuretics. Their toxicity must be balanced against the low chance of benefit. Diuretics are beneficial in controlling oedema associated with mild renal impairment (Table 62.2. 'Risk' & 'Injury' classification.) but rarely improves the volume of urine passed in significant renal impairment (Table 62.2. 'Failure', 'Loss' or 'ESRD' classification).

62.5.2 Nutrition and Growth

In general infants with renal impairment should be feed to the same recommended nutrient intake as for healthy infants. Calorie intake targets are 120–150 kcal/kg/day to avoid the infant becoming catabolic which may result in an increase in urea and acidosis. Dietary protein restriction in not recommended and should be the same recommended intake as for healthy infants to allow growth. Energy intake is difficult to achieve in the oliguric neonate who is dependent on milk or parenteral nutrition. In significant renal impairment daily weight loss of 0.2–1% of body weight may be expected beyond the first week [22]. If sufficient calories cannot be achieved, within an acceptable timescale, because of oliguria then dialysis should be considered to allow a greater volume of feed to be administered. An accurate fluid balance will help differentiate an increase in weight secondary to fluid retention, in the oliguric infant, from nutritional growth.

Poor weight gain may be secondary to sodium wasting which is common in infants with renal hypodysplasia and following treatment of obstructive uropathy. Breast milk and normal infant formula contain approximately 7–10 mmol/1 of sodium. In renal impairment although the volume of fluid intake may be matched, by urine output & insensible losses, the kidneys may not be able to reduce urinary sodium to a correspondingly low concentration and a negative sodium balance will result. Sodium chloride supplements, starting at 1 mmol/kg/day in divided doses, should be given and may improve growth.

62.5.3 Electrolytes

Significant alterations in serum sodium concentrations may occur without neurological compromise in newborn infants. Hyponatraemia is

frequently seen in fluid overloaded infants. The treatment here is fluid (water) restriction. Again, it is not possible to be precise about the volume of 'fluid restriction'. The principle is to achieve a negative water balance, thus output must be greater than input. Careful recording of fluid balance (e.g. weighing nappies), daily (or twice daily weight), clinical examination and frequent measurement of electrolytes will indicate whether the therapeutic goal is being achieved. Rarely the emergency treatment of symptomatic hyponatraemia will require the infusion of hypertonic saline to more quickly increase plasma osmolality, restore intracellular volume and reduce cerebral swelling.

Neonates are remarkably resistant to the effect of hyperkalaemia. Preterm infants may tolerate a serum potassium concentration up the 7 mmol/1 without cardiac symptoms [23]. In this paper only 25% of patients with a serum potassium above 8 mmol/1 had a cardiac arrhythmia. A frequent problem is artefactual hyperkalaemia from mechanical haemolysis during capillary blood sampling. Care must be taken to avoid being falsely reassured when haemolysis is reported and the potassium is elevated. A rise in creatinine, fall in plasma bicarbonate or calcium suggest true hyperkalaemia.

Hyperkalaemia can lead to cardiac rhythm disturbance because of its depolarising effect on the cells of the cardiac conducting pathway. The potassium level at which this occurs is dependent upon acid base variables and other electrolytes, notably calcium. Significant ECG changes are often a late development (Long PR, increased QRS duration) and require prompt treatment [24]. Intravenous calcium gluconate has an immediate stabilising effect on the myocardium. Sodium bicarbonate, to reduce acidosis, can be quickly and easily administered. Nebulised and intravenous salbutamol have appreciable effect upon reducing plasma potassium levels. Insulin and dextrose is useful for life threatening hyperkalaemia but may result in significant hypoglycaemia in newborn infants.

All these measures have only a temporary effect on blood potassium levels, by shifting potassium into cells. Reducing potassium intake is essential. Breast milk and normal infant formula can be exchanged for a low potassium infant milk such as Renastart. Ion exchange resins (Kayexalte and Calicium Resonium) have limited use in the emergency setting and are not without complications, particularly in post operative patients [25]. If the source of potassium cannot quickly be rectified hyperkalaemia associated with renal impairment frequently requires the initiation of dialysis.

Renal tubular unresponsiveness to aldosterone results in hyperkalaemia, hyponatraemia, dehydration and metabolic acidosis. This 'transient psuedohypoaldosteronism' is seen in patients with abnormal renal tracts, such as posterior urethral valves or vesicoureteric reflux, and urinary tract infection [26]. The biochemical features of this condition are indistinguishable from salt wasting congenital adrenal hyperplasia. Aggressive fluid resuscitation with 0.9% sodium chloride and correction of acidosis with sodium bicarbonate will correct hyperkalaemia. The reduced renal tubular response to aldosterone may persist for a long period after surgical correction [27]. Weight gain and electrolytes should be monitored for at least a year [28].

Acidosis due to renal impairment can be buffered by sodium bicarbonate supplements at a dose of 1 mmol/kg/day. Hypocalcaemia must be corrected when treating acidosis to avoid a fall in ionised calcium and tetany or seizures.

Electrolyte abnormalities may be associated with medication [29]. Particular attention should be paid to phosphate, used for the treatment of osteopenia of prematurity or as an enema for constipation. Phosphate containing medication should be avoided when the GFR is below 60 mL/min/1.73 m^2 [30]. to avoid hyperphosphatemia and hypocalcaemia.

The return of normal renal function may be associated with a diuretic phase. This period of excessive urine output requires close attention to fluid and electrolyte balance. It is useful to consider that normal breast milk and infant formula contains about 7–10 mmol/1 of sodium. In neutral water balance, a daily intake of 150 mL/kg/day will be associated with ~30 mL/kg/day transepidermal loss (almost entirely free water) and 120 mL/kg/day urine. This urine will contain ~12 mmol/1 to stay in neutral sodium balance.

Persistently higher urine sodium levels, in the setting of recovering renal function, suggest salt wasting and may need supplementation.

62.5.4 Drug Handling

The dynamic processes of growth, development and renal maturation that occur in the neonate influence the dosing regimens of drugs during early life and childhood. Kidney size, as a percentage of body weight, rises to a maximum at 5 years and then falls steadily until adulthood [11]. This may be one explanation as to why children are usually administered a higher dose of a renal excreted drug, when corrected for size, than adults to achieve targeted therapeutic concentrations.

Knowledge of specific transporters involved in renal drug clearance will enable adjustment of therapeutic doses that avoid toxicity. Several drug are excreted via the same renal pathway as organic acids. The secretion of organic acids is low during the neonatal period and increases over the first few years of life as a result of increasing GFR, increased number of transporter sites and increased metabolic capacity. Organic acid secretion reaches its maximum in the first few weeks of life and then falls to adult levels [31]. Immaturity of the organic anion transport system is more pronounced in the preterm infant. Organic anions frequently administered to the neonate include benzyl penicillin, folic acid, phenobarbitone, ACE inhibitors, antiviral drugs and non-steroidal anti-inflammatory drugs [32]. The neonatal kidney has a greater ability to secrete organic cations than organic anions. Organic cations that may be administered to the neonate include amiloride, morphine and noradrenaline [32].

The weight of the liver relative to the body size is also greater in the infant and younger child than adult. Developmental changes in drug handling are also dependent on the maturation of other hepatic functions such as cytochrome P450 enzymes. Drug toxicity may occur if the P450 enzyme activates the parent drug into its reactive metabolite at a faster rate than the renal excretion pathway. Toxicity may be decreased if renal clearance that removes the active metabolite matures earlier than the P450 enzyme that inactivates the parent drug. To determine optimal therapeutic doses and avoid potential drug interactions the handling of drugs by the developing kidney and liver need to be understood.

Thus particular care should be taken with the dosing of all medication in the presence of known, or suspected renal impairment. Aminoglycosides are frequently administered to neonates with suspected or proven sepsis. A Cochrane review supports the once daily dosing schedule of gentamicin for the beneficial effect on microbial killing without an increase in nephrotoxicity compared to the traditional multiple dose schedule [30, 33]. However, this dosing schedule has not been proven to be safe in the neonate with renal impairment. We recommend a single standard dose (2.5 mg/kg) with close monitoring of therapeutic levels to ensure a trough level below 2 mg/L is reached before a further dose is administered.

Evidence of severe and irreversible renal insufficiency after prenatal exposure to NSAID's has resulted in these drugs being avoided during pregnancy [34]. NSAID's reduce renal perfusion by inhibiting prostaglandins that are vasodilatory. NSAID's, such as Indomethacin, are used for the treatment of patent ductus areteriosus. Other nephrotoxic medication that is frequently encountered in the neonatal surgical unit are Angiotensin Converting Enzyme inhibitors (Captopril, Lisinopril) used for the treatment of congenital heart disease and cardiac failure.

There is no specific medical therapy to improve renal function. The use of low dose dopamine for the prevention or treatment of renal failure in neonates remains controversial [11, 22]. There is little evidence to strongly support its use in the absence of low blood pressure requiring inotropic support. There is some emerging evidence to suggest a benefit from theophylline to prevent AKI following birth asphyxia [35–37]. Treatment appears to reduce frequency of significantly elevated creatinine levels and markers of renal dysfunction. Long term effects were not reported.

62.5.5 Hypertension

Blood pressure in neonates increases with gestational age, post-conceptual age and birth weight [38]. The centile charts produced from this study can be used to define if an infants blood pressure is above the 95th percentile and considered to be hypertensive. These centile charts produce data for infants aged 24–42 weeks gestation. For older infants and children the percentile charts generated from the second Task Force are the most useful [39].

The commonest causes of hypertension in the neonate are renovascular and renal parenchymal disease. Umbilical artery catheter-associated thromboembolism should be considered as a cause of 'renovascular' hypertension in the neonatal ICU [40]. It is therefore important to assess the blood pressure in neonates with nephro-urological conditions **and** also in neonates with abdominal masses or hydronephrosis causing compression of the renal arteries.

Measurement of blood pressure in the NICU is usually performed by an indwelling arterial line. If automated oscillometric devices are used it is important to select the correct cuff size and use the upper limb as normative data is generally obtained from measurements in the right upper arm. An alternative method, which we prefer, is the Doppler technique by skilled nursing staff.

Hypertension in the surgical neonate is usually detected by routine monitoring of vital signs. Classical symptoms and signs include unexplained tachyapnea, irritability, lethargy, failure to thrive and in the more severe case congestive heart failure.

Hypertension in the surgical neonate may require the use of intravenous agents, which have a short half life, and allow the drug to be titrated against the blood pressure to avoid too rapid a reduction in blood pressure leading to cerebral ischaemia and haemorrhage. Intermittently administered intravenous agents, such as hydralazine, may be of use in the neonate with moderate hypertension, who are unable to tolerate oral medication.

Oral antihypertensives are often considered for infants with mild hypertension. An ACE inhibitor should not be used if there is any concern that the neonate has renovascular disease and with caution if the neonate has deranged renal function. The calcium channel blocker Amlodipine is a vasodilator that is available in a suspension and is usually well tolerated in the neonate. It is important that the neonate is not volume depleted before administering a vasodilator as this can result in an unexpected fall in blood pressure. Surgical intervention may be required for patients with an obstructive uropathy or abdominal mass.

62.5.6 Renal Replacement Therapy

62.5.6.1 Peritoneal Dialysis

Renal replacement therapy is indicated when conservative therapy fails to control complications of renal impairment, such as electrolyte and acid-base abnormalities but more commonly progressive fluid overload. Peritoneal dialysis (PD) remains the renal replacement modality of choice. PD provides fluid and solute removal, dependent upon the volume, osmolality and dwell time of the dialysis fluid in the peritoneal space. The major limitation for peritoneal dialysis is related to abdominal pathology. Peritoneal dialysis is unlikely to succeed in a patient with bowel perforation, for example as a consequence of necrotising enterocolitis., Success in this situation is rare with reported attempts representing 'last ditch' attempts in extreme situations [41]. PD can be successfully performed after abdominal surgery and the creation of enterostomies. [Personal Observations] Extra-renal anomalies can significantly complicate the renal course. Patients with VACTERL anomalies are less likely to have peritoneal dialysis because of abdominal surgery [14].

Access to the peritoneal cavity is usually through a Tenckhoff catheter. There are a range of catheters available with different configurations, such as straight, coiled or swan-necked. They may have 1 or 2 'cuffs' for securing to the subcutaneous tissues. None have proven benefits for providing acute, short term dialysis [42]. Insertion technique is important to reduce cathe-

ter related malfunction. In neonates the thin abdominal wall increases the likelihood of leaking dialysis fluid around the catheter. Catheters can be successfully placed using a percutaneous seldinger technique. In our institution short term PD catheters are placed percutaneously. Long term catheters are placed surgically with a subcutaneous tunnel. Peritoneal dialysis catheters with two cuffs requiring a subcutaneous tunnel are recommended for those infants who may need long-term dialysis. This reduces the risk of recurrent peritonitis. These catheters are best placed by an experienced surgeon dedicated to their long term management. The cardiothoracic surgeon place catheters via a trans-diaphragmatic route, at the time of cardiac surgery in patients who are considered at risk for AKI.

There are no accurate automated devices for delivering PD to small children because of the low dialysate volumes required. Manual 'exchanges' of dialysis fluid can be easily managed in the intensive care environment. Standard practice is to start with an initial volume of 10 mL/kg exchanged every hour. This can be progressively increased up to 40 mL/kg. Higher volumes may compromise respiratory function, by splinting the diaphragm. Cardiac function may be compromised, in critically unwell infants, by a reduction in cardiac return through compression to the vena cave. Pericatheter leakage of dialysis fluids is also more likely with larger volumes particularly in the infant with little subcutaneous or oedematous tissues. Small infants, of almost any weight, can be successfully managed, achieving adequate fluid removal, with low volumes (10 mL/kg) PD. [43]

Standard, commercially prepared dialysis fluid is suitable for the majority of patients. Some infants with liver impairment may not metabolise the lactate in these solutions to bicarbonate and failure to control acidosis. Commercial solutions are available with both lactate and bicarbonate buffers. 'Home made' preparations of dialysis fluid using entirely bicarbonate may be required if acid-base homeostasis cannot be maintained.

The most significant challenge remains the 'mechanical' problem of obstruction to fluid flow either during filling or commonly during drainage of dialysate. Small infants can rapidly accumulate significant fluid volumes if several cycles do not drain adequately.. Various PD techniques have been reported to improve PD drainage and include change in the infant's position [44, 45].

62.5.6.2 Blood Based Dialysis

There are several forms of extracorporeal renal replacement therapy. Each has subtle advantages they may be appropriate depending on the clinical situation. Conventional haemodialysis, in which waste product and fluid removal usually occursover a 3–4 h session corrects metabolic abnormalities quickly. This is useful for the treatment on hyperammonemia from urea cycle disorders. Infants are usually unable to tolerate haemodialysis because of the relatively large extracorporeal circuit and the physiological stress associated with fluid removal of a short time. Extracorporeal circuit volumes of more than 10–15% of patient's body weight should be primed with blood.

Continuous therapies, with waste product and fluid removal taking place over a 24 h period, provide more stability. Haemofiltration, dialysis or a combination of both can be employed. Blood is usually taken and returned via a large gauge venous catheter in one of the major vessels. Thus providing the acronym CVVHF (continuous veno-veno haemofiltration). The significant technical challenge with these techniques is vascular access. Even very small infants can be managed provided vascular access can be achieved; At least 6 French catheter is usually required [46]. There are machines that can deliver blood based renal replacement therapy to very small infants, but they are not yet widespread [47]. Using conventional machines the rate of technical complications is low [48]. Although there is a trend towards lower survival rates in infants less than 3 kg [48]. Maintaining vascular access and loss of central veins is a limiting factor for the long term use of blood based dialysis therapies in neonates.

62.6 Long Term Outcome

Neonates who have had an episode renal impairment require follow up. There is limited data on the long term risk of neonatal renal failure [49]. However an underlying principle of the kidney's response to injury supports the need to monitor children. When the number of nephrons is reduced the remaining nephrons increase their GFR in order to compensate. However the compensatory mechanisms within the glomeruli damages the glomerular capillary walls and leads to progressive glomerulosclerosis, proteinuria, hypertension and chronic kidney disease [50]. This phenomena has been demonstrated paediatric patients. Neonates with congenital abnormalities, such as the VACTERAL anomaly, have a greater risk that the renal impairment will continue beyond the neonatal period [14, 51]. Patients who have an elevated creatinine for more than 3 months are classified as having Chronic Kidney Disease. Babies who require long term dialysis are a particular challenge. Although 12% may recover native renal function 25–50% may die before the age of 5 years [52, 53] The presence of oliguria is associated with lower patient survival.

Conclusion

Renal impairment is common in the neonatal period. Frequently the cause is multifactorial with a 'pre-renal' component. Infants may have underlying renal tract abnormalities. For the majority of patients treatment is conservative. Attention to electrolyte abnormalities can maximise the opportunities to achieve adequate nutrition. This will have a beneficial effect on post operative recovery. Active conservative management might avoid the need for dialysis. Renal replacement therapy, primarily peritoneal dialysis is possible and can provide the necessary bridge to renal transplantation in those infants with end stage renal failure. Hard end points regarding renal outcome are lacking but the majority of newborns are likely to have good levels of renal function.

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Newborn Urinary Tract Infections

63

Colin Jones and Joshua Kausman

Abstract

Urinary tract infection (UTI) is among the most common bacterial infections affecting newborns. Urinary tract infection can cause septicaemia or chronic ill health with failure to thrive and is often an indication of an underlying urinary tract malformation.

Keywords

Urinary tract infection • Newborns • Management • Outcomes

63.1 Introduction

Urinary tract infection (UTI) is among the most common bacterial infections affecting newborns. Urinary tract infection can cause septicaemia or chronic ill health with failure to thrive and is often an indication of an underlying urinary tract malformation.

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63.2 Epidemiology and Risk Factors

Neonatal epidemiologic studies have shown that the prevalence of UTI in term infants varies between 0.1 and 1% with a male to female ratio of between 2 and 6 to 1 [1]. Premature infants have a prevalence of 4–25%. The prevalence of UTI in febrile infants under the age of 3 months presenting to emergency departments is up to 20–30% and boys outnumber girls [2–5]. After the age of 3 months the prevalence of UTI in febrile children falls to around 8% in females and 2% in male children [2]. UTI are uncommon in the first 72 h of life [5].

Certain risk factors affect the prevalence of neonatal UTI. Breast feeding has a protective role in this group [4]. Hospital-acquired urinary infections are more common in infants having other infectious diseases (meningitis, omphalitis, pneumonia and generalised sepsis), treatment with broad spectrum antibiotics, mechanical ventilation, parenteral nutrition and those treated using intravascular and

P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_63

urinary catheters [1, 4, 5]. The occurrence of more than one of these risk factors increased the risk of UTI 11 times [5]. One study found maternal bacteriuria at the time of vaginal delivery resulted in colonization of the foreskin and female perineum in neonates and 24% developed bacteriuria with clinical pyelonephritis in 3% [6].

The presence of underlying urinary tract malformations is more common in neonates with urinary infection and more so in nosocomial acquired infection than in community-acquired urinary infection with vesico-ureteric reflux being found in almost 50% of the former and 25% of the latter [1].

63.2.1 Antenatal Abnormalities

The advent of almost routine antenatal scanning at 18 weeks' gestation has led to the detection of approximately 1 in 200 infants having an increased anterior-posterior renal pelvis diameter (APD, >5 mm at any gestation). Postnatal follow-up studies have not shown an increased frequency of UTI in infants with mild to moderate degrees of APD (up to 15 mm) where the hydronephrosis was isolated (i.e. no ureteric, renal cortical or bladder abnormality) even where the infants were not treated with antibiotics [7]. In more severe cases antibiotics have usually been given in a prophylactic manner and UTI have mainly been detected outside the early infancy period [8, 9].

63.2.2 Circumcision

Wiswell et al. [10] found the incidence of UTI in circumcised male infants was 0.11% compared to 1.12% in uncircumcised infants, but the protective effect seems to fall off after infancy. The risk of circumcision is haemorrhage, injury to the glans penis and local infection. The complication rate can be as high as 4% although complications are less common in experienced hands (0.2%) [11]. Thus, 1000 circumcisions may prevent 91 UTI but be associated with 2–40 complications.

The effect of circumcision is presumably related to decreasing the density of bacterial growth and faecal contamination of the urethral meatus. The reduction in UTI with circumcision is one of the stronger pieces of evidence for an ascending route of infection, rather than haematogenous spread, although the latter is said to be more common in the neonatal period than at older ages.

63.3 Diagnosis

63.3.1 Clinical

Non-specific symptoms are the rule in the presentation of a neonate with urinary infection. While fever, vomiting and failure to thrive cover the symptoms the majority of neonates have no specific diagnostic symptoms and irritability, temperature instability, respiratory distress with apnoea or failure to clear secretions are commonly found. While the blood pressure is usually normal, hypotension with tachycardia is common. The newborn may be jaundiced or there may have been an increase in the serum bilirubin, and the hyperbilirubinaemia may be conjugated, unconjugated or mixed. Hepatosplenomegaly may be found. Infection may be asymptomatic. The frequency of symptoms of urinary tract infection in a series of 301 neonates is listed in Table 63.1 [1]. The presentation varies so much because the developmental status of the neonate does not allow specific localizing features that are present at later ages and reflects the systemic response to infection at this age. This results in the majority of urine infections being diagnosed on the basis of a "septic work-up" rather than specifically targeting urine infection as the cause of the neonate's symptoms.

Table 63.1 Frequency of symptoms (%) in neonates with urinary tract infections [1]

Symptom	Community acquired	Nosocomial
Fever	67.6	39.2
Poor feeding	27	13.7
Vomiting	22.4	21.5
Failure to thrive	15.6	11.7
Jaundice	13.7	13.7
Diarrhoea	2	0

The occurrence of meningitis with urinary tract infection is common and examination and culture of the CSF should be made before starting treatment for UTI in this age group. Similarly, a blood culture should be performed. Leucocytosis on blood film examination and a raised CRP are usually found, but the absence of these abnormalities does not disprove the diagnosis.

63.3.2 Rapid Diagnostic Techniques

Microscopy for bacteria with Gram stain has the highest accuracy for rapid detection of urinary tract infection (sensitivity 91% and specificity 96%) but requires laboratory facilities. Phase contrast microscopy is simple and more reliable than standard microscopy [12]. It is a useful adjunct to urine culture and can help discriminate false positive cultures from clean catch urines. The finding of epithelial squamous cells indicates a poorly collected sample and the absence of leukocyturia in a sample with mixed growth or low colony count on culture may indicate a contaminated sample.

Urinalysis for leukocyte esterase is positive in 19–90% of neonates with urine infection, and urinary nitrite, while more specific for urine infection is only present in 10–60% of urine infections [13]. Thus, even achieving the highest success rates for rapid diagnosis and taking the prevalence rates for urine infection into account, a positive test for both nitrites and leukocyte esterase in a child under 3 months of age predicts 90% of urine infections. This is not good enough for clinical purposes as the diagnosis of urine infection would be missed in a significant number of ill infants.

63.3.3 Urine Culture

The diagnosis is dependent upon urinary culture. The two methods for urine culture that are reliable and accurate are catheter sampling and suprapubic aspiration (see Table 63.2) [14–16].

Table 63.2 Comparison of methods of urine collection

Urine collection method	Advantages	Disadvantages
Paediatric bag	Widespread use in primary care paediatrics because considered convenient Collection of urine from infant or toddler at low risk for UTI (not febrile and no known urological abnormality) Only results of $<10^8$ cfu/L[a] are useful in excluding UTI	Contamination with skin flora common Should not be used where immediate antibiotic treatment is required
Clean catch	Non-invasive Method of choice in infants and toddlers where risk of UTI thought to be low Good correlation with SPA/MSU/CSU (can be collected within 1 h) A result of $>10^8$ cfu/L[a] indicates infection Squamous epithelial cells indicate contamination	Perceived to be difficult to collect (majority of samples collected in 40 min)
Catheter sample	Usually results in collection of sample of urine Invasive—poor acceptance by parents and second choice to SPA in infants and toddlers Reasonable for diagnosis especially if 1st drops of urine are discarded Difficult with phimosis $>10^3$ cfu/L taken to indicate infection	Difficult in neonates with some anatomical abnormalities (e.g. posterior urethral valve)
Suprapubic aspirate	Gold standard as avoids contamination Less invasive than CSU Method of choice in neonates with high risk of UTI Any growth significant	'Dry tap' relatively common (confirmation of a full bladder on ultrasound can reduce this)

[a]Quantitative analysis of urine was introduced by Kass [14] recognizing that most UTI's had colony counts 100–1000 times 10^8/1. Significant numbers of asymptomatic premature and term neonates and infants have counts greater than this number in bag or clean catch samples (proven by negative SPA cultures [15, 16]). Conversely there is a time in the development of UTI when the count will be lower

63.3.4 Microbiology

The aetiological agent varies markedly between community- and hospital-acquired infection [1, 15, 17]. In neonates presenting with community-acquired UTI Escherichia coli accounts for 75–90% of pathogens isolated. Klebsiella is frequent (4–15%), and Enterococci and all gram negative enteric bacteria are represented. Infrequent causes are gram positives other than the enterococcus and Candida. Causes of nosocomial UTI comprise a lesser percentage of E. coli, and a greater percentage of Klebsiella, Enterobacter, Enterococci and Candida. Pseudomonas and Proteus species are more frequently isolated in infants with complicated anatomical malformations and in those neonates who have had surgical procedures, especially where foreign materials (e.g. urinary stents) have been left *in situ*. Approximately 5% of children have two organisms isolated. Viral causes of infection have been thought to be rare in neonates who are not immunosuppressed.

Some factors make E. coli that cause UTI more virulent. Certain polysaccharide antigens (K1, K2, K12 and K13) are found more often in neonates with upper tract infection and fimbriated E. coli that attach to glycolipids of the P blood group are more common causes of pyelonephritis in neonates who do not have vesicoureteric reflux. These restricted serotypes adhere to the urothelium avidly, resist serum bactericidal activity and cause increased inflammatory activity (for instance, increased CRP) [18, 19].

63.4 Treatment

63.4.1 Initial Treatment

The newborn with urinary infection will often present as a septic infant with signs such as hypotension, tachycardia and decreased conscious state, and there is frequently vomiting. These neonates may require resuscitation with IV boluses of normal saline and the use of ionotropic agents and intensive care monitoring may be necessary. Even in the well neonate intravenous therapy is always advised to ensure effective absorption of antibiotic.

The electrolytes and creatinine are usually normal. A common finding where obstruction of the urinary tract is an issue, and sometimes without findings of obstruction, is hyponatraemia, hyperkalaemia and normal anion gap metabolic acidosis. This finding can be attributed to failure of collecting duct function with salt wasting and non-responsiveness to aldosterone—a form of hyperkalaemic Type 4 renal tubular acidosis. It usually responds to rehydration and antibiotic treatment rapidly. Where severe hyponatraemia (serum sodium less than 120 mmol/L) is found with a long history (over a week) of symptoms care must be taken to raise the serum sodium slowly (less than 0.5 mmol/L/h) to avoid neurological injury such as central pontine myelinolysis and demyelination of the extrapontine myelin-bearing neurons [7].

Once the urine, blood and CSF cultures and have been obtained a decision on acute antibiotic treatment must be made. The intravenous antibiotics used acutely are listed in Table 63.3. The usual choice is a penicillin (to cover the enterococcus) and an aminoglycoside. The aminoglycoside should be given slowly, over an hour, and blood levels and creatinine monitored. If there is renal impairment cefotaxime may be substituted for the aminoglycoside. Institutional sensitivities of organisms isolated may differ and the regime may need to be modified. The urine culture should be sterile after 48 h treatment. Non response to treatment should lead to reculture of the urine and renal ultrasonography searching for infection with obstruction of urinary drainage or abscess formation, both of which may require surgical drainage and prolonged antibiotic use. Intravenous antibiotics are used for 7–10 days in the usual instance.

63.4.2 Prophylactic Antibiotics

After acute treatment the infant may be placed on prophylactic antibiotics given once each night.

Table 63.3 Antibiotic treatment of urinary tract infection

Acute treatment			
Intravenous benzylpenicillin	30–50 mg/kg/12 h in 1st week of life; 6 hourly after 1st week of life		
And			
Intravenous gentamicin	Wt <1200 g 5 mg/kg given 48 hourly 0–7 days, then 36 hourly 8–30 days, then 24 hourly >30 days of age Wt 1200–2500 g 5 mg/kg 36 hourly 0–7 days, then 24 hourly >7 days Term neonate after 1st week of life: 8 mg/kg day 1, 6 mg/kg day 2 and after Give IV over 1 h Monitoring: trough level <1 mg/1 taken on 3rd day and serum creatinine 3rd day Renal impairment: same dose but redose when trough level <1 ng/mL		
Prophylactic treatment			
1st month of life	Trimethoprim	3 mg/kg/day	40/200 mg/5 mL
>1 month of age	Co-trimoxazole	0.25 mL/kg/night	
	Nitrofurantoin	1–2 mg/kg/night	
	Cephalexin	5 mg/kg/night	

The antibiotics usually used for prophylaxis are listed in Table 63.3. These antibiotics are excreted in the urine, achieve high urinary concentrations and are well tolerated over long periods of time without inducing excessive microbiological changes in the gut (leading to the emergence of resistant organisms or candidiasis). They are usually given until the results of imaging tests are available, and may be used for prolonged periods with the aim of reducing the risk of further UTI. This has been an area of medical controversy but systematic review of higher quality studies has shown a significant reduction in the risk of repeat urine cultures by 50%.

63.5 Investigations

Investigations are aimed at excluding obstructive urinary tract lesions, determining whether there are significant underlying urinary tract malformations and assessing renal injury. The extent of investigation necessary after a first neonatal urinary tract infection has become an area of medical controversy, centred on the role of the cystourethrogram.

All centres perform a renal ultrasound. Most importantly the possibility of obstruction is detected. Secondly, the presence, site, size and shape of the kidneys can be determined. However small lesions can be missed: in the age group under 5 years, only 15% of abnormalities found on DMSA scan ('scars/dysplasia') will be seen on ultrasound examination. The ureters are not visualized unless enlarged. The finding of hydronephrosis or hydroureter leads to further nuclear medical imaging (discussed below) to diagnose obstructive lesions of the urinary tract.

A spinal ultrasound is useful in the first weeks of life for examination of the spinal cord and should be done with bladder abnormalities or if there is abnormality of the spine such as a deep sacral pit.

A spinal radiograph should be done if the sacrum cannot be palpated.

The radiological examination of the urethra and bladder, using a cystourethrogram, was performed in most centres as a routine on neonates until the last decade. However, this investigation is performed less frequently than in the past because the demonstration of vesicoureteric reflux (VUR) does not alter management at many centres. Thus, in the absence of abnormalities of the kidneys, ureters or bladder on ultrasound examination it is often not performed as a routine. This is discussed further below.

Nuclear medicine investigations with technetium-99 m-labelled radioisotopes are useful for a number of purposes.

The *DTPA* radionuclide is injected intravenously, is filtered by the glomerulus and then is neither secreted nor absorbed by the tubule of the kidney. Like creatinine or inulin, it can be used to obtain an accurate measure of the glomerular filtration rate.

The *Mag 3* scan has largely replaced the DTPA scan because, in addition to some glomerular filtration, the isotope is mainly secreted by the proximal tubular cells into the urine so that the signal to background ratio is higher than in the DTPA scan. This is particularly useful in infants in the first 3 months of life when the glomerular filtration rate is low. Both of these investigations are useful for diagnosing the presence of obstruction to urinary flow from the kidneys to the bladder, for determining the 'split' of kidney function (between the right and left kidneys), and for estimating overall renal function.

The *DMSA* radionuclide is filtered by the glomerulus and taken up by the proximal tubular cells. Scanning takes place when it has been taken up by these cells, which are in the renal cortex. Lack of uptake gives a defect on the scan and this can be due to either transient impairment of the tubular cell function (e.g. following acute inflammation with pyelonephritis for a period of up to 3–4 months) or absence of kidney tissue (renal 'scarring/dysplasia').

Delayed uptake of any of these three radionuclides may occur in conditions where perfusion to the kidney is abnormal (e.g. renal artery stenosis in a unilateral case or dehydration in a bilateral case).

The ongoing management depends on the results of investigations. A flow diagram of possibilities is shown in Fig. 63.1.

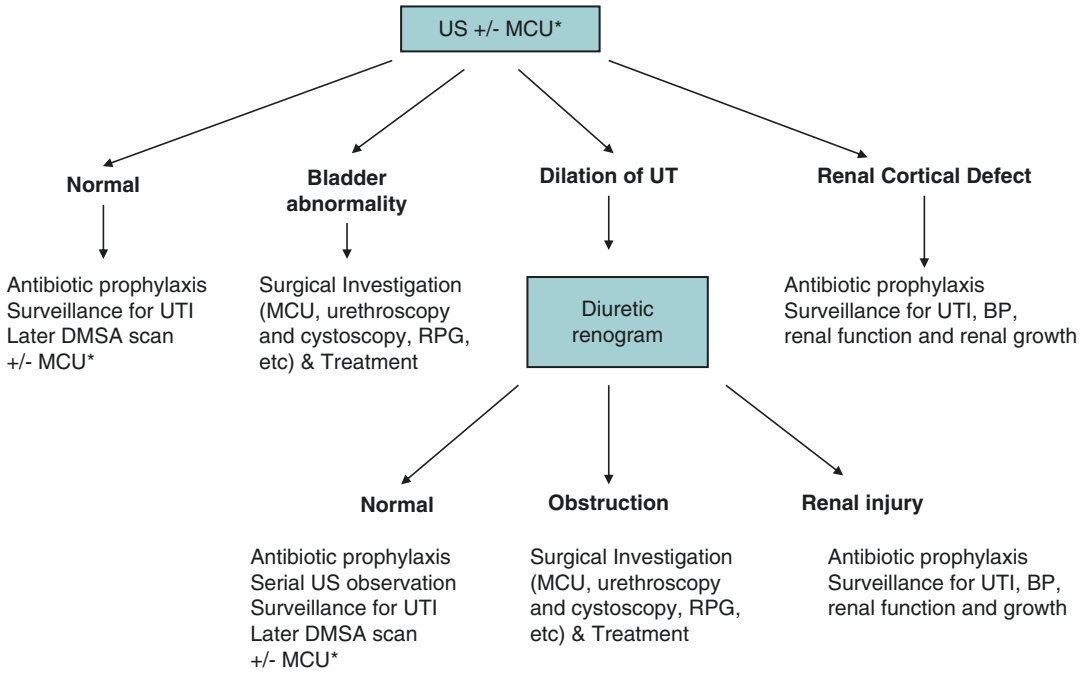

Fig. 63.1 A flow diagram of ongoing management following a proven urinary tract infection. A normal ultrasound does not exclude scarring. This age is chosen for convenience. Boys uncommonly get recurrent infections after 1 year; girls commonly have recurrent infection until about 3 years. Follow-up includes a yearly blood pressure check. The finding of a normal DMSA scan normalizes the risk of developing hypertension. *MCU* micturating cystourethrogram, *US* ultrasound, *VUR* vesicoureteric reflux, *BP* blood pressure, *RPG* retrograde pyelogram. Where indicated by asterisk (*) the results of the MCU do not influence the authors' treatment or investigation of UTI

63.6 Urinary Tract Infection and Normal Renal Ultrasound

If the neonate responds to antibiotics there is no need to perform another urine culture at the end of treatment. Prophylactic antibiotics may be continued for 6–12 months. Long-term follow-up is essential unless DMSA scan is normal. The authors' preferred practice is to follow the infant through childhood clinically and to do a DMSA scan around the age of 5 years. If the scan is normal the child is discharged, and if abnormal the child continues with follow-up for detection of hypertension or development of proteinuria.

63.7 The Diagnosis of Vesicoureteric Reflux

Vesicoureteric reflux (VUR) is a common disorder, affecting 40% of children under 1 year of age who are investigated for a first urinary tract infection. The diagnosis is made by cystourethrogram in neonates.

Vesicoureteric reflux is often a familial trait affecting up to between 30 and 50% of first-degree relatives of index cases. In some cases, it is associated with renal abnormality (variously referred to as renal scarring, dysplasia, reflux-associated nephropathy), excessive dilatation and tortuosity of the ureter, occurrence on the contralateral side and abnormalities of bladder function including premature detrusor contractions (causing urgency symptoms and wetting at older ages) and poor bladder emptying. Higher grades of VUR are associated with higher recurrence rates of UTI.

The treatment of VUR has been controversial. Controlled trials have shown no advantage of either anti-reflux surgery or antibiotic prophylaxis in preventing urinary infections, hypertension, renal injury or renal failure [20–23]. In fact, it is not clear whether these treatments, in turn, are better than episodic treatment of urine infection alone. Much of the renal injury leading to renal failure in a small number of patients with VUR is congenital and the significance of acquired injury is debated [24]. An increasing amount of embryological and genetic data have accumulated that relate congenital abnormalities of the kidney and urinary tract (CAKUT) to vesicoureteric reflux and renal dysplasia and conditions that resemble scarring on radiological or nuclear imaging [25]. Thus, the aim of treatment of VUR is as much or more about prevention of symptomatic UTI, as prevention of renal injury. Attention to reducing and treating precipitating factors for UTI, the use of antibiotic treatment in a prophylactic or episodic manner and the selective use of antireflux surgery for patients with intractable symptoms form the basis of treatment [26–28]. The authors' practice is to continue prophylactic antibiotic until the age of 6–12 months and then to reinstitute them if infections ensue on stopping the antibiotic. For troublesome cases in male infants circumcision can be useful as discussed earlier.

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Indications for Investigation of the Urinary Tract in the Newborn

64

Harriet J. Corbett and Helen Fiona McAndrew

Abstract

The urinary tract in the newborn may require investigation for a number of reasons. The urinary tract is the commonest system in which abnormalities are detected during antenatal ultrasonography (USS). The majority will have isolated hydronephrosis, with mild dilatation detected in as many as 1:100 pregnancies. Others will have more significant urological abnormalities thus investigation of the urinary tract is indicated to interpret the antenatal USS findings. Investigation is also indicated for those neonates presenting with urinary tract related symptoms. Equally, in neonates presenting with non-specific symptoms such as failure to thrive, poor feeding or prolonged jaundice, urinary tract pathology should be considered. Finally, there are neonates with congenital anomalies or syndromes with known associated uropathies who require further investigation. The range of such conditions or syndromes in which the urinary tract may be involved is extensive.

Keywords

Antenatal diagnosis • Urinary tract anomalies • Imaging • Management Outcomes

64.1 Introduction

The urinary tract in the newborn may require investigation for a number of reasons. The urinary tract is the commonest system in which abnormalities are detected during antenatal ultrasonography (USS). The majority will have isolated hydronephrosis, with mild dilatation detected in as many as 1:100 pregnancies [1, 2]. Others will have more significant urological abnormalities thus investigation of the urinary

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_64

tract is indicated to interpret the antenatal USS findings. Investigation is also indicated for those neonates presenting with urinary tract related symptoms. Equally, in neonates presenting with non-specific symptoms such as failure to thrive, poor feeding or prolonged jaundice, urinary tract pathology should be considered. Finally, there are neonates with congenital anomalies or syndromes with known associated uropathies who require further investigation. The range of such conditions or syndromes in which the urinary tract may be involved is extensive.

64.2 Antenatal Diagnosis

In most healthcare systems, modern day antenatal care includes a routine ultrasound scan (USS) seeking structural anomalies between 18 and 20 weeks of gestation [3]. The fetus is examined according to a routine protocol that includes measurement of the amniotic fluid volume. The renal tract examination should document the number and location of the kidneys and the presence and appearance of the bladder. The ureters would not normally be seen so visualisation of either ureter is notable. Other abnormal findings may include dilatation of the renal pelvis, caliectasis, absent or ectopic renal tissue, duplication anomalies, cysts, bladder abnormalities and oligohydramnios. Anomalies in other systems that may be of relevance to the urinary tract include spinal fusion defects such as myelomeningocele, or suspicion of the VACTERL complex.

The most frequently detected urological abnormality on antenatal USS is dilatation of the renal pelvis, which is also known as pelviectasis or hydronephrosis (antenatal hydronephrosis, ANH) [1, 2]. In many this finding will be transitory, but in the others ANH will be a marker of pathology in the urinary tract [1]. Not surprisingly, those with minor degrees of ANH will typically resolve whilst more severe ANH, especially when associated with calyceal dilatation, is more likely to persist postnatally [2]. Table 64.1, adapted from the recent Consensus Statement on the evaluation and management of antenatal hydronephrosis by the Society for Fetal Urology, outlines the aetiology of ANH and the most common causes [4]. Others diagnoses, such as prune belly syndrome, cystic kidney disease, congenital ureteric strictures and megalourethra are uncommon causes of ANH. The presence of abnormalities of renal echogenicity, cortico-medullary differentiation and parenchymal thickness should be noted since these make significant pathology more likely, as does the presence of oligohydramnios, chromosomal defects or multiple anomalies within other organ systems [4]. Overall, fetuses with an abnormality detected in the urinary tract on antenatal USS are predominantly male (male:female ratio of 2:1), particularly in fetuses subsequently found to have obstructive lesions [1].

Table 64.1 The aetiology of ANH

Aetiology	Incidence (%)
Transient hydronephrosis	41–88
Pelviureteric junction obstruction	10–30
Vesicoureteric reflux	10–20
Vesicoureteric junction obstruction/ megaureters	5–10
Ureterocele/ectopic ureter/duplex system	5–7
Multicystic dysplastic kidney	4–6
Posterior urethral valves/urethral atresia	1–2

Adapted from Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, Lee R, Perez-Brayfield M, Metcalfe P, Yerkes E, Cendron M, Campbell JB. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 2010:6:212–31; used with permission

The degree of dilatation of the renal pelvis may be assessed in a number of ways. The simplest grading system of mild, moderate or severe is quite subjective. The Society for Fetal Urology published a system based on *postnatal* appearance in 1993, for which reproducibility is only modest [5, 6]. A more objective, and frequently reported, technique records the transverse antero-posterior diameter (APD) of the renal pelvis at the level of the renal hilum (see Fig. 64.1) [7]. A number of factors influence the degree of ANH, including maternal hydration, the degree of fetal bladder distension and the gestational age at which the dilatation is detected [4]. An increasing degree of dilatation increases the significance, particularly at earlier gestation [7]. However, no single measurement separates normal from abnormal APD measurements. The consensus statement from the Society for Fetal Urology uses a simple grading of

ANH according to the APD and gives recommendations for subsequent prenatal evaluation (see Table 64.2) [4]. In more complex cases, such as those with unclear anatomy, antenatal Magnetic Resonance Imaging (MRI) may be considered (see Fig. 64.2). Severe cases should be discussed on a case-by-case basis, preferably within a multidisciplinary team. Fetal intervention, early delivery or even termination may be considered.

The antenatal scan findings guide the timing and degree of postnatal investigations, bearing in mind that in 30–50% hydronephrosis will persist postnatally and around 30% will be associated with a significant abnormality, particularly in those with more marked ANH [1, 4, 7]. The challenge is to determine which newborns have obstructing lesions and which have simple physiological dilatation. Postnatal USS undertaken at less than 24 h of age have a false negative rate, and this is thought to be due to neonatal dehydration [8]. Significant pathology may be missed in the first few days of life and, hence, very early ultrasound scans are not usually recommended for the majority of infants [8–10]. However, in newborns with bilateral dilation, unilateral dilatation in the presence of bladder abnormality or any uropathy associated with oligohydramnios or lung abnormality, the postnatal ultrasound should be done at 24–72 h of age. If the scan is normal it should be repeated after 3–7 days, and if the scan is still normal, a repeat scan at 4–6 weeks is recommended. In male infants, posterior urethral valves must be considered. A micturating cystourethrogram is usually required in such neonates, after a period of bladder decompression and once the renal function has stabilised.

For all other newborns, the initial postnatal USS should be done at 3–14 days. Again, if this scan is normal it should be repeated at 4–6 weeks of age. In those with an abnormal postnatal USS, further imaging will be indicated according to the antenatal and postnatal findings. The schedule

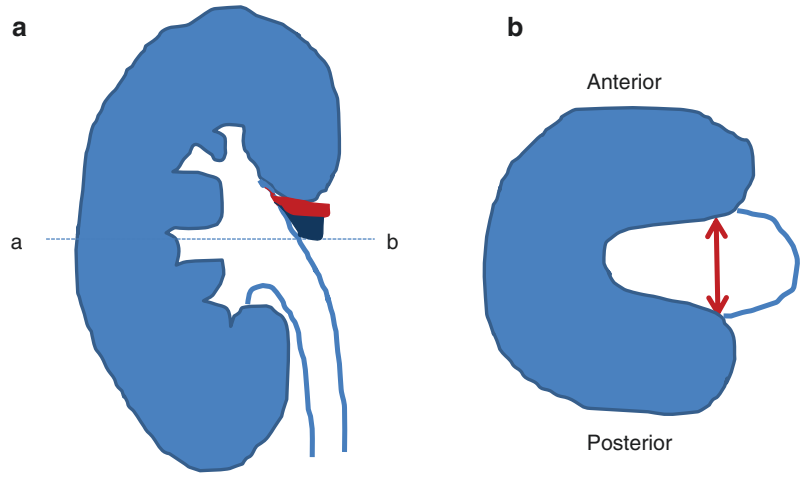

Fig. 64.1 (**a**) Longitudinal view of the kidney. The transverse measurement of the pelvis should be taken at the level of the renal hilum (a, b). (**b**) Transverse antero-posterior view of the kidney and pelvis showing where the APD should be measured (*arrow*)

Table 64.2 Recommendations for the ongoing prenatal evaluation of ANH

Time of detection of ANH	Severity of ANH	APD (mm)	Recommendations
2nd Trimester	Mild	<7	Consider 3rd trimester US
	Moderate	7–10	3rd Trimester US
	Severe	>10	Repeat US in 3–4 weeks
3rd Trimester	Mild	<9	Postnatal evaluation
	Moderate	9–15	Postnatal evaluation
	Severe	>15	Repeat US in 2–3 weeks

From Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, Lee R, Perez-Brayfield M, Metcalfe P, Yerkes E, Cendron M, Campbell JB. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 2010:6:212–31; used with permission

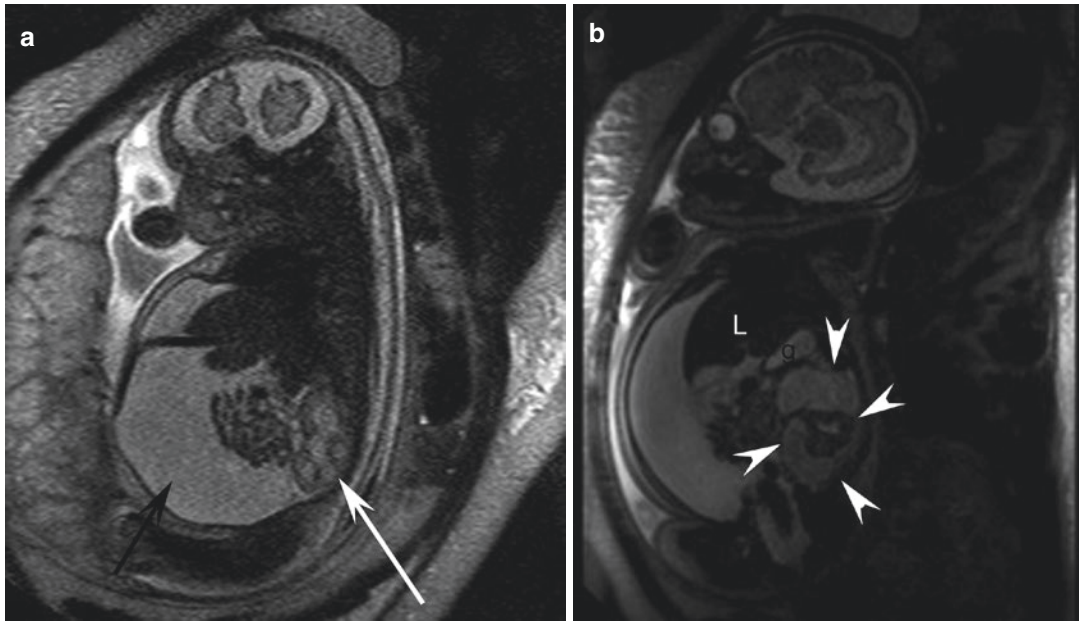

Fig. 64.2 Antenatal uropathy: (**a**, **b**) Sagittal heavily T2-weighted imaging of the fetal abdomen of a hydropic fetus showing a ascites (*black arrow*) and a hydronephrotic kidney (*white arrow*) with b contralateral multicystic dysplastic kidney (*arrowheads*), a loculated urinoma could give rise to similar appearances. Liver (*L*), gallbladder (*g*). Images courtesy of Dr. Gurdeep S. Mann, MRCP FRCR, Alder Hey Children's Hospital, Liverpool.

adopted by the Departments of Urology and Radiology at Alder Hey and the Fetal Medicine Unit and Department of Neonatolgy at Liverpool Women's Hospital is outlined in Fig. 64.3 (adapted from HK Dhillon [11, 12]).

Antibiotic prophylaxis should be given to infants considered to be at increased risk of urinary tract infection due to urinary stasis or vesicoureteric reflux. However, whilst a number of studies have documented the increased risk of UTI in neonates with ANH [13–15], no randomised controlled trials have proven the efficacy of antibiotic prophylaxis [4]; further, UTI are known to occur even with antibiotic prophylaxis. Despite this, most clinicians still deem it appropriate to give prophylactic antibiotics [4, 13–15].

64.3 Postnatal Presentation

Neonates may present with symptoms and/or signs indicative of urinary tract pathology, including an abdominal mass or distension, poor urinary stream, oliguria, or an abnormal appearance of the genitalia, perineum, umbilical cord or abdominal wall. Others will present with non-specific symptoms such as vomiting or sepsis due to urinary tract infection, and some will present with abnormal renal function (see Table 64.3 and Fig. 64.4) [16–19]. In addition, urinary tract pathology should be considered in neonates with failure to thrive, poor feeding or prolonged jaundice, as well as in those newborns presenting with respiratory compromise caused by pulmonary hypoplasia secondary to oligohydramnios [19].

Suspected urinary tract infection in neonates warrants prompt urine microscopy and culture; diagnosis should not be based on dipstick testing in this age group [16, 19]. A standard urine specimen is a 'clean catch' voided sample but this can be difficult to obtain, particularly in girls. Urine collection bags are commonly used but often yield indeterminate culture results so if a clean catch sample is unobtainable, urine should be sampled directly from the bladder by catheter or suprapubic aspiration [19, 20]. Pyuria of more than 5 white blood cells per high-power field or the presence of bacteria on microscopy is highly

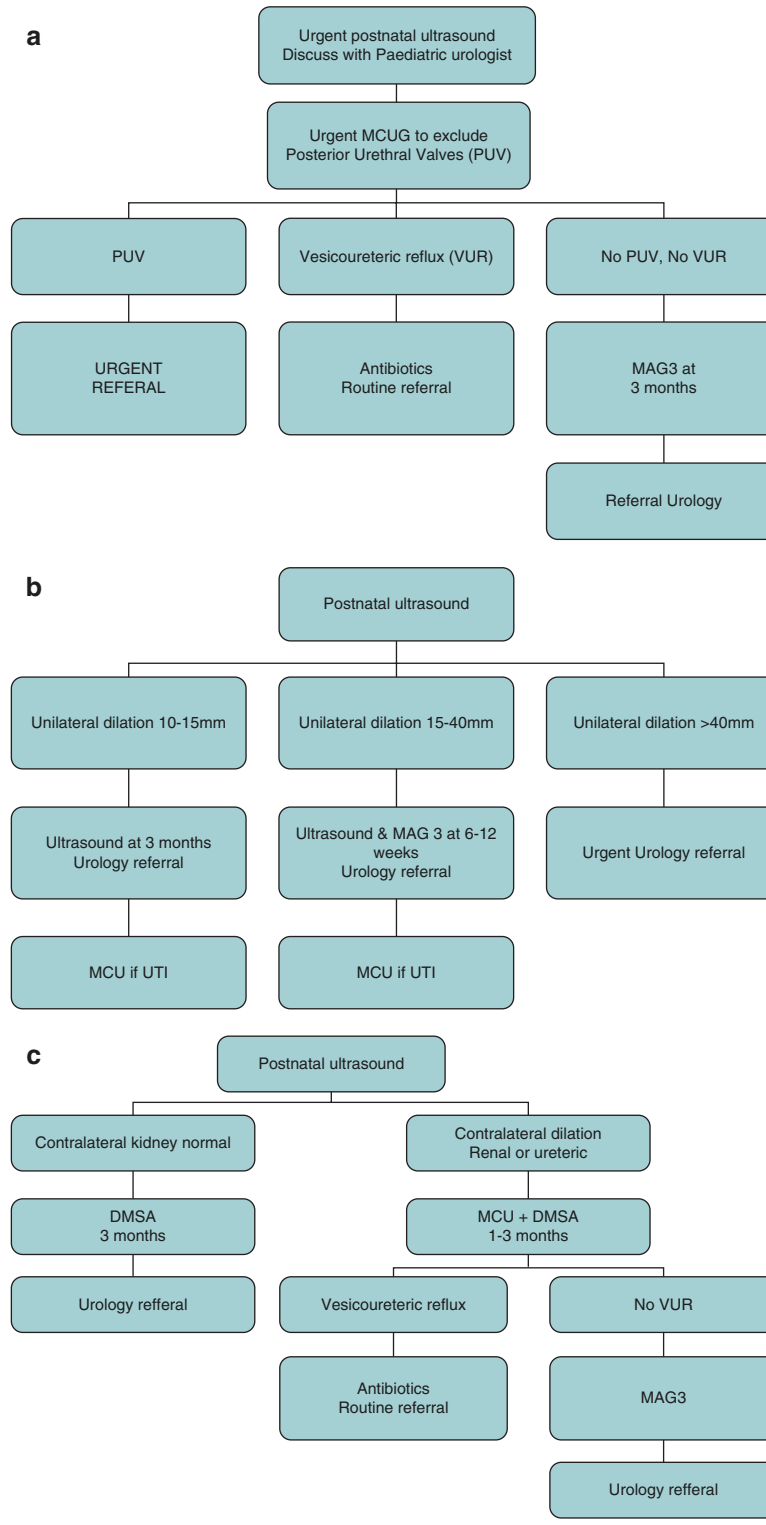

Fig. 64.3 *Protocol 1* (**a**): For (1) neonates with renal dilation with oligohydramnios or lung abnormality, (2) bilateral renal dilation or (3) unilateral renal dilation with ureteric dilation or bladder abnormality or abnormal contralateral kidney. *Protocol 2* (**b**): Isolated Unilateral renal dilation confirmed postnatally (if only has one kidney or bladder or ureteric abnormality, pre or postnatally see protocol 1). *Protocol 3* (**c**). Unilateral cystic kidney confirmed postnatally

Table 64.3 Postnatal signs of urinary tract pathology

Presenting feature	Diagnosis
Poor urinary stream	Bladder outlet obstruction e.g. posterior urethral valves, urethral abnormalities
Abdominal mass or distension	Hydronephrosis Enlarged bladder Vagina (hydrocolpos) e.g. urogenital sinus, persistent cloaca Neuroblastoma Urinary ascites Renal tumour e.g.Mesoblastic nephroma
Abnormal abdominal wall	Prune belly syndrome / eagle-Barrett syndrome Bladder or cloacal exstrophy
Abnormal umbilical cord	Urachal or allantoic anomalies
Abnormal perineum	Disorders of sexual development Urogenital sinus Persistent cloaca Ureterocele Spinal dysraphism
Haematuria	Urinary tract infection Renal vein thrombosis

suggestive of a UTI [20]. A pure growth of $>10^5$ bacteria/mL on culture in association with pyuria is diagnostic although a growth of $>10^4$ bacteria/mL from catheter or suprapubic samples is also highly suggestive of UTI. It is worth mentioning that in neonates with urinary tract obstruction above the bladder, the urine from the may be clean if the infection is contained within the obstructed part of the system. As such, a specimen may only be obtained when the obstruction is relieved. A high index of suspicion is therefore required and urgent USS is recommended.

Around 14% of infants with a urinary tract infection will have a previously undetected urinary tract anomaly, hence all such infants should undergo timely investigations [18]. Indeed, any newborn presenting with suspected urinary tract pathology must have an USS in the first instance; subsequent imaging will be guided by the clinical course as well as the USS findings [19]. A thorough history and examination is also mandatory, seeking clues to underlying pathology such as a poor urine stream, a family history of vesicoureteric reflux (VUR) or renal disease, constipation, an abdominal mass, poor growth, high blood pressure or an abnormal spine (see Table 64.3) [19].

Newborns with spinal dysraphism or congenital anomalies including anorectal malformations and the VACTERL association all require urinary tract screening with USS in the newborn period as associated anomalies are common [20–23]. Spinal dysraphism encompasses a wide spectrum of anomalies from the clinically obvious myelomeningocele through sacral agenesis to occult spinal cord tethering or syringomyelia. Cutaneous stigmata of spinal dysraphism include a hairy patch, sacral lipoma and an abnormal gluteal cleft [21]. USS can be used as a screening tool for abnormalites of the lower spinal cord in neonates but any abnormality suggestive of dysraphism warrants Mangetic Resonance Imaging (MRI) of the spine to delineate the anatomy in detail [24]. Such babies may have a neuropathic bladder so bladder emptying should be assessed in the newborn period. This is readily achieved by placing an alarmed pad in the nappy; the alarm is triggered when the baby voids and a portable ultrasound is used to ascertain the bladder's residual volume. Alternatively an intermittent catheter may be passed, any residual urine drained and the volume measured.

64.4 Imaging Modalities

64.4.1 Ultrasound Scan

Ultrasonography is the first choice of investigation as the scans are relatively easy to perform and involve no radiation, and as such can be repeated frequently (see Fig. 64.5) [4]. USS can show the anatomy in detail, although the scan findings will be dependent upon the degree of hydration, the degree of bladder filling and the experience of the sonographer. Doppler studies will give information regarding blood flow, particularly important in infants suspected to have pyelonephritis or at risk of renal vein thrombosis. And whilst USS are typically static scans, dynamic information can be captured if, for example, reflux is seen to occur during the Doppler scan. Portable scan machines can be taken to the cot or bed-side which is particularly useful in very sick infants or children. USS is operator dependant and therefore should be repeated whenever there is diagnostic doubt or unexpected clinical course.

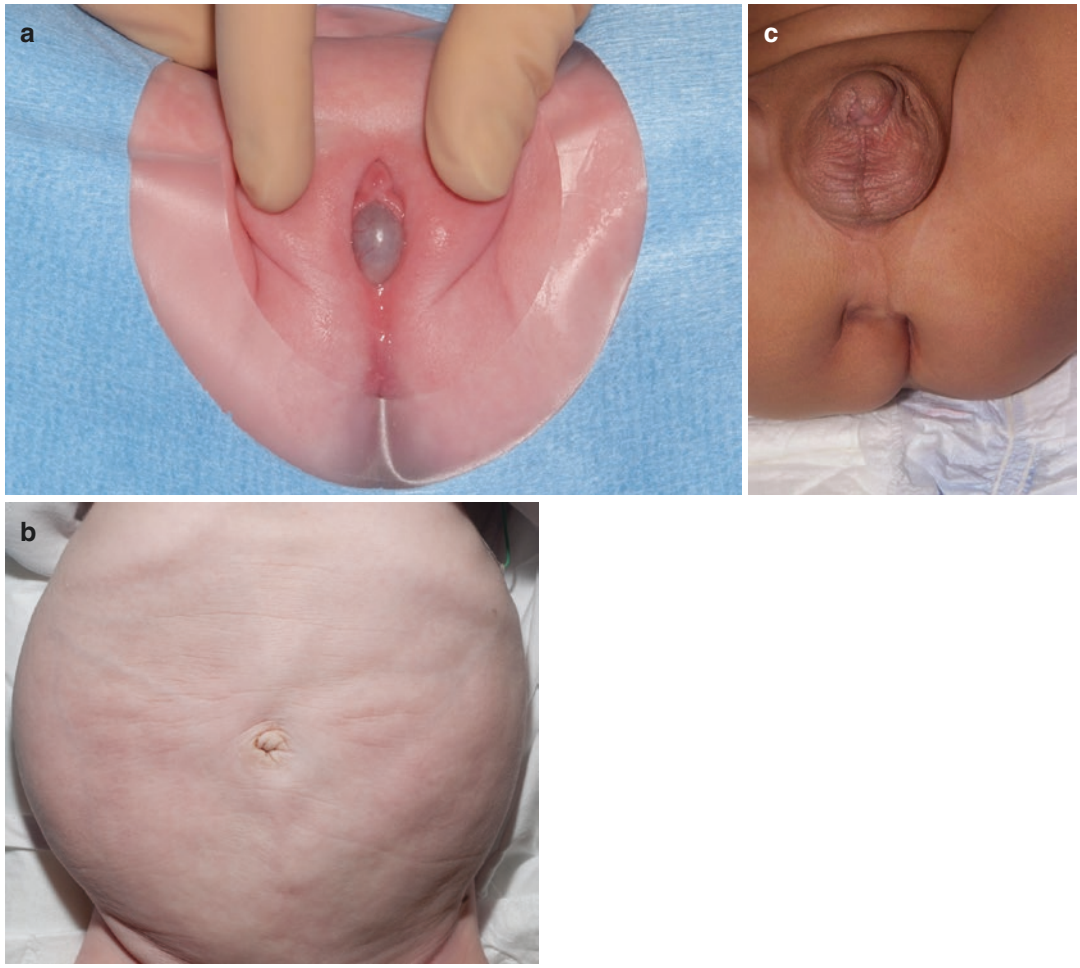

Fig. 64.4 Clinical examination findings that should prompt investigation of the urinary tract: (**a**) Caeco-ureterocele protruding through the urethra. (**b**) Prune belly syndrome. (**c**) Asymmetrical perineum in spinal dysraphism

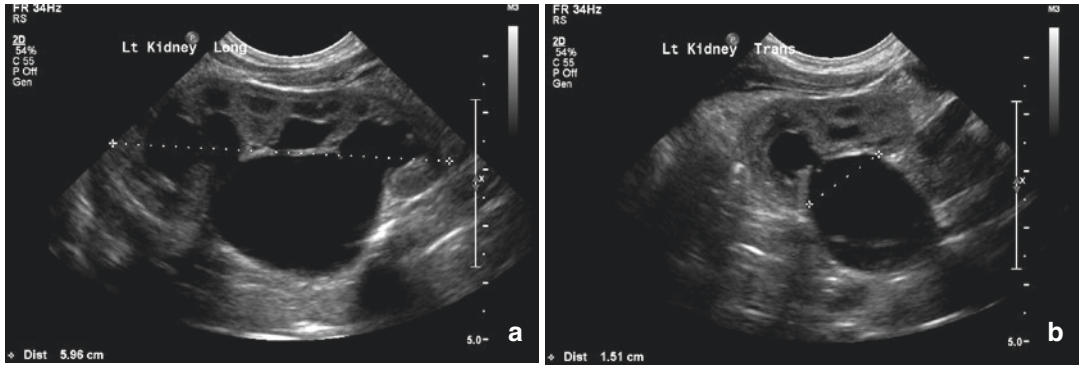

Fig. 64.5 Ultrasound scan in a neonate with significant hydronephrosis (**a**) longitudinal view (**b**) transverse view—the APD is 15 mm

64.4.2 Micturating or Voiding Cystourethrogram

The micturating (or voiding) cystourethrogram (MCUG or VCUG) is uncommonly required in the neonatal period. There is a risk of introducing infection during the study, so antibiotic cover should be considered particularly in neonates in whom intravenous administration is recommended. A MCUG is indicated for delineation of the anatomy of the lower urinary tract and diagnosis of bladder outflow obstruction and vesicoureteric reflux (VUR) (see Fig. 64.6). The study involves catheterisation, which will usually be per urethra but the study may be performed via a suprapubic catheter if clinical circumstances have required one. Water soluble contrast is slowly instilled via the catheter, with intermittent fluoroscopic screening to guide the dynamics of the study. The study should capture both filling and voiding phases; complete views of the male urethra are essential to look for posterior urethral valves.

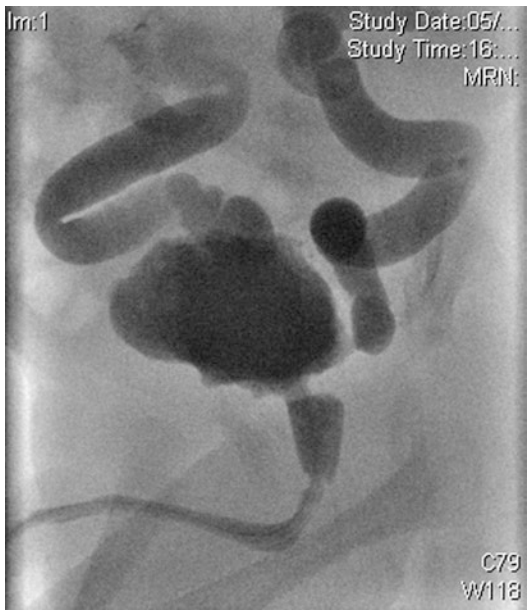

Fig. 64.6 Micturating cystourethrogram showing unilateral vesico-ureteric reflux and an enlarged posterior urethra secondary to Posterior Urethral Valves

64.4.3 Nuclear Medicine Imaging/ Isotope Scans

Renal isotope scans may be dynamic or static studies, using technetium-99 (Tc-99) bound to mercapto acetyl tri-glycerine (MAG3), dimercaptosuccinic acid (DMSA) or diethylenetriamine pentaacetic acid (DTPA). These studies are rarely utilised in the newborn period as the neonatal kidney is relatively immature. The European Society for Paediatric radiology recommends monitoring of the renal tract in the newborn with USS over 3 months prior to performing a renal isotope scan whilst in the USA, scans are rarely performed prior to 6 weeks of age [4]. Ideally all such scans should be performed in a standardised manner but many units will still use local protocols.

64.4.4 DMSA (Dimercaptosuccinic Acid) Scan

Dimercaptosuccinic acid binds to the cells of the proximal tubule, giving a static image of the renal parenchyma. In older children the scans are used primarily to identify focal defects or scars within the kidneys. In neonates DMSA scans have a high background count and there is a high degree of urinary excretion. DMSA scans may occasionally be required to confirm function where ultrasound raises the question of a need for neonatal intervention or when it is necessary to confirm or exclude acute pyelonephritis (see Fig. 64.7) [19].

64.4.5 MAG3 (Mercapto Acetyl Tri-Glycerine) Scan

Tri-mercaptoglycerine is chiefly bound to plasma proteins and is subject to tubular secretion. The scan provides dynamic information relating to the collecting system and drainage of the kidney. The parenchyma is also outlined reasonably well in the early stage of the scan and so the MAG3 serves to give an estimate of split function. The dose of radiation is low and for this reason a MAG3 scan may be used in the occasional newborn in whom information is required about drainage of the kidneys.

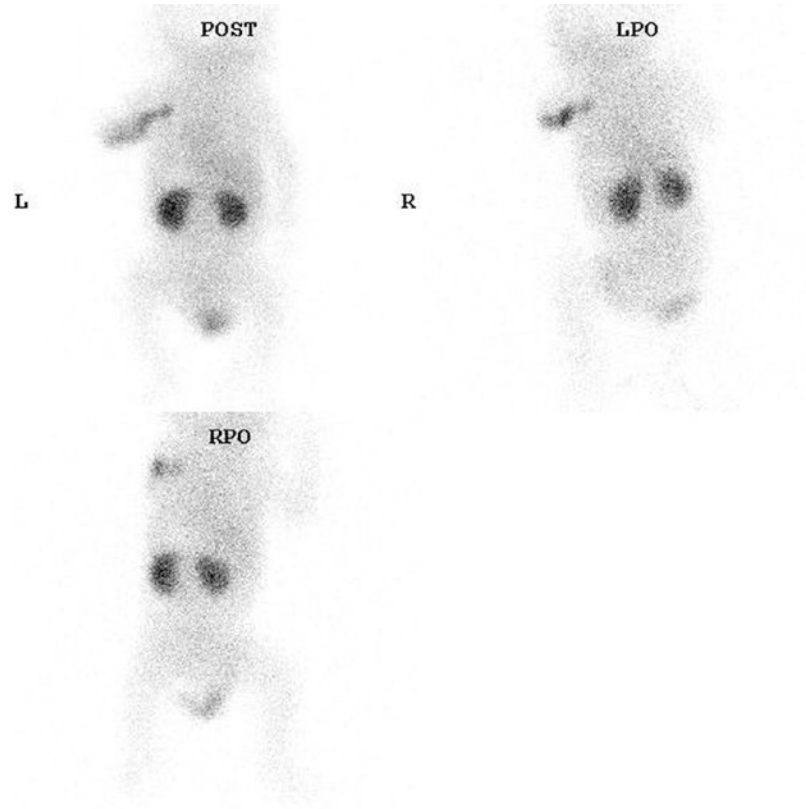

Fig. 64.7 Preterm infant with right nephrostomy in situ: DMSA showed a split function of Right 45%, Left 55%. (*POST* posterior, *LPO* left posterior oblique, *RPO* right posterior oblique)

64.4.6 DTPA (Diethylenetriamine Pentaacetic Acid)

DTPA is cleared by filtration, and in the immature neonatal kidney visualisation of the renal parenchyma is poor. It is of very limited use in infants and has largely been replaced by DMSA.

64.4.7 Magnetic Resonance Imaging (MRI)

MRI can give excellent anatomical information, and can be specifically targeted at the urinary tract through the MR urogram (MRU). The scans take a long time to acquire and for older children this will often require general anaesthesia. In infants however, scans may be acquired in 'natural' sleep, after a feed. As there is no radiation involved, MRU is becoming the investigation of choice if cross sectional imaging is required. However, MRU is rarely indicated in neonates due the quality of USS which, when combined with MCUG and nuclear medicine usually gives sufficient information.

64.4.8 Computed Tomography (CT)

CT scans provide useful cross-sectional information but at the expense of very high doses of radiation so are utilised infrequently in the newborn. Tumours are a rare indication.

64.5 Summary

Antenatally detected urinary tract anomalies are the commonest indication for urological investigations in the newborn. Ultrasound confirmation of the abnormality is followed by further investigations as indicated. Paediatric Urologists play a central role in this group as it is important not to over-investigate these newborns yet critical not to miss those with significant pathology. Neonates

will all present postnatally with a wide range of symptoms and signs; once again the Paediatric Urologist must tailor the investigations accordingly.

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Urinary Tract Obstruction and Dilatation

65

Anju Goyal

Abstract

Congenital anomalies of the kidney and urinary tract (CAKUT) has an incidence of 3–6 per 1000 birth and is a common cause of chronic kidney disease in children. While most CAKUT are believed to be sporadic, recent studies have suggested a high incidence (upto 50%) of CAKUT in families of index cases of urinary tract anomaly (Renkema et al. Nephrol Dial Transplant. 26:3843–51, 2011; Bulum et al. Pediatr Nephrol. 28:2143–7, 2013). This suggest a genetic basis and various genes such as HNF1 β[beta], PAX2, RET and ROBO2 have been implicated. Commonly CAKUT result in dilatation and/or obstruction of the urinary tract anywhere from the kidney down to the bladder and urethra. There can be isolated dilatation of the pelvicalyceal system (hydronephrosis [HDN]) or associated ureteric dilatation (hydroureteronephrosis [HDUN]) with or without bladder abnormality. HDN/HDUN can be secondary to obstructive or non-obstructive pathology. Obstruction is defined as 'some impedence to the flow of urine, which causes gradual and progressive damage to the kidney' (Dhillon. Essentials of paediatric urology. Informa Healthcare, p. 133–42, 2008). The non-obstructive dilatation can be due to vesico-ureteric reflux (VUR) or it can be non-obstructive, non-refluxing dilatation. Non-obstructive non-refluxing pathology, which is usually due to inherent dysplasia of the developing urinary tract, is more difficult to define and to differentiate from obstruction. Occasionally obstruction and reflux can coexist.

Keywords

Urinary tract anomaly • Prenatal diagnosis • Investigations • Surgical management • Outcomes

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_65

65.1 Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) has an incidence of 3–6 per 1000 birth and is a common cause of chronic kidney disease in children. While most CAKUT are believed to be sporadic, recent studies have suggested a high incidence (upto 50%) of CAKUT in families of index cases of urinary tract anomaly [1, 2]. This suggest a genetic basis and various genes such as HNF1 β[beta], PAX2, RET and ROBO2 have been implicated. Commonly CAKUT result in dilatation and/or obstruction of the urinary tract anywhere from the kidney down to the bladder and urethra. There can be isolated dilatation of the pelvicalyceal system (hydronephrosis [HDN]) or associated ureteric dilatation (hydroureteronephrosis [HDUN]) with or without bladder abnormality. HDN/HDUN can be secondary to obstructive or non-obstructive pathology. Obstruction is defined as 'some impedence to the flow of urine, which causes gradual and progressive damage to the kidney [3]. The non-obstructive dilatation can be due to vesico-ureteric reflux (VUR) or it can be non-obstructive, non-refluxing dilatation. Non-obstructive non-refluxing pathology, which is usually due to inherent dysplasia of the developing urinary tract, is more difficult to define and to differentiate from obstruction. Occasionally obstruction and reflux can coexist.

The landscape of neonatal urinary tract dilatation and obstruction anomalies has been transformed by the introduction of routine antenatal ultrasound (US) screening. A mid-trimester ultrasound scan to detect fetal structural anomalies has been undertaken in the UK since the 1980s. A fetal anomaly screening scan is offered to all pregnant women from 18 to 20(+6) weeks. High-resolution 2D ultrasound scan provides detailed assessment of urinary tract from early 2nd trimester onwards. It can detect renal pelvic (Fig. 65.1) and/or ureteric dilatation/anomaly and/or bladder distention (Fig. 65.2) along with other associated non urinary tract abnormalities. Many of the detected anomalies might never have come to attention clinically in childhood but often generates disproportionate parental anxiety during the pregnancy [4].

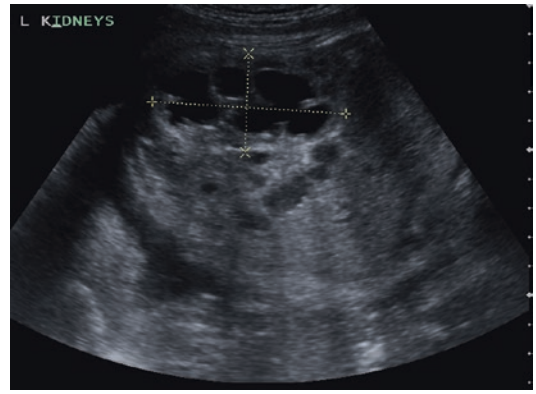

Fig. 65.1 Antenatal scan demonstrating left hydronephrosis

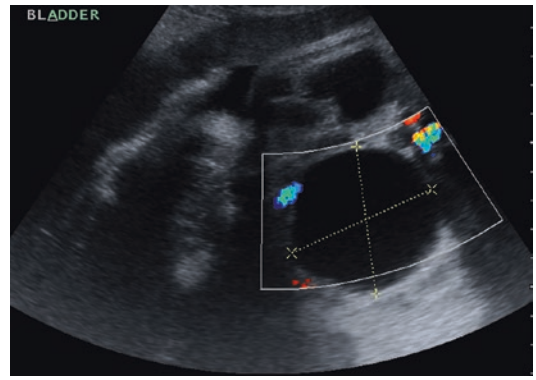

Fig. 65.2 Distended bladder on antenatal scan

Antenatal detection has created a whole new field in the practice of paediatric urology. It deals predominantly with healthy children with no obvious clinical problem who have a potential for morbidity in the form of urinary tract infection (UTI) and renal functional deterioration. There are management dilemmas as to how far to investigate in an apparently healthy child, especially where natural history of the abnormality is not clear and management may not yield satisfactory outcomes. This is especially brought to focus when managing cases with megaureter and non-specific renal pelvic dilatation. Natural history studies are limited. Some

anomalies such as antenatal HDN and megaureter are better studied than others and this has led to majority of these being managed conservatively with careful monitoring [5].

Most neonates are asymptomatic at birth and have a benign pathology, which needs antibiotic prophylaxis, careful and optimally timed investigations and monitoring. In the medium term, only 7% of these antenatally detected anomalies require surgery [5]. A recent long-term outcome study demonstrated that one third each showed normalization, need of surgery or persistence of anomalies without need of surgery [6]. And further few of these such as those with posterior urethral valves (PUV), severe pelvi-ureteric junction (PUJ) obstruction and obstructing duplex ureterocoele, will require intervention in the neonatal period.

The challenge for the medical community is to differentiate those, which need treatment to prevent renal deterioration from those that are unlikely to have any consequences. In order to make this differentiation, the optimum level of investigations that a child should be subjected to, continue to be refined. As demonstrated by trends in management of HDN, the pendulum has swung from aggressive surgical correction to non-interventional observation for majority [5, 7].

65.2 Antibiotic Prophylaxis

Urinary tract dilatation and obstruction, on account of stasis of urine predisposes the child to urinary tract infection. In some pathology, prophylaxis has been proven to be helpful where as in others, the benefit is debatable. Antibiotic prophylaxis reduces the risk of UTI and prevents renal scarring in selected cases [8, 9]. Regardless of the need for intervention, antibiotic prophylaxis is started in most neonates with suspected urological anomaly while awaiting investigations and it remains the mainstay of urological management in a significant number of refluxing, obstructive and non-refluxing, non-obstructive pathologies. In our practice, trimethoprim at 2 mg/kg is the most commonly used antibiotic, followed by cefalexin.

65.3 Prenatally Detected Urinary Tract Anomalies and Their Antenatal Management

65.4 Incidence

A significant proportion of congenital urinary tract anomalies are diagnosed antenatally on detailed fetal anomaly scan done at 20 weeks gestation. About 20% of the anomalies are detected at a later gestation scan despite an apparently normal 20 weeks scan [5]. A small proportion escapes antenatal detection and may present in early infancy with symptoms of abdominal mass or UTI.

The reported incidence of antenatal urological anomalies is increasing due to improved detection. A variable incidence has been reported depending upon the threshold for diagnosing pelvicalyceal dilatation with most citing incidence of 1 in 100 or higher [4, 5, 10, 11]. A consensus statement by the Society for Fetal Urology (SFU) suggests that up to 5% of fetuses might be affected by HDN [12]. Most of these are mild dilatation and incidence of significant uropathy is around 1 in 500 [4].

The most commonly detected anomalies are—non-specific dilatation (NSD) of pelvicalyceal system (48.6%), VUR (12%), PUJ obstruction (10.6%), multicystic dysplastic kidney (MCDK) (6%) [5]. Apart from urinary tract dilatation, antenatal screening may detect—absence of kidney, absence of bladder, renal dysplasia, amniotic fluid volume increase or decrease, associated other system anomalies such as haematocolpos, etc. (Table 65.1). Though antenatal findings suggest the possible diagnosis, it is not always accurate and hence prognostic predictions are fraught with pitfalls. Any advice about antenatal intervention or progression or otherwise of pregnancy has to be very cautious with recognition of limitations of imaging techniques [13].

Table 65.1 Features and possible aetiology of antenatally detected urinary tract dilatation/pathology

Pathology	Features on antenatal scans	Aetiology
Upper urinary tract pathology	Renal pelvic dilatation	Non specific dilatation, PUJ obstruction, duplex kidney
	Ureteric dilatation ± Renal pelvic dilatation	Megaureter (obstructed or non-obstructed), Vesico-ureteric reflux, duplex kidney
	Other renal pathologies	Renal aplasia, dysplasia, MCDK, duplex
Lower urinary tract pathology	Bladder distention ± renal pelvic and ureteric dilatation	PUV, Isolated Megacystis, Neuropathic bladder (unusual), urethral atresia
	Bladder not seen	Bladder exstrophy / Cloacal exstrophy
Entire urinary tract malformation	Renal pelvic and ureteric dilatation along with bladder distention	PUV, Prune belly syndrome, Megacystis megaureter syndrome, MMIHS
Associated with complex urogenital tract malformations	Usually renal pelvic and ureteric dilatation ± bladder distention	Cloacal anomaly, Vaginal atresia, Urogenital sinus, Imperforate anus

65.5 Antenatal Investigations

Most antenatally detected anomalies require monitoring during pregnancy with ultrasound scan. The frequency of monitoring depends upon the severity of pathology. In unilateral renal dilatation follow up scan at 30–32 weeks gestation would suffice but in bilateral PCS dilatation or solitary kidney, serial scans at 4 weekly intervals are required (see Fig. 65.3a). In case of associated oligohydramnios, referral to specialist fetal therapy unit must be made. In selected cases such as when kidneys are not seen clearly due to maternal habitus or low liquor volume, magnetic resonance (MR) scan of fetus may be helpful to assess anatomy. In some instances, when pathology detected might warrant consideration of termination, MR may be done to be absolutely sure of the pathology—such as in cloacal exstrophy [13]. Depending upon the findings of antenatal scan, other investigations such a karyotyping, amniotic fluid analysis might be required. There is up to 22% reported incidence of chromosomal abnormalities in antenatal lower urinary tract obstruction (LUTO) [14–17].

65.6 Antenatal Intervention

Intervention can be diagnostic or therapeutic. Alternatively it may be termination of pregnancy (TOP). TOP is recommended only if bilateral severe renal dysplasia/solitary dysplastic kidney with or without oligohydramnios or in very severe anomalies with poor quality of life such as cloacal exstrophy.

Antenatal intervention is most commonly considered in cases of LUTO because if untreated, it carries a mortality of up to 45% mainly due to the severe oligohydramnios and resulting pulmonary hypoplasia [18]. One third of survivors may develop end-stage chronic renal impairment [19]. Because of this prognosis, there is a termination rate of up to 50% in severe LUTO [20, 21]. LUTO is amenable to therapeutic fetal intervention and it is considered if there is predicted poor prognosis with some anticipated salvage consequent to intervention. The aim of therapeutic antenatal intervention is prevention of renal failure and pulmonary hypoplasia. The prognostic criteria for case selection for intervention include echogenicity of kidneys and liquor volume. Biochemistry of fetal urine gives information about the prognosis but a systematic review [22] demonstrated that none of the analytes of fetal urine yielded clinically significant accuracy to predict poor postnatal renal function. Also fetal urine for analysis is obtained by vesicocentesis, which carries its own risk; hence it is not routinely performed. As a preparation for therapeutic intervention, it is mandatory to perform a detailed anomaly scan, determine fetal sex and offer fetal karyotyping.

There are different modalities of therapeutic intervention. Though fetal cystoscopy, open shunt insertion and repeated vesicocentesis have been utilised [23, 24], percutaneous vesico-amniotic shunt (VAS) placement is the most commonly used modality. VAS involves the placement of a double pig-tailed catheter under ultrasound guidance and local anaesthesia, with the distal end in the fetal bladder and the proximal end in the amniotic cavity to allow drainage of fetal urine. Since the first report of VAS in human fetuses in 1982 [25], many case series have suggested that

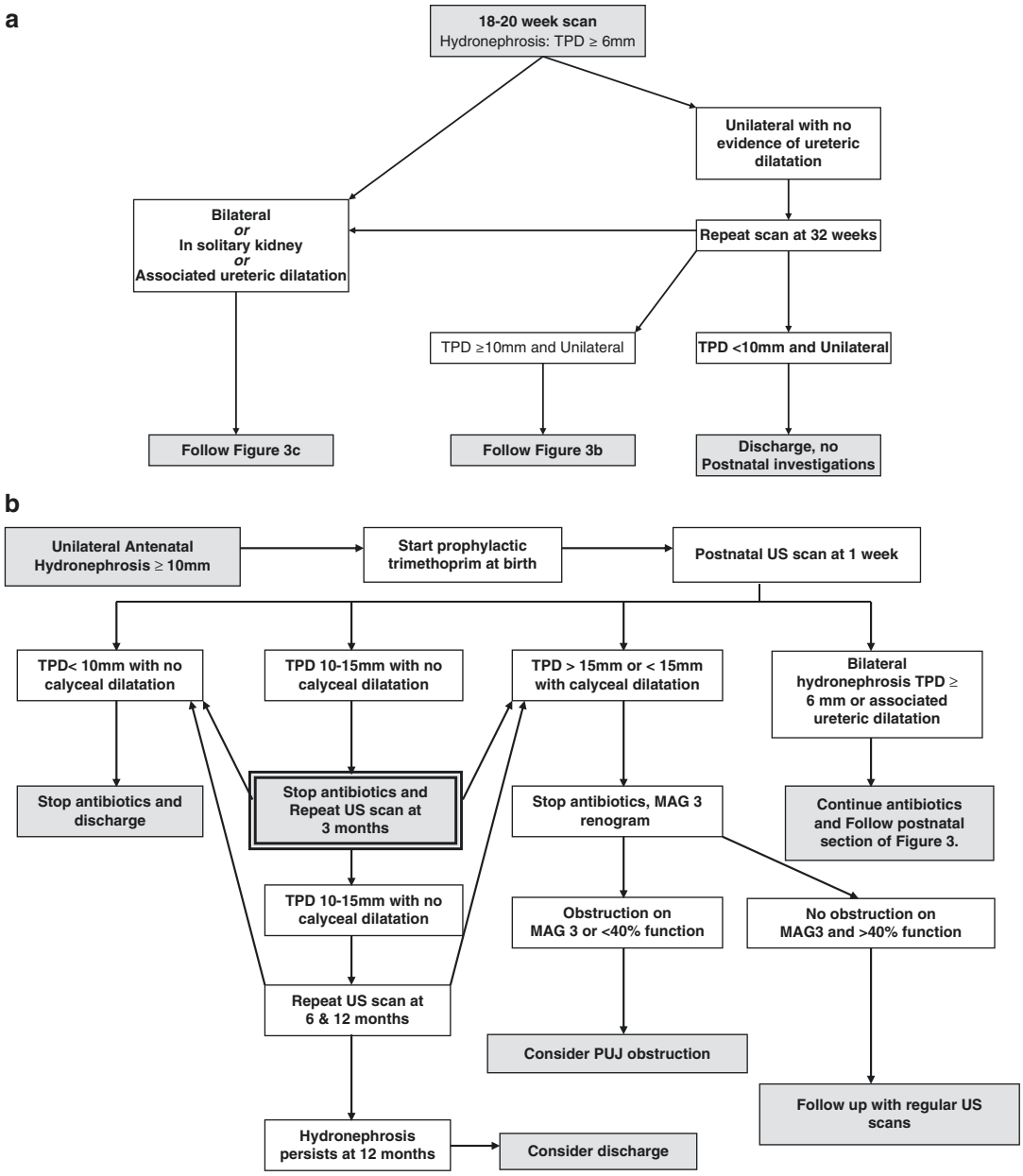

Fig. 65.3 Institutional management protocol for antenatal hydronephrosis. (**a**) Antenatal scan findings and pathway for management, (**b**) Postnatal management for unilateral hydronephrosis, (**c**) Pathway for bilateral hydronephrosis, hydronephrosis in a solitary kidney or associated ureteric dilatation

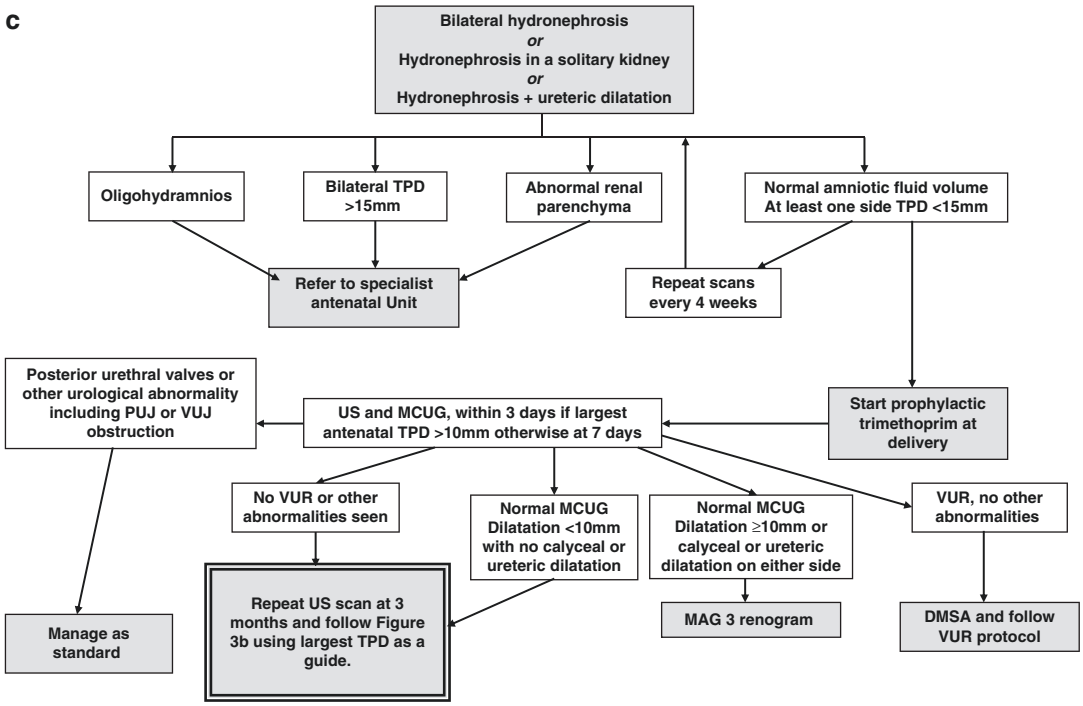

Fig. 65.3 (continued)

survival could be improved with this [26]. VAS has a significant incidence of complications: shunt displacement/occlusion (upto 34%), preterm labour, chorioamnionitis, traumatic injury and fetal/neonatal death [27]. Despite initial promise of good results, outcomes have not been very positive and VAS is not in vogue any more. Systematic review of observational studies showed a role for VAS in reduction of perinatal mortality but long-term mortality and morbidity remains high. It suggests that amelioration of oligohydramnios by shunting reduces mortality due to pulmonary hypoplasia, but the renal damage is not reversible [27]. A multi centre randomised controlled trial (PLUTO—The Percutaneous shunting in Lower Urinary Tract Obstruction) conducted by The University of Birmingham, UK compared in-utero VAS with conservative management [28]. The as-treated analysis of 31 pregnancies showed that fetuses that underwent bladder shunting had a three-time higher chance of postnatal survival than non-shunted fetuses, though very few survived with normal renal function. These findings are in line with results from studies in animals, which have shown that renal damage occurs rapidly after the onset of obstruction and might be only partly reversible [29]. The dysplastic changes seen in fetal kidneys are probably a different pathological process, rather than just a consequence of obstruction [30].

65.7 General Principles of Postnatal Management

A thorough clinical examination of the newborn remains very relevant. The necessity of investigations is clear when a neonate presents with symptoms of UTI or mass or urinary stream problems. However formulating a rational investigation protocol for antenatally detected anomalies that is appropriate and is tailored to the urgency of concerned pathology is more difficult. The aim is to investigate urgently those, which are likely to result in infection or nephron damage if left untreated. Others can be investigated at a pace that is suitable for the child, family and is likely to give best information. Fig. 65.3a–c shows the pro-

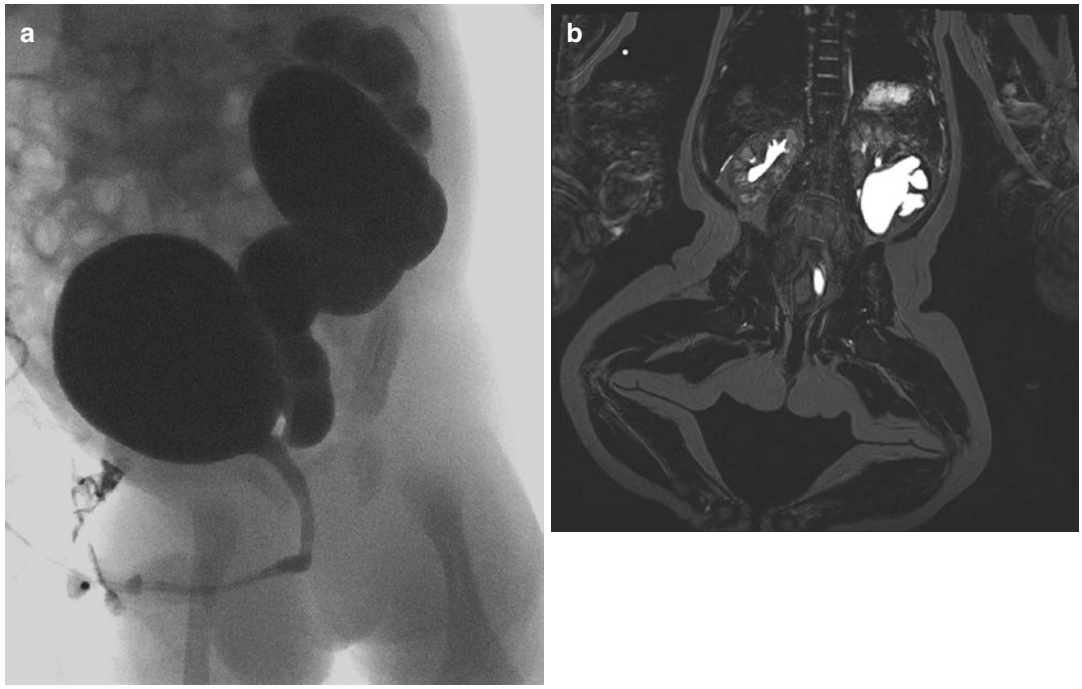

Fig. 65.4 (**a**) MCUG showing left VUR in an apparently simplex system but is actually lower pole reflux in duplex kidney, (**b**) MR scan showing left duplex in the same patient

tocol for investigation and management of antenatally detected hydronephrosis at our institute.

Due to renal immaturity, a nuclear medicine scan in first 2 months might not give accurate information about renal function and drainage. Similarly an ultrasound scan done in first 48 hours may miss important pathology as diuresis is not established as yet. Hence in most cases ultrasound should be delayed till at least 1 week of age. The indication for earlier ultrasound in first 2–3 days would be palpable mass, bilateral HDN or HDN in a solitary kidney or suspected LUTO. Micturating cystourethrogram (MCUG) is being used more selectively now whereas earlier it was performed in most cases with HDN and MCDK. MCUG is warranted in cases of suspected LUTO or if there is any ureteric dilatation. Bilateral HDN in boys even in the absence of ureteric dilatation could be due to LUTO and should be investigated with MCUG. An MR scan may be helpful to delineate anatomy in selected cases such as in duplex kidneys (Fig. 65.4a, b), horseshoe kidney, etc.

65.8 Multicystic Dysplastic Kidney

MCDK constitutes 6% of the antenatally detected anomalies. Overall Incidence has been estimated at 1 in 2400. Previously most common presentation was postnatally with abdominal mass but now most are detected antenatally.

MCDK develops due to failure of induction of metanephric blastema by the ureteric bud leading to replacement of whole kidney with multiple non-communicating cysts with no discernible parenchyma. There may be associated ureteric atresia, dilatation of ureter or ureterocoele. Confirmation is done with a postnatal ultrasound (Fig. 65.5a). If there are multiple cysts with big central cyst then a PUJ obstruction with huge pelvicalyceal dilatation (Fig. 65.5b) must be considered in differential diagnosis. Differentiation can be made with a DMSA scan which shows no function in a MCDK.

Natural history of MCDK is well documented [31]. Based on the natural history stud-

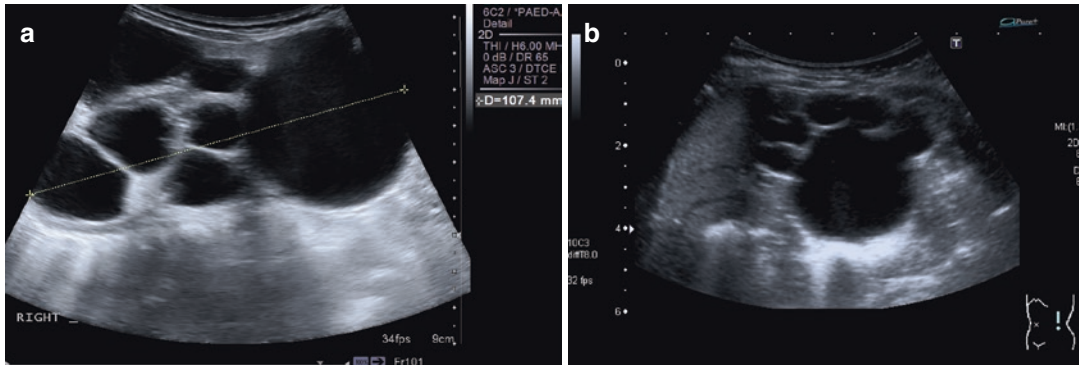

Fig. 65.5 (**a**) MCDK with multiple non-communicating cysts on US, (**b**) MCDK with dominant medial cyst mimicking severe PUJ obstruction

ies, significant changes in investigations and management have happened in last 2 decades. In MCDK there is associated VUR with reported incidence of contralateral reflux being 4.5–20% and ipsilateral reflux is present in 3–16%. It was a standard practice to do a MCUG to assess for reflux. However, it is an invasive investigation involving radiation and risk of UTI. Reflux is however low grade and mostly clinically inconsequential. Hence MCUG is no longer routinely recommended [31–34]. It may be considered in selected cases when there is contralateral kidney pathology or ureteric dilatation or family history of VUR or if there is UTI in infancy.

MCDK are managed conservatively with monitoring of blood pressure, urinalysis for protein, Glomerular Filteration Rate (GFR) estimation and follow up US to check for MCDK involution and contralateral kidney growth. Spontaneous complete involution rate is 60% at 10 years [31]. Nephrectomy is no longer recommended. Hitherto, one of the rationales for nephrectomy was to prevent risk of hypertension, malignancy and the argument that removing MCDK allowed child to be discharged from follow up. However large long-term studies have identified small but important risk of contralateral pathology (PUJ obstruction, Vesico-Ureteric Junction (VUJ) obstruction, VUR, abnormal echogenicity with low GFR) mandating follow up in early childhood regardless [29].

65.9 Isolated Pelvicalyceal Dilatation

Hydronephrosis in newborn does not equate with obstruction. Pelvicalyceal system (PCS) dilatation can be due to non-specific dilatation (NSD) or PUJ obstruction [5]. In NSD there is no hold up on MAG3 scan. While some NSD are result of fetal polyuria and resolve with time, others are consequent to kinks, folds and narrowings at PUJ, which straighten/settle over time. About 50% of antenatal PCS dilatation is transient and post natal ultrasound scan is normal. In PUJ obstruction there is delayed drainage on MAG3 scan. These are more difficult to manage, as they are a different entity to PUJ obstruction presenting later in childhood with symptoms. The standard investigations for diagnosing obstruction such as MAG3 scan and severity of dilatation on ultrasound are not applicable to this group [35, 36]. Evidence of obstructive injury to kidney in the form of decrease in function of >10% and increasing hydronephrosis, is currently the accepted way of differentiating between those needing surgery and those who can be managed conservatively. Only 22–30% of PUJ obstructions require surgical intervention [5, 35] and intervention is rarely required in neonatal period. Most neonates can be investigated as per the protocol shown (Fig. 65.3 b). Only indication for urgent investigations would be in cases of severe dilatation bilaterally or in a solitary kidney (Fig. 65.3c). Even severe unilateral hydronephrosis can be observed safely non-operatively with regular imaging (Fig. 65.6a, b)

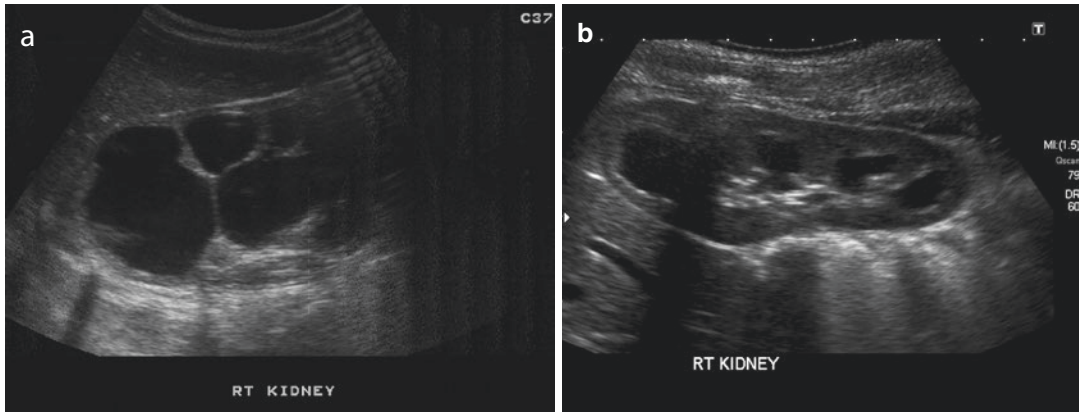

Fig. 65.6 (**a**) Severe PCS dilatation SFU grade 4, (**b**) Same patient, PCS dilatation now improved on conservative management

Table 65.2. SFU grading of Hydronephrosis

Grade	Characteristics of central renal echo complex
0	Closely apposed
1	Slight separation
2	Further separation; one or few calyces may be visualized
3	Pelviectasis and fluid filled calyces seen throughout kidney
4	Grade 3 with parenchyma over calyces thinned

and need for intervention seems to be independent of initial severity of HDN, degree of renal function and renogram pattern [35].

Thirty years after commencement of antenatal detection and management, we are still debating the indications and timing of surgical intervention. Protocols and guidelines in various centres are derived from natural history studies, which had arbitrary cut-off points for surgical interventions; hence many current indications continue to be arbitrary.

Hydronephrosis can be graded on the basis of pelvic dilatation assessed as transverse anteroposterior diameter (TAPD) with separate specific reference to calyceal dilatation and cortical thinning. Society for Fetal Urology (SFU) recommends grading on the basis of dilatation and renal cortex thickness [37] (Table 65.2). Only grades 3 and 4 are felt to be clinically significant with respect to obstruction. In our centre and in most UK centres, radiologists prefer to assess hydronephrosis with TAPD. A new classification system—Urinary Tract Dilation (UTD) Classification System has been proposed which can be applied both prenatally and postnatally [38].

Two most debated aspects of antenatal HDN are initial assessment protocol of antenatal HDN and indication for intervention in PUJ obstruction.

65.10 Assessment of Antenatal HDN

Different parameters have been proposed. The maximum antero-posterior diameter at the hilum in the transverse plane (TAPD) is the crucial measurement. After detection of isolated HDN on 20 weeks scan, it is recommended that repeat scan should be done around 30 weeks gestation. TAPD at this scan correlates closely with the need for surgery [39] and hence is the basis of postnatal management. Some including our institution protocol (Fig. 65.3a–c) recommend no postnatal scanning for those who have TAPD of less than 10 mm on >30 week scan. But with this cut-off parameter, a small proportion of urologically significant anomalies (mostly non-dilating reflux but some PUJ obstruction) may be missed. Hence some recommend at least one postnatal scan for those with TAPD more than or equal to 7 mm [5].

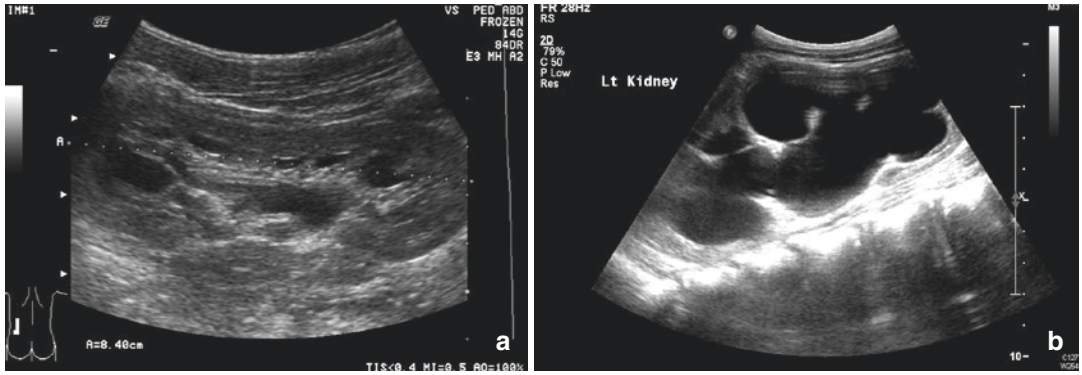

Fig. 65.7 (**a**) Ultrasound scan showing PCS dilatation which settled on conservative management and thus discharged, (**b**) Same patient presented 3 days later with acute obstruction and pain

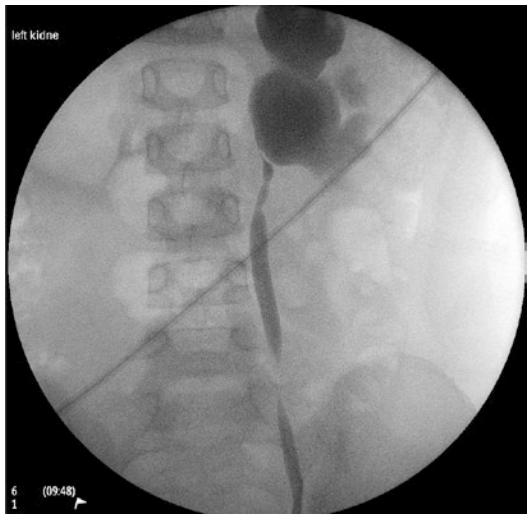

Fig. 65.8 Retrograde pyelogram demonstrating narrowing at the PUJ

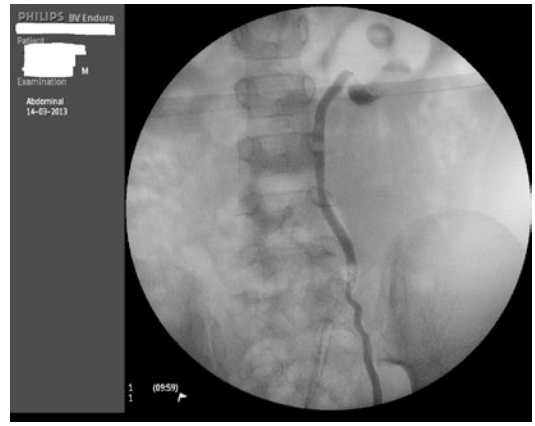

Fig. 65.9 Retrograde pyelogram showing a kink at the PUJ due to aberrant lower pole vessel

It is important that postnatal ultrasound should be viewed in light of antenatal scans. If antenatal scans showed huge dilatation but postnatal scans do not, they should be viewed with suspicion and a further ultrasound scan should definitely be performed. MCUG is usually indicated if there is any ureteric or bladder dilatation and is usually done few weeks after birth. An urgent MCUG should be considered in first week of life, in cases of bilateral dilatation or dilatation in a solitary kidney and should be adequately covered with antibiotics. When indicated, MAG 3 scan should be performed at 2–3 months of age. Again it may be indicated earlier in bilateral/solitary kidney cases.

Early natural history studies of PCS dilatation [35, 40–42] demonstrated that majority of these can be managed conservatively. A very small proportion of antenatal HDN that has resolved fully or partially may develop obstruction at a later date (Fig. 65.7a, b) and families should be counselled about it at the time of discharge from follow up.

65.11 Pelvi-Ureteric Junction Obstruction

PUJ obstruction is the most commonly detected anomaly on antenatal scans after NSD. It is defined as PCS dilatation with impaired drainage on MAG3 scans. It can be unilateral or bilateral. It is

more common in males and left side is more common. About 10% may be bilateral [5]. Occasionally there may be a familial predisposition with cases found in different generations and in siblings.

Usually there is an intrinsic PUJ narrowing of variable length (Fig. 65.8), rarely it may be due to aberrant lower pole vessel (Fig. 65.9). In intrinsic PUJ, the proximal ureter is bound to the lower renal pelvis by flimsy adhesions. Once the ureter is dissected free, it is usual to find a narrow segment, 2–10 mm in length immediately below the pelvi-ureteric junction and that urine does not escape from the renal pelvis until an incision is carried proximally above the narrow segment [43]. PUJ usually shows histological features of narrowing with decreased smooth muscle and increased collagen and elastin.

PUJ obstruction usually remains asymptomatic despite increasing dilatation. Very rarely it may present in infancy with mass, UTI, sepsis, hypertension or haematuria.

65.12 Diagnosis and Indication for Intervention in PUJ Obstruction

Initial assessment is with an US and MAG3. Delayed drainage pattern or a non-draining curve should not be taken as a mark of obstruction [36]. Peters [44] has defined obstruction as "a condition of impaired urinary drainage which, if uncorrected, will limit the ultimate functional potential of a developing kidney." The dilemma facing urologists managing these patients is that are we loosing nephrons because we are waiting for too long [45] or are we intervening when we did not need to. Certainly the trend over the years is more towards conservative management following results from natural history studies. Dynamic functional MR is being investigated for its utility to provide more accurate assessment of obstruction [46].

65.12.1 Management

The most commonly accepted indications for intervention are: serial ultrasound scans showing increasing PCS dilatation, MAG3 scan showing deterioration in kidney function by >10% and symptoms of UTI/haematuria or echogenic fluid in pelvis on US (Fig. 65.10). Intervention if the differential renal function on first assessment is below 40% is debatable [35].

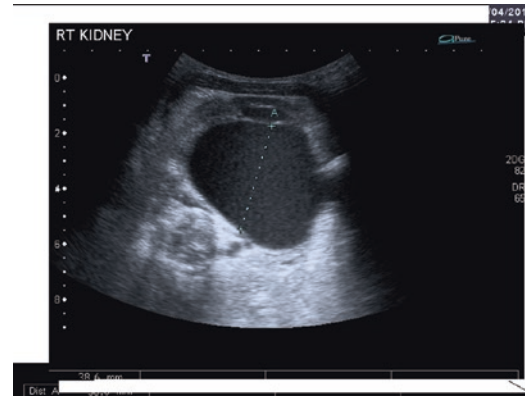

Fig. 65.10 Echogenic debris on US in a child with PUJ obstruction

Anderson Hynes pyeloplasty is the standard procedure performed. Occasionally if there is some uncertainty about the level of obstruction, a retrograde pyelogram can be done on the table to delineate anatomy better before proceeding to pyeloplasty (Fig. 65.11a, b). Though laparoscopic/robotic pyeloplasty is gaining acceptance and becoming more common in older children, open surgery is still the procedure of choice in infants. If there is massive pelvic dilatation, a reduction of pelvis is important to prevent kinking at the PUJ. In our practice, a transanastomotic stent is kept and patient is usually discharged the next day of the operation. Stent is removed approximately 6 weeks later.

A percuatenous nephrostomy may occasionally be done before pyeloplasty when there is poor function or if there is presentation with pyonephrosis. Post-nephrostomy nuclear medicine scan will provide better assessment of function to guide towards nephrectomy or pyeloplasty. If there is an acute presentation with pain which does not settle, emergency stent insertion might be considered but proceeding straight to emergency pyeloplasty is another option.

Post operative scans if done early often show preoperative level of PCS dilatation causing

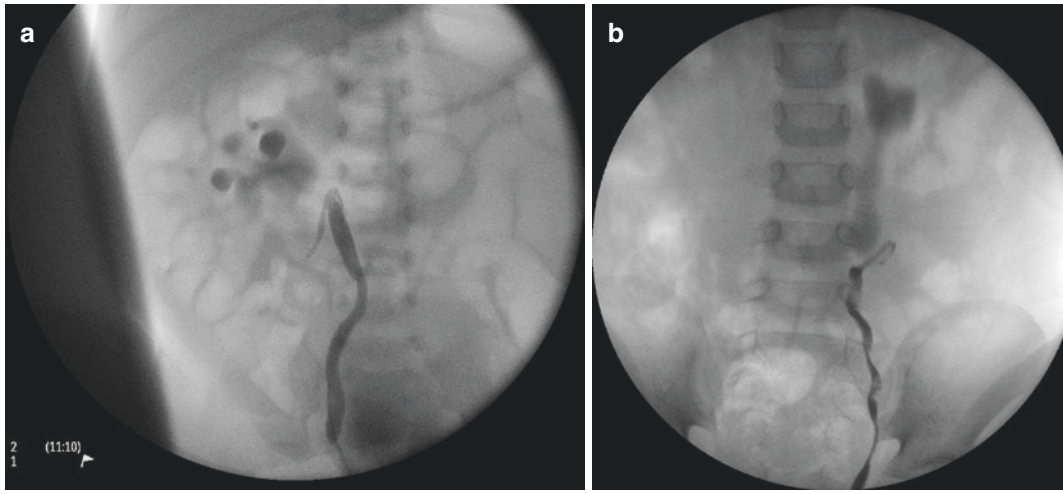

Fig. 65.11 Retrograde pyelogram. (**a**) narrowing at the PUJ, (**b**) mid-ureteric stricture

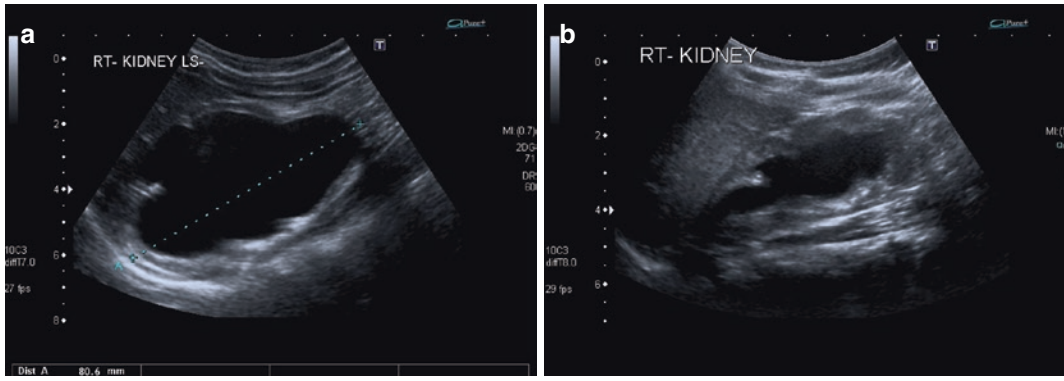

Fig. 65.12 Post pyeloplasty imaging. (**a**) US scan 4 weeks following stent removal demonstrating severe PCS dilatation, (**b**) repeat scan after 10 weeks showing that dilatation has settled without any intervention

unnecessary anxiety. It takes some time for dilatation to settle down. For this reason we defer follow up scan till about 3 months following removal of stent (Fig. 65.12a, b).

65.12.2 Vesico-Ureteric Reflux

Vesico-ureteric reflux is the retrograde flow of urine from the bladder up into the ureter and upper urinary tract. Postnatally VUR usually present as UTI. Prenatally diagnosed VUR refers to a diagnostic sequence in which the dilatation of the fetal urinary tract initiates postnatal investigations confirming VUR. An indicator of reflux on antenatal scan is ureteric dilatation. A significant proportion of infantile VUR escape antenatal detection and present with UTI [47]. Prenatal VUR constitutes 12–15% of all prenatal HDN and the protocol for investigation of antenatal HDN determines the proportion of VUR in any series. Prenatal VUR tends to be more in males and higher grade and bilateral and is known to follow a benign course [5, 48–51]. Approximately 80% is in males [51, 52]. Prenatal VUR is bilateral in 60–80% [47, 49, 51, 52]. Upto 50% VUR is grade IV and V [50, 52].

Bilateral high-grade reflux in boys is a distinct entity, which is known to have a high rate of spontaneous resolution. Up to 30% of grade 4 and 5 VUR resolve in first year of life. Transient functional urethral obstruction has been suggested as a

cause for high grade VUR in males [53]. VUR can be primary due to an anatomical abnormality of the vesico-ureteric junction, which weakens the normal anti-reflux mechanism. Secondary VUR is associated with abnormal bladder such as the neuropathic bladder, posterior urethral valves or anatomical variants such as duplex kidneys.

65.12.3 Investigations

MCUG is the gold standard investigation for VUR and allows grading (Fig. 65.13). A DMSA scan informs about the kidney function and any scarring or global dysplasia. Global atrophy might be seen without any UTI and is usually associated with high-grade reflux and is reflective of intrinsic developmental anomaly of the renal units [48, 50]. UTI usually results in focal scarring [51]. Follow-up is usually with US and DMSA. In our unit we do not do a formal assessment of VUR resolution. If the child is infection free on antibiotic prophylaxis, a trial of discontinuation is given at attainment of potty training. A proportion of HDN due to low grade VUR picked up antenatally may never have presented postnatally [54]. There is a trend towards a more select approach to MCUG in antenatal HDN due to low yield in NSD without ureteric dilatation. Rather than exposing every child with HDN to the invasive procedure of MCUG, indications have been rationalised and we advocate it only in cases with dilated ureter or bilateral HDN (see Fig. 65.3c). This approach tends to detect high grades of VUR which are clinically relevant [5].

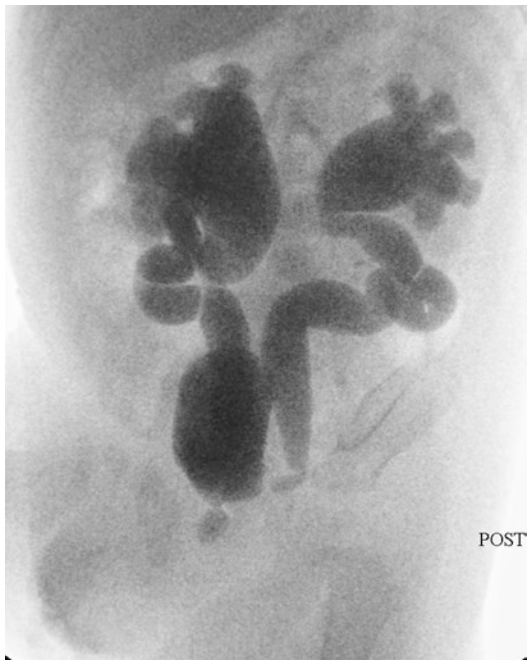

Fig. 65.13 MCUG demonstrating bilateral grade 5 VUR

65.12.4 Treatment

The goal of management of VUR is to prevent UTI. Antibiotic prophylaxis is the mainstay of VUR management for all grades. Evidence for this has been limited but some good observational, long term studies have provided insight into the best treatment options for VUR and provided evidence base for current management. In children with non-dilating reflux, antibiotic prophylaxis is an option but its efficacy is not established [55]. Recently Swedish reflux trial demonstrated that in dilating reflux, antibiotic prophylaxis result in a significant decrease in infection rate and scarring [8, 9].

All grades of VUR have a tendency for spontaneous resolution with up to 3/4th improving or resolving [47, 48, 50–52]. Recurrent UTI and bladder dysfunction predicts non-resolution [47, 48]. 16–52% breakthrough infection rate has been reported in prenatal VUR while on antibiotic prophylaxis [47, 48, 50, 51, 56]. Up to 20% have recurrent UTI.

A surgical intervention is rarely required in infancy. For recurrent UTI in boys, circumcision reduces the risk. An endoscopic correction of reflux may be done in cases of recurrent UTI. In high grade reflux—ureteric reimplantation can be done but is technically difficult in infants; ureterostomy or vesicostomy can be a temporary option [51].

65.12.5 Primary Non-refluxing Megaureter

Primary non-refluxing megaureter is mostly detected antenatally. It may be obstructed or non-obstructed and the distinction between them is very difficult. VUJ obstruction constitutes

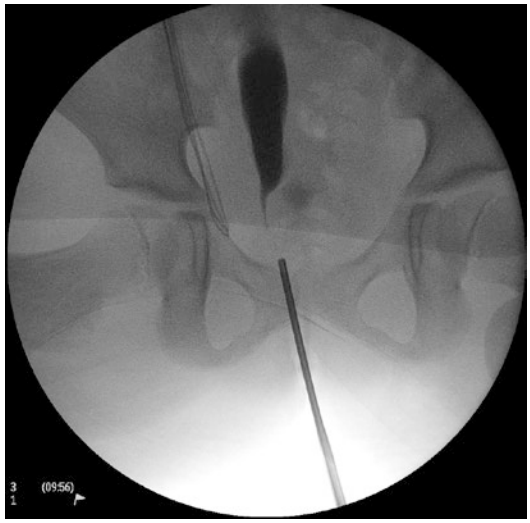

Fig. 65.14 Retrograde study showing an adynamic segment of the lower ureter in a megaureter

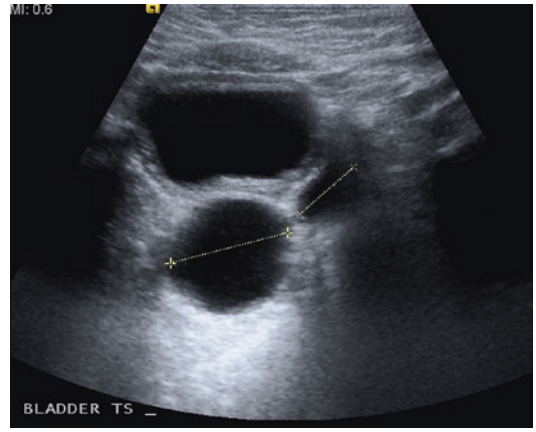

Fig. 65.15 Bilateral dilated ureters behind the bladder

2.3% of all antenatally detected urinary tract anomalies [5]. Most are asymptomatic but some may present with UTI. Non-refluxing megaureter has an incidence of about 1 in 1500 with a male preponderance and is more common on the left [57–59]. It can be bilateral in 13–42% of cases [58, 59].

The obstruction may be functional with an adynamic segment at the VUJ (Fig. 65.14) or may be due to narrow VUJ. Histological studies of the VUJ show increased collagen with reduction in muscle component [60]. The pathology is thought to result from congenital defective vascular development at the vesicoureteric junction [60]. Other mechanism might be dysplastic development of the entire ureter and PCS. Spontaneous resolution in majority supports a maturational causation [61, 62].

Ultrasound (Fig. 65.15) and MAG3 (Fig. 65.16) scans give anatomical and functional details. A MAG3 may show draining kidney in the presence of obstruction if area of interest in drawn over the kidney as the isotope is draining into the dilated ureter. A MCUG rules out VUR. An MR urogram might be done to evaluate further if needed. Similar to dilemmas in PCS dilatation management, the most important challenge is to define and identify obstruction in megaureter. Nevertheless, the relevant pathophysiology is stasis of urine. The walls of dilated ureter cannot coapt to generate effective peristalsis leading to stasis related complications such as infection and stone formation.

Antibiotic prophylaxis needs to be commenced at birth. The concept of management has changed from surgical intervention to close observation. Currently 70—90% can be managed conservatively [58, 63]. Conventional surgical option is ureteric reimplantation. However despite ureteric reimplant, the ureteric and PCS dilatation might not improve due to developmental dysplasia of the system. Minimally invasive procedures such as stent insertion, balloon dilatation and cutting balloon endoureterotomy of VUJ have been reported with variable success rates [64–69]. The rationale for stenting is that a period of drainage would allow the ureteric dilatation to come down to such an extent that following removal of the stent effective peristalsis would continue [58]. However, sometimes the narrow VUJ may not allow a guidewire insertion precluding endourological intervention. Occasionally an ureterostomy may be required if obstruction is leading to sepsis. A refluxing reimplantation is another option in infants [70]. There is a great debate on the best interventional modality.

Even more keenly debated is the indication for surgical intervention. Most commonly agreed indications include renal function deterioration on nuclear medicine scan and development of

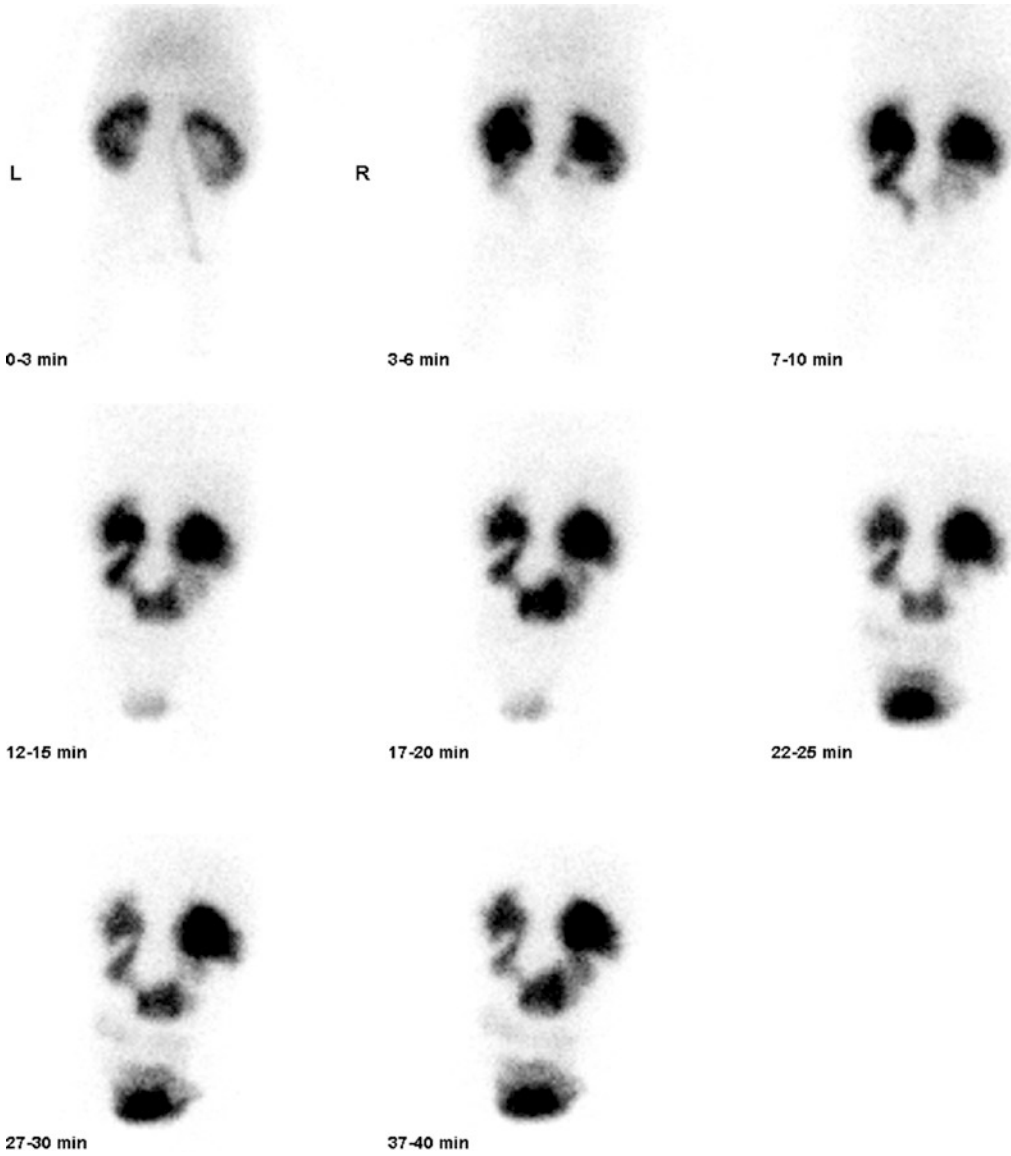

Fig. 65.16 MAG 3 scan showing bilateral megaureters

symptoms such as UTI or pain [57, 58, 63]. An increasing hydronephrosis or hydroureter can be monitored closely. A recent long term observational study from our institute [58] confirmed that conservative management is highly successful especially when the ureteric diameter was less than 10 mm with virtually all resolving completely. When ureter was more than 10 mm size, complete resolution is not common and 25% developed complications. Still the majority remains asymptomatic.

65.12.6 Duplication Anomalies

They constitute 2.6% of antenatally detected anomalies [5]. The commonly identified features are hydronephrosis, dilated ureter, duplex appearance and ureterocoele. But majority of duplication anomalies are uncomplicated where there is no associated dysplasia or dilatation and they remain undetected.

Those that are detected on antenatal scans or which present postnatally have either dysplastic/

dilated one moiety or both. Upper moiety is usually associated with obstruction due to ureterocoele or narrow VUJ. Upper moiety ureter may have an ectopic opening outside the bladder. Lower moiety is usually associated with VUR and rarely PUJ obstruction.

Duplication anomalies rarely cause symptoms in infancy. A large ureterocoele (Fig. 65.17) may give rise to obstructive bladder symptoms. Child may present with sepsis/pyonephrosis of the dilated obstructed upper pole or have UTI due to refluxing lower pole. Girls may present with wetting due to ectopic ureter opening in urethra, perineum or vagina but it is usually noted after potty training. Boys with ectopic ureter are never incontinent as opening is always above the sphincter but may present with UTI/epididymo-orchitis when ectopic ureter is opening into the vas/seminal vesicle.

Antibiotic prophylaxis is commenced at birth. Ultrasound delineates the anatomy. MCUG is done to assess for reflux. A MAG 3/DMSA scan should be done in 2–3 months time. In complex cases a MR scan may be done (Fig. 65.18).

Ureterocoele associated with a dilated upper pole may be non-obstructive and can be managed non-operatively [71]. Intervention is required early if the obstructed upper pole gets infected. An urgent endoscopic incision of ureterocoele relieves the obstruction [72–75]. Ureterocoele incision may prove to be the definitive management in 2/3rd of patients. In our series of 39 patients who had incision of ureterocoele, further surgery was necessary in only 13%. Incision may result in reflux into the upper pole. Heminephrectomy is the treatment of choice when the function of upper moiety is poor. If there is reasonable function then excision of ureterocoele with ureteric reimplantation is an option [75, 76]. If there is persistent obstruction/infection in infancy following incision of ureterocoele or if obstruction is due to narrow VUJ without associated ureterocoele, then an urgent ureterostomy may need to be done. Another option is to do uretero-ureterostomy but non-refluxing lower pole is the prerequisite [77].

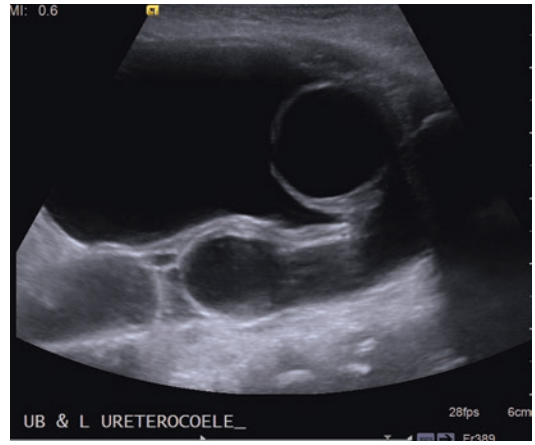

Fig. 65.17 A large ureterocoele obstructing the bladder neck on US

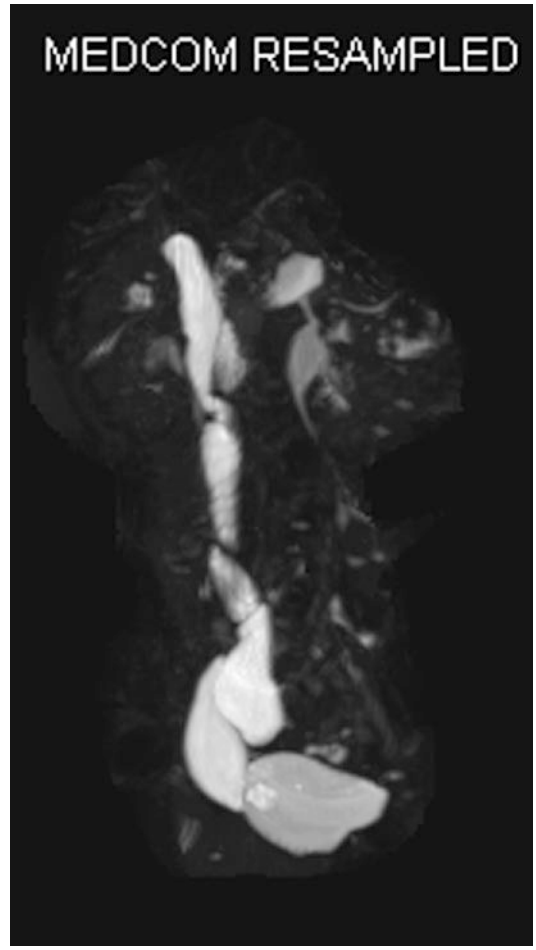

Fig. 65.18 MR urogram demonstrating an ectopic ureter associated with cryptic upper pole

VUR associated with lower pole is managed with antibiotic prophylaxis. It can be treated endoscopically or with ureteric reimplantation if there are recurrent UTI despite antibiotics. If lower pole is dysplastic with poor function then lower pole heminephrectomy can be carried out, preferably laparoscopically.

65.12.7 Megacystis

A large bladder may be detected on antenatal scans and its presence along with findings of HDN commonly suggest lower urinary tract obstruction, which is predominantly due to posterior urethral valves and urethral atresia. A small proportion is due to non-obstructive pathology such as isolated megacystis, megacystis associated with severe dilating VUR (also called Megacystis Megaureter Syndrome (MMS)) [74], Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (MMIHS) and Prune Belly syndrome (PBS). Isolated megacystis is a distinct entity where a large bladder exists without VUR or any obstructive pathology (Fig. 65.19) and may be detected antenatally [78, 79].

The pathophysiology of megacystis in MMS is proposed to be consequent to the inability of the bladder to stay empty completely after voiding due to reflux into extremely voluminous ureters [78]. But existence of isolated megacystis without VUR and detection of large bladder in MMS as early as 15 weeks of gestation [80] contests this theory. An alternative hypothesis is that it is due to dysplasia of the developing urinary tract, which can range from involvement of the kidney (HDN), ureters (megaureter), bladder (isolated megacystis), whole urinary tract (MMS, PBS), to involving the gastrointestinal tract (MMIHS).

In megacystis, a MCUG to assess bladder volume and VUR is done (Fig. 65.20a, b). Urodynamic study gives information on bladder storage and emptying function. The bladder is usually large capacity, hypotonic and may have poor emptying (Fig. 65.21). DMSA scan informs about the degree of renal dysplasia.

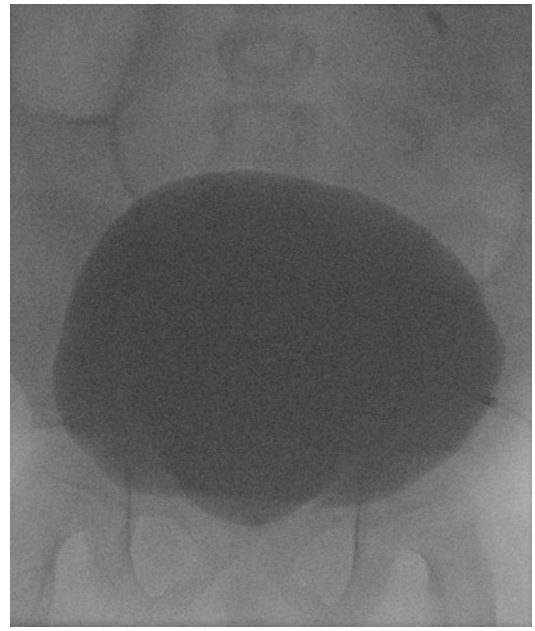

Fig. 65.19 Large bladder—isolated megacystis

65.12.8 Management

The concept of management has evolved from surgical reduction of bladder [81] to antireflux surgery [82] to conservative management. Long-term outcome series are lacking. The prognosis depends upon the extent of inherent dyplasia of the system including kidneys. Management goals are prevention of infection by ensuring complete bladder emptying. Surprisingly, a good proportion has good bladder emptying but a minority might require ISC. Our series [83] demonstrate that bladder dynamics tend to stabilise over time as long as UTI's can be prevented by antibiotic prophylaxis and complete bladder emptying. A few went on to develop deterioration of bladder dynamics and these had poor bladder emptying.

65.12.9 Posterior Urethral Valves

Posterior urethral valves are an important cause of antenatally detected and postnatally presenting lower urinary tract obstruction which carries a 50% fetal and neonatal mortality [18]. PUV is a congenital obstructive uropathy where there is

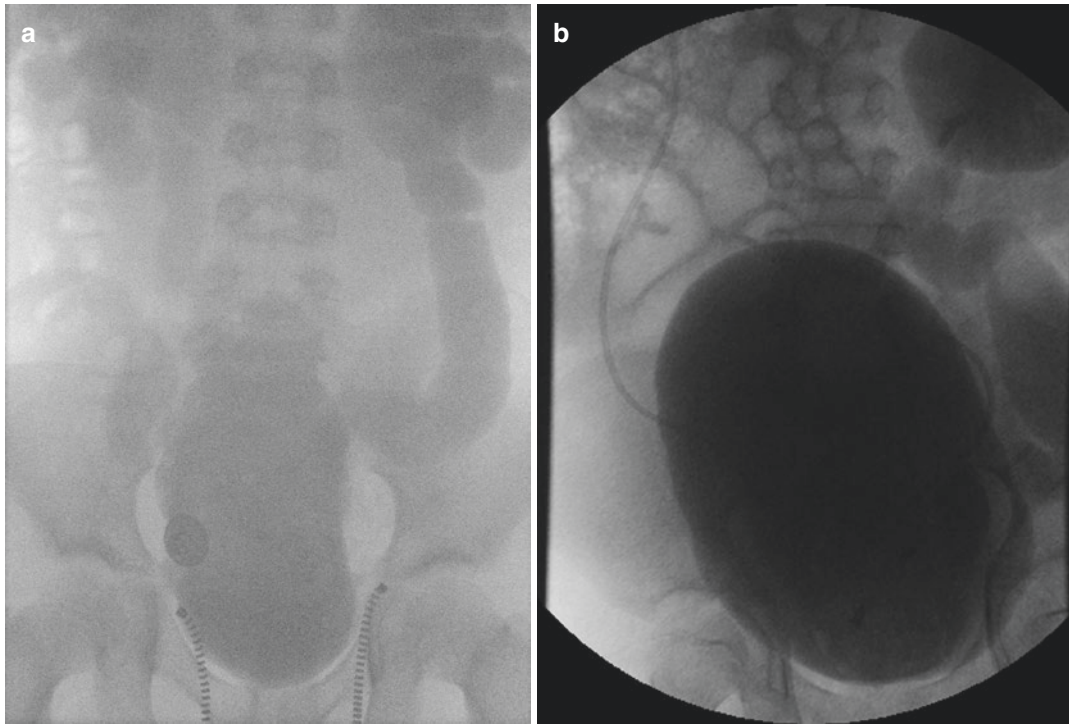

Fig. 65.20 Megacystis megaureter syndrome. (**a**) bilateral VUR, (**b**) unilateral VUR

obstruction in the posterior urethra and there is associated variable developmental dysplasia of the entire urinary tract. An incidence of 1 in 5000 live births has been reported. Anecdotally its incidence has been thought to be declining because of antenatal detection and subsequent terminations. But a recent study refutes this assumption [84]. It is an important cause of renal failure in paediatric population. UK Renal registry shows that obstructive uropathy accounts for 15% of end stage renal disease (ESRD) and that PUV is responsible for 25–30% of paediatric renal transplants [85]. There is a known association with Downs syndrome [86, 87]. A familial predisposition to PUV is rare but it may be associated with other CAKUT in family members [1, 2].

65.12.10 Pathology

Historically Young classified PUV into 3 types—Type 1, II and III [88]. But this classification is not accepted any more. Typical valves are mucosal folds, which arise from the lower end of verumontanum and go down to meet in midline anteriorly and cause obstruction to antegrade flow and correspond to type I valve. Rarely one may find a transverse membrane across the urethra immediately below the verumontanum with a centrally or eccentrically sited aperture (Type III). Type II valves are not recognized as a pathology. Dewan [89] postulated the concept of congenital obstructing posterior urethral membrane (COPUM) and proposed that typical configuration of valve results from rupture of this membrane by a catheter. But this configuration can be seen in uncatheterised urethra as well. Embryologically valves result from abnormal integration of wolffian ducts into the developing urethral wall. It is an early event and can be detected in early second trimester.

There may be minimal involvement of upper urinary tract or there may be associated disordered development of entire urinary tract resulting in dysplastic kidneys and ureters with thickened hypertrophied bladder. In some cases

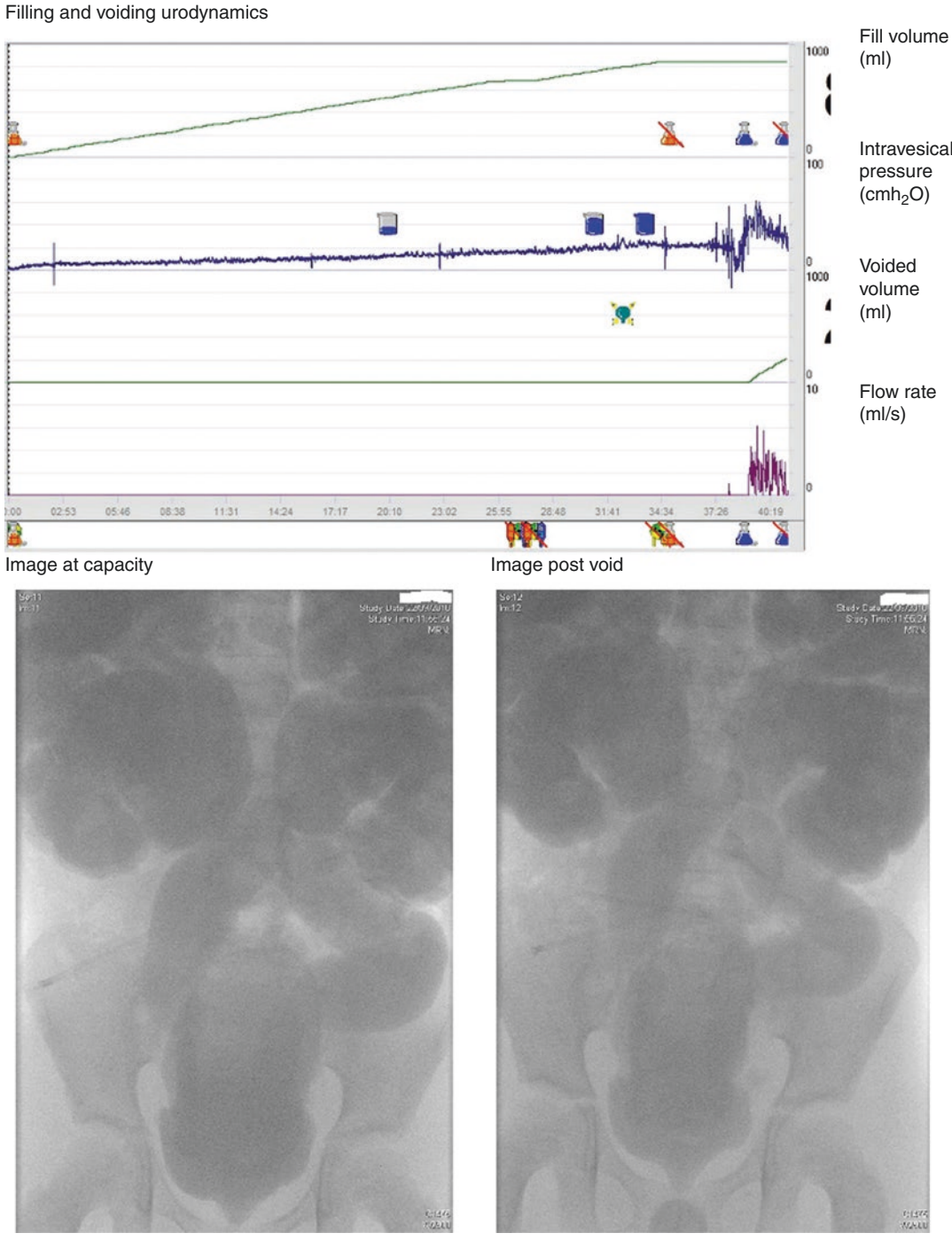

Fig. 65.21 Urodynamic study in a 7 year old boy with MMS showing 850 ml capacity with bilateral VUR, compliance of 55 mls/cm of H_2O and poor emptying

only one kidney might be dysplastic with very poor function and almost normal function on other side—termed Vesico-Ureteric Reflux and Dysplasia (VURD) syndrome. In mild variant of PUV, both kidneys might be well developed with only bladder distension. VUR is present in 40–60% cases and is bilateral in half of these.

65.12.11 Clinical Presentation

Antenatal detection is the most common presentation with two-third of PUV detected to have abnormal findings on prenatal scans though specific diagnosis of LUTO has been made in only 3/4th of these [90]. Rest present postnatally with poor urinary stream, large bladder, UTI's. A few still present with sepsis and renal failure. A good urinary stream does not exclude posterior urethral valves. Very occasionally child may present with urinary ascites either due to leak from bladder or more commonly from kidney and this is protective for renal development. Those who have had antenatal intervention may get ascites due to displacement of the bladder stent into peritoneal cavity.

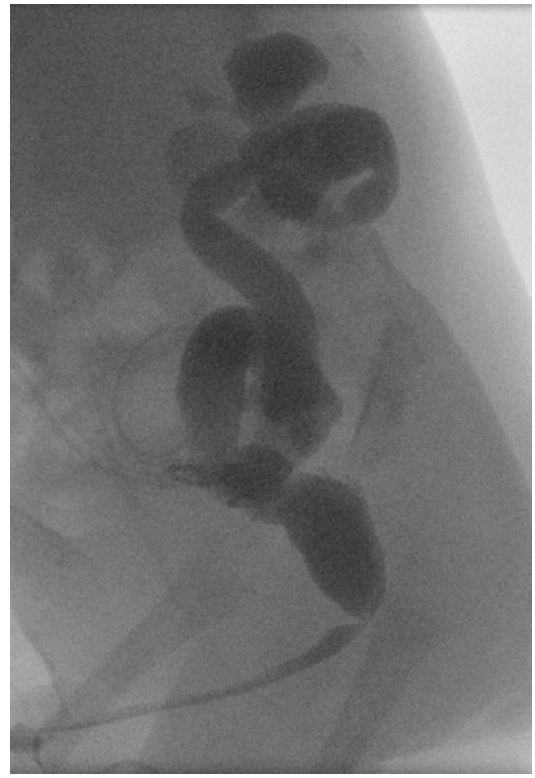

Fig. 65.22 Dilated and elongated posterior urethra along with VUR on MCUG in a neonate with posterior urethral valves

65.12.12 Diagnosis and Investigations

On antenatal scans, a keyhole sign is suggestive of PUV. Spectrum of findings may include bilateral HDUN, unilateral HDN, bilateral HDN with no ureteric dilatation or only bladder dilatation. Similar features on postnatal ultrasound supports diagnosis but definitive diagnosis is made on MCUG, which shows a dilated elongated posterior urethra with or without associated trabeculated bladder and VUR (Fig. 65.22). Bladder neck may be prominent leading to impression of constriction at the bladder neck.

Cystoscopy provides the final answer and the valves are best observed endoscopically with the tip of the cystoscope situated approximately 1 cm distal to the verumontanum. With antegrade flow through the proximal urethra obtained by opening the draining channel and stopping the flow of irrigation fluid, the valve margins can be seen to co-apt in the midline [43].

65.12.13 Management

Antibiotic prophylaxis is started after birth in antenatally detected or postnatally suspected cases. The urinary tract is obstructed from the first trimester of gestation and catheterisation can usually wait until transfer to a specialist paediatric surgical centre. Negotiation of catheter past the valves may be slightly awkward or more commonly it can curl in the dilated posterior urethra. It is not uncommon to damage the urethra when balloon is blown in the urethra by an inexperienced person. If it is imperative that child be urgently catheterised in the non-specialist unit to relieve obstruction, then a fine polythene catheter is safer than a balloon catheter.

These patients should be ideally be jointly managed along with a paediatric nephrologist as the neonate needs close monitoring of electrolytes, acid-base balance, fluid balance and renal function due to associated renal dysplasia and tubular dysfunction. Catheterisation results in post-obstructive diuresis and appropriate fluids should be supplemented, usually orally. A period of catheterisation stabilises the renal function. A MCUG under appropriate antibiotic cover should be done to confirm the valves and assess the bladder and VUR. If there is UTI or sepsis, appropriate antibiotic management should be instituted.

Once renal function is stabilised, resection can be attempted with a 9 Fr resectoscope and in older patients. 11/13 Fr resectoscope can be used. A diathermy hook or a cold knife may be used and valve may be ablated at 5 and 7 o'clock position or at 12 o'clock position. Nd YAG and Ho YAG [91, 92] laser have also been used for valve ablation with claims of lower risk of stricture. Where urethra does not accept a resectoscope or one is not available, a ureteric catheter or a cold knife can be utilised through a cystoscope to ablate the valves. Post-operative catheter drainage for a short duration may be employed if there is some trauma or oedema to urethra during the ablation but is not necessary. A post-operative MCUG or check cystoscopy to check completion of ablation is optional.

Further follow up is with regular monitoring of renal function, DMSA scan and US.

65.12.14 Bladder in PUV

Typically the bladder may be small capacity and poorly compliant with detrusor overactivity. Bladder dysfunction in PUV may progress from detrusor overactivity to normal function to low compliance and in later stages detrusor hypocontractility [93]. Short term anti-cholinergic therapy may be warranted in initial stages and usually results in improvement. Most bladders normalize with time. However some bladders go on to develop valve bladder syndrome. Valve bladder syndrome is characterized by persisting or progressive HDUN in the absence of obstruction [93–95]. This is attributed to constant bladder overdistention due to a combination of polyuria and incomplete emptying, bladder insensitivity and VUR. Polyuria due to renal dysplasia and consequent concentration defect is known to be present in 60% of PUV [96]. Resolution of valve bladder after renal transplant supports the role of polyuria in aetiopathogenesis of valve bladder. Where renal function dose not warrant transplant, ensuring effective bladder emptying by regular voiding, double voiding and overnight catheterisation has been reported to have good outcomes [94]. In severe cases, bladder augmentation or urinary diversion might be required.

65.12.15 Urinary Diversion

A short term urinary diversion may occasionally be required when a premature baby's urethra is unable to accept a resectoscope; a suprapubic catheter may be inserted or a temporary vesicostomy might be fashioned.

After valve ablation if there is recurring UTI and poor renal function and accurate assessment of obstruction at the VUJ is precluded by dysplastic dilated urinary tract, ureterostomy may provide relief. A low, loop ureterostomy can be done easily via a Pfannensteil incision and will allow some bladder cycling as well. It can be simply reversed. An end ureterostomy will warrant reimplantation at closure. A high ureterostomy may be preferred if very dilated tortuous ureters are causing stagnation of urine with recurrent UTI's, as it ensures the best unobstructed drainage of urine. Once done, ureterostomy is best left for at least 1 year or preferably 2 years to allow growth of kidney without any obstruction and UTI. There have been concerns about bladder dysfunction due to non-cycling of urine but in our experience bladder function quickly recovers after ureterostomies are closed. A vesicostomy has the advantage of bladder cycling and is preferable to ureterostomy under appropriate circumstances where obstruction at the VUJ is not an issue.

65.13 Long Term Outcomes

65.13.1 Renal Failure

Development of renal failure depends on the degree of urinary tract dysplasia at birth. If kidneys are dysplastic then they are more likely to develop ESRD. Further continuing damage may occur due to persistent obstruction, VUR, UTI or bladder dysfunction. Historically 1/3rd developed renal failure but better management has led to improved results with latest data suggesting that only 13% progress to ESRD [97, 98]. 31% of PUV have severe bladder dysfunction which can contribute to it [99].

65.13.2 Sexual Function and Fertility

Many factors in PUV can affect sexual function including renal failure, bladder neck procedure, abnormal reflux into ejaculatory system leading to epididymo-orchitis, and cryptorchidism. While concerns have been raised about fertility and sexual function, a recent long-term study of 67 adult PUV patients did not show any particular difference compared to normal controls regarding fertility, and erections [99, 100]. Again abnormal sperm parameters have been identified by few studies, but no significant semen abnormality has been identified and reported fertility is comparable to controls [101].

65.13.3 VUR

VUR tends to resolve after ablation of valve and is managed with antibiotic prophylaxis. Ureteric reimplantation is rarely required. Circumcision is protective against infection and should be considered as first line of management for recurrent UTI. But when VUR is associated with poorly functioning kidney as in VURD (Fig. 65.23a, b), it tends to persist causing recurrent UTI and requires nephrectomy.

65.13.4 Urinary Incontinence

Patients with posterior urethral valves achieve daytime and night-time urinary continence significantly later than their healthy peers [102]. Continued urinary incontinence might be a consequence of bladder dysfunction or rarely may be related to sphincter damage during valve ablation. Urethral stricture may also occur after valve resection.

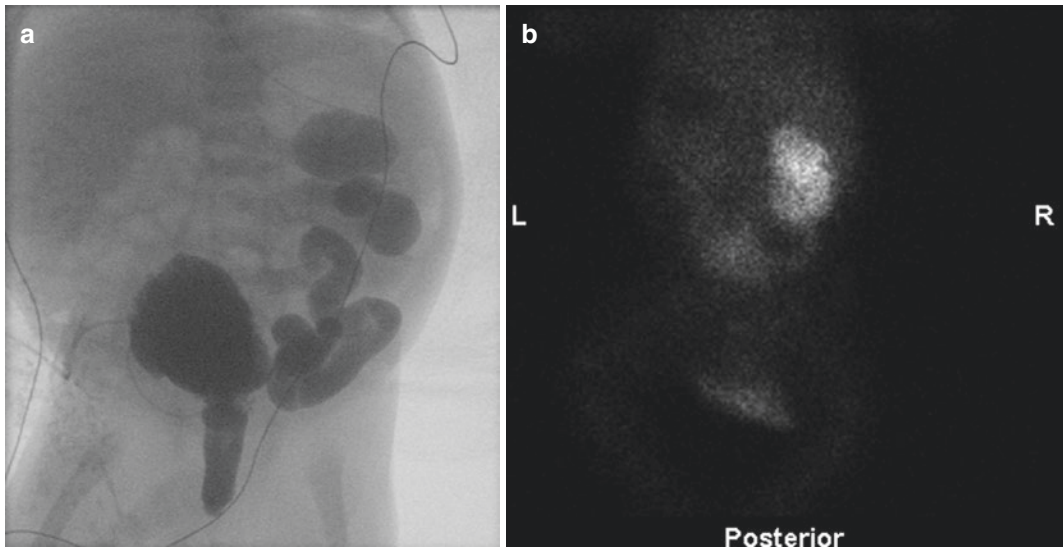

Fig. 65.23 VURD syndrome in PUV. (**a**) Left high grade reflux, (**b**) no function on the side of reflux on DMSA

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Renal Cystic Disease and Vascular Lesions of the Adrenal and Kidney

66

Kelvin K.W. Liu and Michael W.Y. Leung

Abstract

Multicystic dysplastic kidney (MCDK) is the most common renal cystic disease in neonates. Autosomal recessive polycystic kidney disease (ARPKD) is an uncommon condition that can present in utero or early infantile period. Autosomal dominant polycystic kidney disease (ADPKD) and solitary renal cyst are rarely seen in newborns. Localized adrenal haemorrhage may occur in infants but massive haemorrhage is rare and is often confined to newborn. Renal vein thrombosis leading to haemorrhagic infarction has become much less common due to improved perinatal management. Renal artery thrombosis and stenosis are the main causes of renovascular hypertension in neonate

Keywords

Renal cystic disease • Adrenal lesions • Adrenal haemorrhage • Renal vein thrombosis • Renovascular hypertension • Management • Outcomes

66.1 Renal Cystic Disease

Multicystic dysplastic kidney (MCDK) is the most common renal cystic disease in neonates. Autosomal recessive polycystic kidney disease (ARPKD) is an uncommon condition that can present in utero or early infantile period. Autosomal dominant polycystic kidney disease (ADPKD) and solitary renal cyst are rarely seen in newborns.

66.1.1 Multicystic Dysplastic Kidney

Multicystic dysplastic kidney (MCDK) was first described by Schwarz in an infant with kidney replaced by a "bunch of grapes" [1] (Fig. 66.1). The incidence of MCDK is about 1 in 4000 live births with a male to female ratio of 3:2 [2, 3]. Left MCDK is slightly more common. Bilateral MCDK occurs in about 20% of cases leading to fetal loss, stillbirth

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_66

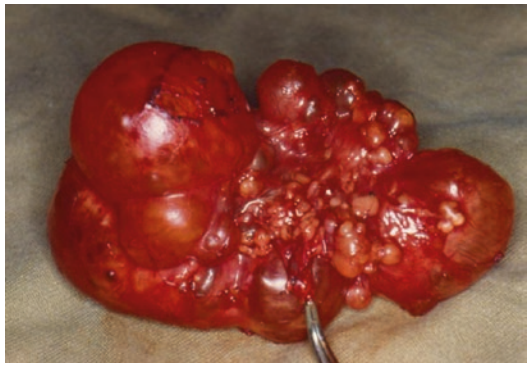

Fig. 66.1 Multicystic dysplastic kidney

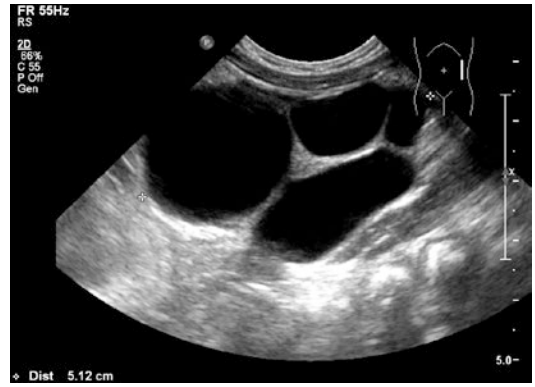

Fig. 66.2 Multicystic dysplastic kidney with almost complete replacement of renal parenchyma with cysts (Courtesy of Dr. Sunny Tse)

or early neonatal death as a result of oligohydramnios, pulmonary hypoplasia and renal failure [4].

66.1.1.1 Pathogenesis

MCDK is a variant of renal dysplasia. According to the ureteric bud theory of Mackie and Stephens, MCDK may be a consequence of abnormal induction of metanephric mesenchyme by the ureteric bud [5]. It is also hypothesized that MCDK can be caused by urinary tract obstruction during early gestational period [6].

Most MCDK occurs sporadically although familial occurrence has been reported. The *EYA1, SIX1 and PAX2* genes play important roles in ureteric bud development [7]. Mutations of these genes have been identified in Branchio-oto-renal syndrome and renal-coloboma syndrome associated with renal dysplasia [8–10]. In utero viral infections including cytomegalovirus may be associated with MCDK development [11].

66.1.1.2 Clinical Presentation and Diagnosis

Prenatal diagnosis by fetal ultrasound is the most common presentation of MCDK. Next to hydronephrosis, MCDK is the second most common aetiology of incidentally palpable abdominal mass in neonates. The two diagnoses can be differentiated by postnatal ultrasonography. The sonographic appearance of MCDK consists of haphazardly arranged multiple non-communicating cysts with variable size, separated by hyperechoic dysplastic stroma (Fig. 66.2). There is no pelvicaliceal structure. Atresia of the ureter can occur. When

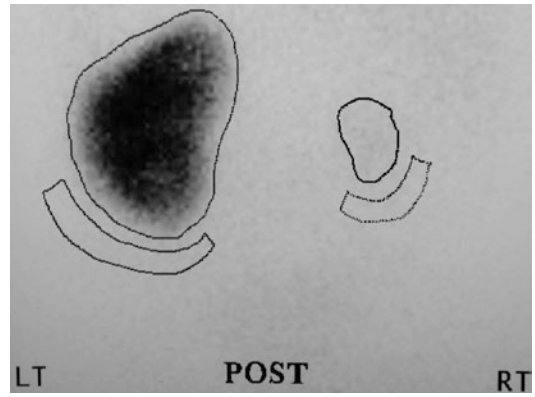

Fig. 66.3 Non functioning right kidney demonstrated on DMSA

an isotope mercaptoacetyltriglycine (MAG3) dynamic diuresis renography or dimercaptosuccinic acid (DMSA) scintigraphy is performed, MCDK is non-functional and can be distinguished from other causes of hydronephrotic kidney (Fig. 66.3).

The contralateral kidney can be abnormal. Vesicoureteric reflux (VUR) occurs in 4–43% of patients and pelviureteric junction (PUJ) obstruction can be found in up to 15% of cases [12–15]. As the contralateral kidney is the only functioning unit, its management is crucial. Micturition cystourethrography (MCUG) should be considered in MCDK patients [16]. Fortunately, majority of contralateral VUR is of low grade with tendency of spontaneous resolution [17].

66.1.1.3 Natural History

Less than 20% of prenatally diagnosed MCDK is clinically palpable [14]. Without antenatal detection, most patients with MCDK can be asymptomatic. Outcome of MCDK is variable. Spontaneous involution of MCDK can occur in up to 60% of patients, after a period of few months to 10 years [18, 19]. The involution velocity is higher in infancy period [20]. Small size of MCDK (<6 cm length) and presence of compensatory hypertrophy of contralateral kidney are positive predictors for complete involution [21, 22].

Urinary tract infection (UTI) is not common in MCDK as the associated ureteric atresia prevents ascending infection. The US National Multicystic Kidney Registry reported a UTI prevalence of 4.6% in 5 years follow-up [14].

The risk of developing hypertension is low in patients with MCDK. In a systemic review, Narchi reported six cases of hypertension developed in 1115 children [23]. Other series also suggested that the risk of hypertension development is lower than 3% on long term follow-up [14, 24]. Once hypertension has developed, conversion to normal blood pressure after nephrectomy can occur in only about one-third of cases [2, 25].

Concerning the risk of malignant change, there are case reports of Wilms tumour in patients with MCDK [26, 27]. The non-involuted intervening stroma of dysplastic kidney may be a focus for malignant degeneration. The higher prevalence of nodular renal blastema in these patients comparing with the general population may be related to the development of Wilms tumour [28]. However, in a systemic review of 26 studies for 1041 children with MCDK, none developed Wilms tumour [29]. Renal cell carcinoma and transitional cell carcinoma have been reported in adults with MCDK [30–32].

In conclusion, most children with unilateral MCDK do not have any long term consequences. However, the patients and parents should be informed of the implications of only one functioning kidney for lifetime.

66.1.1.4 Treatment

The role of nephrectomy in MCDK is controversial. In general, nephrectomy may need to be considered in cases of enlarged renal mass, persistent symptoms such as pain, development of complications including UTI or hypertension, suspicion of malignancy, concomitant surgery and poor compliance to long term follow-up. With recent advances in minimal invasive surgery, laparoscopic nephrectomy can be performed from either trans-peritoneal or retro-peritoneal route with evolution to single port operation [33, 34] (Fig. 66.4).

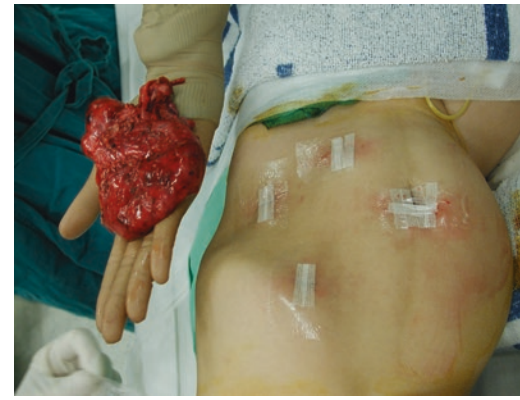

Fig. 66.4 Multicystic dysplastic kidney removed via trans-peritoneal laparoscopy

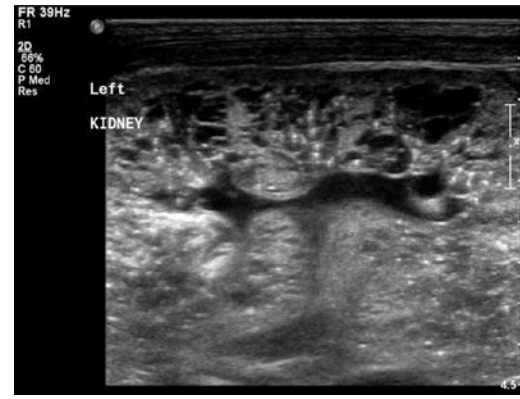

Fig. 66.5 Multiple cysts in autosomal recessive polycystic kidney (Courtesy of Dr. Sunny Tse)

66.1.2 Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD) occurs one in 10,000–40,000 live births [35]. It is previously also known as infantile polycystic kidney disease which is not an accurate ter-

minology as some patients can present at late childhood [36]. A single gene, *Polycystic Kidney and Hepatic Disease 1 (PKHD1)*, mutation on chromosome 6p was identified to account for the disease [37]. The disease affects both kidneys and liver invariably, characterized by the cystic changes of renal collecting tubules and congenital hepatic fibrosis (CHF) [38] (Fig. 66.5). Age of presentation and severity of renal symptoms depend on the number of abnormally dilated collecting ducts involved [39]. Antenatal diagnosis of bilateral renal masses, oligohydramnios and Potter sequence is common [40]. In neonates, patients will present with bilateral flank masses, impaired renal function and respiratory insufficiency. Neonatal death is usually caused by pulmonary complications. More than 70% of patients can survive beyond neonatal period, with progression to end stage renal disease and hypertension. The renal collecting tubules are affected, resulting in polyuria and polydipsia [41]. For long term survivors, hepatic manifestation as a result of CHF by abnormal ductal plate development will cause symptoms of hepatosplenomegaly, cholangitis, portal hypertension and oesophageal variceal bleeding [39].

Postnatal USG should be performed in neonates suspicious of ARPKD. Bilateral homogenously enlarged kidneys are seen with hyperechogenicity and poor corticomedullary differentiation. Renal cysts are small in neonates, different from those in MCDK and autosomal dominant polycystic kidney disease (ADPKD) [42]. Macrocysts are more common in older patients [43]. Hepatic parenchymal hyperechoic texture, cyst formation and occasionally intrahepatic ductal dilatation resembling Caroli's disease are found. If portal hypertension develops in juvenile period, splenomegaly and reverse hepatic venous flow can be demonstrated. If USG findings are equivocal, more sensitive imaging studies including computed tomography (CT) and magnetic resonance imaging (MRI), should be considered [44].

Treatment of ARPKD is mainly supportive. Recent advances in neonatal intensive care especially ventilation support decrease neonatal mortality from pulmonary hypoplasia. Patients will require treatment for chronic renal failure and hypertension. As the patients grow older, treatment for hepatic complications such as portal hypertension are necessary.

66.1.3 Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited human renal disease affecting one in 400–1000 people [45]. The age of onset is usually in third to fifth decades. Neonatal and early infantile presentations can occur that are not clinically distinguishable from ARPKD [46].

In 85–90% of patients with ADPKD, mutation of *PKD1* gene on chromosome 16p occurs [45]. Mutation of *PKD2* gene on chromosome 4q is found in rest of cases [47].

Extra-renal cysts in liver and pancreas, cardiac and cerebral manifestations are rare in neonates. USG may show enlarged hyperechoic kidneys, presence of macrocysts and increased corticomedullary differentiation [48]. Similar to ARPKD, management of early onset ADPKD is mainly supportive.

66.1.4 Solitary Renal Cysts

Contrary to adult population, solitary renal cyst is uncommon in children and extremely rare in neonates. It can occur sporadically or exist in patients with urinary tract obstruction such as posterior urethral valve [49]. USG is useful to differentiate it from other neonatal renal cystic diseases and hydronephrosis. Treatment of isolated solitary renal cyst is usually conservative. Image guided percutaneous aspiration of cysts had been reported in symptomatic children with loin pain [50].

66.2 Vascular Lesions of the Adrenal and Kidney

66.2.1 Adrenal Haemorrhage

The adrenal gland is vulnerable to haemorrhage due to its large size and high vascularity [51, 52].

Localized adrenal haemorrhage may occur in infants and children under stress [53, 54]. This condition is more frequently seen in term infants delivered vaginally [51, 55–57]. Massive adrenal haemorrhage, however, is much rarer and is often confined to newborns [58].

66.2.1.1 Aetiology

Birth trauma, prolonged labor, intrauterine infection, perinatal asphyxia or hypoxia, large birth weight, septicaemia, haemorrhagic disorder and hypothrombinemia are the most common predisposing causes of adrenal haemorrhage [52, 53, 56, 59]. In term infants, it is often related to large size following a difficult and traumatic delivery whereas in premature infants, perinatal hypoxia is often the predisposing cause. However it can also occur spontaneously [59]. Prenatal occurrence has also been documented [60].

66.2.1.2 Clinical Features

Clinical features vary depending on the amount of blood lost. The most common clinical presentations are persistent jaundice and flank mass [51, 52, 56, 57, 61]. However, adrenal haemorrhage may also present with scrotal haematoma, anaemia, adrenal insufficiency, shock [51, 55, 56, 59, 62], and as an incidental finding [63]. Macroscopic haematuria can occur if there is associated vascular lesion affecting the kidney. Breakdown of the red blood cells in haematoma causes jaundice. Adrenal insufficiency due to adrenal haemorrhage is rare [51, 52, 56, 57, 63] and is usually seen in premature infants [64]. As the adrenal gland has a considerable regenerative capacity, most adrenal haemorrhage is not associated with significant adrenal insufficiency. When adrenal insufficiency occurs, prematurity and severe underlying diseases such as sepsis, disseminated intravascular coagulation, perinatal hypoxia and intraventricular haemorrhage are also potential causes. Cytokine-related suppression of adrenocorticotropic hormone or cortisol synthesis, inadequate perfusion of the adrenal gland, a limited adrenocortical reserve or immaturity of the hypothalamic-pituitaryadrenal axis may also contribute to the development of adrenal insufficiency [65].

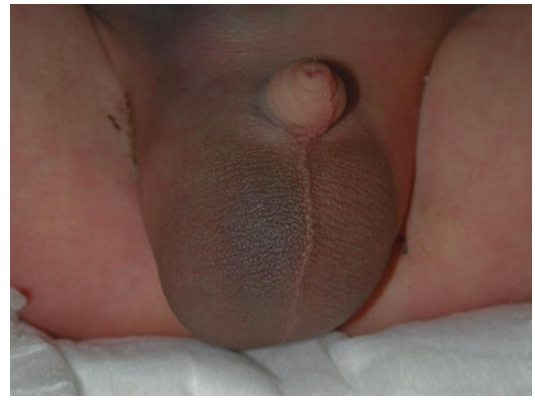

Fig. 66.6 Acute bluish discolouration and swelling of the right scrotum

Adrenal haemorrhage may present with swelling and bluish discoloration of the scrotum [51, 55, 56, 59, 62, 66] (Fig. 66.6). When adrenal haemorrhage occurs with rupture of the capsule, blood can easily reach the scrotum via the patent processus vaginalis or along the retroperitoneum [55, 62]. Swelling and discoloration of the scrotum in newborns may arise from other disorders, including torsion of the testis, epididymitis, scrotal or testicular edema, strangulated inguinal hernia and meconium peritonitis. Ultrasonography of the abdomen and scrotum should be performed in infants with scrotal swelling and ecchymosis to exclude adrenal haemorrhage [62]. If differential diagnosis between adrenal haemorrhage and torsion of the testis cannot be established, nuclear scanning or color Doppler analysis is required [62]. The right adrenal gland is the frequent (38–100%) site of adrenal haemorrhage [51–53, 55–57, 63]. This may be related to the direct drainage of the right adrenal vein into the inferior vena cava thus exposing the gland to the raised intravenous pressure that may occur during birth compression. Frequencies of 8–38% for bilateral adrenal haemorrhage have been reported [53, 56].

66.2.1.3 Diagnosis

Differential diagnosis of adrenal haemorrhage includes adrenal abscess, cystic neuroblastoma, cortical renal cyst, obstructed upper cortical renal cyst and an obstructed upper moiety of a duplicated kidney [67]. Measurement of urinary vanil-

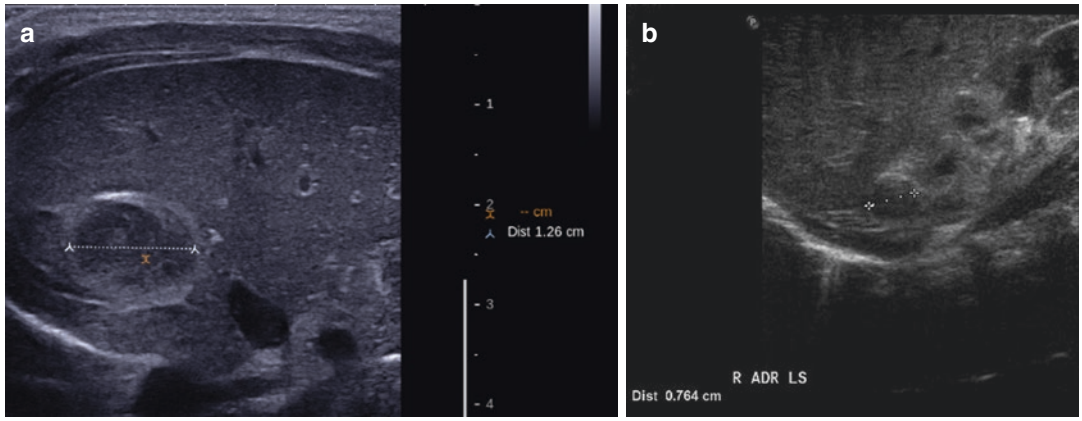

Fig. 66.7 Adrenal haemorrhage in a neonate (Courtesy of Professor Winnie Chu). Predominately cystic lesion with internal echoes over the right adrenal region. Interval reduction in size of the cystic lesion appearing more homogeneous and anechoic after 3 months

lylmandelic acid (VMA) levels assists in the differentiation of adrenal haemorrhage from neuroblastoma. The ultrasonographic appearance of adrenal haemorrhage depends on the age of haematoma, and this gradually resolves with time [61]. Diagnosis and follow-up of adrenal haemorrhage using ultrasonography is the most effective modality and avoids unnecessary laparotomy. Serial ultrasonography can demonstrate decrease in size and echogenity (Fig. 66.7), multiloculated cystic mass, calcifications and complete resolution of adrenal haemorrhage [55, 68]. Adrenal haemorrhage usually resolves between 3 weeks to 6 months [55–57, 59, 61]. For the case of neuroblastoma, the lesion remains solid in appearance and may enlarge over several weeks [51, 52]. In patients suggestive of adrenal insufficiency, cortisol and adrenocorticotropic hormone (ACTH) are measured and ACTH provocative test is performed. Rarely, adrenal haemorrhage may be associated with renal vein thrombosis. This may be due to the connection between the two venous systems or the same causative factor affecting both organs. It is therefore worthwhile to do imaging study to determine if the kidney has been affected by similar vascular lesion.

66.2.1.4 Treatment

Most cases of adrenal haemorrhage can be managed conservatively particularly in term infants. Occasionally blood transfusion for hypovolaemia, antibiotics for sepsis and hormonal treatment for bilateral involvement may be required. Most cases treated conservatively usually resolve with time. Occasionally the haematoma may calcify [69] and rarely becomes infected [70]. Surgery is seldom indicated except for dangerously high level of serum bilirubin or very extensive haemorrhage. Late sequelae of adrenal haemorrhage are uncommon.

66.2.2 Renal Vein Thrombosis

Renal vein thrombosis (RVT) leading to haemorrhagic infarction of the kidney was first described by Rayer [71] in 1837. It is predominantly a disease of the paediatric age group, primarily newborn infants [72, 73]. Between 60 and 75% of the cases are observed in the first month of life [72, 73] and about one third of all cases are diagnosed in the first week. Male infants are slightly more often affected than female. The number of surviving patients has increased, but at the same time, late complications are now being recognized with greater frequency [74–79].

66.2.2.1 Pathogenesis

It is now believed that the thrombus starts in an arcuate or interlobular vein, and it may spread in both directions to involve the renal cortex and to

occlude the main renal vein [80]. The thrombus may extend into the vena cava. However, spread to involve the contralateral kidney is unusual. Bilateral renal involvements are usually caused by thrombi arising from each kidney. Microthrombi found in small caliber veins of other organs in young infants support a generalized disease.

66.2.2.2 Aetiology

RVT occasionally occurs in previously well babies but dehydration has been implicated most commonly [73, 81, 82]. Infants of diabetic mothers seem to be susceptible [83, 84], and it has been observed as a complication of congenital heart disease, nephrotic syndrome, acute blood loss, sepsis, shock, or asphyxia at birth [85]. These associated factors together with the sluggish perfusion in the neonatal kidney and the relative polycythaemia render the neonate susceptible to RVT [73, 82].

66.2.2.3 Clinical Manifestations

RVT has a wide range of clinical manifestations. The complex of flank mass, gross haematuria, and thrombocytopenia should always alert the possibility of RVT. Swelling and cyanosis of the legs are indicative of thrombus within the inferior vena cava. Bilateral loin swellings, severe oliguria, anuria and azotaemia suggest bilateral renal involvement. In the first month of life, haematuria has been reported in 64% of cases and in older children in 49% [73]. Vomiting, diarrhea, pallor, cyanosis or shock, and the clinical signs of metabolic acidosis, occur in some infants. Prenatal RVT is a less common entity and has been found incidentally on prenatal imaging [86, 87].

Although the biochemical findings can vary greatly, decreased renal function is usually indicated by an increase in serum creatinine and blood urea nitrogen concentrations. At the same time, the serum bicarbonate level is decreased. The level of plasma potassium is significantly increased in about one third of the patients. The serum sodium level is variable, ranging from normal to high or low concentrations.

Renal venous thrombosis can sometimes be confused with hydronephrosis or a tumour within the kidney or adjacent tissues. Although rare in infants, a mesoblastic nephroma or hamartoma is an important differential diagnostic consideration. Furthermore, neuroblastoma and cystic disease of the kidneys are also palpated as abdominal masses in the newborn period.

66.2.2.4 Diagnosis

The clinical diagnosis of RVT can be supported by ultrasonographic and radiologic examinations. The plain film of the abdomen may show enlarged renal outlines. Ultrasonography is the technique most commonly used in the evaluation of neonates with suspected RVT [88]. The ultrasound appearances depend on the stage at which the examination is performed and the extent of the thrombus. Initially the thrombi in the peripheral small renal veins appear as highly echogenic streaks which only persist for a few days. In the first week the affected kidney swells and becomes echogenic with prominent echopoor medullary pyramids. Later, the swelling increases and the kidney becomes heterogenous with loss of corticomedullary differentiation. Grey scale ultrasound readily demonstrates thrombus within the renal vein and inferior vena cava. Colour Doppler may demonstrate absent intrarenal and renal venous flow in the early stages of RVT. Computed tomography (CT) can demonstrate both renal anatomy and function and is of help in the evaluation of a thrombotic process within the kidney [89]. Renal scintigraphy that measures glomerular filtration rate and renal plasma flow have been used in newborn infants to diagnose RVT and to estimate the renal function in the initial assessment and in monitoring upon the return of function during therapy. Tc-99 m mercaptoacetyltriglycine (MAG3) renal scintigraphy provides superior images because of its greater extraction and faster clearance and this is especially helpful in the neonates who inherently have immature renal function [90]. Similarly, renal nuclear magnetic resonance may be useful in evaluating the kidney, and particularly RVT. This technique demonstrates the anatomy, as well as the function, of the kidney and also any disease in the retroperitoneum. The intravenous pyelogram (IVP) in many cases shows no or minimal function on

one side while the other functions normally. Because of rather nonspecific and inconclusive findings, an IVP is of limited value in acute RVT. Renal angiography is an invasive study and is seldom required nowadays in the diagnosis of RVT.

66.2.2.5 Treatment

All children with RVT should be treated medically in the acute phase. Immediate treatment consists of correction of shock, metabolic acidosis, anaemia, sepsis, and cyanosis with or without hypoxia. Normal hydration must be achieved as soon as possible. If azotemia is present, fluid administration should be calculated to avoid overload. Anticoagulant therapy is still controversial [91, 92] Since extensive thrombosis is almost always present by the time of diagnosis, the usefulness of heparin is in doubt. Heparin probably should be used if RVT is diagnosed early [92] and in cases with evidence of intravascular coagulation or bilateral disease. If there is complete renal shutdown or the patient's condition deteriorates, early dialysis is beneficial. Haemodialysis is rarely used except in older patients with anuria. Surgery has only limited value in the treatment of RVT. Neither exploration of the kidney nor nephrectomy should be performed during the acute phase because the prognosis is generally favorable. Surgical intervention may be necessary in bilateral RVT, which usually also involves the inferior vena cava. Patients have recovered after thrombectomy [93], but even spontaneous recovery is known. Any other surgical procedure should be delayed for at least 4–6 months, when damage to the kidney can be defined more clearly after complete reevaluation and the appropriate procedure can be selected. Nephrectomy may be necessary for secondary complications such as hypertension, frequent infections of an atrophic kidney, or nephrotic syndrome.

66.2.2.6 Late Sequelae

Although the majority of neonates who receive supportive treatment can survive, structural or functional renal abnormalities are found in up to 90% of survivors [74–79]. Recanalization of occluded vessels or development of extensive collateral circulation may explain the functional recovery. There is a wide spectrum of complications including renal atrophy, renal tubular defects, growth retardation and hypertension. Hypertension seems to develop in only a few cases [74, 76]. It is usually accompanied by a high plasma renin level and is practically always relieved by nehrectomy. Recognition of these complications is important because early treatment can avoid many disturbing or debilitating diseases. The nephrotic syndrome has been diagnosed in older children with history of RVT. Present evidence favors the theory that the nephrotic syndrome is a precondition for the development of renal venous thrombosis rather than its late sequelae [94].

66.2.3 Renovascular Hypertension in Neonate

Hypertension in neonate may be seen in up to 2% of all infants cared for in neonatal intensive care unit [95]. It is increasingly recognized because of improved techniques of measurement and monitoring. Defining what is considered a normal blood pressure in newborn infants is a complex task. Studies in both term and preterm infants have demonstrated that blood pressure in neonates increases with both gestational and post-conceptual age, as well as with birth weight [95–97]. An infant's blood pressure is considered to be elevated if it falls above the upper limit of the 95% confidence interval for infants of similar gestational or post-conceptual age, size and gender.

The causes of hypertension in neonates are numerous, with the two largest categories being renovascular and other renal parenchymal diseases [98, 99]. Renal artery thrombosis accounts for 75% of cases of neonatal hypertension and renal artery stenosis for a further 18% [100]. Other renovascular problems may also lead to neonatal hypertension including renal vein thrombosis and diseases involving the renal artery either by direct involvement such as mid-aortic coarctation [101], idiopathic arterial calcification [102], congenital rubella infection [103], renal artery aneurysm [104], renal artery

embolism [105], or by compression of the renal artery such as hydronephrotic kidneys and other abdominal masses.

Although apparently spontaneous renal artery thrombosis has been reported [106], majority of cases occur as a consequence of umbilical artery catheterization used in the management of critically ill infants. A clear association between use of umbilical arterial catheters and development of arterial thrombi was first reported by Neal et al. [107] The association between umbilical arterial catheter-associated thrombi and the development of neonatal hypertension was confirmed by others [108, 109] though the rate of thrombus formation has been much lower than that reported by Neal. Thus, it is possible that the cause of hypertension in such cases is related to thrombus formation at the time of line placement, probably related to disruption of the vascular endothelium of the umbilical artery. Such thrombi may then embolize to the kidneys, causing areas of infarction and increased renin release. Isolated renal arterial stenosis is mainly caused by fibromuscular dysplasia. Although the main renal artery may appear fairly normal on angiography but there may be significant branch vessel disease that can cause severe hypertension [110].

66.2.3.1 Clinical Presentation and Diagnostic Approach

In many infants, hypertension will be discovered on routine monitoring of vital signs. However, other classic presentations of neonatal hypertension have been described. Congestive heart failure and cardiogenic shock represent life-threatening consequences of hypertension [111]. In the less acutely ill infant, feeding difficulties, unexplained tachypnea, apnea, lethargy, irritability, or seizures may constitute symptoms of unsuspected hypertension. In older infants unexplained irritability or failure to thrive may be the only manifestations of hypertension. In case of renal artery thrombosis, haematuria, azotaemia and proteinuria are the cardinal features. It is important that blood pressure is being measured accurately so that hypertension will be correctly identified. In most acutely ill neonates, blood pressure is usually monitored directly via an indwelling arterial catheter either in the radial or umbilical artery. Automated, oscillometric devices are less invasive and the more common alternative method of blood pressure measurement in most NICUs.

The correct cause of neonatal hypertension is usually suggested by careful history and physical examination. Relevant laboratory tests and diagnostic studies are then performed to confirm/exclude other non-renovascular causes. Determination of plasma renin activity is frequently performed in the assessment of neonates with hypertension. Although renal arterial stenosis and thromboembolic phenomenon are typically considered high renin forms of hypertension, a peripheral renin level may not be elevated in some infants despite the presence of significant underlying pathology. Selective renin level may yield more accurate information. Ultrasound and Doppler sonography should be performed and may detect potential correctable causes of hypertension such as renal vein thrombosis, renal artery thrombosis and renal artery stenosis. Renal scintigraphy may demonstrate abnormalities of renal perfusion. For infants with extremely severe blood pressure elevation, angiography may be necessary. A formal angiogram offers the most accurate method of diagnosing renal arterial stenosis, particularly given the high incidence of intrarenal branch vessel disease in children with fibromuscular dysplasia [110]. In extremely small infants, it may be appropriate to defer angiography, managing the hypertension medically until the baby is large enough for an angiogram to be performed safely. Because of the invasiveness of conventional renal angiography, magnetic resonance angiography has been reported by some to be of use in evaluation of renovascular cause of neonatal hypertension [111, 112]. Similarly, computed tomography angiography has been reported to be of help in the diagnosis of renovascular hypertension [113, 114] (Fig. 66.8).

66.2.3.2 Treatment

Immediate and urgent treatment consists of correction of hypertension. An antihypertensive agent should be chosen that is most appropriate for the specific clinical situation. For the majority of acutely ill infants, particularly those with severe hypertension, continuous intravenous

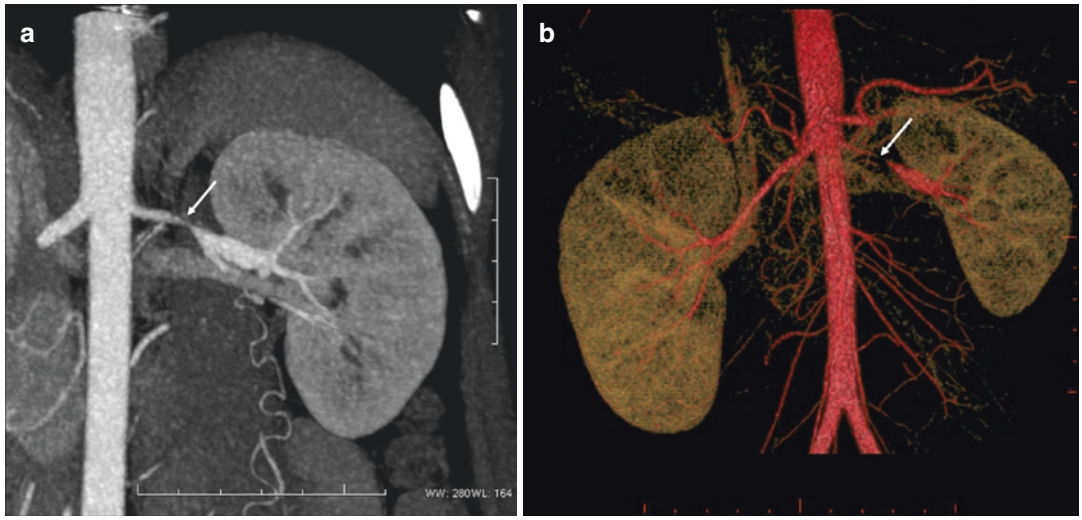

Fig. 66.8 Renovascular hypertension caused by renal artery stenosis (Courtesy of Professor Winnie Chu). (**a**) Coronal Reformat Contrast enhanced CT shows a focal stenosis (*arrow*) at the proximal left renal artery. (**b**) 3D volume rendering renal arteriogram shows again left renal artery stenosis (*arrow*) and relative smaller size of the left kidney when compared with the normal right side

infusion is the most appropriate approach. It is important to avoid too rapid a reduction in blood pressure [110] to avoid cerebral ischemia and hemorrhage, a problem that premature infants in particular are at increased risk. Surgery is indicated for treatment of neonatal hypertension due to renovascular cause in selected cases. For infants with renal arterial stenosis, it may be necessary to manage the infant medically until it has grown sufficiently to undergo definitive repair of the vascular abnormalities [115, 116]. Surgical reconstructive procedures include surgical dilatation, renal artery resection and reanastomosis, autologous or synthetic bypass grafts and autotransplantation. Good long term results have been reported but may sometimes result in primary or secondary nephrectomy [117, 118]. Percutaneous transluminal angioplasty for renal artery stenosis has been proven to be safe and effective in older children [119]. Generally good results outweigh the risks of recurrent stenosis and the rare but severe complications of dissection, rupture, bleeding, occlusion and aneurysm formation [119, 120]. Its successful use in neonate has also been reported [121]. For cases of severe hypertension with poor response to medical therapy, nephrectomy may have to be performed [122]. For cases of renal artery thrombosis that fail to respond to medical therapy, nephrectomy has to be performed as a lifesaving intervention [123, 124].

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Prune Belly Syndrome

67

John M. Hutson

Abstract

Prune Belly Syndrome (PBS) is a rare anomaly of the anterior abdominal wall, urinary tract and undescended testes. It is thought to be caused by transient obstruction of the urethra between 10 and 20 weeks of gestation, leading to massive dilatation of the bladder which resolves in the third trimester. The atrophic abdominal wall and cryptorchidism are secondary to the enlarged bladder. Management primarily requires treatment of the intraabdominal testes.

Keywords

Prune belly syndrome • Management • Outcomes

67.1 History

A case of congenital deficiency of the abdominal muscles, now known as prune belly syndrome, was recorded in the mid nineteenth century [1], but the first description of the association of the condition with urogenital tract anomalies was made by Parker in 1895 [2].

Prune belly syndrome (PBS) was previously called Eagle-Barrett or Triad syndrome, because it included the triad of congenital deficiency of the abdominal musculature, massive dilatation of the urinary tract and intra-abdominal undescended testes [3]. Stephens proposed that there was a defect in mesodermal development affecting the anterior abdominal wall, urinary tract and the genital tract of males [4, 5].

Development of antenatal ultrasonography has shown that the characteristic anomaly in midgestation is massive dilatation of the fetal bladder, which may be larger than the fetal head [6].

67.2 Epidemiology

This is a rare morphological anomaly in males, now easily identified on antenatal ultrasonography with an incidence of 1/25,000 [7]. In many centres, the number of live-born infants with PBS has decreased dramatically in recent years, because of selective termination of pregnancy. The anomaly is extremely rare in females, and is usually associated with massive dilatation of the

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_67

urogenital tracts in a cloacal anomaly, or even more rarely, with massive abdominal distention associated with bowel obstruction such as meconium ileus caused by cystic fibrosis. In the latter case the other features are absent.

67.3 Pathogenesis

Opinions remain divided between a primary mesodermal disorder affecting the abdominal wall and pelvic organs on one hand and temporary obstruction of the male urinary tract in midgestation on the other [5, 8, 9].

Primary deficiency of mesodermal migration into the lower anterior abdominal wall has been proposed as the cause of bladder exstrophy and epispadias [10] and there is preliminary evidence that mutations in the P63 gene may be responsible [10]. However, this idea does not readily explain the massive dilatation of the bladder, which suggests distal obstruction (see below).

PBS has been reported as part of the Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome (EEC) where a mutation in the P63 gene (p R204W) has been identified [11]. Another gene associated with PBS is the hepatocyte nuclear factor-1β[beta] gene [12].

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) has an overlapping phenotype with PBS, and has been reported within the same family, consistent with a common genetic cause [13].

Most post-mortem studies of fetuses with PBS show some form of urethral obstruction, which may or may not have resolved by the time of examination [9]. A flap-like obstruction between the prostatic and penile urethra is a relatively common finding [14, 15], but severe phimosis has also been suggested as the cause [15]. Urethral atresia with complete obstruction at the level of the membraneous urethra is well-reported [16, 17].

In a detailed study of 21 PBS specimens and 23 specimens of posterior urethral valve (PUV) (Young types 1 and 3) there was an obvious difference in development of the seminal vesicles and ducts. In the PBS specimens the prostatic glands and seminal vesicles were atrophic, while in the PUV specimens the prostate and seminal vesicles were developed normally. These differences are consistent with a primary abnormality in the intermediate and lateral plate mesoderm in PBS, leading to Wolffian duct maldevelopment as well as defects in the abdominal wall musculature and urinary tract [18].

Deletion of the hepatocyte nuclear factor-1-β [beta] gene has been reported in association with PBS [19]. This is a transcription factor that is expressed in a number of tissues derived from the urogenital ridge including Wolffian duct, renal tubules and urethra, leading to the "renal cysts and diabetes" syndrome with mutations. Other reports of transient neonatal diabetes and PBS have been associated with DNA hypomethylation [20].

The massive enlargement of the fetal bladder in midgestation with resolution in the third trimester is characteristic of PBS, and is consistent with temporary bladder-outlet obstruction [21]. In a study of urethral diameters, as measured on micturating cystourethrograms, we were able to show that the anterior urethra was dilated in PBS, consistent with transient distal urethral obstruction [8, 9, 21] (Fig. 67.1).

67.4 Antenatal Presentation

Most babies with PBS are now diagnosed by antenatal ultrasonography because of the massive bladder enlargement at 15–20 weeks of gestation [17]. Because of the gross disturbance of the urinary tract and abdominal wall, as well as 25% have co-existing anomalies in the cardiovascular system, termination of pregnancy is a common outcome [7]. This trend has caused a significant drop in the number of live-born infants with PBS in many centres (Fig. 67.2).

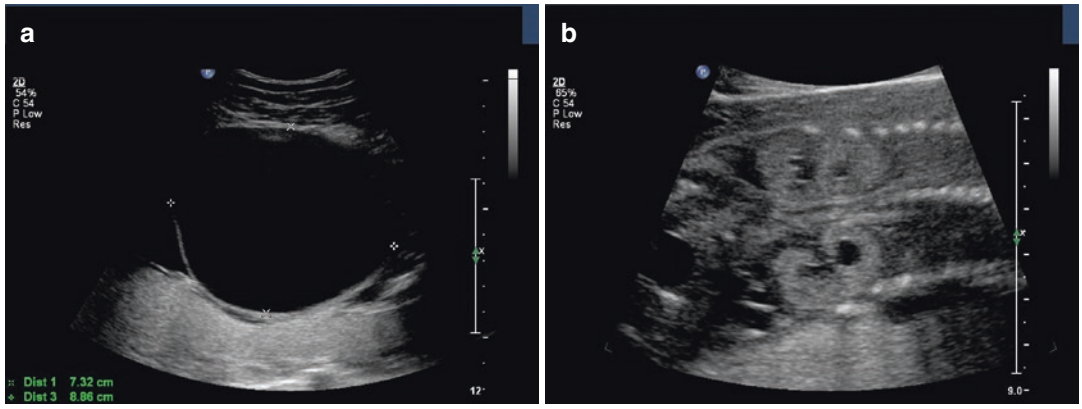

Fig. 67.1 (**a**) Antenatal ultrasound (20 + 4 weeks) showing massively dilated and tense bladder. (**b**) Echogenic kidneys with caliectasis

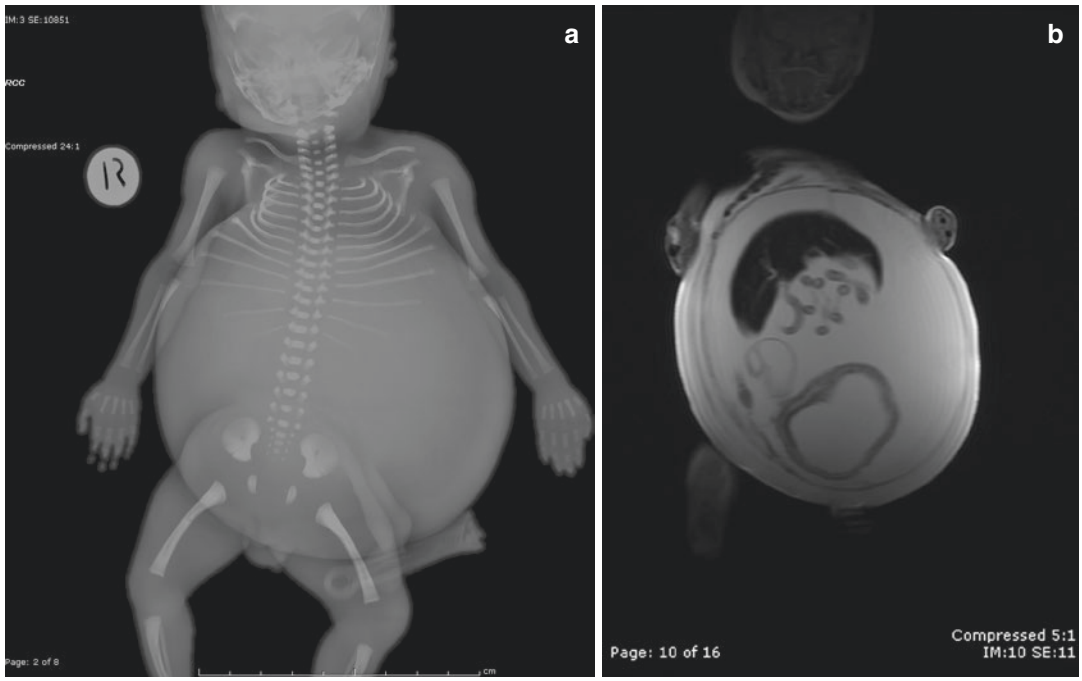

Fig. 67.2 (**a**) Postmortem X-ray of same foetus as shown in Fig. 67.1 after termination. The massively enlarged abdomen is obvious. (**b**) Postmortem MRI of same foetus showing thick-walled bladder, massive ascites and thin anterior abdominal wall

67.5 Clinical Presentation

67.5.1 Urinary Tract

The bladder is massively enlarged and there is often a urachal diverticulum extending to the umbilicus. The vesical muscle is hypertrophied but there is not usually any trabeculation. The urethra is dilated and there may be an associated enlargement of the utriculus. Megalourethra is relatively common.

The upper tracts show significant hydronephrosis and hydroureter, with high-grade vesicoureteric reflux being very common (Fig. 67.3).

Renal function is extremely variable, from normal at one extreme to renal failure at birth at the other. In the latter circumstance there may be oligohydramnios or anhydramnios and Potter facies.

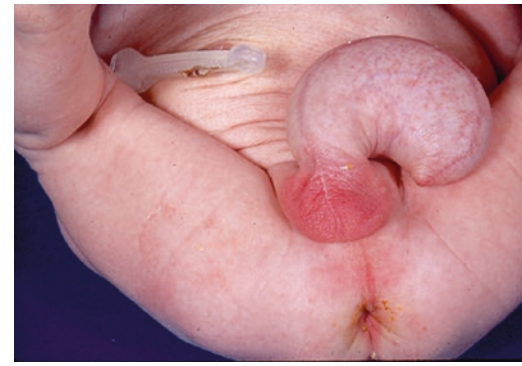

Fig. 67.3 Megalourethra in a newborn with prune belly syndrome, consistent with distal urethral obstruction in mid gestation. Note also the hypoplastic, empty scrotum

67.5.2 Genital Tract

The testes are impalpable, and are usually on the back of the bladder, which reached such a size in midgestation that the gubernaculum was (presumably) torn out of the inguinal abdominal wall. Hence the processus vaginalis is usually absent and there is no recognisable inguinal canal (Fig. 67.4) In other respects the testes are normal histologically and functionally, as the intra-abdominal cryptorchidism is caused by the enlarged bladder rather than a primary gonadal dysplasia. Postnatally, however, secondary degeneration of the testes will develop in the first year if orchidopexy is not carried out.

In the rare female neonate with PBS, there is usually a complex anorectal or cloacal anomaly leading to hydrometrocolpos and/or bladder outlet obstruction [22].

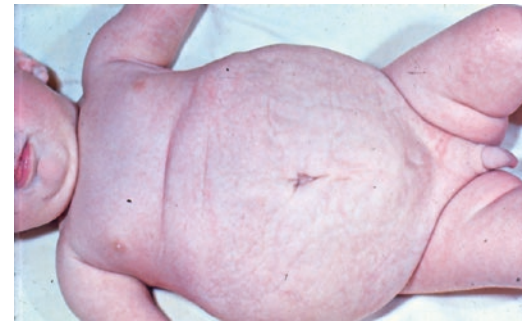

Fig. 67.4 The flabby, wrinkled anterior abdominal wall at birth that gives the condition its name, after decompression of the obstructed bladder in midgestation

67.5.3 Abdominal Wall

The thin and wrinkled anterior abdominal wall that is characteristic of PBS is quite variable depending on the maximum size of the bladder at 15–20 weeks of development (Fig. 67.1a). The area affected undergoes pressure atrophy so that the anterior muscles are replaced by a thin fibrous sheet. The most severely affected part is the central hypogastrium which is stretched most severely by the enlarged bladder. The epigastric component of the rectus abdominis and oblique muscles are relatively well preserved, as are the flanks. Secondary spinal deformity may accompany the wrinkled abdominal wall because the massive bladder enlargement may deform the fetal posture.

67.5.4 Orthopaedic Anomalies

Massive bladder enlargement in midgestation can be associated with congenital dysplasia and dislocation of the hips, as well as congenital amputation of the leg [23].

67.5.5 Cardiovascular Anomalies

Heart defects occur in about 25% of babies, although these are more likely caused by coincidental genetic anomaly rather than postural or pressure effects of the enlarged bladder [7].

67.6 Surgical Management

Most infants with PBS do not need surgical treatment of the dilated urinary tract, although the nephrologist may be involved to manage any renal insufficiency.

By contrast, the intra-abdominal testes need orchidopexy, which is usually carried out laparoscopically [24]. The timing of surgery should be the same as for other babies with impalpable testes: 6–12 months, on the premise that this has the best chance of preserving fertility [25].

Orchidopexy may be achieved by radical mobilisation of the testicular vessels laparoscopically, but a 2-stage Fowler-Stephens procedure may be required [26], with reasonable long-term results. The surgical details do not need to be described, as the procedures have been well documented elsewhere.

There is controversy about whether surgery is required for the abdominal wall. Many centres advocate total surgical reconstruction as initially championed in the 1970s [27, 28] and subsequently in recent decades [29, 30]. However, in some centres it has been found that minimal surgical intervention is required [31].

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Disorders of Sex Development

68

John M. Hutson

Abstract

Disorders of sex development (DSD) are rare, complex anomalies of genital development that often present with an ambiguous genital appearance at birth. Rapid recognition and diagnosis are essential to prevent inappropriate gender assignment in the neonatal ward. After morphological and molecular assessment is complete a management plan is developed by a multidisciplinary team in the tertiary and/or quaternary referral centre.

Keywords

Intersex • Ambiguous genitalia • Disorders of sexual development • Surgical management, outcomes

68.1 Introduction

Disorders of sex development (DSD) are rare and complex anomalies affecting sexual differentiation, and cause significant stress for the new parents, as well as life-long issues for the patient. There have been rapid changes recently in the nomenclature and also in the approach to management, with the development of regional referral centres to permit multidisciplinary care at an appropriate level. Gender assignment and surgical intervention remain controversial, while legal issues now need to be considered in some societies. Meanwhile we have learnt more about the genes controlling normal sex development, and now understand the normal and abnormal embryology much better than previously.

68.2 History

Fascination with abnormalities of sexual differentiation is very ancient, as evident in the word "hermaphrodite" (from the Greek: hermaphroditos), used to describe the unfortunate individual with both male and female genital anatomy. Babies with ambiguous genitalia were thought to have "intersex", but there was little medical understanding of underlying disorders prior to the discovery of congenital adrenal hyperplasia (CAH) by Dr. Lawson Wilkins in Baltimore in 1953. There was an explosion of knowledge in the 1960s and 1970s, as surgical and medical ther-

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_68

Table 68.1 Classification of DSD

Level of anomaly	XY	XX	Mixed chromosomes
Chromosome	46,XY DSD	46,XX DSD	Mixed chromosome DSD (aneuploidy) (Klinefelter/ Turner)
Gonad	MGD	Partial/complete	Partial/mixed
Development	Complete dysgenesis	Dysgenesis	Dysgenesis
Partial/complete/mixed	Partial dysgenesis Ovotesticular DSD Denys Drash syndrome Frasier WAGR	Ovotesticular DSD Denys Drash syndrome Frasier WAGR	Ovotesticular DSD
Abnormal Androgen action	Androgen biosynthesis defect Androgen insensitivity (receptor defect) (partial/complete)	Androgen excess (CAH)	
Syndromic and non-hormonal	Abdominal wall defect Anorectal/perineal anomalies Hypospadias	Abdominal wall defect Vaginal agenesis	

apies evolved. In the 1980s and 1990s the first cohort of adult patients with DSD began campaigning for better care, and patient-support groups appeared. Long-term follow-up studies began appearing in the last 10 years, and showed varied outcomes, from reasonable to poor, and this led to intense public scrutiny on the quality of care. There were calls for irreversible surgery to be delayed until children were old enough to make their own decisions. In some places all surgical intervention ceased. In 2004 a consensus meeting was held in Chicago to address some of the issues raised by the support groups, and this led to nomenclature change and articulation of a set of principles for management, which have been developed further since [1].

68.3 Classification

Following the 2004 consensus, a new classification was adopted, based on the underlying chromosomal status. The main groups are now called 46,XX DSD, 46,XY DSD, ovo-testicular DSD, mixed chromosomal DSD, 46, XY complete gonadal dysgenesis and 46, XX testicular DSD (Table 68.1).

68.4 Prognosis

Most forms of DSD cause abnormalities of sexual function and/or fertility, but are not fatal, except for congenital adrenal hyperplasia (CAH). In the latter case, a salt-losing adrenal crisis may occur in the second or third week of life, with the baby presenting with sudden vomiting and shock from lack of cortisol production by the adrenal glands. Glucocorticoid (and usually mineralocorticoid replacement therapy) is required for life, but overcomes this.

68.5 Epidemiology

Although uncomplicated hypospadias has an incidence of 1 in 100–200 live male births, more significant DSD occur rarely, at about 1 in 5000

live births. Most are recognised at or shortly after birth as having ambiguous genitalia, but some disorders do not present until after childhood, puberty or in adult life.

68.6 Genetics

The genetic regulation of sexual differentiation was unknown until the discovery of the sex-determining region on the Y-chromosome, now known as the SRY gene [2]. Recently it has been shown that SOX9 is one of the early downstream genes regulated by SRY, with SOX9 in turn stimulating FGF9 and down-regulating WNT4 and β-catenin to trigger development of a testis. In the absence of SRY, WNT4 activates β-catenin and blocks SOX9 and FGF9 to initiate ovarian development. Steroidogenic factor 1 (SF1) and Wilms tumour 1 (WT1) both have roles in early development of the ambisexual gonad.

Mutations in the gene DAX1 cause gonadal dysgenesis, although the mechanism is not yet determined, and no doubt many more genes will be found in future to have a role on testicular and ovarian differentiation.

Apart from the genes controlling gonadal development, mutations in the genes coding for steroid synthesis enzymes, particularly in the androgen pathway, are well known. These lead to 46,XY DSD with inadequate production of testosterone, with the common lesion being in 17β-hydroxysteroid dehydrogenase-3 (17β-HSD3), In this case the androgen levels may be too low to virilise prenatally, causing female external genitalia, so that the affected girl presents in early adolescence with primary amenorrhoea, virilisation, and palpable gonads in the inguinal region.

Anomalies in the androgen receptor gene interfere with androgen signalling and cause partial or complete androgen insensitivity syndrome. As the androgen receptor gene is on the X-chromosome, the inheritance is X-linked. In some families the mother is a heterozygote carrier, but spontaneous mutations are common. Another genetic anomaly in androgenic function is in the gene for 5α-reductase-2, the enzyme that converts testosterone to dihydrotestosterone (DHT) in peripheral tissues, especially the prostate and external genitalia. Infants with this anomaly are mostly found in societies with inbreeding, although subtle mutations may be more common than previously appreciated. Babies have ambiguous or feminine external anatomy, but increasing androgen production at puberty bypasses the need for conversion to DHT, leading to virilisation and, often, gender-change to male at puberty [3].

68.7 Embryology

The genital tract arises from the urogenital ridge that is formed from the intermediate mesoderm in the early embryo. Prior to the onset of sexual differentiation the mid section of the urogenital ridge contains the mesonephros (or "middle kidney", present from 4–8 weeks, the mesonephric (Wolffian) duct and the paramesonephric (Műllerian duct) and also the ambisexual gonad. The latter is colonised by germ cells migrating from the caudal stalk of the yolk sac between 3 and 5 weeks of development.

At 7–8 weeks, the SRY gene on the Y-chromosome activates a still mostly unknown chain of genetic signals to initiate development of a testis in a male embryo [2]. The testis begins making anti-Műllerian hormone (AMH; also called Műllerian inhibiting substance, MIS) from the Sertoli cells, and this is secreted down the mesonephric or Wolffian duct (which becomes the duct of the testis after the mesonephros regresses) to cause regression of the immediately adjacent ipsilateral Műllerian duct [4]. Testosterone is synthesised in the Leydig cells and secreted into the Wolffian duct to initiate its differentiation into epididymis, vas deferens and a distal bud that forms the seminal vesicle [5]. Testosterone is also secreted into the bloodstream

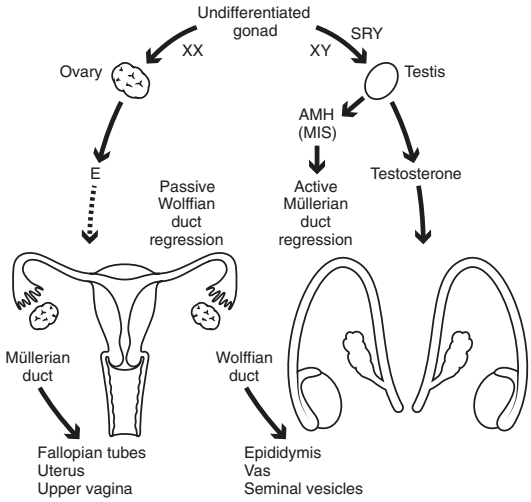

Fig. 68.1 Sexual differentiation of internal genitalia. At 7–8 weeks the undifferentiated gonad develops into an ovary or a testis. SRY gene on the Y-chromosome triggers testicular development. Testosterone (T) and anti-Műllerian hormone (AMH) produced by the testis are secreted down the mesonephric (Wolffian) duct to induce its preservation and development into epididymis, vas deferens and seminal vesicle (by T) and regression of the adjacent Műllerian duct (by AMH). In the female, ovaries develop that begin making oestrogen (E). As AMH is absent the Műllerian duct persists to form Fallopian tubes, uterus and upper vagina. In the absence of testosterone the Wolffian duct regresses and the lower vagina develops

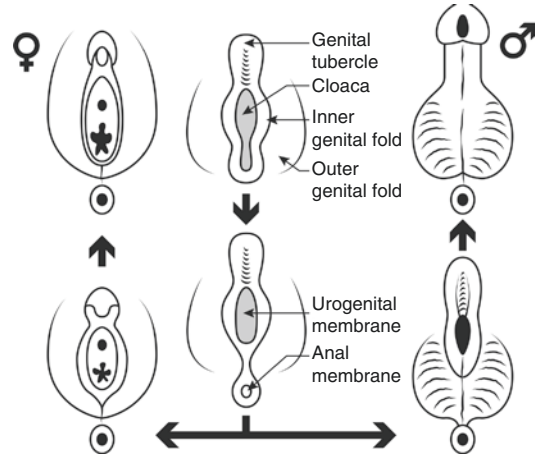

Fig. 68.2 External genital development requires testosterone to be converted to DHT, which triggers genital tubercle enlargement to form the penis, canalisation of the urethral plate to form the anterior urethra and fusion of the labial folds to make a scrotum. In the female, absence of DHT allows the lower vagina to develop, while there is apoptosis in the urethral plate to cause the natural bend in the clitoral shaft

to reach the future prostate and external genitalia. Between 8–12 weeks of gestation however, the serum levels are still low, so virilisation of the external genitalia at this time is mediated by conversion of testosterone itself. This local tissue conversion to DHT effectively increases the activity of testosterone 5–10-fold, enabling growth of the genital tubercle to form a penis, canalisation of the urethral plate to make the male anterior urethra, fusion of the outer genital folds to form the scrotum, and regression of the lower vaginal primordium which formed after the Műllerian ducts reached the cloaca. Coincidentally with lower vaginal involution, the DHT activates prostatic development (Fig. 68.1).

During this same period (8–12 weeks) the Leydig cells make another hormone, insulin-like hormone (Insl 3), which stimulates the genito-inguinal ligament (gubernaculum) to enlarge in males, thereby anchoring the developing testis to the future inguinal canal as the fetus enlarges [6, 7]. Later in development (25–35 weeks) testosterone controls the migration of the gubernaculum from the inguinal canal to the scrotum, enabling the testis to arrive in the scrotum shortly before birth (Fig. 68.2).

68.8 Associated Anomalies

Genital abnormalities caused by gonadal and hormonal defects form the primary group of DSD, but there are also a large group of abdominal wall and perineal anomalies that have associated deformities of the internal and external genitalia [8]. Defects in fusion of the Műllerian ducts are often accompanied by atresia, leading to the Rokitansky sequence, where there is atresia in one half of the unfused vagina and absence of the ipsilateral kidney.

Anorectal malformations may be associated with genital anomaly if the cutaneous fistula is in the vestibule or between the bifid scrotum [9]. Complete agenesis of the genital tubercle may also occur, leading to agenesis of the penis in

boys, with the urethra opening into the anterior wall of the anal canal [10].

Abdominal wall defects affecting the pubic region lead to secondary genital anomaly when there is failure of fusion in the midline. These conditions include bladder exstrophy and epispadias, and the rare cloacal exstrophy, or OEIS association (omphalocele, exstrophy, imperforate anus and spinal anomaly).

One of the rarest anomalies of the genitalia is that associated with severe caudal regression, such as in sirenomelia, with hypoplastic fused lower limbs like a mermaid. Another extremely rare anomaly is partial duplication of the caudal embryo, where there may be duplication of the external genitalia.

Where the genital anomaly is caused by inappropriate hormone levels, there are a few recognisable multiple malformation syndromes. These include Smith-Lemli-Opitz syndrome with developmental delay and microphaly, hypotonia, fusion of the second and third toes with incomplete virilisation in boys [11]. Another syndrome is Denys-Drash syndrome, where the mutation has been found in the WT1 gene on chromosome 11. There are abnormalities in all the structures derived from the urogenital ridge, including the kidneys and the gonads. In 46,XY babies there is gonadal dysgenesis and the related ambiguous genitalia from incomplete virilisation, while the kidneys are predisposed to progressive glomerulosclerosis, causing renal failure in infancy. There is also a significant risk (75%) of developing Wilms tumour [12]. Different mutations in the WT1 gene can lead to Frasier syndrome, where the 46,XY fetus has complete or almost complete gonadal dysgenesis, leading to a female phenotype. The intra-abdominal streak gonads are at high risk of gonadoblastoma and there is also some focal glomerulosclerosis [13]. In yet another syndrome affecting the WT1 gene there is a major deletion of the chromosome 11p13, causing a cluster of anomalies called WAGR syndrome (Wilms tumour, aniridia, genitourinary anomalies, and retardation of development). The ocular anomaly is caused by the close relationship between WT1 and PAX6 on chromosome 11 [14].

ATRX syndrome is a disorder causing 46,XY DSD because a mutation in the gene for the chromatin-remodelling enzyme, helicase, which is on the X-chromosome. There is severe gonadal dysgenesis associated with developmental delay and thalassaemia, and a range of other defects.

Opitz syndrome is characterised by hypertelorism, hypospadias and a cleft between the larynx and trachea and the oesophagus, and occasionally oesophageal atresia [11].

The frequency of multiple malformation syndromes is high in babies with 46,XY DSD, and there is a significant risk of potentially fatal cardiac anomalies [15].

68.9 Antenatal Presentation

The increasing use of ultrasonography has led to predictions of gender of the fetus, based on the external anatomy. However, in DSD prenatal diagnosis is extremely uncommon except in those families with a previous infant with a DSD. In the most common of these circumstances, where there is a previous infant with CAH, the mother can be treated with dexamethasone to prevent virilisation in the fetus. When chorion villus biopsy at 10–12 weeks determines the gender, as well as whether or not the fetus is affected, the steroid treatment can be ceased in a male. Termination of pregnancy is possible in this circumstance but remains controversial.

68.10 Clinical Presentation

DSD present at birth in three broad categories: obviously ambiguous genitalia, a female phenotype with some clitoromegaly and an apparent male with hypospadias with or without undescended testes. The first situation is readily identified in the labour ward, and should trigger immediate referral to the DSD referral centre, while the latter two circumstances require significant skill and experience to determine the diagnosis (Fig. 68.3).

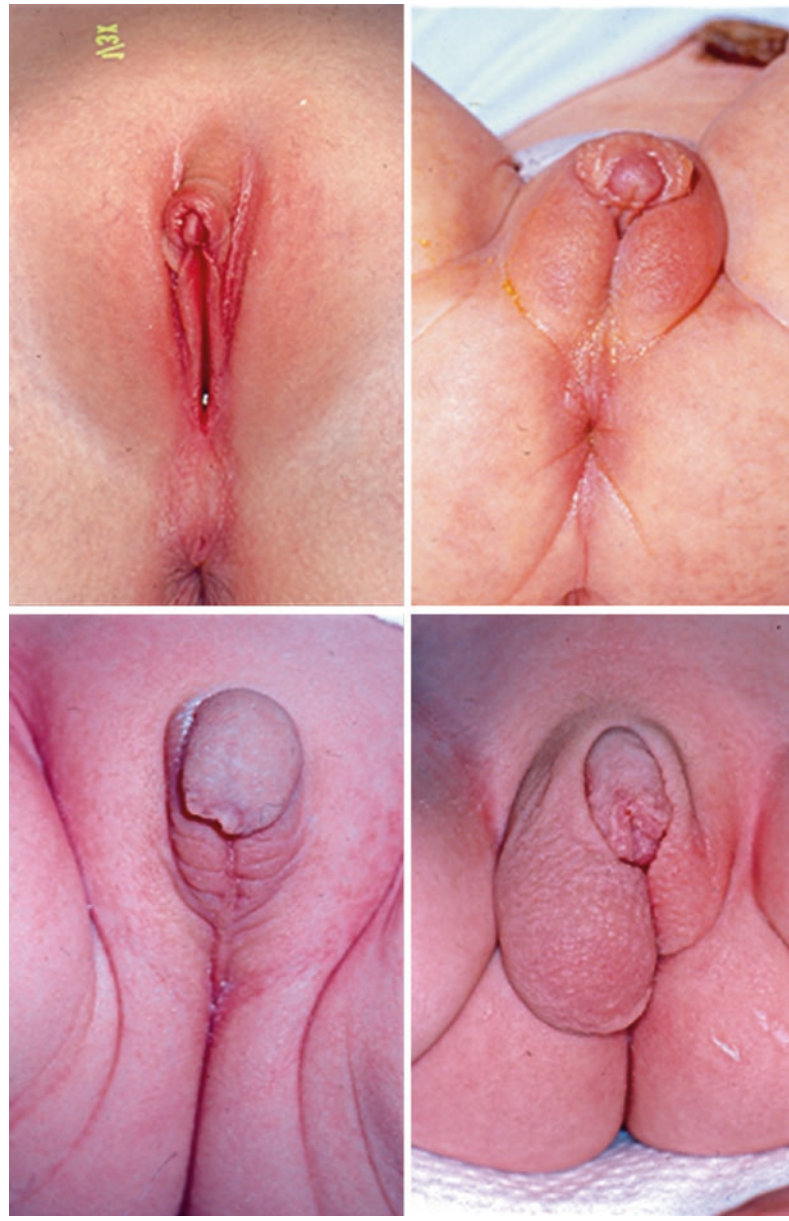

Fig. 68.3 The four broad categories of DSD: (1) apparent female phenotype with minor clitoral enlargement (CAH, Prader 1) (2) clearly ambiguous genitalia (CAH, Prader 2) (3) apparent male phenotype with "hypospadias", with absent testes (CAH, Prader 4) (4) apparent male phenotype with "hypospadias" with bifid scrotum and absent testis (45X, 46XY MGD)

The clinical examination includes a careful history of pregnancy and possible prenatal factors, as well as the family history. The physical examination is based on a deep understanding of the normal embryology, which allows a prediction of the underlying hormonal status from the anatomy. The first step is to establish the degree of masculinisation using the Prader scale (0—normal female to 5—normal male phenotype), which is an estimate of the amount of androgenic action (Fig. 68.4). The next step is to determine the status of the urogenital opening, which in ordinary hypospadias is smaller than the normal male urethral meatus, but in DSD is often a funnel-shaped opening. At the apex of the funnel the presence of bluish mucosal folds indicates the hymen, and hence the presence of the vagina where the genital and urinary tracts diverge. Then the presence and site of the gonads should be determined, which if palpable

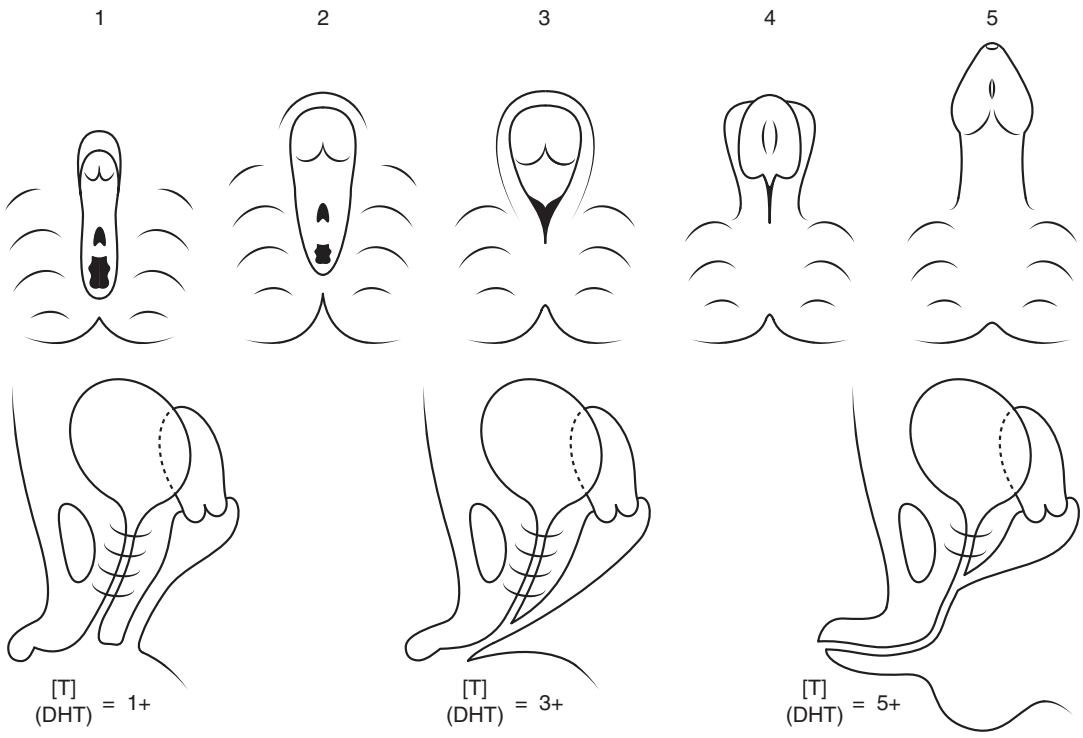

Fig. 68.4 (**a**) The Prader classification of the degree of virilisation of the external genitalia is from O (normal female) to 5 (normal male appearance). Prader 1 is clitoromegaly alone. Prader 2 is clitoromegaly and a funnel-shaped urogenital opening showing 2 orifices (urethra and vagina). Prader 3 is more virilised where only one opening is visible inside the urogenital opening. Prader 4 is more masculinised still, where the opening is on the proximal shaft of the enlarged phallus. The increasing virilisation from 1 to 5 is directly related to levels of androgens the fetus is exposed to, and also inversely related to the degree of regression of the developing lower vagina. (**b**) The regression of the lower part of the vagina is directly related to the amount of androgens present and the degree of external genital virilisation. From Hutson JM. The neonate with ambiguous genitalia. In Hutson JM, Warne GL, Grover SR (eds), Disorders of Sex Development. Springer-Verlag; Berlin, Heidelberg; 2012: 103–114; used with permission from Springer

are almost always testes. If the gonads are impalpable, the external inguinal ring should be felt to see if it is open, which may indicate the testes are within the inguinal canal. The final step in the clinical examination is to determine the status of the internal genital tract by rectal examination with the little finger. If a uterus is present, the cervix is palpable against the back of the pubic bone and feels like the eraser on the end of a pencil. Understanding how to interpret the clinical findings can be aided by using a set of rules based on the embryological processes (Table 68.2) [15].

Further investigations include pelvic ultrasonography to document the status of the internal genitalia. Then it is important to obtain a full karyotype, which might take several days, and an urgent fluorescent *in-situ* hydridisation (FISH) test to detect a Y-chromosome can be done within a few hours. Serum levels are obtained of the electrolytes (abnormal in CAH with hyponatraemia and hyperkalaemia), 17-hydroxyprogesterone, testosterone, FSH and LH. The serum level of AMH is also useful if available in the local laboratory. Second line tests include the hCG stimulation test to assess the androgenic synthesis pathway. An ACTH stimulation test can be useful to assess steroid hormone synthesis in both the adrenal gland and the testis. A 24-h urine collection enables the urinary steroid profile by gas chromatography and mass spectrometry, and will identify the

Table 68.2. Rules for diagnosis

Rule No.	Rule	Implication
1	Testes descend, ovaries don't	A palpable gonad is a testis
2	Testis descent + Mullerian ducts linked	A palpable gonad means Müllerian duct (on that side) is regressed
3	Uterus present = Sertoli cells poor/ absent (PR or ultrasound)	Persisting Müllerian ducts only occur in absent/dysgenetic testis (or rare PMDS)
4	Internal ducts mirror ipsilateral testis	MD/WD controlled by exocrine hormones from ipsilateral testis
5	Circulatory (adrenal) androgens cannot masculinise Wolffian duct	Endocrine levels too low and needs exocrine (high) levels
6	External genital development proportional to amount of effective androgens	Clitoral enlargement (erectile tissue) only caused by androgen exposure
7	External masculine development inversely proportional to lower vaginal regression	Vaginal remnant will be present in ambiguous genitalia
8	Masculinisation externally complete by 12 weeks but penis needs androgen up to 40 weeks	Absent androgens after this (in hypothalamic defects) cause micropenis
9	"hypospadias" assumes male gender Therefore only use if scrotum fused and testes descended	= Boy with normal hormone levels
10	Nonhormonal genital anomalies outside spectrum from male to female	Perineal anatomical anomalies include genitalia as well as other features

level of any enzyme defect in the steroid synthesis pathway.

A useful anatomical test to augment the pelvic ultrasonography is the urogenital sinugram, to outline the urogenital sinus and connection between urethra and vagina, and whether or not the cervix is present. The final test available in some referral centres, is molecular genetics to identify specific gene mutations.

68.11 Management

The medical and surgical approach to DSD first requires consideration of the degree of risk to the baby. Most importantly, there is a risk of death from adrenal failure in the second or third week of life if there is congenital adrenal hyperplasia (CAH) which is present in about half the affected babies. Where the baby has XY DSD, there is a risk of germ cell malignancy in the dysgenetic testis, as well as a significant risk of infertility and osteoporosis in adulthood from hormonal deficiency. In 46,XY DSD there is a risk of early onset renal failure or Wilms tumour if there is a WT1 mutation (Denys-Drash, Frasier, WAGR syndromes). In 46,XY DSD with incomplete virilisation the common urogenital sinus poses a risk of recurrent urosepsis if there is pooling of urine in the vaginal cavity. In all babies with a hormonal cause for DSD there is a risk of gender dysphoria in adolescence, as well as rejection by traumatised parents.

These potential risks have led to the development of a set of ethical principles on which to base the gender assignment and subsequent medical and surgical treatment plan for patients with DSD [16]. In the Royal Children's Hospital, Melbourne, these principles are now used by the ethics committee to oversee all decision-making for DSD patients, so that there is some external and transparent review of decisions that have lifelong consequences. The principles are: (1) Minimisation of physical harm to the child; (2) Minimisation of psycho-social harm to the child; (3) Maximising the potential for fertility; (4) Maximising opportunities for satisfying sexual relations, if required; (5) Keeping options open for the future; (6) Respecting the wishes and beliefs of the parents and (7) Considering the views of older children and adolescents where they are the patient.

Parents of babies with DSD suffer significant stress from the situation, and need not only definitive and frank information about the diagnosis, its implications and prognosis, but also counselling and support from a social worker and/or psychologist [17]. Another key requirement for reducing parental stress is a common message

from all team members, so there is no confusion or contradictory views about the management plan.

The surgical treatment of DSD requires a high level of expertise because the operations are complex, and have life-long impact on the person if done poorly.

The surgical timing remains controversial, with proponents of early surgery in infancy (between 6/52 and 6/12) and those recommending delay until puberty, or at least until the patient is able to decide for themselves [18, 19]. In our own centre we still offer early surgery, as our long-term results support this approach [20–22].

Female genital reconstruction is the most controversial, because of a poor outcome for clitoral appearance and sensation, as well as persisting vaginal stenosis requiring revision in adolescence [18]. We have a 30-year history of performing the clitoroplasty with a specific technique that preserves neuronal and vascular supply to the glans clitoris by not dissecting the dorsal surface of the clitoris [23, 24]. This has given very reliable long-term results. For the vaginoplasty, we have found that more complex operations such as the Passerini procedure [25] or total urogenital mobilisation (TUM) [26] do not seem to be necessary as long as the posterior skin flap in a standard Y-V vaginoplasty is inserted high enough up the posterior vaginal wall, to overcome the congenital stenosis present in the lower third of the vagina secondary to the masculinisation.

Male genital reconstruction follows standard guidelines for hypospadias repair, although initial laparoscopy may be required to excise any streak gonad or ovotestis, as well as address the urogenital confluence. Most authors have advised excision of the redundant internal female genital tract in patients being raised as boys to prevent development of a urine-storing vagina after hypospadias repair. Recently, we have opted to merely disconnect the retained vagina from the urinary tract and leave it *in-situ*, based on the ethical principles described above, which recommend keeping options open for the future. There appears to be no measurable malignancy risk, but long-term follow-up will be essential to determine this.

68.12 Long-Term Follow-Up and Prognosis

Women with CAH have a reasonable prognosis for fertility, if the surgery allows normal sexual intercourse without significant discomfort. As hormone treatment of the adrenal defect improves the side-effects have decreased, with Cushing syndrome from excess steroid replacement now less common than previously. However, there remains a risk of polycystic ovaries as well as the residual anatomical or psychosocial issues.

In boys with 46,XY DSD fertility is lower, as poor androgenic function may prevent normal spermatogenesis, in addition to the anatomical defects where the vas deferens would normally enter the prostate to reach the posterior urethra. Sexual function, however, is still reasonable despite the small size of the penis, and the problem may be lessened with professional counselling. Fertility may be possible in some patients with the assistance of reproductive technology, if a viable sperm can be retrieved from the epididymis.

Gender dysphoria remains an issue for partial androgen insensitivity syndrome (PAIS), 5α-reductase-2 deficiency and 17β-hydroxysteroid dehydrogenase-3 deficiency. In patients with CAH who were commenced on steroid therapy at birth, gender dysphoria later in life is extremely rare and only occurs when the treatment is ceased, allowing physical (and mental) virilisation to recur.

Long-term outcomes from Royal Children's Hospital, Melbourne show a quality-of-life score in adulthood that is similar to patients with Hirschsprung disease or childhood-onset diabetes mellitus [21]. Outcome results from other centres show more varied results, perhaps reflecting a less cohesive and stable team that has been our strength for 3–4 decades [27].

The key requirement for optimal outcomes is a cohesive, multidisciplinary team in a quaternary referral centre, so that patients receive "best practice" treatment for their DSD. The appearance of Support Groups has enabled many issues to be addressed, as the groups perform an invaluable role for advocacy, distribution of information, lobbying and open communication with the medical team.

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Male Genital Tract

69

Mike O'Brien

Abstract

Until the 12th week of gestation it is difficult to ascertain the sex of a human embryo based on the appearance of the external genitalia and yet the process is complete by 16–17 weeks. Our understanding of the complexity of the genetic and endocrinological interactions controlling this process continues to develop. There is emerging evidence that penile development has much in common with the development of limb buds. The developmental direction the indeterminate external genitalia take is driven by gonadal development which in turn is controlled by genetic sex determination. Though presented as sequential events, much of this happens in parallel. Between the 4th and 6th weeks the cloaca becomes divided into a posterior anorectal canal and an anterior urogenital sinus by the formation of the urorectal septum, the tip of which will eventually form the perineum. Simultaneously the mesoderm antero-lateral to the developing urogenital sinus expands to create the genital tubercle. When the cloacal membrane ruptures it exposes the floor of the urogenital sinus that will form the urethral plate. The mesoderm on either side of the urethral plate expands to form urogenital folds that extend into the genital tubercle. These are flanked by a pair of labioscrotal swellings. During the 6th week the urethral plate develops into a urethral groove which becomes the penile urethra as a result of fusion of the urogenital folds from proximal to distal, and is usually complete by 14 weeks. The formation of the glanular urethra is still under investigation and it is still unclear if it occurs by tubularization of the endoderm as in the penile urethra or through

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_69

canalization of ectoderm distally. The prepuce itself develops as a result of ectodermal folding and cellular ingrowth resulting in the glans penis and inner prepuce sharing a common mucosal lining which gradually separates over years.

Keywords
Male genital tract • Newborns • Phimosis • Buried penis • Hypospadias
Undescended testes • Varicocoele • Acute scrotum

69.1 Penis

69.1.1 Phimosis

Until the 12th week of gestation it is difficult to ascertain the sex of a human embryo based on the appearance of the external genitalia and yet the process is complete by 16–17 weeks. Our understanding of the complexity of the genetic and endocrinological interactions controlling this process continues to develop. There is emerging evidence that penile development has much in common with the development of limb buds [1]. The developmental direction the indeterminate external genitalia take is driven by gonadal development which in turn is controlled by genetic sex determination. Though presented as sequential events, much of this happens in parallel. Between the 4th and 6th weeks the cloaca becomes divided into a posterior anorectal canal and an anterior urogenital sinus by the formation of the urorectal septum, the tip of which will eventually form the perineum. Simultaneously the mesoderm anterolateral to the developing urogenital sinus expands to create the genital tubercle. When the cloacal membrane ruptures it exposes the floor of the urogenital sinus that will form the urethral plate. The mesoderm on either side of the urethral plate expands to form urogenital folds that extend into the genital tubercle. These are flanked by a pair of labioscrotal swellings. During the 6th week the urethral plate develops into a urethral groove which becomes the penile urethra as a result of fusion of the urogenital folds from proximal to distal, and is usually complete by 14 weeks. The formation of the glanular urethra is still under investigation and it is still unclear if it occurs by tubularization of the endoderm as in the penile urethra or through canalization of ectoderm distally [2]. The prepuce itself develops as a result of ectodermal folding and cellular ingrowth resulting in the glans penis and inner prepuce sharing a common mucosal lining which gradually separates over years.

The penile condition for which most medical opinion/intervention is sought is phimosis, which derives from the Greek phimoo (=muzzle) or phimos (=gag) and the suffix -osis (= process or state). Over the millenia since its original description by the Greeks it's meaning has been extended to include normal physiological states such as a non-retractile prepuce, residual glanulo-preputial adhesions and even 'excessive' or 'redundant' preputial length [3]. This unfortunate confounding with a genuine pathological process such as Balanitis Xerotica Obiterans has resulted in innumerable unnecessary circumcisions and even more unnecessary medical consultations. Rickwood's efforts to restrict the use of the term to BXO are doomed to fail and the more pragmatic approach is to adopt a classification into physiological or pathological phimosis.

Physiological phimosis describes normal anatomical findings that tend to disappear/resolve with growth. At birth a small minority of boys (4%) will have a foreskin that is fully retractable over the head of the penis, a further 54% will have a partially retractable foreskin but in the remaining 42% the glans is not at all visible [4]. The rate of separation of the glans and prepuce is exponential such that 20% of boys had a fully retractable foreskin by 6 months of age, 50% by 1 year, 80% by 2 years and 90% by 3 years. Oster took Gairdner's work and extended to older boys

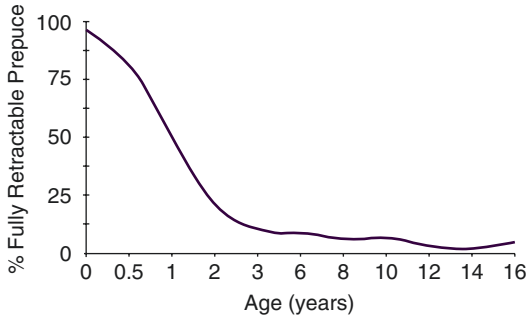

Fig. 69.1 Percentage of boys with a fully retractable foreskin [4, 5]

(see Fig. 69.1) and a significantly larger study population (>9500) of which a subset, 173 boys were reviewed annually for 7 years confirming that they had a similar trend to the graph for the overall population [5]. I would agree with Gairdner that the term 'preputial adhesions' is misleading as it implies that the glans and prepuce were previously separated and have adhered together. This misunderstanding perpetuates the false impression that forcible retraction of the prepuce from an early age is necessary for penile hygiene to clean a space that does not yet exist.

That said physiological phimosis is associated with some pathological and non-pathological processes. Smegma pearls are collections of shed epithelial cells, keratin and natural oils that accumulate in the developing space between the glans and prepuce and present as a mobile, non-tender, non-fluctuant swelling on the penis. Their formation contributes to the natural separation of the prepuce occasionally presenting as a non-offensive 'discharge'. Ballooning on micturition, especially if fusiform along the shaft of the penis, rather than spherical at the base as discussed below, is often a presenting complaint. Hutton and Babu found no evidence of obstructed urine flow when comparing uroflowmetry of uncircumcised boys when comparing those with and without ballooning [6]. After non-retractability the most common reason for referral for circumcision is recurring balanitis often misdiagnosed as recurrent UTIs when in fact it is posthitis! Posthitis is an inflammation of the prepuce, balanitis inflammation of the glans and balanoposthitis inflammation of both. The 'redundancy' of the foreskin encourages retention of urine subpreputially which then develops an ammoniacal dermatitis or inflammation which if left untreated may develop a secondary cellulitis. The initial posthitis, because of its association with dysuria is often diagnosed as a UTI, is best treated with topical barrier agents, simple hygiene advice and patient, parent and GP education.

Paraphimosis is an acquired condition thought to result from failure to reduce a tight foreskin that has been withdrawn over the glans and causes glanular oedema secondary to constriction which then makes spontaneous reduction unlikely. It tends to occur at the extremes of life in children whose foreskin has been retracted 'to clean', post sexual intercourse and in the elderly post urethral catheterization. It is a surgical emergency as failure to reduce has been associated with necrosis, gangrene and necrotising fasciitis. There are a number of treatment options including manual reduction with or without the aid of an ice glove, multiple needle punctures (The Dundee technique) to facilitate evacuation of oedema [7], injection of hyaluronidase or the topical application of granulated sugar [8]. All methods have been shown to work with no comparative studies to demonstrate superior efficacy of any individual technique [9]. That said topical osmotic agents (sugar etc.) take a long time to work and are probably best used where there is a delay in manual reduction [10]. Occasionally surgical intervention in the form of a dorsal slit is required especially where there is a delay in seeking medical attention. Once reduced there are mixed opinions on the merits or necessity of circumcision as recurrence of paraphimosis is notably uncommon.

The majority of cases of pathological phimosis can be attributed to Balanitis Xerotica Obliterans or BXO. More correctly known as penile lichen sclerosis it is a progressive sclerosing condition that affects the prepuce, glans and if left untreated, the urethra. It has a reported incidence of 0.07% [11]. Clinically it is distinguishable from physiological phimosis by virtue of the indurated pallor of the prepuce that prevents retraction of the foreskin in patients presenting in acute urinary retention or with a penile discharge.

However it is rare for referring doctors to make the diagnosis [12]. Its exact aetiology is unknown but it largely occurs in uncircumcised males thought possibly to be due to chronic irritation/inflammation from sub-preputial epithelial debris or an as yet unidentified infectious agent. In the paediatric population at least circumcision is curative in half [12] but may need supplementation with topical steroids especially if the glans/meatus is affected. Glanular lesions usually disappear within 6 months in >99% of patients [13]. Treatment with topical or intra-lesional steroid therapy may be sufficient in milder cases [14]. Topical steroid therapy alone was associated with resolution of symptoms and signs in 17% of boys with mild BXO after 3 months of therapy and this increased to 30% after 17 months [15].

The topical application of steroid ointment to treat both physiological and pathological phimosis has its origins here in Melbourne when proposed by Kikiros, Beasley and Woodward. Since that time there have been multiple publications of control trials of topical steroid versus placebo demonstrating statistically greater efficacy [16–18]. Despite this the optimal steroid treatment regimen has not been determined. Twice daily application appears to be as effective as three-times (without the need for application during the school day) with success rates approaching 85% [19]. Success is enhanced when application is coupled with routine preputial retraction. Topical steroid ointment has been shown to significantly more cost-effective than circumcision with potential annual savings in France in 2001 of 150 million Francs. One of the problems with topical steroid therapy is accurate dose application/administration sometimes resulting in non-compliance from steroid phobia, as has been demonstrated in up to a third of patients [20]. Of greater concern to physicians is over administration resulting in exogenous Cushing's syndrome or suppression of the hypothalamic-pituitary-adrenal axis. This has been demonstrated in infants treated with potent steroids for nappy rash i.e. a large area. Similarly absorption of preputially administered oestrogen cream has been shown to have systemic effects in a boy with phimosis [21]. However no evidence of H-P-A axis suppression was found in a study of topical Clobetasol [22]. Clobetasol proprionate is a Class I super potent topical steroid so the more commonly used Betamethasone valerate, a Class II or potent agent, should have even fewer side effects provided administered correctly.

69.1.2 Circumcision

For an operation to remove a few cm [2] of skin, practised for over 5000 years and carried out on over 1/3rd of the world's male population, circumcision still manages to generate a great deal of debate and controversy. No one knows exactly when circumcision was first practised. Sir Grafton Elliot Smith a British Egyptologist suggests it started over 15,000 years ago. Egyptian mummies as far back as 2300 BC were found to have been circumcised [23]. It has been demonstrated on 6000-year-old reliefs on the wall of the tomb of Ankh-Mahor at Saqqara near Cairo, Egypt [24]. There are many theories as to the origins of circumcision from a necessity in arid/desert regions to address the accumulation of sand under the prepuce through a humiliating 'branding' of slaves in ancient Egypt to a 'rite of passage' into adulthood [23]. Whatever the origins or indications circumcision continues to be performed amongst Jewish and Muslim cultures for religious reasons and for cultural reasons amongst some western societies.

In Judaism circumcision (*Brit Milah*) is a commandment (a *mitzvah*) from God representing a covenant between God and Abraham and all of Abraham's descendants—Genesis 17:10–14:

> 10. This is my covenant, which ye shall keep, between me and you and thy seed after thee; Every man child among you shall be circumcised.
>
> 11. And ye shall circumcise the flesh of your foreskin; and it shall be a token of the covenant betwixt me and you.
>
> 12. And he that is eight days old shall be circumcised among you, every man child in your generations, he that is born in the house, or bought with money of any stranger, which is not of thy seed.

> 13. He that is born in thy house, and he that is bought with thy money, must needs be circumcised: and my covenant shall be in your flesh for an everlasting covenant.
>
> 14. And the uncircumcised man child whose flesh of his foreskin is not circumcised, that soul shall be cut off from his people; he hath broken my covenant.

It is the father's obligation to perform the circumcision himself or as is more usual to appoint a *mohel* to carry it out. The rules and requirements are set out in the *Talmud* including the requirement that the entire glans be uncovered when the penis is flaccid [25]. In the UK *mohelim* are trained and regulated by the Initiation Society, under the guidance of the Chief Rabbi of Great Britain. Training takes 6 months, they have to see 40–50 before being permitted to perform one and have to pass a two-part practical and theoretical exam before being licensed. As has happened in those cultures that practice social circumcision there are people in the Jewish community who question its validity and relevance in modern society [26].

Among the six schools of Islam only one, the Shafiite school considers circumcision obligatory (*wajib*). The remaining five consider it to be recommended as a tradition (*Sunnah*) attributed to the Prophet Abraham [27]. Unlike Judaism a specific age, technique or person is not designated. This in part explains why, with the exception of bleeding, more complications are seen in circumcisions performed on Muslim boys than in Jewish boys.

It was in the nineteenth century that circumcision as a 'treatment' for widespread ills became increasingly common. Circumcision was advocated as a treatment for impotence, sterility, priapism, masturbation, 'wet dreams', syphilis, epilepsy, spinal paralysis, bedwetting, club foot, crossed eyes and even to prevent black men from raping white women (Dunsmuir:1999wd, http://www.icgi.org/medicalization). The sequelae from this can still be seen in the estimated 1.25million boys circumcised annually in the USA or one child every 26 s! [28]. That said there has been a reduction, in recent years, in the number of circumcisions performed annually in the western societies such as USA, UK and Australia. Circumcision rates in the USA have fallen from 65% in 1980 to 57% in 2009, continuing a downward trend from ever higher rates in the 1960s [29]. There is still marked regional variation with more circumcisions carried out in the mid-west that on the coast, with the exception of Maryland where the rate approached 83% [29, 30]. A similar downward trend though starting from a very low initial level has demonstrated in the UK. Korea where non-medically indicated 'social' circumcision is believed to be an after-effect of American occupation, is the one developed culture that is bucking this downward trend [31]. The reasons for this trend are varied. Given that the main reasons for circumcising one's child, outside of religious indications, are because his father is circumcised or because of a belief that it is cleaner or more hygienic [32]. As fewer fathers are circumcised, naturally the rate will fall and similarly position statements such as that released by the American Academy of Pediatrics suggesting that circumcision was unnecessary will have both a direct effect and an indirect one by influencing Medicaid to no longer reimburse the cost in some American states. In Australia a similar government initiative to not reimburse hospitals for carrying out non-medically indicated circumcision has had a similar effect. That said circumcision rates for phimosis in Western Australia are more than seven times the expected incidence of phimosis [33].

There is an ever growing anti-circumcision lobby driven, to be fair, by men who have been circumcised. Groups such as NOHARMM (National Organization to Halt Abuse & Routine Mutilation of Males), NORM (The National Organization of Restoring Men) and NoCirc (National Organization of Circumcision Information Resource Centers). Their objections are based on reports (from selected series of men) of dissatisfaction with penile appearance following circumcision in 1/3–1/2 men, due to scarring, or insufficient penile skin restricting erections and erectile curvature [28]. A number of women also object to routine circumcision primarily because of the pain it causes their child and some because of concerns regarding its impact on

sexual function later in life for both their child and his potential female partner [34].

There is an equally strong pro-circumcision lobby promoting the public health benefits of circumcision. Ever since the first report in 1989 describing an association between circumcision status and susceptibility to HIV infection [35] there have been a number of randomized control trials in sub-Saharan Africa demonstrating a 50–60% reduction in HIV susceptibility [36–38]. Furthermore research has shown that circumcision in areas with a high prevalence of HIV is cost effective [39]. Given the high rates of circumcision required to have a significant impact, circumcision in the neonatal period has been shown to be even more effective given the potential higher take-up rates, lower procedural costs and lower complication rates [40]. Male circumcision has been shown to associated with a reduced risk of sexually transmitted diseases, penile cancer and urinary tract infections [41–43]. Despite some predictions there is no evidence that circumcision as an adult to mitigate HIV risk is associated with increased sexual risk taking behaviour. What is not clear is the protective effect on male-to-female HIV transmission of male circumcision. In the only trial to-date looking at this, what was found was an increased susceptibility of female partners of HIV-positive males who underwent circumcision and resumed sexual intercourse before complete wound healing [44]. Other advantages for female partners are a reduced susceptibility to Human Papilloma Virus infection and cervical carcinoma [45].

Extrapolating data from sub-Saharan African trials with a very high prevalence of HIV among heterosexuals to more developed westernized cultures with a higher rate of male-to-male infection is prone to error. Many of the trials had difficulty distinguishing the relative impacts of circumcision status and genital ulcer disease and hence the ongoing need to wear a condom cannot be underestimated. The high complication rates of 17–35% in adults undergoing circumcision, compared with 0.2% of neonates [46], give cause for consideration when proposing population-wide intervention [47]. Though the neonatal period is the best time to circumcise [48], the ethics and legality of performing circumcision on infants without their consent as a public health measure to minimize the risk of contracting a disease for which there are readily available and credible prevention strategies is still under discussion [49–53]. The psychological impact of circumcision both on the neonatal patient and subsequently as an adult is still being calculated [54].

Whatever the indication or justification there are a limited number of circumcision techniques. A detailed discussion of operative technique is beyond the scope of this text. Most open operative techniques are modifications of the 'sleeve resection' originally described by Treves in 1903 [23], normally carried out under general anaesthesia [55, 56]. The techniques carried out under local or regional anaesthesia generally make use of some form of clamp such as the Gomco, Winkleman or Mogen removed once the foreskin has been excised or the Plastibell designed to fall off within a week.

Whatever the technique employed circumcision, as with any procedure, is associated with some complications though the risks are largely overstated. Wiswell looking retrospectively at over 100,000 neonatal circumcisions performed at army hospitals over a 5-year period found a complication rate of 0.19% [42]. The majority of these were bleeding (43%), of which half required surgical haemostasis and only 3 (0.003% of total) required blood transfusion. Infection was a close second in 42% and only 25 boys (0.025% of overall) suffered any surgical trauma. The complication rate for circumcisions performed outside the hospital system is hard to quantify given the unknown denominator. What little is published suggests that Plastibell circumcision is associated with a higher complication rate, especially in obese children [57]. Other less frequent complications include recurrent phimosis leading to a buried penis, inclusion cysts, skin bridges and fistula. More significant but less frequent are glanular injuries. Meatal stenosis, thought to be due to contact with urine in the diaper and, historically reported to occur in 8–31% of boys is rarely seen nowadays possibly due to advances in diaper technology [24]. This is supported by the

still relatively high incidence (20%) of meatal stenosis in Iran, possibly related to use of more traditional diapers [58].

Preputioplasty is an option for those boys with recurring preputial inflammation or restriction, despite topical steroids and who wish to keep an uncircumcised appearance. Not an operation to be considered in the presence of BXO, preputioplasty offers the possibility of increasing preputial girth at the expense of preputial length. There are a number of different publications advocating one, three or multiple longitudinal incisions which are closed transversely (alá Heineke-Mikulicz) [59]. A Y-V preputioplasty has been shown to be associated with higher success rates [60] and to be finding acceptibility with adult surgeons [61]. Preputioplasty as a credible alternative to circumcision is finding an expanding role in the management algorithm of phimosis [62]. It must be remembered that as with topical steroids much of the success relates to regular post intervention preputial retraction and hence patient age at selection is a crucial determinant.

Despite the absolute wealth of information, albeit largely conflicting, it would appear that providing information to parents has little impact on their decision to circumcise their newborn son or not as their decision had been made before the third trimester [32, 63].

69.1.3 Paraphimosis

Paraphimosis is an acquired condition resulting from retraction of the prepuce proximal to the coronal sulcus with consequent oedema and engorgement and entrapment of the glans. It is associated with failure to return the foreskin after male urethral catheterisation, post-coitally and post-masturbation but the majority in adolescents have no clear aetiology. The presumed association with phimosis is not born out by the fact that post reduction and resolution of swelling only 29% of patients have evidence of phimosis [10].

There are a number of differing techniques described to enable reduction, none of which have any proven superiority [9]. The most common method, initially trialled with topical anaesthesia but proceeding to penile block or general anaesthesia as necessary involves sustained manual compression of the prepuce and glans to reduce swelling (can take 15 min or more!) [64]. Then with a firm grip on the preputial ring the glans is invaginated. Others have suggested augmenting this approach with use of an ‘ice’ glove to help reduce the swelling. The use of topical osmotic agents such as glycerine magnesium sulphate, granulated sugar [8] or 50% dextrose. Others report the use of multiple needle punctures (the Dundee technique) to facilitate reduction of the oedema [7], enhanced by others by injection of hyalurinidase.

A failure of these methods especially under general anaesthetic may precipitate the need for a dorsal slit and either immediate or delayed circumcision. For those that did reduce without surgery it is no longer considered imperative to circumcise to prevent recurrence which is very rare [10].

69.1.4 Hypospadias

A condition that appears to be increasing in incidence, typically presenting at birth to obstetricians but occasionally detected antenatally, especially when severe [65, 66]. The term hypospadias is derived from the Greek for rent or defect “spadon” and ‘hypo’ meaning below. It is usually composed of three elements—a ventral opening of the urethra, ventral curvature (chordee) of the penis and an incomplete or hooded foreskin.

The development of the external male genitalia begins in the 7th week of gestation and is completed by 16–17 weeks [2]. The process begins earlier in the 4th–7th weeks with differentiation of the primitive sex streaks into testes under the influence of the SRY gene on the Y chromosome. The initial development of Sertoli cells triggers the development of germ cells and Leydig cells which in turn produce testosterone that is converted to dihydrotestosterone to exert its effect on the genital tubercle. Over the past decade a number of similarities between limb bud development and that of the genital tubercle

have been discovered. The penis develops from ecto-, meso- and endodermal layers. The endodermal layer gives rise to the urethral folds on either side of the urethral groove, which fuse to form the urethra from the veru-montanum to the glans. The glanular urethra is formed by canalization and joins the tubularizing urethral plate. There is some evidence that this endodermal layer is crucial to penile development—endodermal differentiation—thus explaining the association of incomplete urethral development with incomplete preputial development [67]. These have been shown at a molecular level to interact through a number of signalling mechanisms including *Sonic hedgehog, BMP, WnT, Fgf* etc. [1]. How systemically circulating testosterone interacts with these signal transduction genes is still being elucidated.

For a long time hypospadias has been classified according to the position on the phallus of the meatal opening into Anterior (glanular and subcoronal)—50%, Middle (Distal penile, midshaft and proximal penile)—30% and Posterior (Peno-scrotal, scrotal and perineal)–20%. It is well recognized that this classification underestimates the severity of hypospadias as the meatal opening tends to adopt a more proximal position once the chordee has been released. Furthermore the quality of the urethral tissue immediately proximal to the meatal opening is highly variable and tends to be hypoplastic or atretic proximally to the level of the bifurcation of the Corpus Spongiosum [68]. They describe a method of estimating the bifurcation of the spongiosum by drawing intersecting lines between the preputial skin and inner preputial mucosa. This understanding has prompted a new classification based on division of Corpus Spongiosum and pubic symphysis [69]. This changes the proportions to Middle 21% and Posterior 30%, of relevance when deciding whether the defect is best managed with a single or staged repair. This classification has the potential to enable more accurate comparisons between differing series of patients. It must be remembered though that this remains only one descriptive parameter of a complex anomaly that should also include an assessment of peno-scrotal transposition, penile size, glans size, nature of glanular groove, penile torsion and degree of chordee. Even by their own admission Orkiszewski have identified that in hypospadias with the most proximal meatal openings the division of the corpus spongiosum may be more distal on the penis than the meatal opening. Ultimately the classification of hypospadias is finalized intra-operatively. It is important that surgeons undertaking hypospadias repair be able to operate on all severities of hypospadias as pre-operative assessment will occasionally be an under-estimate.

There is marked variability in the incidence of hypospadias worldwide with 32 cases per 10,000, in 1992, reported from Southampton [70] and only 10 per 10,000 from South America [71]. In line with other male genital anomalies there are numerous reports of increasing incidence of hypospadias in recent years and this has been linked to increased environmental exposure to endocrine disrupting pollutants. Some of this variability will be due to under-reporting in less developed countries of minor degrees of hypospadias, however there is evidence of a genuine increase in the incidence of hypospadias in the developed world with a doubling of the incidence in America from 20 per 10,000 in 1970 to 39.7 per 10,000 in 1993. The majority of the increased incidence appears to be in less severe degrees of hypospadias which is consistent with some theories that the increase is not due to a real increase but rather due to increased reporting, previous under-reporting or a lowering of the threshold for reporting [72, 73]. Because of the confusion surrounding changing trends in the incidence of hypospadias there have been calls for more accurate registration of patients especially if endeavoring to link to potential emerging epidemiological data [74].

There is increasing evidence suggestive of an association between the incidence of hypospadias and environmental pollution by compounds with endocrine disrupting activity [75]. There are a large number of compounds with oestrogen-like activity (xeno-oestrogens—found in insecticides such as DDT, and industrial chemicals, phyto-oestrogens—plant derived chemicals with oestrogenic activity found in grains, nuts, Soya

etc.) or with anti-androgenic activity [76]. For example the odds ratio of developing hypospadias is 2.4–3.4 if the patient's mother worked in agriculture in the month prior to conception [77, 78] and is 1.96 if the patient lives within 3 km of a landfill site [79]. A maternal professional exposure to hair spray products including phthalate is associated with a 2.4-fold increase risk of having a son with hypospadias [80]. An exclusive vegetarian diet has been demonstrated to have an almost fivefold increased risk of hypospadias [81]. The latter is felt to be due to an increased consumption of phyto-oestrogens especially found in Soy-based foods [76], hence their recommended intake in peri- and post-menopausal women. There are however a few reports that question the increased incidence and association with vegetarianism etc. [80, 82, 83]. Interestingly epidemiological data have unveiled a protective effect of folate supplementation during the first trimester [80].

There are a number of associated anomalies such as cryptorchidism (9%), persistent utriculus masculinus (10–57%), bifid scrotum and scrotal transposition all of which again suggest a common aetiology due to ineffective androgenisation. Severe forms of hypospadias can present as ambiguous genitalia. In some series up to 50% of patients with hypospadias and cryptorchidism had an underlying genetic, gonadal or phenotypic abnormality. All patients with hypospadias and cryptorchidism should be investigated to exclude congenital adrenal hyperplasia, a potentially lethal condition if undetected but eminently treatable. Apart from *in-utero* exposure [84], other risk factors for the development of hypospadias include placental insufficiency evidenced by an association with prematurity, very low birth weight, small for gestational age and multiple births [77].

A familial or genetic predisposition to hypospadias has been well described with a presumed multifactorial model of inheritance dependent on genetic-environmental interactions. The risk of a sibling developing hypospadias has been estimated to be between 6–10% [85]. It has been reported that as many as one in four boys with hypospadias will have a family member with hypospadias, and 1 in 14 will have two [86]. The more extensive the hypospadias the more likely for a family member to be affected with 3.5% of mild, 9% of moderate and 17% of severe cases having an affected relative. As our knowledge of the genetic mechanisms that underly development of the external genitalia increases so too does the ever expanding list of candidate genes associated with the development of hypospadias. These genes are not exclusively restricted to androgen development, conversion and effect such as 5 alpha-reductase type 2 gene (SRD5A2), 17 Beta-Hydroxysteroid dehydrogenase type 3 (HSD17B3) or Mastermind-like domain containing1 (MAMLD1) also known as Chromosome X open reading frame 6 mutation (CXorf6) to name but a few. They also include sonic hedgehog, fibroblast growth factors, bone morphogenic proteins (BMP), homeobox genes (HOX) and WnT/Beta catenin. For a detailed review the reader is directed to Kojima et al. and Kalfa et al. [87, 88]. There is some emerging evidence from in-vivo modelling of up-regulation of some of the candidate genes in response to exposure to oestrogen providing initial evidence to support the genetic-environmental interaction theory [89].

Hypospadias is a diagnosis that is almost always made at birth and generally investigations are not required. Exceptions include boys with associated undescended testes and those with proximal hypospadias who are known to have an increased incidence of utricular and renal abnormalities. Cryptorchidism is found in 8–10% of boys who have hypospadias [90]. The incidence of cryptorchidism increases with more severe forms of hypospadias such that almost a third of boys with a proximal hypospadias have an undescended testis. This latter group have a much greater incidence of chromosomal abnormalities (22%) than those with simple hypospadias (5–7%) or those with isolated hypospadias (3–6%). More severe degrees of hypospadias are also associated with an increased risk of disorders of sexual development, and persistent or enlarged utricular remnants. Boys with associated cryptorchidism or proximal hypospadias should at least undergo karyotyping. Endoscopic examination at the time of hypospadias repair

may reveal an enlarged prostatic utricle in more than half of those with severe hypospadias. Whilst not mandating surgical immediate surgical intervention it may portend urinary tract infection, epididymo-orchitis, stone formation or urinary incontinence.

Despite the immortal words of Durham Smith "There is nothing new in surgery not previously described" [91], there have been over 250 described operations for hypospadias. All aim to produce a penis that is straight when erect, voids from the tip with a terminal meatus and looks cosmetically acceptable, whether that be with a circumcised or uncircumcised appearance. Broadly speaking the operative techniques can be subdivided in single or staged procedures, tubularised or grafted repairs and pedicled or free grafts. The majority of surgeons will only undertake half a dozen or so different types of hypospadias operation and a detailed operative description is best obtained elsewhere. For distal hypospadias the author's approach is dictated by the nature of the urethral plate, the depth of the glanular groove, the extent of any associated chordee and the parental desire for preputial reconstruction or not. The author prefers not to perform a preputial reconstruction in association with a Snodgrass repair [92, 93] and in that setting or where the urethral plate is deemed too narrow (<6 mm) prefers to use a meatal-based flap repair or Mathieu. Foreskin reconstruction as an option is being increasingly requested by parents who wish a cosmetic result more aligned with the general population.

For more proximal or severe hypospadias we perform a two-stage free graft or Bracka repair. For the Bracka repair we prefer to use inner preputial skin from the hooded prepuce as this is non-hair-bearing epithelium that is used to being in contact with urine. Other options for graft material include buccal mucosa—our next choice, bladder mucosa, as a last resort and never taken to the tip as constant exposure to a dry environment has lead in the past to unsightly mucosal overgrowth through the meatus, and finally posterior auricular skin graft. A necessary consequence of the Bracka repair is that the patients will ultimately end up looking circumcised. Again there are a wide range of alternative operations including but not limited to the single stage Koyanagi or modified Koyanagi [94], the Macedo 'three-in-one' [95] or the Duckett Onlay [96] or the two-stage Durham-Smith [97].

The ideal timing of hypospadias surgery continues to be debated with a trend towards surgery at a younger age. It is the author's preference to undertake hypospadias repair between 10 and 14 months of age for a number of reasons. Firstly there is a period after birth lasting approximately 6 months, often referred to as 'mini-puberty' where under the influence of circulating testosterone there is penile growth in excess of the remainder of the baby. Secondly, there are some emerging concerns regarding the impact of volatile anaesthetic agents on the developing brain. Thirdly, the surgery still takes place before the patient becomes 'genitally aware'. Finally, it is occasionally necessary in some patients to increase penile size prior to surgery and this can be achieved through the topical application of testosterone gel or intra-muscular depot testosterone. This can take as long as 3 months. When surgery is undertaken at around 1 year of age, the fact that the baby is still in diapers and yet to start toilet-training makes post-operative care simpler.

In part the wide variety of hypospadias operations is a response to a desire to improve functional and cosmetic outcomes but also a response to a need to reduce the complication rate associated with this surgery. The most common complication is urethrocutaneous fistula. There is marked variability in the reported incidence rate for fistula ranging from 2–30%. Fistulae account for 75% of complications [98] and have a 25–50% recurrence rate following repair [99, 100]. Other rarer complications include stricture, meatal stenosis, both of which should be excluded prior to fistula repair to minimize recurrence, meatal retraction, glans dehiscence, urethral diverticulum, residual chordee and unsatisfactory cosmesis with Bracka reporting up to 50% requesting further surgery. Most paediatric urologists believe that the repairs being currently performed have a much better cosmetic outcome than repairs performed 15–20 years ago and that Bracka's report

is not applicable to current repairs. It is widely recognized however that there is poor agreement between patient and surgeon in relation to cosmetic outcome. It has also been reported that up to 33% of hypospadiacs are inhibited in seeking sexual contact compared to 12% of controls. For these reasons Bracka believes it is not appropriate to discharge these patients until they are fully grown and sexually active to allow time for both physical and psycho-sexual complications to manifest.

69.1.5 Inconspicuous or Concealed Penis

In 1986 Maizels developed a classification to describe a group of conditions resulting from or giving the appearance of a small penis. They consist of (1) poor penile suspension; (2) buried penis; (3) webbed penis; (4) trapped penis; (5) concealed penis; (6) dimunitive penis and (7) micropenis.

While the majority present in infancy there is a second peak in later childhood/early adolescence (pre-pubertally) [101]. The latter group tend to be primarily buried in excess pre-pubic fat [102]. For this group time to allow penile growth, diet and exercise to encourage weight loss and only in a selected group is surgical intervention appropriate or required. When surgery is indicated it usually involves some form of lipectomy or liposuction and fixing of the penile shaft skin at the base of the penis [103]. Increasingly frequently a penis buried in excess pre-pubic fat is seen in infants, presenting prior to learning to walk, for whom surgical intervention is inappropriate and parents should be reassured that with weight loss the appearance will approve [104].

A buried penis, sometimes referred to as a Congenital Megaprepuce, tends to present between 6 and 12 months of age with a history of significant, spherical ballooning on micturition (not to be confused with the fusiform ballooning seen in physiological phimosis). Parents will usually report the need to manually express urine from within the prepuce. The exact aetiology of congenital megaprepuce is unknown. Most theories focus on abnormal attachments of fascial layers, others on penile skin deficits or crural abnormalities [105]. The overwhelming majority do not present at birth rather they become apparent over 6–12 months and hence whilst there is a congenital predisposition the act of micturition must play a contributing role in the progression of the condition. The natural history is unknown as most undergo some form of surgical intervention with generally speaking good outcomes [101]. There are a number of different surgical approaches all of which emphasize the importance of not removing external shaft skin, which tends to be deficient, and focusing instead on the inner preputial and Dartos layers [105–108].

Webbed penis is a form of peno-scrotal fusion anomaly for which surgical intervention may be necessary in severe cases. El-Gohary and El-Koutby recently proposed a classification of webbed penis into primary or secondary to circumcision and into simple or compound [109]. Simple merely describes a web that extends for variable lengths along the shaft of the penis. Compound is either a broad based web or one associated with scrotal transposition or chordee. The nature of the repair is based on the severity of the problem ranging from simple excision to the use of skin flaps [102, 110].

Trapped Penis is a post-operative complication following circumcision that if detected early may respond to topical steroid application [111]. It has been reported to occur in as many as 2.9% of boys circumcised as neonates [112]. More often surgical release is required which may be a simple scar revision or rarely a complex staged repair with skin grafting [113].

A concealed penis is one of the more poorly defined entities and could conceivably be any of those listed above. It would also include those that are masked by large herniae or hydroceles in neonates and infants.

Micropenis differs from other forms of concealed penis in that the underlying problem is the size of the penis which by definition is a stretched penile length of more than 2.5 standard deviations less than the mean for age [114]. For neonates this means less than 1.9 cm and for an adult 9.3 cm. This reference range does not take

account of some ethnic differences and for that reason <7 cm is advocated for diagnosis of micropenis in adults [115]. It is essentially an endocrinological rather than a surgical problem resulting from a failure to produce gonadotrophins (hypogonadotropic hypogonadism), a failure of the testis to respond (hypergonadotropic hypogonadism) or idiopathic. For a more detailed review readers are directed to Wiygul and Palmer [114]. Treatment is essentially medical and aimed at improving appearances not restoring normality. When medical therapy fails surgical intervention may be appropriate with increases in length varying from 1 to 4 cm [115].

Peno-scrotal transposition describes the appearance when the penis is partially or completely enveloped by the scrotum. It can be an isolated presentation but more often appears in association with hypospadias and chordee. Primarily a cosmetic condition, more severe cases may have functional implications especially when associated with chordee. Most repairs involve flap rotation of the scrotum to drop it back but others move the penis [116].

69.2 Undescended Testis/ Cryptorchidism

69.2.1 Introduction

Cryptorchidism is the most common congenital abnormality. The incidence is increasing and currently stands between 2.4 and 6.9%, averaging around 5% of all boys born at full term [117, 118] and being more common in pre-term and low birth weight infants. Descent of the testes has been the subject of extensive research. Despite this there are still large gaps in our knowledge of the aetiology of this condition.

69.2.2 Embryology

Currently the unifying theory describes testicular descent as occurring in two stages, the abdominal and the inguino-scrotal phase. Development of the gonads begins during the 4th intrauterine week. During the 6th week Testis Determining Factor, encoded by the SRY (sex-determining) region of the Y chromosome the developing gonad differentiates into a testis. Testicular descent begins during the 7th week. This phase, the abdominal phase, said to be under the control of Mullerian Inhibiting Substance (MIS) released from Sertoli cells, is attributed to regression of Mullerian structures and enlargement of the gubernaculum under the influence of Leydig cell produced insulin-like hormone 3 [119]. In addition testosterone causes regression of the Cranial Suspensory Ligament permitting the testis to remain near the internal inguinal ring during somatic growth and hence apparent trans-abdominal movement, complete by 15 weeks gestation.

The second or inguino-scrotal phase is largely under the control of testosterone and takes place during the 28th–35th intra-uterine weeks. During this phase testosterone is believed to act on the nucleus of the genitofemoral nerve in the spinal cord to cause the ipsilateral release of Calcitonin-gene related peptide (CGRP) from the end of the Genitofemoral nerve [120]. It is postulated that CGRP induces swelling and cavitation of the Gubernaculum into which the Processus Vaginalis protrudes. The growth and expansion of the gubernaculum has been shown to have a number of similarities with developing limb buds [121, 122]. This provides a space through which the testis can pass into the scrotum possibly driven by intra-abdominal pressure.

69.2.3 Classification

A fully descended testis is one that normally resides in the scrotum. An undescended testis is best described as one that cannot be manipulated to the bottom of the scrotum without undue tension on the cord. Undescended testes can be classified on the basis of whether they have become arrested in the line of normal descent and are described as intra-abdominal, canalicular or emergent. Testes that are not in the line of normal descent are called ectopic and can be Femoral, Perineal, Pre-penile, Transverse Testicular Ectopia. Histological examination of testicular

biopsies suggests that ectopic and undescended testes have similar pathological origins [123].

The cremasteric reflex serves to elevate the testis in the scrotum either to help with the maintenance of testicular temperature in cold weather or to protect it from trauma. This reflex, weak at birth, becomes stronger in infancy and diminishes again after age 10. Retractile testes are those with a marked cremasteric reflex. They can be seen in the scrotum when the child is warm and fully relaxed, but retract into the superficial inguinal pouch with the slightest provocation. They can usually be diagnosed clinically in the out-patient department as the testes can be brought to the bottom of the scrotum, without tension on the cord. Occasionally this cannot be demonstrated in the OPD and may require examination under anaesthesia. Retractile testes per se do not require surgical intervention as the weakening of the reflex with age and the increase in testicular size make retraction in latter life unlikely. These patients should be followed up annually, until after puberty, as some will go on to develop acquired cryptorchidism, often referred to as Ascending Testes. Of boys diagnosed at 5 yo with retractile testes 1/3 will descend, 1/3 will remain retractile and 1/3 will ascend or become an acquired undescended testis [124]. With growth the distance from the bottom of the scrotum to the external inguinal ring increases and the excessive cremasteric reflex may prevent the spermatic cord from lengthening with age. It is more common in boys whose retractile testes are diagnosed before 7 yo rather than after 7 yo. Acquired cryptorchidism has been reported as occurring in almost 50% of post-pubertal boys with spastic diplegia. The other form of acquired cryptorchidism is that which occurs after inguinal surgery and can be referred to as iatrogenic testicular ascent. This has been reported to occur in 1.2% of boys following inguinal herniotomy.

What is relevant from a clinical point of view is whether the undescended testicle is palpable or impalpable. A palpable undescended testicle can usually be dealt with at open surgery. Unilateral or bilateral impalpable testes may require further investigation and laparoscopic techniques (described below).

69.2.4 Incidence

A large population-based study by the John Radcliffe Hospital Cryptorchidism Study Group reported that in the 1980s the incidence at birth was 5.4%, which fell to 1.85% by 3 months [125]. Those testes that had not descended by 3 months of age were unlikely to do so spontaneously. This represents a doubling of the incidence of undescended testes in 3-month-old boys since Scorer's report in 1964 [126]. The frequency of undescended testes is higher in premature infants. Approximately 45% of infants weighing less that 2000gms at birth will have undescended testes, many will descend spontaneously such that at 3 months of age 7.7% have persistent cryptorchidism.

There is worldwide concordance in the prevalence of cryptorchidism with no geographical sparing. There is a peculiar peak incidence in the UK amongst children born in March/April and a trough in boys born between June and October [127]. Similar Spring peaks and summer troughs have been reported in Austria, Sweden and Hungary. Additional associations include other congenital anomalies, low birth weight, twins, pre-eclampsia and previous stillbirth. These associations may be due to placental insufficiency, intrauterine infection, maternal pituitary hypogonadism and *in-utero* oestrogen or anti-androgen exposure.

69.2.5 Diagnosis

69.2.5.1 History

The history is usually straightforward when the absence of testes is noted at delivery or at the routine 6-week check-up. Children with a unilateral undescended testis can usually be seen at a routine OPD appointment at or after 3 months of age, by which stage the majority of those testes that will descend spontaneously will have done so. One must beware the newborn male with bilateral impalpable undescended testes and these must be seen more urgently. A diagnosis of bilateral cryptorchidism in association with Hypospadias must

never be made on clinical grounds alone, as there is a very real possibility that these children may actually be over-androgenised females with Congenital Adrenal Hyperplasia (CAH), one form of which can be life-threatening if not treated.

69.2.5.2 Examination

When examining the scrotum a lot can be learned from inspection alone. With a relaxed patient in a warm environment both testes may be seen in the scrotum and observed to retract under the threat of palpation. Obvious scrotal asymmetry would suggest a unilateral undescended testis. The penis itself can be considered a "bio-assay" for testosterone and if a normal phallus is seen it is very suggestive that the developing penis was exposed to normal amounts of testosterone *in-utero*. Assessment of testicular size is helpful, especially in unilateral cryptorchidism, as there may be compensatory hypertrophy of a solitary testis; however this is not sufficient evidence that one would not actively look for the other testis. Testicular size can be measured by comparison to a Prader Orchidometer. In pre-pubertal boys the testes should be approximately equivalent to the size of the glans penis. When palpating for the 'impalpable' testis it is important to have a non-threatening approach and warm hands. Starting lateral to the superficial inguinal ring and 'milking' the contents of the inguinal canal towards the scrotum using the other hand to prevent retraction. Once located the testis is grasped between thumb and forefinger and under gentle traction an assessment is made of the distance into the scrotum that the testis can be drawn. If not palpable, remember to examine all potential sites (perineum, femoral, penile, other hemiscrotum) for an ectopic testis.

69.2.5.3 Investigation

Imaging investigations and biochemical tests are usually of little benefit in the pursuit of the impalpable testis particularly in the presence of a normally descended contralateral testis. The investigation of choice for an impalpable undescended testis is laparoscopy.

69.2.5.4 Pathological Changes in UDTs

Testes that remain out of the scrotum undergo tubular dysplasia, evident on Electron Microscopy at 6–12 months of age, light microscopic changes at 3–4 years, macroscopic testicular atrophy in school-aged children and irreversible azoospermia if still not in the scrotum at puberty. There is some evidence to suggest that cryptorchid testes that are higher in the line of descent have more significant reductions in fertility index (spermatagonia per seminiferous tubule) than testes that have progressed further or fully descended testes [128]. Furthermore there is evidence that the longer a testis spends in an undescended position the more significantly the fertility index is negatively affected [129]. As well as a greater reduction in germ cells the longer a testis is undescended Cortes et al. found that reduction in germ cells starts from 28th week of gestation suggesting that there is more at play here than merely testicular location [130].

69.2.6 Management

69.2.6.1 Medical

Hormonal manipulation of undescended testes enjoyed a brief flurry of interest with the use of two differing regimens. Patients received either Human Chorionic Gonadotropin (HCG) by intramuscular injection twice weekly for 6–8 weeks or intra-nasal Leutenising Hormone Releasing Hormone (LHRH) up to 6 times a day for 3–4 weeks. Randomised trials showed no difference in incidence of testicular descent compared to untreated boys. Where hormonal studies are particularly useful are in boys with bilateral cryptorchidism [131]. In this group of patients if there are no palpable testes, a HCG stimulation test may be undertaken to detect functioning testicular tissue. A positive test suggests the presence of testicular tissue, however a negative test does not obviate the need for laparoscopy to look for the gonads, as they may be present but abnormal/dysplastic. One fifth of those testes that descend with hormonal therapy reascend at a later date [132]. There is also some evidence of

testicular damage following HCG treatment and therefore hormonal treatment.

69.2.6.2 Surgical

Aims of Surgery

The purpose of orchidopexy is to locate the testis and place it in its normal environment. Testes are located in the scrotum so that they are 2–3° cooler than body temperature. This is possible because of the scrotal rugosity, which gives a large surface area relative to scrotal volume from which to lose heat, the absence of subcutaneous fat and a counter-current heat exchange mechanism—warm testicular arterial blood looses heat to the returning cooler blood of the pampiniform plexus of veins which surrounds it, with greater than 90% efficiency [133].

As well as achieving a cosmetically normal scrotum, placing the testis in the scrotum enables earlier detection of malignant transformation should it occur and may have some beneficial effect on fertility.

69.2.6.3 Palpable UDTs

The first successful orchidopexy was carried out by Thomas Annandale in Edinburgh in 1877 [134]. The surgical management of palpable undescended testes is reasonably straightforward with patients usually undergoing a single-stage, day-case open orchidopexy under general anaesthesia. Traditionally the testis is exposed via a groin crease incision but particularly for ascending testes some surgeons prefer a lateral scrotal margin incision or a trans-scrotal (Bianchi) approach with similar outcome results [135]. Whatever the approach the testis is identified, mobilized by dividing the gubernaculum, maximum length is obtained by separating and suture transfixing the associated patent processus vaginalis. The testis is delivered from within the tunica vaginalis and a Hydatid of Morgagni, if present, excised. The testis is then placed in the scrotum and secured. The most common method of securing is to place in an extra-Dartos or Sub-Dartos pouch where it is secured by co-apting the Dartos layer around the spermatic cord [136]. Whilst still commonly used I do not place sutures through the testicle to secure in the scrotum as I believe this to be unnecessary and have potential complications.

69.2.7 Impalpable Testis

Laparoscopy is the diagnostic test of choice for the impalpable testis. Open insertion of the umbilical port, CO_2 insufflation and a second port to manipulate the intestines are necessary [137]. Once visualized the vas must be followed throughout its full extent, as must the testicular vessels. There are a number of possible findings: (1) blind ending vas and vessels with no evident testis—so called 'vanishing testis'; (2) Normal or attenuated vas and vessels entering the inguinal canal through the internal ring—these patients require open surgical exploration of the inguinal canal with orchidopexy of a normal testis or more likely excision of a testicular remnant. The nubbin is excised as it provides no useful reproductive or endocrine function but retains its enhanced malignant potential. A single-stage orchidopexy, utilizing a pre-peritoneal or Jones approach is suitable for a normal sized-testis; (3) Good-sized testis within the peritoneal cavity that cannot be brought to the scrotum in a single stage—the surgical options for these patients are either a single stage microvascular transfer with the gonadal vessels being divided high near the renal vessels and anastamosed onto the inferior epigastric vessels or a two stage Fowler Stevens Orchidopexy. We favour the latter approach the basis for which is division of the gonadal vessels as a first stage; encouraging collateralisation of the remaining gonadal blood supply i.e. the cremasteric and vasal vessels. Followed 6 months later by the second stage, where the testis is mobilized on a pedicle of peritoneum that includes the vas and its now enhanced blood supply. This is brought through the abdominal wall medial to the inferior epigastric vessels (the Prentiss maneuver [138]) to reduce tension and placed in an extra-dartos scrotal pouch. Both of these stages can be performed as open operations, as originally described. However, we favor a laparoscopic approach for both. The first stage is an extension

of the diagnostic laparoscopy with the addition of simple dissection of the gonadal vessels prior to their ligation. The second stage requires laparoscopic mobilization of the testis and then the introduction of a 10 mm port through the scrotal wound through which the testis is drawn into the scrotum and secured in the usual manner. A large meta-analysis by Elyas et al. has demonstrated that a 2-stage Fowler-Stephens approach is marginally better than recent attempts to undertake a single-stage orchidopexy with division of testicular vessels [139], with no difference between the open and laparoscopic approaches.

69.2.8 Complications of Surgery

Fortunately post-operative complications are rare and include the usual culprits of wound infection and bleeding. Testicular ascent occurs but the rate varies in relation to the extent of mobilization needed such that it is <1% for testes that are in the superficial inguinal pouch pre-operatively but close to 30% for those testes managed with a 2-stage Fowler-Stevens approach. Injury to the vas and vessels is very uncommon but vasal injury may be underestimated. Animal studies have demonstrated vasal injury from simple handling. Intimal vasal injury may never be detected therefore extreme care must be taken when mobilizing the vas off the sac to protect and preserve its patency.

69.2.9 Outcome Following Surgery

69.2.9.1 Testicular Size and Position

Testes that have undergone orchidopexy are usually smaller than normal testes and in general the higher the position of the testis initially, the smaller the final volume. Approximately 85% of all testes remain in the scrotum long term, 3% undergo testicular atrophy and 12% retract to a higher position requiring further surgery.

69.2.9.2 Fertility

Undescended testes have an obvious implication for fertility and it is difficult to get an accurate measure of this as the most commonly used indicator is paternity which is clearly prone to error in the absence of genetic testing. Remember that 15–20% of married couples have difficulty conceiving and of these 1/4–1/3 are identifiable as being due to an abnormality in the prospective father. When looking at couples who have attempted to conceive a child in the preceding 12 months Lee et al. [140] found that compared with controls (93.2% successful) men with a history of unilateral undescended testis were 89.7% successful and those with a history of corrected bilateral cryptorchidism were 65.3% successful [141]

69.2.9.3 Semen Analysis

Semen analysis would be a more objective way of assessing the effect of cryptorchidism on fertility. Only 25% of men with a history of bilateral UDTs have normal sperm counts and more than 50% have azoospermia. Amongst men with a history of unilateral orchidopexy, 20—70% have subnormal and about 50% have normal sperm counts. These figures are based on men who underwent surgery more than 25 years ago at which time surgery was often delayed until later in childhood. Recent studies are more optimistic of a benefit for testicular function with earlier orchidopexy such that 100% of those men whose orchidopexy was carried out at less than 4 years of age had normal semen analysis. The implications for fertility are equally optimistic with a report by McAleer who developed a fertility index based on the number of spermatagonia per cross-section of tubule in 50 tubules on histological examination of testicular biopsies [129]. When compared with normal controls patients whose orchidopexies were carried out at less than 1 year of age had a normal fertility index while those >5 years old had a decreased fertility index.

69.2.10 Malignancy

The absolute risk of developing malignancy in an undescended testis is hard to quantify. The majority does so in the third and fourth decades of life and 60% of the tumours are seminomas. The

frequency for testicular malignancy in the population in general is 0.07%. The relative risk of developing cancer in an undescended testis has been calculated at between 5 and 10 times higher. There is no evidence of an association between likelihood of developing malignancy and initial location of testis. More importantly, there is no evidence of a reduction in malignant transformation with earlier surgery. Given the long lag-time of 30- to 40 years it may be some time yet before we are in a position to ascertain the impact of orchidopexy on those less than 2 years old on the subsequent development of malignancy.

69.3 Acute Scrotal Pathology

69.3.1 Introduction

A child who presents with an acute scrotum is the most urgent of urological emergencies. A torted testis may show signs of atrophy after 6 h and viability is compromised with a longer history. Surgery can be avoided if a confident diagnosis of torsion of an appendix testis, idiopathic scrotal oedema or epididymo-orchitis can be made but if in doubt—explore.

69.3.2 Torsion of Appendix Testis

Torsion of a testicular appendage almost always affects the appendix testis or Hydatid Cyst of Morgagni, a remnant of the cranial end of the Müllerian duct, present in 90% of boys. Other appendages include the appendix epididymis, the vas aberrans of Haller and the Paradidymis or Organ of Giraldes, all remnants of the Wolffian duct [142]. The peak incidence is between 10 and 12 years of age. The appendix testis is pedunculated and peri-pubertally may increase in size in response to hormonal stimulation. The pain is typically more gradual in onset, of longer duration and less severe than that of testicular torsion. If seen early in their clinical course it may be possible to distinguish between these two conditions. Torsion of the appendix testis has discrete localized tenderness, a palpable nodule and visible 'blue dot' of the infarcted appendix testis. With a history of longer duration it can be impossible to distinguish from testicular torsion and surgical exploration is imperative.

The diagnosis is clinical, substantiated with Doppler Ultrasonography if appropriate. Where doubt exists it is prudent and more rapid to explore the scrotum. Where a diagnosis of a torted appendix testis has been made the treatment options can be discussed. The choices are symptomatic management using oral analgesia and anti-inflammatory drugs. The alternative is surgical exploration under general anaesthesia with excision of the torted nodule, that is sent for histological examination. Contra-lateral scrotal exploration is not indicated [143]. Surgery is generally associated with a more rapid resolution of the patient's symptoms.

69.3.3 Testicular Torsion

The peak incidence occurs between the ages of 14 and 16 years and accounts for 90% of acutely presenting scrotal symptoms in post-pubertal boys. The annual incidence has been estimated at approximately 1 in 4000 males below 25 years of age [144]. The left side is more commonly affected than the right. Exercise, trauma, cold weather and cryptorchidism are possible predisposing factors. Testicular torsion takes two main forms, intravaginal and extravaginal.

69.3.4 Intravaginal Torsion

Intravaginal torsion is the more common, occurring at any age. It occurs because of a high attachment of the tunica vaginalis to the cord resulting in what is often referred to as a 'bell-clapper' testis. This allows the testis to rotate around the axis of the spermatic cord inside the tunica vaginalis. The testis may rotate internally or externally through one or more complete revolutions i.e. 360° or 720°. Manual detorsion is not recommended.

Numerous studies support prompt surgical exploration and detorsion. There is evidence that

if torted for 6–8 h a testis will show signs of atrophy and after >8–10 h ischaemic necrosis is almost inevitable. However all acute scrotums should be explored given the often inaccurate nature of the duration of symptoms and the occasional occurrence of intermittent torsion where testes are said to have twisted and untwisted spontaneously.

Less than 50% of boys with testicular torsion present with a classic history of sudden onset of severe scrotal/testicular pain and swelling associated with a high riding, tender testis on physical examination. Because of the pathways of testicular innervation the initial pain is often referred to the groin or lower abdomen. The association of lower abdominal pain and vomiting can be misleading causing a misdiagnosis of acute appendicitis if the scrotum is not examined.

69.3.5 Extravaginal Torsion

Extravaginal torsion, also referred to as intrauterine or neonatal torsion is thought to occur pre-natally or during birth. The anatomical arrangement is normal but a lack of fixation between the tunica vaginalis and the scrotal/dartos tissues permits the testicle and tunica to rotate about the spermatic cord. Typically these patients present in the early neonatal period with an indurated and discoloured scrotum that is not tender. Published reports would suggest that testicular salvage is not possible is this setting. The anatomical arrangements are such that contra-lateral torsion is extremely unlikely. Rare cases of synchronous or metachronous extravaginal torsion have been reported. Our current policy is to not explore these testes immediately but to proceed to an elective exploration as soon as it can be arranged. This provides an opportunity to fix the contra-lateral side, remove the dead testis and exclude the rare possibility of a congenital testicular tumour.

The management of testicular torsion is based on immediate surgical exploration. The scrotum may be entered via a transverse scrotal crease incision over the affected side or through a midline sagittal incision in the raphe. Once exposed the testis and spermatic cord is untwisted and assessed for viability based on the prompt return of perfusion as evidenced by a change in colour or bleeding of oxygenated blood when the tunica albuginea is incised. In prepubertal boys there is no contraindication to detorting an apparently non-viable testis. However, in post-pubertal boys there is evidence of impaired fertility following testicular torsion. It may be that detorting and preserving a testis of dubious viability predisposes to the production of anti-sperm antibodies (there are no sperm present pre-pubertally) and may explain the reduced sperm quality, up to 50%, in later life. It is our policy to detort all testes and give the benefit of the doubt to the testis where possible. Once detorted and deemed viable the testis should be fixed, the contralateral side explored and prophylactically fixed to reduce the likelihood of torsion. There is much debate as to the method of fixation with some authors advocating placement in an extradartos pouch without suture fixation and others who support intra vaginal 3-point fixation with a non-absorbable suture. We employ the latter approach. All patients must be warned that testicular fixation makes recurrent testicular torsion very unlikely but not impossible and they should take the recurrence of sudden and severe testicular/scrotal pain seriously, seeking urgent medical attention.

69.3.6 Idiopathic Scrotal Oedema

Sometimes this idiopathic and enigmatic condition represents a cutaneous infection spreading forward from the anus, others that it is an allergic phenomenon and still others that it perhaps results from an insect bite. It usually presents with an asymptomatic patient whose parents have noticed a marked oedema and erythema of the scrotum. Typically the erythema involves one hemi-scrotum, but may be bilateral, extends beyond the confines of the scrotum up onto the anterior abdominal wall or back towards the anal verge. The usual age range is 5–6 years but it has been seen in up to 10 year olds. It is often confused with testicular torsion or cellulitis. The

absence of testicular tenderness, pyrexia and malaise mitigate against these diagnoses. Treatment usually consists of reassurance but antibiotics and anti-histamines, of no proven benefit, have been advocated in the past. It resolves in 1–2 days and recurrence is unusual.

69.3.7 Epididymitis

Epididymitis or epididymo-orchitis, is the consequence of the retrograde passage of urine along the patent vas deferens. Because patency of the vas is critical to its aetiology it tends to occur either in early infancy (<6 months) or in adolescence as the vas is generally occluded in the intervening years becoming patent again with the onset of puberty. Though usually associated with reflux of infected urine it may occur with vasal reflux of sterile urine usually in patients with a predisposing anatomical abnormality such as ectopic ureter or persistent Müllerian remnant. All patients with epididymo-orchitis should at least undergo ultrasound examination of the urinary tract; additionally infants should have a micturating cystourethrogram.

As testicular torsion is significantly more common, a clinical diagnosis of epididymo-orchitis must be reached very carefully and ideally supported by evidence of a urinary tract infection; up to 50% of patients will have fever and pyuria, urinary tract abnormality or sonographic evidence that the testis has not torted. Management is based on administration of analgesia and antibiotics, usually intravenous Gentamicin or Ciproflaxacin, until the results of urine culture have been. If epididymo-orchitis is found at surgical exploration it is customary to take a swab or fine-needle aspirate from the epididymis for culture and sensitivity.

69.3.8 Orchitis

True orchitis is very rare but may occur in association with Mumps or septicaemia. Mumps orchitis, unilateral in 80% of patients, is extremely rare prior to puberty. In orchitis the testis tends to be larger and harder than in epididymitis. Approximately one third of patients will develop testicular atrophy and have an increased risk of infertility and malignancy.

69.3.9 Other

69.3.9.1 Hernia/Hydrocoele

Incarcerated inguino-scrotal herniae or a hydrocoeles may present as an acute scrotum but an experienced clinician can usually easily distinguish these conditions.

69.3.9.2 Malignancy

Testicular malignancy is rare but it may be primary as in adenocarcinoma, seminoma or secondary as in the malignant infiltration seen in leukemia.

69.3.9.3 Henoch-Schönlein Purpura

This vasculitic condition typically presents with a purpuric rash that extends from the buttocks and lower limbs to the remainder of the body. In addition to scrotal discolouration it occasionally affects the testis itself causing tenderness. A history of rash preceding the testicular symptoms may help with the diagnosis. Treatment is generally supportive though some paediatricians advocate steroid therapy.

69.3.10 Summary

As a general rule unless the diagnosis of testicular torsion can be confidently and completely excluded urgent surgical exploration should be undertaken in all cases. Investigations such as Doppler Ultrasonography and Isotope Scintiggraphy should not delay prompt exploration and rather are usually used to provide reassurance where testicular torsion has been clinically excluded.

69.4 Varicocele

A varicocele is an abnormal dilatation of the testicular vein and pampiniform plexus within the spermatic cord and scrotum leading to the classic

description of "a bag of worms". It is rarely seen before 10 years of age but approximates 15% by late adolescence, similar to the rate seen in adults. They are typically asymptomatic, presenting as an incidental finding, although occasionally associated with vague symptoms of 'heavy scrotum' or 'dragging pain'. They are more commonly found (40%) in men with primary infertility [145] and it is the implications for fertility that cause the greatest confusion regarding treatment.

Varicoeles are graded clinically into one of three grades:

- Grade 1—small and only palpable with Valsalva
- Grade 2—easily paplable when patient examined upright
- Grade 3—visible when patient upright

Patients must be examined when both erect and supine. Varicoceles that do not resolve when the patient is recumbent and/or right-sided varicoceles are more likely to be secondary to intra-abdominal pathology and should prompt an abdominal examination and further imaging. More than 90% of varicoceles are on the left side. There are a number of possible reasons for this—the longer course of the left gonadal vein, valvular incompetence of the gonadal vein, the left vein drains into the smaller left renal vein than the right which joins the IVC, the 'nutcracker effect' where the left gonadal vein is compressed between the superior mesenteric artery and the aorta [146].

During physical examination testicular volume, using an orchidometer or an ultrasound, and testicular consistency must be assessed. The role of ultrasound is controversial. It is highly accurate, repeatable and non-invasive and more accurate than orchidometer at detecting volume differentials [146, 147]. However the cost implications of implementing Diamond et al.'s suggestion for annual surveillance ultrasonography would be somewhere between $364 and $795 million per annum [148]. For adolescent boys with equal sized testes at time of diagnosis of varicocele 25% will have demonstrable testicular growth arrest, regardless of the grade of their varicocele [149]. For those patients with right sided or non-reducing varicoceles a combined abdominal and scrotal ultrasound may yield additional benefit however for others regular self-examination and annual review with clinical examination and orchidometry makes the most sense.

Biochemical tests reported in the literature but rarely used include Gonadtrophin releasing Hormone stimulation assay, serum Inhibin levels and FSH stimulation test [146]. Semen analysis on the other hand is of immense practical use in adults and late adolescence and possible in early adolescence, however there no established norms for early adolescence [150].

The clinical significance of varicocele lies in its relation to male infertility after all 40% of men with primary infertility have a varicocele yet only 20% of men with a varicocele are infertile [150]. There are a number of theoretical pathophysiological mechanisms by which varicoceles amy impact fertility—poor venous drainage with resultant interference with counter-current heat exchange and relative hyperthermia causing oxidative stress impairing spermatogenesis [150], endocrine disruption with reduction in intratesticular testosterone and reduced Sertoli cell response to FSH [146].

Deciding on whom to surgically intervene continues to remain controversial. The American Urological Association [151] recommends treatment for:

- Male partners in a couple attempting conception where the varicocele is palpable, they have documented infertility, the female has normal fertility or potentially correctable infertility and there are demonstrated abnormalities on semen analysis.
- Adult males with a palpable varicocele and abnormal semen analysis but are not currently attempting to conceive.
- Young men who have a varicocele and normal semen analyses should be followed with annual semen analysis.
- Adolescents who have a varicocele and objective evidence of reduced ipsilateral testicular size

should be offered repair. Those without testicular size discrepancy should be followed annually with assessment of size and semen quality.

In adults with fertility issues and poor semen analysis the decision to intervene is relatively simple however in adolescents there is still significant uncertainty of the indications for and outcome of surgery. It is the most common correctable cause of male infertility with improvement in semen qualities, especially motility, in 66% and 40% of female partners conceiving [146]. That said a Cochrane review by Evers et al. found no significant impact on fertility where the treated varicocele was the only abnormality found in either partner [152].

In adolescents a testicular discrepancy of 20% between sides is considered an indication for surgery and there are numerous studies demonstrating catch-up growth in 85% of those undergoing surgery compared with 30% when observed [150]. Given that surgery alters venous and lymphatic drainage it has been postulated that the reduction in size discrepancy may reflect testicular oedema rather than true growth [150].

Once a decision to intervene has been made next is a decision about the best approach: whether it is to be embolization by an interventional radiologist [153] or surgery. There are a number of surgical approaches—subinguinal (Marmar), inguinal (Ivanissevich) and retroperitoneal (Palomo) that may be augmented by the use of microsurgical instruments [154] in the inguinal and distal approach or laparoscopic for the retroperitoneal (Table 69.1 (A detailed discussion of the various surgical approaches is beyond the scope of this text).

Table 69.1 Comparison of surgical approaches [158]

Approach	Failure rate	Hydrocele rate
Embolization	4.3% (1.9–9.3%)	
Inguinal	15.6% (3.5–17.5%)	7.5% (4.3–17.5%)
Microscopic	2% (1.4–14.8%)	0.3% (0–0.7%)
Retroperitoneal	12.5% (7.3–15.5%)	7.6% (4.6–9%)
Laparoscopic	11% (4–26.5%)	7.5% (1.7–12.7%)

Once a decision to operate has been made and a choice of approach made all that remains is the timing and for those in whom infertility is the indication operating in those with <1 year history of infertility does not result in an increased pregnancy rate above untreated males and given the rate of spontaneous resolution of infertility in couples with a history of less than 2 years then it has been suggested to reserve surgical intervention for those with more than 2 years of fertility struggles [155].

69.5 Epididymal Cyst/ Spermatocele

Epididymal cysts are benign cystic lesions of the epididymis that contain serous fluid in pre-pubertal boys and spermatoceles which are seen post-pubertally contain sperm. These are benign lesions that for the most part (80%) are asymptomatic and incidental pick-ups [156]. The remaining 20% were either discovered on self examination or rarely presented clinically with acute torsion. The incidence of epididymal cysts increases over time from 3.3% in boys <5 yo, 4.2% in 5–10 yo, 20.1% in 10–15 yo and 35% in boys >15 yo. Surgical intervention is generally reserved for large cysts.

For a more detailed review of other intrascrotal lesions the reader is referred to Rubenstein et al.*'s* review article [157].

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Part X

Outcomes in Newborn Surgery

Long-Term Outcomes in Neonatal Surgery

70

Risto J. Rintala and Mikko P. Pakarinen

Abstract

Paediatric surgery and neonatal surgery as a part of it started to develop to an independent surgical speciality after World War II simultaneously in many Western countries. The first paediatric intensive care units and neonatal surgical units were opened in 1950s. These factors lead to rapid change in the mortality of patients with congenital malformations. Specialised paediatric surgeons and, surgical wards and operation theatres dedicated to care for children enabled survival of increasing numbers of patients with congenital defects and acquired neonatal surgical problems.

Keywords

Neonatal surgery • Paediatric surgery • Long term outcomes • Quality of life

70.1 Introduction

Paediatric surgery and neonatal surgery as a part of it started to develop to an independent surgical speciality after World War II simultaneously in many Western countries. The first paediatric intensive care units and neonatal surgical units were opened in 1950s. These factors lead to rapid change in the mortality of patients with congenital malformations. Specialised paediatric surgeons and, surgical wards and operation theatres dedicated to care for children enabled survival of increasing numbers of patients with congenital defects and acquired neonatal surgical problems. During the last 50 years the mortality of patients with congenital defects, also those with malformation complexes has continued to decrease (Figs. 70.1 and 70.2). This development is due to improved neonatology and paediatric intensive care and especially due to improved treatment possibilities of congenital cardiac defects. The downside of decreased mortality is that a significant percentage of survivors today have permanent morbidities and long-term handicaps.

Until recently there has been too little information about long-term consequences of repaired congenital defects or acquired neonatal surgical problems. For paediatric surgeons the end point and final outcome measure is the functional outcome in an adult patient. Recent research has indi-

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_70

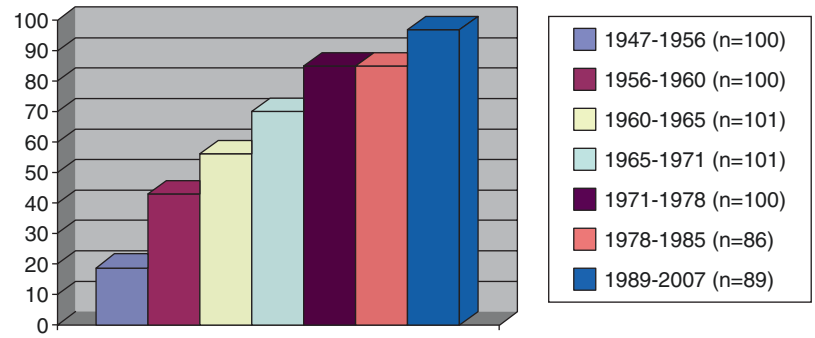

Fig. 70.1 Survival of 677 oesophageal atresia patients undergoing surgery at Children's Hospital, University of Helsinki from 1947 to 2007

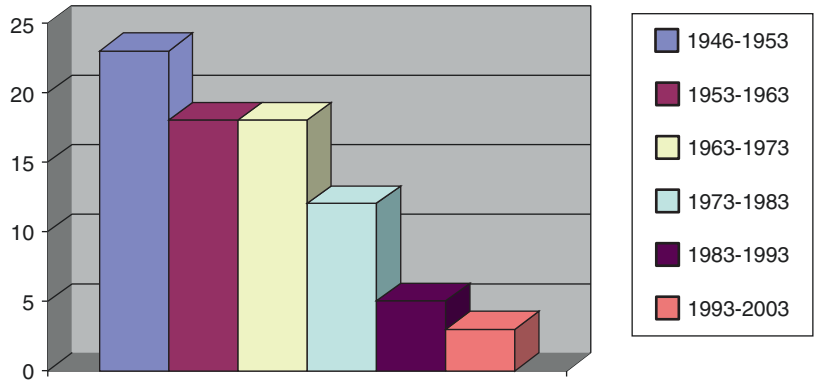

Fig. 70.2 Overall mortality of patients with anorectal malformations at Children's Hospital, University of Helsinki from 1946 to 2003

cated that a significant proportion of patients suffer from abnormal organ functions during childhood and many of these abnormalities are carried on to adulthood. These have often a significant impact on quality of life. Long-term functional results and quality of life are today as important outcome measures as early mortality and morbidity.

70.2 Rationale of Long-Term Follow-Up Programmes

There are several involved parties that are concerned on long-term outcomes of neonatal surgery. The patients' parents need to get a realistic picture on what is going to happen to their newborn child requiring surgery. The information has to be as accurate as possible without giving inappropriately positive expectations concerning functional outcomes. The parents tolerate well bad news on future problems of the patient as long as the given information is honest and consistent.

The patient himself/herself needs to get reliable information, as early as this can be given, of potential problems during later life. The information needs to include clarification of management modalities available to treat these problems. The parents may adopt to the handicaps of the patient and may not consider these as major functional problems. On the other hand, the patients may experience these handicaps as major factors that limits their social activities. For example even minor soiling in a teenager with an anorectal malformation may segregate the patient from many social activities such as sports and overnight visits to friends although the parents may consider that the patient's continence has greatly improved since earlier childhood.

The surgical team caring for newborn patients needs long-term follow-up data to guide clinical practice. In many neonatal surgical conditions the final functional outcome is not evident until the child has reached adolescence or adulthood. Longitudinal follow-up studies are required to determine the natural history of a neonatal

surgical condition. Profound knowledge of possible complications that may develop during the development period of a neonatal surgical patient may guide primary treatment and definitely modifies the follow-up of the patient. For example, the recent finding of increased incidence of thyroid cancer in adult patients with Hirschsprung's disease [1] suggests that screening of thyroid cancer, especially medullary thyroid cancer, may be indicated in all patients with Hirschsprung's disease.

Health care administration need to be aware of the consequences and costs of neonatal surgery. Although the numbers are not high, the management costs of a newborn surgical patient are very high. There is a need for highly specialised intensive care facilities. In many cases the intensive care period may be lengthened significantly, e.g. patients with severe congenital diaphragmatic hernia may require weeks of intensive care. Patients with multiple malformations, especially those with combined cardiac and oesophageal anomalies may remain longer periods in the intensive care unit. On the other hand, the mortality of practically all neonatal surgical conditions has decreased significantly during the last decades. This implicates that more sick children survive with more handicaps. It is likely that these surviving children with serious primary conditions have more needs for medical care during their growth period than those with less stormy start. For planning of resource expenditure of long-term care of paediatric surgical patients, it is essential that data on long-term functional outcome and morbidities is available.

70.3 How to Analyse Long-Term Outcomes

The main problem in analysing long-term outcomes on paediatric surgical patients is the lack of standardization of surgical procedures. Although paediatric surgical conditions are usually well defined and classified, there are no standardization of procedures used to repair congenital or acquired defects in neonates. It is likely that the type of surgical procedure plays a significant role but this is very difficult to demonstrate.

The length of the follow-up period is also a crucial factor. The most valid endpoint is the outcome beyond childhood, at maturity. There is, however, paucity of long-term follow-up data in adults with congenital defects, therefore, short-term studies, often with variable age ranges of patients, have been used as measures of long-term outcome. This kind of studies have often had significant methodological problems. There has commonly been a lack of a healthy control population. Healthy controls with similar age, sex and municipality distribution as the patients are crucial for reliable outcome analysis.

Long-term outcome data, in terms of function and quality of life, is usually based on clinical history and examination. A major problem is the validity and agreement of the information attained from children and parents. Reliable data can be collected only from older children. The parents may not be able to provide truly reliable functional data for several reasons. They may not want to report unfavorable results to a surgeon who has been responsible for the treatment of their child. The parents may also ignore minor and moderate functional defects in a child who has had a congenital problem from birth or, in the case of smaller children, may consider them to be part of normal functional maturation.

The low incidence of neonatal surgical conditions poses a significant problems for outcome analysis. Institutional series are commonly too small to allow reliable comparisons between different management modalities. Pooling data from multiple centres could be a powerful tool also for long-term outcome studies but there is an increased opportunity for bias. Standardized management and follow-up protocols are very difficult to set up and long-term outcome studies commonly require many years of follow-up that is very difficult to organize in a multi-centre setting.

The study design in the evaluation of long-term outcomes is inherently problematic. Randomized controlled trials with enough power are usually unavailable for long-term outcome studies; the patients series are too small and there are to many confounding factors such as variable

surgical skills and techniques, inhomogeneous patient material and problems in recruiting patients for follow-up visit/examinations. Observational studies are more commonly used for analysis of long-term outcomes. Observational studies can be performed prospectively, retrospectively or as a cross-sectional study. Prospective matched, controlled cohort studies are powerful in providing information on natural history of a congenital defect or disease. Case control studies are useful for cross-sectional studies e.g. gastrointestinal morbidity in adult oesophageal atresia patients. The critical point in case control studies is the matching of controls [2].

Recently, measures to assess the functional status and quality of life have become widely available also for children. These instruments are designed to measure health related quality of life (HRQoL) and are today validated for many languages and cultural backgrounds. Quality of life instruments can usually be divided in two categories: generic instruments that assess overall HRQoL and disease specific instruments that are validated and available for patients with for example renal diseases, gastrointestinal disease etc. A typical generic HRQoL instrument is SF-36 [3] that has 36 items and assess seven domains. SF-36 is not validated for children under 16 years of age, therefore, other instruments need to be used. Of the commonly used paediatric HRQoL generic instruments CHQ (Child Health Questionnaire) [2] includes 87 items and 11 dimensions, and PedsQL (paediatric Quality of Life Inventory) [4] that is a very flexible and easy to use tool has 23 items in four domains. Both of these come in several forms for different age groups and also for parents/caregivers. A typical disease specific instrument is GIQLI (gastrointestinal quality of life index) that has 36 items in five domains [5].

70.4 General Long-Term Consequences of Neonatal Surgery and Anaesthesia

There is very little published data concerning overall long-term effects of neonatal surgical procedures and anaesthesia. More data is available of the effects of prematurity on the incidence of disabilities later in life. Brain development is particularly vulnerable during the second and third trimesters of pregnancy. Very low birth weight (VLBW, birth weight 500–1500 g) infants have a high risk for hypoxic brain injury and intraventricular haemorrhage that are frequently associated with long-term neurodevelopmental sequelae [6]. Although the mortality of these patients has decreased during the last 20 years, the incidence of cerebral palsy has increased significantly [7]. There is an inverse correlation between the incidence of neurological damage and gestational age. Overall, 20–25% of children born with a birth weight under 800 g have at least one major disability [7].

Many studies have suggested that the prevalence of children with neurological disabilities has increased because of better survival of VLBW infants. The main problem in the assessment of neurological outcome is that the abnormalities may not become fully manifest until school age. In a follow-up study of children born at 25 weeks or earlier many, who showed no disability at the age of 30 months, demonstrated mild to moderate disabilities at the age of 6 years. The overall prevalence of neurodevelopmental disabilities in this group of extremely low birth weight children was between 90–100% depending on the gestational age [8].

Recent findings in neonatal rodents have revealed that many commonly used paediatric anaesthetic agents and sedatives are neurotoxic. Excessive neuronal apoptosis has been found to develop in rat pups immediately after exposure of standard anaesthetics [9]. The apoptosis has affected several regions of the developing brain including hippocampus and cerebral cortex. In the experimental animals the detected apoptotic effect was significant also at physiological and behavioural levels persisting into adulthood. It is controversial whether the apoptosis was caused by derangements of physiological homeostasis secondary to anaesthesia or by the direct effect of anaesthetic agents. These findings in experimental animals have raised concerns regarding safety of anaesthesia and surgical procedures in immature infants [10]. Epidemiological studies in human infants have yielded conflicting findings, some studies have suggested an association

between neonatal anaesthetic exposure and later learning or behavioural problems [11], others have not shown any association [12].

The long-term neurodevelopmental effects of surgery early in life has been studied in premature infants who have developed necrotising enterocolitis. In a large meta-analysis concerning 7843 infants with necrotizing enterocolitis the median follow-up was 20 months [13]. Necrotizing enterocolitis was associated with significantly worse neurodevelopmental outcome than prematurity alone. Overall, 45% of infants with necrotizing enterocolitis were neurodevelopmentally impaired. Moreover, the need for surgery increased the risk of neurological impairment. Another study concerning surgically treated patients with necrotizing enterocolitis suggested that patients who initially underwent enterostomy formation had a worse neurodevelopmental outcome than those with primary anastomosis despite comparable severity of illness [14].

It is clear that a neonatal infant requiring surgical management is exposed to numerous adverse factors related to anaesthesia and surgical stress that can have a significant neurodevelopmental impact in future life. The effect of these factors have been demonstrated in premature infants, especially in those suffering from necrotizing enterocolitis, who are extremely ill and more vulnerable to central nervous system injuries than full-term infants. On the other hand, it is obvious that these adverse factors affect also full term surgical infants, although the long-term impact has largely not been investigated. For example, surviving infants with critical congenital diaphragmatic hernia who were treated with extracorporeal membrane oxygenation have a high incidence of developmental delay and central nervous system abnormalities [15]. Developmental delay occurs also in patients not treated with ECMO but ECMO is a very strong risk factor for adverse neurocognitive and psychomotor outcome [16].

The effect of neonatal surgery on cognitive and psychological development has been addressed only in a few studies. Most studies concern patients who have undergone neonatal correction of cardiac malformations, resulting in cyanosis, such as transposition of great arteries by arterial switch in cardiopulmonary by-pass [17, 18]. These studies have shown that these patients have lower general intelligence, more motor impairments and behavioural problems than healthy children. Risk factors for cognitive problems were the duration of operation and postoperative complications.

Ludman et al. [19, 20] studied non-cardiac neonatal surgical patients one and 3 years after surgery comparing the cognitive and developmental progress of the patients with those of healthy infants. At 1 year the surgical infants performed within normal range but less well than the controls in most areas of development. At 3 years the cognitive functioning of children whose condition resolved during first months of life was similar to the controls. Those requiring further treatment and surgery functioned at lower levels than controls. The number of operations under general anaesthesia was most strongly associated with poorer outcome.

70.5 Factors that Influence the Long-Term Outcome

70.5.1 The Type of the Malformation/ Condition

The severity of the defect that is repaired in the neonatal period has a significant impact on long-term outcome. Benign conditions presenting during the neonatal period such as inguinal hernia and hypertrophic pyloric stenosis are successfully repaired with simple procedures with few complications. The long-term outcome of these conditions is usually excellent. Late complications of inguinal hernia repair include recurrence, testicular ascent and atrophy and damage to vas deferens or Fallopian tubes. These complications are uncommon but occur more frequently following neonatal repair [21] and in patients with incarcerated inguinal hernia [22]. Late surgical consequences of pyloromyotomy for hypertrophic pyloric stenosis are rare. Adhesive bowel obstructions are very uncommon as are significant dyspeptic symptoms [23, 24]. Probably the most important long term risk is inheritance; the risk of

offspring of patients to inherit the disease is 20% of sons and 7% of daughters of a female proband and 5% of sons and 2.5% of daughters of s male proband [25].

The long-term outcome of defects that are life-threatening in the newborn period is influenced by severity of the anatomy, success of the anatomic reconstruction and occurrence of operative complications. Associated anomalies have a significant impact on the outcome, also. There is, however, scarcity of long-term follow-up data of many neonatal surgical conditions. In the following section examples of neonatal surgical conditions with recent consistent long-term follow-up data are considered, illustrating the factors that are involved in the outcome, especially beyond childhood.

70.5.1.1 Oesophageal Atresia

Patients with oesophageal atresia have multiple long-term consequences that are carried to adult life. One important consequence is the inherent abnormality of the oesophagus in these patients. No matter how perfect the original repair is there will always be a significant degree of oesophageal dysmotility [26]. The dysmotility is intensified in patients that have had anastomotic complications or long gap atresia. The dysmotility is associated with the incidence of epithelial metaplasia that predisposes to oesophageal malignancy [26]. Cases of oesophageal cancer in relatively young patients with repaired oesophageal atresia have been reported during the last decades [27, 28]. The dysmotility is also associated with a significant incidence of oesophageal symptoms. Symptoms of gastro-oesophageal reflux occur on average in 45% of adult patients with repaired oesophageal atresia [26, 29–31] and dysphagia in up to 85% of the patients [26, 32].

Thoracic deformities and scoliosis occur in a significant percentage of adults patients with repaired oesophageal atresia. Clinical and radiological scoliosis has been reported in more than half of patients [33]. The risk factors for developing scoliosis are thoracotomy-induced rib fusions and occurrence of associated malformations. Chest wall and shoulder asymmetries are also common occurring in 30–80% of patients [33, 34] and are associated with rib fusions and paralysis of serratus anterior and latissimus dorsi muscles.

Some of the associated defects in oesophageal atresia patients may go undetected during infancy and early childhood. In a recent report on adults with repaired oesophageal atresia 45% had vertebral anomalies that were detected at adult age [33]. Cervical spine was most commonly affected (38% of patients), many of these abnormalities were Klippel-Feil type of vertebral fusions. The radiographs obtained during the primary surgical care had revealed vertebral anomalies in only 3% of the patients. The high incidence of undetected cervical spinal anomalies is a significant and worrying finding as fused cervical vertebrae may later in life result in cervical instability and spinal stenosis. Cervical instability is associated with increased risk of spinal cord injury [35].

The overall quality of life of oesophageal atresia has been reported to be comparable with healthy peers [36, 37]. However, when disease-specific quality of life scores have been used (GIQLI: gastrointestinal quality of life; RSRQLI: respiratory quality of life), oesophageal atresia patients have obtained significantly lower scores than healthy controls [38]. Age and occurrence of associated malformations predicted poor gastrointestinal quality of life and occurrence of associated anomalies and tracheomalacia poor respiratory quality of life.

70.5.1.2 Hirschsprung's Disease

There are conflicting data regarding long-term outcome of surgery for Hirschsprung's disease. A traditional assumption has been that a great majority of patients gain more or less normal bowel function at least beyond childhood. This widely held view has been strongly challenged by several recent reports, where the follow-up has been extended to late childhood or adult age [39–43]. The reasons for this disparity remains somewhat unclear. In some older reports the data concerning patients' bowel function was retrospectively retrieved from hospital notes, that may underestimate problems in bowel function [41]. There is also an inherent bias when telephone and

letter inquiries without structured questionnaires are used. Some more recent studies have used structured scoring systems that are based on questionnaires validated by healthy age- and sex-matched controls [43]. A common finding in these studies has been that the scores of Hirschsprung's disease patients are significantly lower than those of the controls.

It is commonly believed that bowel function in patients with operated Hirschsprung's disease improves with age. This is confirmed by most studies [39, 44, 45]. The critical age for final improvement is puberty [44]. Most reports describing outcome in adults or adolescents show few limitations in social functioning, occupation or sport activities despite overall reduced continence scores when compared with healthy controls [43, 44, 46]. In adults with operated Hirschsprung's disease, the gastrointestinal quality of life as measured with the GIQLI score, has been found to be marginally lower than in healthy controls [43]. The questions that gave the lowest scores were disease specific questions that were related to anorectal function. A worrying finding in this study was, however, that the only finding that correlated with poor bowel function was age. This suggests that the bowel control in patients with Hirschsprung's disease deteriorates by growing age.

A recent finding in patients with Hirschsprung's disease is that the incidence of thyroid cancer, especially medullary thyroid cancer, is significantly increased [47]. The cancer cases are often related to mutations in RET proto-ocogene in chromosome 10 and occurrence of associated MEN 2A syndrome [48]. The absence of MEN 2A does not rule out the possibility of medullary thyroid cancer, therefore, clinical and genetic screening of adults with operated Hirschsprung's disease need to be considered.

70.5.1.3 Anorectal Malformations

Anorectal malformations form an extremely diverse group of anomalies where the diversity of severity ranges between a simple and mild displacement of the anus that have little or no early or long-term consequences and extremely severe caudal regression syndromes that are often incompatible with life. Therefore, overall statements concerning long-term outcomes are not possible.

There are still very few reports on outcomes of ARM in adults. Most adult series include patients that have been operated by traditional methods, such as abdominoperineal or sacro-abdomino- and sacroperineal pull-throughs [49, 50]. There are no reports on adult outcomes following posterior sagittal anorectoplasty, the gold standard of ARM repair today.

Another problem is lack of uniformly accepted standardized methods to evaluate outcomes. Reliable comparison between reports is difficult, therefore, the outcomes can be expressed only in very general terms. Moreover, the criteria used to evaluate long-term outcome are variable and mostly designed for high anomalies [51–53]. The most recent assessment criteria are based on a consensus meeting in Krickenbeck 2005 [54]. These have, however, not gained overall acceptance. The likely reason for this is that the Krickenbeck criteria are mainly descriptive and relatively crude, and difficult to use in comparing the results.

In high anomalies a good result means usually socially acceptable continence which is not equivalent to normal anal function. A patient with a high anomaly and a good functional result rarely has normal bowel function and although socially continent may have some degree of smearing or soiling associated with physical straining or loose stools. Although many patients with low malformations have normal bowel function at long term, a method designed to assess long term outcome in high anomalies may underestimate minor defects in bowel function that are not uncommon in these patients,. These defects may become significant when the patient leads a life of an independent adult individual.

There are several prognostic factors that have impact on the long-term outcome. The level of the anomaly is an important prognostic factor in terms of bowel function. Males with a bladder neck fistula and females with a high confluence cloaca [55] have significantly poorer prognosis than patients with a lower urogenital connection

[56]. The obvious cause of worse prognosis in very high anomalies is the more marked hypoplasia of the voluntary sphincter muscles, especially the infralevator part the muscles [55].

The presence of severe sacral abnormalities is associated with hypoplastic sphincters. If more than two sacral vertebrae are missing or if the patient has other major sacral deformities, such as hemivertebrae and vertebral fusions the functional outcome is worse than in patients with normal sacrum or lesser degree of sacral maldevelopment [55, 56].

The role of the internal sphincter in anorectal malformations is a topic which has been debated for decades. The functioning internal sphincter can be demonstrated by the presence of rectoanal relaxation reflex at anorectal manometry. Most patients with a low anomaly have positive rectoanal reflex [57, 58]. In patients with high malformations rectoanal relaxation reflex has traditionally been present in only a minority of patients [58, 59]. However, when the rectourogenital fistulous connection has been preserved at the anorectal reconstruction the percentage of patients with preserved functional internal sphincter has been between 40–80% [56, 58, 60]. The presence of internal sphincter has been clearly shown to correlate with favorable functional outcome [56, 58, 59, 61].

Colonic motility disorders presenting usually as constipation have been earlier reported to be a problem in patients with low anorectal malformations and in females with a vestibular fistula [55]. Chronic constipation is also the main functional complication following repair of high anomalies by posterior sagittal anorectoplasty [55, 62, 63]. The incidence of constipation following PSARP procedure has varied between 10% [64] and 73% [63]. Constipation seems to be more common when internal sphincter preserving techniques have been used [63]. The cause of constipation is unclear; the extensive mobilization of the anorectum may cause partial sensory denervation of the rectum and impair the awareness of rectal fullness. Also, rectosigmoid hypomotility and generalized colonic motility disturbance has been suggested [55, 65].

It is likely that the surgical method of anorectal reconstruction in high malformations is a significant prognostic factor. However, this is very difficult to prove since randomized controlled studies are completely missing. Significantly better continence outcome was found in 21 patients who had posterior sagittal anorectoplasty compared with 16 patients having abdominoperineal pull-through [62]. Others [64, 66] have found no difference between patients who had undergone sacroabdominoperineal operation and those who had posterior sagittal anorectoplasty.

Associated defects may have a significant impact on life of patients with anorectal malformations. The urinary tract is the most commonly affected organ system. Urinary incontinence is today uncommon in patients that have undergone posterior sagittal anorectoplasty. Urinary incontinence occurs mainly in patients with neurogenic bladder that is caused by partial or complete sacral agenesis. In females with complex cloacal malformation continent urethral reconstruction may not be possible. Social continence, however, can be achieved by intermittent catheterizations or catheterizable continent urinary stomas. Tethering of the spinal cord is common in patients with anorectal malformations, however, neurological symptoms are uncommon. Untethering should be considered only in symptomatic patients [67]. Gynecological complications occur frequently in patients with cloacal malformations. Agenesis or duplication of Mullerian structures are found in approximately half of the cloaca patients. Uterovaginal agenesis and vaginal septum are not uncommon also in patients with vestibular fistulae [68]. Gynecological symptoms arise mostly from menstrual obstruction that occurs typically in cloaca patients. In these patients symptomatic adnexal cysts as well as endometriosis are not uncommon.

Patients with low malformations such as perineal fistulas have normal fertility [69]. The fertility of patients with more severe anomalies is a more complicated issue. Pregnancy is possible even in patients with complex cloacal malformation [68], but requires careful monitoring and delivery by caesarean section. In a long-term follow-up study concerning adults high

malformations, only 39% of the patients had children, which was significantly less than healthy controls, 60% of whom had offspring [56]. Obviously, the low frequency of offspring in patients with high anomalies reflects true infertility in a significant percentage of patients. On the other hand, some patients may avoid sexual contacts because of defective fecal continence.

At adult age, defective fecal continence that is a reality in many patients with anorecatal malformations has significant social consequences. The continence related social problems are more common in patients with high lesions. The main problem is fecal soiling that restricts social activities. In a report [56] on the adult patients with high ARM 85% experienced social disability related to soiling. Other problems disturbing especially occupational life were inability to hold back flatus and fecal urgency. Hassink et al. [70] have reported that adult patients had significantly lower educational level than expected.

The literature reports on quality of life of adult patients with ARM show significant incidence of emotional problems [56, 69–74]. Up to rate of 58% of psychiatric diagnoses has been reported by Diseth et al. [74]. Psychosocial functioning also appears to be more affected in patients with severe anomalies and worse fecal continence [75].

70.5.2 Aging

The effect of aging in the outcome of neonatal surgical conditions is poorly studied. A common belief has been that most functional problems in congenital or acquired surgical conditions occur during the growth period with a general trend of global improvement in various domains of function. At adulthood the functional status stabilizes to the level that was reached at the end of the growth period. The overall health and quality of life appear to remain stable in some neonatal surgical conditions such as oesophageal atresia [37, 38]. In some conditions such as Hirschsprung's disease there is evidence that functional outcome might deteriorate by aging [43]. This is probably true also in patients with anorectal malformations.

The patients with spina bifida are vulnerable to deterioration of health at adulthood. The mortality is clearly increased in adult spina bifida patients when compared with healthy population. Those with hydrocephalus are especially at risk, the most common cause of death is unrecognized shunt malfunction. The need for repeat shunt surgery is not abolished in adulthood. The ambulatory status tends to decrease also after childhood [76, 77]. One of the greatest challenges in paediatric medicine today is to establish a network of transitional care for spina bifida patients that reach adulthood.

Biliary atresia is another condition where aging significantly affects outcome. After Kasai portoenterostomy operation the survival with native liver typically decreases to 20—40% or less until adult age. Although increasing numbers of patients with biliary atresia survive to adulthood with native liver, there remains a significant possibility of hepatic deterioration requiring liver transplantation at adult age [78]. Most surviving patients with native liver have not normal liver function. Cirrhosis and portal hypertension are typical findings and these are reflected in the laboratory parameters of hepatic synthetic capacity [79]. These patients require meticulous lifelong follow-up to detect those patients that require liver transplantation at adult age for recurrent jaundice or complications of liver cirrhosis.

70.5.3 Risk for Malignancies

Malignant degeneration occurring with advancing age is a risk that is clearly associated with congenital malformations. This is a central topic that commonly emerges when long-term outcomes are discussed. In addition to above discussed risks of malignancy that is associated with Hirschsprung's disease and possibly with oesophageal atresia, there are numerous examples of malignancy complicating congenital malformations. There is a risk of malignancy with undescended testes [80], asymptomatic cystic adenomatous malformation of the lung [81] and multicystic degeneration of the kidney [82]. Cancer may arise from a duplication cyst at any

level of the gastrointestinal tract [83–86]. A unique anomaly complex is the Currarino syndrome where an anorectal anomaly and sacral defect are associated with presacral mass that is usually an anterior meningocele or presacral teratoma or a combinations of the two. The teratoma component has traditionally been considered as a benign tumor but accumulating data has confirmed that there is a significant risk of malignant degeneration both during childhood and in adults [87]. The author has encountered two malignant presacral masses in adult Currarino syndrome patients. Malignancy of the bile ducts, mainly cholangiocarcinoma; is a well established complication associated with choledochal cyst in adults. The risk is less that 1% if the cyst presents during first decade of life but increases to 14% in the third decade. Abnormal pancreaticobiliary junction probably plays a role in the pathogenesis. A possible pathogenic sequence is pancreatobiliary reflux because of pancreaticobiliary ductal malunion, inflammation, dysplasia with or without intestinal metaplasia, and invasive carcinoma. A combination of biliary stasis due to poor drainage of a stagnant pool of bile and increased mutagenicity of the bile acids may be ultimately responsible [88].

70.5.4 Undefined Factors

There are many conditions and management modalities in a newborn surgical patient of which very little is known in terms of long-term consequences. Many of these consequences may affect the neurocognitive and psychological prognosis of the patients. Little is known of long-term effects of multiple general anaesthesias that are quite commonly required in the postoperative management of neonatal surgical conditions. A typical procedures requiring multiple general anaesthesias are anastomotic dilatations of strictures following oesophageal atresia repair. Anal dilatations are usually necessary following repair of anorectal malformations. There is evidence that the duration of anal manipulation in patients with anorectal malformations is inversely related to mental and psychosocial outcome [89]. Later in childhood many of these patients undergo long-term bowel management regimens that often include invasive anal manipulations such as enemas. Psychosocial consequences of these procedures are completely unknown. It is self-evident that permanent and frequent soiling during childhood is deleterious to patients mental health, therefore, bowel management regimens are required. However, these regimens should avoid long-term anal enema administrations and use antegrade enema routes instead as they are usually well tolerated and associated with improved quality of life [90].

Intra-abdominal surgery during the neonatal period is associated with long-term complications that are related to adhesion formation. The overall risk of adhesive obstruction is less than 10% [91] but significantly higher reaching almost 20% in some conditions such as congenital diaphragmatic hernia [92]. The implications of neonatal pelvic and lower abdominal surgery in conditions like sacrococcygeal teratoma, Hirschsprung's disease and anorectal anomalies on fertility and fecundity in females is largely unknown at the moment.

Conclusions

The development of neonatal surgery after World War II and rapidly improving early outcomes has brought into light a growing group of individuals that in the past would have died or suffered from serious functional defects. The early operative and functional outcomes in these patient groups are usually well recognized, however, amazingly few reports on long-term outcomes beyond childhood are available. The medical teams and especially neonatal surgeons taking care of neonatal surgical patients have the responsibility to follow-up their patients throughout their growth period to study the true long-term outcomes. The caregivers of the patients have the right to know about possible late complications, effect of the neonatal surgical condition on growth and development, and also possible cognitive and psychosocial consequences. Proper follow-up gives also tools for development of management guidelines and surgical practice.

The follow-up of neonatal surgical patients should not end when the patients reach adulthood as congenital anomalies and neonatal surgical conditions may affect fertility and sexuality. The potential risks of malignancy and future inheritance need also be considered. The research on long-term outcomes is facilitated by development of patient registries and tracking systems. Reliable long-term outcome studies require also validated and standardized research tools and healthy control materials.

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Long Term Outcomes in Pediatric Urology

71

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Abstract

Pediatric urology has evolved in the last decades as an independent specialty from pediatric surgery covering several congenital and acquired diseases and interacts with other pediatric specialties for an early diagnosis and adequate treatment. However, in many places from all over the world, pediatric urology remains under performance by pediatric surgeons. Prenatal diagnosis has become a reality in urological pathologies and some procedures can be performed as early as fetal surgery or immediately after birth.

The long-term outcomes in the most common urological problems are presented and we look forward for new therapies and robotics in the pediatric population for the next years.

Keywords

Newborn surgery • Paediatric urology • Long term outcomes

71.1 Vesicoureteric Reflux

71.1.1 Background

Age at diagnosis has two peaks with different demographic features and distinct modes of presentation. The first group is antenatal, predominantly male and identified on ultrasonography, or if there is a family history there is no gender predominance. This vesicoureteric reflux (VUR) resolves or improves in the vast majority by 4 years of age [1]. The second group is diagnosed later, after a urinary tract infection (UTI) and is predominantly female.

71.1.2 Long-Term Outcome

Long-term follow-up studies in relation to VUR cover various scenarios; children presenting with acute UTI, VUR with renal scarring followed into adulthood, girls with asymptomatic bacteriuria and VUR and scarring, and children

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_71

with VUR nephropathy who had ureteric reimplantation. To summarize, there is no evidence that recognition and treatment of VUR has any impact on the development of end-stage renal disease.

The primary objective in the management of VUR is the prevention of ascending pyelonephritis secondary to bacteriuria. It has been a long held belief that antibiotic prophylaxis prevents parenchymal damage in patients with VUR, and that long-term administration is well tolerated and is the treatment of choice for all infants regardless of severity of VUR [2] and that older children with mild to moderate (I–III) reflux can be maintained infection free because spontaneous resolution is common, although recent studies [3] have shown no significant results. Approximately, up to 50% of VUR patients have renal scarring at the time of initial presentation, but relatively few new scars develop after medical or surgical treatment and no child with normal kidneys initially developed scarring. However, once deterioration in renal function commences, it progresses even when UTI are successfully prevented or treated and hypertension satisfactorily controlled. VUR repair at this stage does not affect the development of renal failure [4].

Minimally invasive endoscopic injection has been in use for more than 20 years and while highly successful for grades II–IV, its role in grade V is questionable with no effect on the subsequent incidence of UTI [5, 6].

For surgical intervention there seems to be a great discrepancy between effective and ineffective treatments, but no obvious difference between effective treatment and no treatment. There is a general trend for children over 2 years of age with persistent high-grade VUR (IV–V) to have surgery to decrease complications secondary to pyelonephritis. Cohen and Leadbetter-Politano are most commonly performed procedures with Cohen associated with lowest failure and complication rates. Again, while surgical correction can be highly successful and prevent renal damage, the overall incidence of infections is not reduced, and prophylactic antibiotics are usually required. To summarize, antireflux surgery should be reserved for patients who have high grades of reflux refractive to medical treatment, and for those with social circumstances or particular problems, which make medical treatment difficult to supervise or administer.

71.2 Pelvicuretero Junction/ Ureteropelvic Junction Stenosis

71.2.1 Background

There is no imaging or urodynamic modality that can accurately distinguish pelviureteric junction (PUJ)/ ureteropelvic junction (UPJ) obstruction from patients with inconsequential hydronephrosis, so the current approach is to observe conservatively in the short-term, reserving surgery for cases who deteriorate or become symptomatic. Symptomatic hydronephrosis in children occurs much less commonly than antenatally diagnosed hydronephrosis, but long-term follow-up studies of adults who underwent pyeloplasty many years earlier clearly identify the benefit of surgical intervention for alleviating symptoms [7, 8]. Surgery should be performed immediately regardless of age once the diagnosis of true obstruction is made [9]. Otherwise the added benefit of surgery in less severe cases is not clear since the same improvement may be observed without surgery.

71.2.2 Long-Term Outcome

The challenge for the clinician in the management of hydronephrosis is to decide who should be observed, who should be medically managed, and who requires surgery. This decision is complicated further by the challenge of cost containment. While open pyeloplasty is the gold standard for treatment, minimally invasive surgery/robotic surgery are gaining momentum but are less cost effective compared with open surgery. Earlier surgery has better results.

71.3 Megaureters

71.3.1 Background

Management of megaureter has changed markedly over the past 20 years and most patients are often entirely asymptomatic with kidneys that are functioning well [10]. Antenatal diagnosis of hydroureteronephrosis raises concern because of uncertain indications for surgical intervention. The current consensus is that megaureter represents non-obstructive dilation and therefore careful observation with antibiotic prophylaxis is all that is needed for most children [11, 12].

71.3.2 Long-Term Outcome

Should there be evidence of deteriorating renal function, worsening dilatation or breakthrough urinary tract infections, surgical intervention is mandatory and involves excision of the stenotic ureteral segment, reduction in caliber of the dilated distal ureter and ureteral reimplantation. The timing of surgery affects preservation of renal function. Ureteric reimplantation in infants below 1 year of age may be challenging due to the discrepancy between the grossly-dilated ureter and the small infantile bladder, and concern regarding possible iatrogenic bladder dysfunction [13].

71.4 Bladder Exstrophy

71.4.1 Background

Classic bladder exstrophy accounts for 60% of patients with defects in ventral coverage of several organs while cloacal exstrophy and epispadias are far less common.

Reconstruction of exstrophy-epispadias complex remains one of the greatest challenges facing the pediatric surgeon. Many modifications in surgical procedures have improved outcome, but as no formal assessment of staged repair versus total reconstruction with respect to function and cosmesis has been performed to date, the definitive approach has yet to be established. Depending on severity, surgical intervention may commence early with closure of the bladder, posterior urethra, pelvis and abdominal wall at birth, followed by genital reconstruction, and some form of continence procedure that may proceed through to adolescence. The current trend is clearly toward augmentation in patients who do not have adequate bladder capacity or in whom continence procedures involving simple closure and bladder neck reconstruction fail. Genital reconstruction that used to be common in adolescent exstrophy patients is now uncommon [14, 15].

71.4.2 Long-Term Outcome

Survival rates in bladder exstrophy patients today are normal. Long-term follow-up shows that staged repair has better outcome and less complications [16, 17], and urinary continence is achievable in at least 65% with males doing better than females [18, 19].

The psychological effects of a major congenital genitourinary malformation such as bladder exstrophy can be devastating. Although urinary continence and genital cosmesis are major issues, long-term goals for sexual function have considerably modified the surgical procedures performed in infancy over the past 20 years. Despite severe epispadias associated with exstrophy, most patients completing staged reconstruction can expect to enjoy sexual relations. Sexual response and libido of males with bladder exstrophy is normal although fertility through conventional procreation is very low because of penile shortening, dorsal chordee, poor erections and retrograde ejaculation. However, only a small proportion classify these as distressing [18]. Females tend to fare better in all aspects of sexual health with most being satisfied with the appearance of their genitalia and all being sexually active. In fact, women with bladder exstrophy have delivered children, with the commonest complication being cervical/uterine prolapse, and future urinary reconstruction should include

prophylactic anterior fixation of the uterus. Cesarean section should be considered for all exstrophy patient deliveries [20].

Now that patients who have undergone modern exstrophy treatment techniques have been followed into adulthood, it is gratifying to see the successful lives these patients enjoy—a sharp contrast to lives before successful bladder closure was common.

Adenocarcinoma is approximately 400 times more common in patients with bladder exstrophy than in the normal population, accounting for up to 93% of the bladder tumors seen in these patients. Long-term monitoring with cystoscopic evaluation is recommended. Long-term follow-up of patients who have completed modern staged reconstruction with successful bladder closure is expected to reveal a diminished risk for cancer [21, 22].

71.5 Epispadias

71.5.1 Long-Term Outcome

The defect in epispadias can be closed successfully and satisfactory continence achieved without loss of renal function or normal drainage. In fact, continence can be expected in up to 90% of complete epispadias patients managed successfully. In other words, results in both complete epispadias and bladder exstrophy have improved to the point where functional closure and bladder neck reconstruction should be the aim of initial surgery, and only those patients who are proven to have special problems or who fail in achieving success at each step need to be considered for alternatives of internal or external urinary diversion or augmentation cystoplasty [21, 23].

71.6 Neuropathic Bladder

71.6.1 Background

Over the past 20 years the survival rate of these children has improved with the primary goal of treatment being preservation of renal and bladder function. Practical and functional substitutes for native bladder tissues are constantly being researched in view of the detrimental combination of intestinal tissue and urine.

71.6.2 Long-Term Outcome

Clean intermittent urethral catheterization (CIC) itself does not necessarily guarantee continence and usually requires the addition of pharmacotherapy in the form of anticholinergics and alpha adrenergics, or surgery [24, 25]. There is limited data on the long-term follow-up of children with neuropathic bladder taking medications. Oral and intravesical oxybutynin both cause side effects, more prominent in children taking oral oxybutynin. Injection of botulinum in the detrusor muscle is effective for detrusor hyperreflexia in the short term requires anesthesia for administration [26].

Prophylactic bicarbonate is mandatory, as is orthopedic follow-up to combat the impact of acidosis on growing children to prevent bone demineralization and loss of growth potential.

Symptomatic UTIs are relatively infrequent with CIC and in the absence of significant preexisting reflux, fresh renal scarring is unusual.

Surgical intervention must match the needs of the patient with those of the primary care giver. If for example, a third party is the primary care giver, then a conduit urinary diversion with collecting bag is far easier to manage than trying to assess when a bladder is full.

The most commonly performed diversions are vesicostomy, refluxing ureterostomy, and ileal conduit, usually performed temporarily for deteriorating upper tracts or failure of CIC [27, 28]. Otherwise, procedures performed with good outcome include suprapubic diversion via a suprapubic tube or button often followed by a Mitrofanoff stoma or button vesicostomy as an alternative to a Mitrofanoff channel [29].

For bladder neck surgery, revision rates are similar for all procedures performed but the incidence of complications appears highest with the Kropp procedure. Artificial urinary sphincter (AUS) should be the initial treatment of choice

for the surgical management of neurogenic sphincter incontinence. However, there is limited long-term published data [30–35].

There are very few reviews of long-term outcome of augmentation cystoplasty specifically in the pediatric age group and many patients with cystoplasties performed years ago, have never been followed-up properly, and present with complications that could have been managed simply as they arose. Careful follow-up for monitoring voiding efficiency and timely use of CIC are vital to prevent decompensation. Voiding inefficiency after augmentation cystoplasty is common and can be managed by CIC especially in neuropathic bladder and is due to associated sphincter weakness that after surgical intervention can improve continence greatly [36, 37]. The competence of bladder outflow is often overlooked [38, 39].

Augmentation cystoplasty will continue to require the use of gastrointestinal tract segments until such time as an entirely urothelial bladder substitute is available. Current composite enterocystoplasties where demucosalized intestine is seeded with urothelial cells propagated in vitro could evolve to create a synthetic substitute for augmentation.

Gastrocystoplasty is an alternative and is advantageous because of decreased chloride absorption and mucus production, with lower incidence of urinary infections, stone formation, and perforation [40, 41]. However, up to 89% have decreased urinary continence postoperatively and hematuria dysuria syndrome amenable to proton pump inhibitors has been described in up to 25% of children. Suture line bleeding is the most serious surgical complication. Long-term follow-up documents improved urodynamics with increased bladder capacity and compliance [41, 42].

71.7 Mitrofanoff

71.7.1 Background

Mitrofanoff conduit is the most commonly performed continent catheterizable conduit in patients with a neuropathic bladder. Creation of a Mitrofanoff channel is usually performed concomitantly with an augmentation cystoplasty in children with neuropathic bladder and occasionally with the Malone antegrade continence enema (MACE) procedure [43].

71.7.2 Long-Term Outcome

Long-term follow-up of the Mitrofanoff channel has shown its robustness in the ability to be catheterized. High continence rates have been achieved when combined with an augmentation cystoplasty and bladder neck procedure [44].

Stomal stenosis is the most frequent complication requiring revisional surgery. Other long-term problems include UTI, bladder calculi, urine leakage, and progressive bilateral upper tract dilation [45, 46], and kinking of the channel, long stenosis of the channel, and difficulty in catheterization [47].

71.8 Posterior Urethral Valves

71.8.1 Background

Posterior urethral obstruction more than any other urinary anomaly has the capacity to affect the development and function of the whole urinary tract and can range from conditions incompatible with postnatal life when severe, to extremely mild conditions that may not manifest until later in life [48–50]. Posterior urethral valves (PUV) can be detected prenatally by ultrasonography (US) from 24 weeks' gestation when urinary tract dilation, hydronephrosis and/or a distended thick-walled bladder can be identified with a sensitivity of close to 100%. However, if prenatal US findings suggestive of PUV are noted before 24 weeks' gestation, or if there is severe bilateral hydronephrosis with oligohydramnios or renal dysplasia with oligohydramnios in the second trimester, the risk for postnatal chronic kidney disease is increased and perinatal mortality can be as high as 90–95% [51].

71.8.2 Long-Term Outcome

Although most infants with PUV are diagnosed in utero, underlying primary renal dysplasia cannot be altered by postnatal intervention, and provided bladder function can be preserved, the progressive decline in renal function associated with persistent high bladder pressures can be impeded [52, 53]. Impairment of renal function is found in around 70% of boys at presentation and over 80% of boys less than 3 months old. Although renal dysplasia is irreversible, adequate attention to urinary infections and bladder dysfunction can decrease or delay ongoing renal deterioration, and recent evidence would suggest that dysplastic kidneys do not affect infection rates or function of the remaining kidney and may be left in place. After initial management, 60% of patients recover normal biochemical renal function on short-term follow up [54]. However, renal failure can occur in up to 40% of PUV patients. In most countries transplantation is a viable treatment option and attention to bladder dysfunction and treatment of high bladder pressures associated with urge incontinence with anticholinergic therapy and frequent voiding are important to protect transplanted kidneys and prevent further deterioration. Dilated ureters attached to dysplastic kidneys may also have potential use during bladder augmentation in those rare cases of high-pressure bladder refractory to standard therapy [55, 56]. In bladders that have progressed to myogenic failure and incomplete emptying, clean intermittent catheterization (CIC) and/or overnight bladder drainage may be necessary. It must be remembered that patients with PUV do not have altered urethral sensation, and for the majority, catheterization through the penis is painful [57–59].

The presence of reflux should not change the initial overall treatment of PUV and probably does not change the long-term prognosis unless there is recurrent infection. Ureteral reimplantation is indicated only in those patients with recurrent urinary tract infection despite appropriate chemoprophylaxis and after appropriate therapy to treat bladder dysfunction.

Bladder dysfunction manifesting as incontinence, can complicate up to 38% of patients with PUV. Daytime catheterization can often be avoided in older boys if they can adhere to a strict schedule of timed voiding. Night time indwelling catheterization optimizes bladder drainage with documented improvement in hydronephrosis and bladder compliance. Compliance with catheterization can be difficult and creation of a continent catheterizable channel to the anterior abdominal wall could improve quality of life greatly and improve compliance. Patients with high-pressure voiding dynamics often benefit from the use of anticholinergic medications and conservative measures are usually effective enough for modifying bladder dynamics (i.e., keeping bladder volumes sufficiently low to maintain acceptable bladder pressure) in the medium term, but careful follow-up to assess renal dysfunction is mandatory [60–62].

Sexual function may be impaired due to higher incidence of undescended testes, the impaired function of the posterior urethra and ejaculatory mechanism and the effect of urethral surgery and renal failure. However, semen samples are fertile and fathering children is possible [63, 64].

The overall infant mortality rate has improved from about 50% to less than 3% in the past 3 decades. Early infant mortality in PUV is related to pulmonary hypoplasia and can be as high as 63% in boys less than 1 month old. With earlier, often prenatal diagnosis, possible future treatment options may include fetal cystoscopy and in utero treatment of PUV, or amnioinfusion to allow normal pulmonary development, already proven successful in bilateral renal agenesis [65, 66]. Longer follow-up has shown that chronic renal failure can cause death in up to 6.4% of boys between 3 and 12 years after presentation while end-stage renal disease can cause death between 10 and 15 years after presentation. Early management will certainly result in increasing numbers of patients surviving to be recruited into renal replacement programs. However, renal dialysis and transplantation are associated with morbidity and mortality, and prognosis may in fact prove to be closer to renal failure once follow-up extends to several decades [67].

71.9 Hypospadias

71.9.1 Background

The results of hypospadias surgery can be assessed objectively with urography or subjectively with respect to cosmesis, sexual function, psychosocial adjustment, and body image [68, 69]. Hypospadias should be repaired within the first year of life preferably around 6 months of age [70, 71]. It is an age well accepted by parents, reliable for the surgeon, and not remembered by the patient.

The most significant advance in surgical technique over the past 10 years is Snodgrass' primary tubularized urethroplasty. Reports of the success of tubularized incised plate urethroplasty are favorable and concern about strictures and meatal stenosis are unfounded [72, 73]. However, tubularized island flap urethroplasty appears to be associated with a high complication rate of up to 40% even in experienced hands and is not now commonly performed [74–76], while a vascularized preputial flap used as an onlay to preserve the urethral plate will provide a more secure result long-term. Other observations that appear to enhance outcome include: the neourethra in single-stage repairs using vascularized preputial pedicle flaps is functionally equivalent to a normal urethra in most boys using preputial island flaps; multi-stage surgery for severe hypospadias and redo surgery is acceptable if one-step surgery appears to be difficult, although additional procedures are often required to achieve an optimal outcome [77].; dorsal plication of the tunica albuginea to correct curvature has stood the test of 17 years follow-up with minimal recurvature, and is a simpler technique than ventral grafting of the corpora; buccal mucosa grafts are the best urethral replacement for redo surgery and for stricture, and the meatus will be durable [78]; an apical meatus is usually preferred, allows a good stream, and is worth the extra effort despite data to the contrary [79]; while urography is a good objective measure of caliber, observation of a good stream of urine at follow-up is more satisfying to both the patient and treating surgeon. Ideally one should have both; redundant skin after hypospadias repair in the child will often fill out and be unnoticeable after puberty [80]; utricles are not of great concern when they are small, however, they may cause inflammation or stone formation and treatment is difficult if they are large.

71.9.2 Long-Term Outcome

Long-term evaluation of surgical procedures has been largely hindered by the constant modifications made over time. What long-term results are available concern procedures that have now been abandoned. Data would suggest that most men have no lasting effects, but up to 40% of those with severe hypospadias have some degree of voiding difficulties. Although objective assessment of appearance after hypospadias surgery is also difficult, a recent study found TIP to be most cosmetically appealing [81].

Hypospadias patients appear to be inhibited when seeking sexual contact, are more likely to have a negative opinion of their genitals, and often fail to adjust sexually [82]. Size of the hypospadias penis will most often be perceived as small by the patient and parents but may not be so when compared to the range of normal. An absolutely straight erect penis is not necessary for enjoyable sex; gentle curvature is within the norm, and fixation on perfect straightness with hypospadias is unwarranted [83, 84]. The majority would appear to enjoy conventional sexual activity [85, 86]. Fertility is theoretically unaffected, but if associated with cryptorchidism, patients are unlikely to be fertile.

Complications are common and should be treated at least 6 months after the initial procedure, to allow the tissues to heal properly. Onlay urethroplasties used in severe cases would appear to be associated with a lower overall complication rate of 28.6% [87]. Unsatisfactory appearance related to irregular suture lines, scars, unevenness, or redundant skin can deflate confidence and invoke comment, but if the ventral aspect of the glans is short and there is no mucosal collar around the glans, the cosmetic result is

disastrous and is related directly to the artistry of the surgeon not technical prowess [88].

Fistulas are the second most common complication of hypospadias repair, and can be seen during the first month after operation [89, 90]. Urethrocele is often related to a difference in urethral compliance between the native urethra and the reconstructed urethra.

71.10 Intersex

71.10.1 Background

Almost 90% of ambiguous genitalia patients are managed by some form of feminizing genitoplasty. While the immediate goal is to provide a feminine appearance to the external genitalia, long-term goals are to create a functional vagina sizable enough for comfortable sexual intercourse, to retain sexually sensitive tissue to allow orgasm and, if internal genitalia permit, to preserve potential for fertility.

71.10.2 Long-Term Outcome

Intersexuality does not threaten a patient's life, but rather their psychosocial status. Body image and psychosexual identification are often profoundly disturbed because despite tests that objectively define chromosomes and internal genital anatomy [91], decisions about sexual assignment and choices for treatment are made quite subjectively.

While vaginoplasty techniques have advanced to allow a responsive natural looking vagina to be fashioned, such surgery is planned in infancy to enhance social adjustment and family acceptance without any real consideration of the best interests of the patient. Unfortunately, future adjustment issues cannot be resolved in advance, and long-term follow-up data is lacking because unless patients have persistent problems, they tend to be lost to follow-up. Little is known about how adults adjust to genitoplasty, or whether the genitoplasty expresses their sexual preference. After many years of genitoplasty experience and technical revisions, gender identification mismatch tends to be consistently problematic and requires close monitoring with good counseling. Recent trends indicate that patients are not so much disturbed by unusual looking genitals but are more concerned about sensation and potential for fertility [92]. Thus, if the chromosomal and gonadal sex are compatible with fertility, gender assignment should be made to preserve fertility, if the external phenotype allows [93].

No studies of clitoral surgery address the long-term results of erotic sexual sensitivity. Sexual orgasmic response is multifactorial; however, the extent to which sexual orgasm and response is dependent on the clitoris is unknown [94].

71.11 Cloacal Malformation

71.11.1 Background

Urinary incontinence seen in patients with cloacal malformation is multifactorial. It may be secondary to structural abnormalities of the bladder, bladder neck and urethra, sacral dysplasia or agenesis, and intrinsic or iatrogenic neurovesical dysfunction (surgical denervation) [95, 96]. Despite obvious anomalies, accurate diagnosis is not always made before referral, which can potentially place the newborn at risk for sepsis, with preoperative renal scarring or dysplasia present in up to 25%.

71.11.2 Long-Term Outcome

Urinary continence after cloacal repair is often difficult to achieve and is only possible after several procedures, including bladder neck reconstruction. Associated congenital anomalies such as tethered cord and renal malformations are common, adversely affecting continence as well as general renal function [97]. Some 60% of cloacal malformation patients have an atonic type of neurogenic bladder, requiring CIC [98]. In a recent follow-up study, 66% of children had dry intervals of over 4 h; 62.5% using CIC through a Mitrofanoff channel and 12.5% through the ure-

thra [97, 98]. Upper tract deterioration is a concern in cloacal malformation secondary to persistent hydronephrosis (in up to 60%), the need for bladder augmentation and the presence of reflux requiring reimplantation (in up to 75%), make it extremely difficult to reach an overall conclusion about renal dysfunction [99, 100]. Research data would indicate that 60% of children with common channels of at least 3 cm required bladder augmentation associated with bladder neck closure and Mitrofanoff conduit, compared with none of the patients who had common channels less than 3 cm. Thus explaining the high rate of dryness achieved after all these procedures [99, 101].

71.12 Robotics

Robotic surgery can generate extremely delicate movements in a confined working space such as are found generally in the pediatric population [102]. Initial results with robotic assistance are encouraging and have demonstrated safety comparable to open procedures and outcomes at least equivalent to standard laparoscopy, although it should be regarded as an assisted form of open surgery rather than an evolution of laparoscopy. Future development of smaller instruments, incorporating tactile feedback, will likely overcome current limitations related mainly to lack of tactile sensation or feedback to the surgeon [103, 104]. Currently, robot-assisted surgery must rely on visual clues surrounding the operative site to adjust for orientation and tactile input [105]. Ultimately, the efficacy and role of robotic surgical systems will require definition following comparison with standard procedures of choice performed open or laparoscopically.

71.13 Stem Cells

Embryonic stem cell research is generally controversial and newer semi synthetic stem cell development programs have had varying success with no real potential for active application established. Human embryonic stem (hES) cells are derived from the inner cell mass of the blastocyst stage embryo, and human embryonic germ (hEG) cells are obtained from primordial germ cells. Formation of embryoid bodies is an important intermediate step for hES and hEG cells, before differentiation into various cell types [106, 107]. With embryoid body formation, the markers of pluripotentiality decline, and ectodermal, mesodermal, and endodermal markers appear. Some research on urologic tissue engineering has been promising but has been hindered because form does not always equate with function, especially for bladder tissue.

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Evidence Based Neonatal Surgery

72

Nigel J. Hall, Simon Eaton, and Agostino Pierro

Abstract

Surgical intervention has, quite rightly, a well-established role in the management of a number of congenital and acquired neonatal conditions. Surgical approaches have been developed over a period of time, from the initial endeavours of pioneering neonatal surgeons, to the procedures commonly in everyday use today. Such development has been predominantly a result of necessity, learning from past experience and translation of techniques in use in other surgical fields into neonatal surgery. As neonatal surgical experience has grown, surgeons have begun to develop alternatives to what were once thought to be traditional techniques such that for a number of conditions we now have the luxury of choice in the treatment of these often fragile infants. With choice, there comes a dilemma. Which approach should be used? How should we make the decision?

Keywords

Evidence based neonatal surgery • Evidence based paediatric surgery Systematic review and meta-analysis • RCTs

72.1 Introduction

Surgical intervention has, quite rightly, a well-established role in the management of a number of congenital and acquired neonatal conditions. Surgical approaches have been developed over a period of time, from the initial endeavours of pioneering neonatal surgeons, to the procedures commonly in everyday use today. Such development has been predominantly a result of necessity, learning from past experience and translation of techniques in use in other surgical fields into neonatal surgery. As neonatal surgical experience has grown, surgeons have begun

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_72

to develop alternatives to what were once thought to be traditional techniques such that for a number of conditions we now have the luxury of choice in the treatment of these often fragile infants. With choice, there comes a dilemma. Which approach should be used? How should we make the decision?

The practice of evidence based medicine means integrating clinical expertise with the best available external clinical evidence from systematic research. Given that evidence based medicine is now an integral part of routine practice, we are required to draw on the available evidence to guide us in our decisions and justify them. The application of such evidence to surgical specialties, termed *evidence based surgery (EBS)*, has lagged behind our non-surgical counterparts. In the field of paediatric and neonatal surgery we are hindered further in our ability to perform evidence based surgery by a paucity of patient numbers from which we are able to draw high quality evidence. Compared with adult general surgeons, who may perform many hundreds of similar operations, general paediatric surgeons perform a great variety of different operations, but each of them may be in relatively small numbers. One consequence of this is that the evidence base for many paediatric and neonatal surgical procedures is limited compared with comparable procedures in adults. However, this problem is not just related to number of operations, as some very frequently performed paediatric operations such as hydrocele repair are also performed with very little evidence base.

This lack of evidence has been highlighted previously by Baraldini et al., who performed a study to determine the type of research evidence supporting operations in a tertiary referral paediatric surgical unit [1]. All patients admitted over a 4-week period to two surgical teams were enrolled in the study and all major operations carried out on each patient since birth were evaluated. Twenty-six percent of the operations were supported by a randomised controlled trial (RCT, level 1 evidence), but the vast majority of these trials had been conducted on adult patients. At that time, the only operation supported by an RCT *in children* was repair of congenital diaphragmatic hernia. The majority of the operations (68%) were based on evidence from non-randomised, prospective or retrospective studies.

More recently, Ostlie and St Peter scrutinised the Paediatric Surgical literature searching for RCTs in the field of Paediatric Surgery [2]. They identified only 56 RCTs relating to paediatric surgical conditions over a 10 year period and only four relating to neonatal conditions. A Paediatric Surgical RCT comprised just 0.04% of the manuscripts published in the 26 journals containing at least one RCT during the study period. An updated study of the Baraldini paper has recently been published, in which the evidence base for paediatric surgical operations, including specifically neonatal operations, was reviewed, in which it was concluded that although there had been an improvement in evidence base, more than one third of the procedures still lacked evidence-based literature support [3].

Whilst these three studies highlight the lack of EBS within the field of paediatric surgery as a whole and within the field of neonatal surgery in particular, a number of groups are striving to improve the evidence base on which Paediatric Surgeons base their daily practice.

This review examines the current available evidence for neonatal surgical procedures. We focus on those conditions of the term and preterm neonate which would be managed by the general paediatric and neonatal surgeon, excluding conditions affecting the cardiovascular, genitourinary and nervous systems. The evidence that we present will be primarily of level 1. There are many retrospective reviews and case series amongst the literature which may give some guidance as to which approach to a given condition may be superior. By their very nature, these have internal flaws and are subject to bias. We are firmly of the view that the correct way to determine the best approach to a condition where a choice exists is by means of a RCT. We have therefore reviewed primarily RCTs as they relate to neonatal surgery and we include non-randomised studies only where no RCTs exist and the alternative evidence is of sufficient quality or interest to make it noteworthy. We present

the published evidence up relating to the more common surgical conditions of the neonatal period is presented. It is hoped that in future editions of this book further evidence will be available in neonatal surgery.

72.2 Oesophageal Atresia

Following the first classic description of oesophageal atresia with tracheo-oesophageal fistula by Gibson in 1697, it was not until the early twentieth century that the first attempts at repair of this congenital anomaly were made. Initially mortality remained high but during the course of the twentieth century oesophageal atresia was changed from a condition incompatible with life to a condition having a survival rate in excess of 90% [4]. With high survival rates now commonplace, surgeons have looked for interventions to refine both operative technique and outcome. The introduction of minimally invasive surgery has presented one such opportunity and thoracoscopic repair of oesophageal atresia has been performed, reportedly with good results [5, 6]. However, concern has been raised regarding acidosis during thoracoscopic repair of oesophageal atresia and congenital diaphragmatic hernia in infants, although a pilot randomised controlled trial suggested that this acidosis was not as severe in oesophageal atresia as in congenital diaphragmatic hernia [7]. In this pilot randomised controlled trial, there was no significant difference in outcomes between those operated thoracoscopically and those operated via a thoracotomy, although it should be noted that only ten oesophageal atresia patients were included and that clinical outcomes were not the primary aim of the study [7].

A proportion of infants with oesophageal atresia are born such that the interruption of the oesophagus between upper and lower pouches is too great to permit a primary anastomosis ("long-gap"). This may be managed in a staged manner using techniques including delayed primary repair with gastrostomy, cervical oesophagostomy, oesophageal replacement, and continuous extracorporeal tension of the oesophageal ends to encourage longitudinal growth (Foker technique [8]). Despite the lack of quality evidence, it is interesting that the United Kingdom National Institute of Clinical Excellence (NICE) has reviewed the evidence relating to the Foker technique and approved its use despite the unclear evidence considered relating to a limited number of infants who underwent this procedure [9]. Although experience with the technique is increasing it remains predominantly limited to a few centres [10]. Whilst the Foker technique may have a role in the management of selected infants with oesophageal atresia, we feel that this technique should be used cautiously and due consideration given to alternative approaches. It has not been subjected to the true scientific interrogation required to unanimously support its use.

Post-operatively the main challenges faced are anastomotic leakage, the development of anastomotic strictures requiring dilatation, gastro-oesophageal reflux, oesophageal dysmotility and tracheomalacia. Various techniques have been proposed to minimise the incidence of these post-operative complications. Elective paralysis and ventilation [11, 12] has been proposed as effective method of minimising anastomotic leakage following 'tight' oesophageal anastomosis. Both elective oesophageal dilatation and the routine use of anti-reflux medications [13] have been proposed to reduce the incidence of anastomotic strictures. None of these methods of treatment have been subjected to the rigorous scientific interrogation of a RCT.

72.3 Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) remains one of the most interesting and challenging congenital anomalies of the newborn. Once a condition that carried an extremely poor prognosis, overall survival rates are now in the range of 40–70% with some centres reporting mortality of less than 20%. Central to our understanding of this condition has been the recognition that early surgical repair is not crucial for survival but that delayed surgical approach following improvement in

cardiorespiratory function is preferable. However, even though most centres now delay repair until stabilisation, the evidence base for delayed repair is limited. Only two small RCTs of emergency early repair vs. delayed repair have been performed, neither of which showed a significant advantage of delayed repair [14, 15], and a systematic review concluded that a large multicentre RCT should be performed [16]. Such a trial would be very difficult to perform, however, because of the widespread perceived benefit of delaying surgery until haemodynamic stability is established. Survival rates are still far from desirable. This has prompted the pursuit of alternative strategies including extracorporeal membrane oxygenation (ECMO) and fetal intervention. A number of groups worldwide have led these pursuits and several RCTs performed. This is the neonatal condition that boasts the highest number of RCTs investigating various aspects of its treatment.

Prenatal diagnosis of CDH has permitted the identification of those fetuses with characteristics suggestive of poor prognosis and high postnatal mortality. A number of prenatal interventions have been suggested in attempts to improve outcome. Whilst technically feasible, prenatal repair of CDH by means of open fetal surgery failed to improve outcome and resulted an increased incidence of premature birth with no survival benefit [17]. Fetal endoluminal tracheal occlusion (FETO) has been investigated as a means of promoting prenatal lung growth in the anticipation that this would improve survival. Following *in-utero* FETO in experimental models of CDH, investigators found an increase in lung growth, improvement in lung compliance and improved postnatal oxygenation and ventilation. Initial reports [18–21] in the human suggested great promise using this technique but a recent RCT investigating FETO in what were considered to be high risk infants with CDH (lung to head ratio <1.4) was stopped before completion due to a higher than anticipated survival in the control (untreated) group [22]. This resulted in the study being underpowered to demonstrate any benefit in the treatment group. Another RCT investigating the effect of a modified FETO technique, in infants deemed to be at particularly poor prognosis (liver herniation and significantly reduced lung to head ratio), is currently ongoing [23].

Post-natally, it has been suggested that alternative ventilator strategies may improve outcome from CDH. Studies (some of them RCTs) have been performed investigating the effect of inhaled nitric oxide (NO) [24], routine ECMO [25], surfactant usage [26], partial liquid ventilation [27] and high-frequency oscillatory ventilation [28] in CDH infants. At present there is no evidence of improved outcome in infants with CDH following any of these interventions.

The technique of surgical repair of the diaphragmatic defect is of far lesser importance than management of the infant's cardio-respiratory compromise secondary to pulmonary hypoplasia and associated pulmonary hypertension. Surgical repair of the defect can proceed once the infant's cardio-respiratory status has stabilised. Following the return of the abdominal contents from the thorax to the abdomen, the defect is repaired primarily when possible but using a patch when the defect is too large for primary repair. Retrospective evidence suggests that a biological patch may confer a lower recurrence rate when compared with a synthetic alternative [29]. Surgical repair is possible through a traditional laparotomy incision or via minimal access techniques through both the abdomen and thorax. There is no evidence of improved outcome following minimal access repair when compared with conventional open surgical approach; and a recent meta-analysis of retrospective data suggests that the recurrence rate may be higher following minimally invasive repair [30], and the pilot randomised controlled trial of thoracoscopic vs. open repair of oesophageal atresia and congenital diaphragmatic hernia described above under oesophageal atresia showed that acidosis was significant during thoracoscopic repair of congenital diaphragmatic hernia [7].

72.4 Atresia of the Mid and Hind Gut

The surgical principle behind operative repair of duodenal, jejuno-ileal and colonic atresias is restoration of continuity from mouth to anus

whilst maintaining as much intestinal length as possible. In the majority of cases, primary repair of the defect is possible. A laparoscopic approach to repair of duodenal atresia has been reported [31] but there is no evidence to support the preferential use of either open surgery or laparoscopy. The most significant long term adverse outcome following intestinal atresia is that of short bowel syndrome in a small group of infants. The underlying aetiology of this is usually the anatomical nature of the underlying anomaly rather than the technique of surgical repair. The high (>90%) survival rates and acceptable long term gastrointestinal function in the majority of infants provide evidence in support of current techniques [32]. Controversy does exist, however, in post-operative feeding strategies; some surgeons advocate parenteral feeding for some types of atresia whereas others do not [33]. There is no good quality evidence base either for or against parenteral nutrition.

72.5 Anorectal Malformations

The management of anorectal malformations remains a challenge for paediatric surgeons mainly due to the high incidence of functional long-term impairment including faecal incontinence, urinary incontinence, sexual dysfunction and fertility problems. The introduction and widespread use of the posterior sagittal anorectoplasty (PSARP; [34]) is generally perceived to have improved functional outcome from this complex group of anomalies. However, gathering reliable evidence to support this statement is difficult due to the diversity of anomalies, the functional (and therefore often subjective) nature of the outcomes of interest and indeed the widespread usage of the PSARP procedure thereby precluding meaningful comparison with alternative surgical approaches. A laparoscopically-assisted anorectoplasty has also been advocated, with the rationale of minimising perineal dissection [35]. However, whether there is advantage of the laparoscopically-assisted anorectoplasty over the PSARP remains a matter of debate.

72.6 Anterior Abdominal Wall Defects

The anterior abdominal wall defects (gastroschisis and exomphalos) are often considered together due to their anatomical similarities and similarities in their management strategy. The principles of surgery relating to these conditions are to protect the bowel and other eviscerated organs and to achieve their return to the abdominal cavity as soon as possible so that the defect in the abdominal wall can be closed. Reduction and closure may be undertaken as single stage primary procedure or as a staged approach with the use of a silo.

Infants in whom primary closure is possible have traditionally had the procedure performed under general anaesthetic. However, the need for this in selected infants with gastroschisis (but not exomphalos) has been questioned and the concept of primary reduction without anaesthesia at the bedside has been reported [36]. There is a lack of quality evidence in support this approach. A Cochrane review failed to identify any RCT addressing this issue and recommended that they be undertaken [37]. None has been.

When a staged approach is required this involves the use of a protective bag known as a ‘silo’ into which the eviscerated abdominal contents are placed. The silo serves to protect the bowel from the outside environment particularly preventing the bowel from dehydration. It also facilitates reduction of its contents into the abdominal cavity by containing it in such a way that gravity and external pressure can be applied to enhance reduction. Traditionally silos were attached to the abdominal wall musculature surgically but recently the ‘preformed silo’ product has become available that can be tucked under the musculature and held in place without the need for general anaesthesia or surgical attachment. Following return of the abdominal contents to the abdomen, the abdominal wall defect is closed. This has usually been a surgical closure under general anaesthetic but a number of centres are now performing this at the bedside without the need for anaesthesia and achieving excellent cosmetic results.

The advent of the preformed silo has led clinicians to consider whether such a technique should be used for all cases of gastroschisis and that attempted primary closure should be avoided altogether. The potential complications of primary closure include a sudden rise in intra-abdominal pressure which may result in respiratory compromise, organ failure and significant complications. Pastor and colleagues [38] have performed a RCT comparing routine placement of a preformed silo without anaesthetic at the bedside with attempted primary closure either under general anaesthetic or at the bedside. In the group randomised to undergo attempted primary closure, a preformed silo was placed if primary closure was not possible either due to a large discrepancy between volume of eviscerated contents and abdominal capacity or due to an unacceptable increase in intra-abdominal pressure. Unfortunately their study was stopped early due to poor recruitment and analyses demonstrated no difference between the groups in outcome measures of number of days on a ventilator, duration of PN dependency, length of hospital stay, incidence of sepsis and NEC and intra-abdominal pressure at the time of closure. However due to the smaller than anticipated numbers in this study, the trial was significantly underpowered to detect any difference in this outcome measures between the groups. Previous retrospective studies have demonstrated improved outcomes following routine use of preformed silos although there are significant biases in patient allocation attributable to the retrospective nature of these reports [39, 40]. More recently however, a national non-randomised cohort study from the UK [41] has not shown any proven benefit of one approach over the other and has raised some concerns about the safety of pre-formed silos based on a higher incidence of intestinal ischaemia in cases treated with a pre-formed silo. A systematic review and meta-analysis on this topic suggested although that routine use of a pre-formed silo is associated with fewer days on a ventilator, strong evidence to support either strategy was not available [42].

One of the most challenging aspects of the treatment of the infant with gastroschisis is the management of intestinal dysfunction following return of the bowel to the abdomen and abdominal wall closure. The precise aetiology of this dysfunction is unclear but it is proposed that there is a degree of intestinal damage sustained *in utero*. A number of interventions have been proposed to improve the intestinal dysfunction including prenatal amniotic fluid exchange, elective pre-term delivery [43, 44], elective Caesarian section delivery [45], early onset of enteral feeds [46] and administration of pro-kinetic agents [47]. The efficacy of early delivery and of pro-kinetic agents has been investigated in RCTs. Logghe et al. performed a RCT comparing elective delivery at 36 weeks gestation with spontaneous onset of labour [43]. They found no clear benefit in terms of time to full enteral feeding or hospital stay in infants who were electively delivered at 36 weeks although the sample size was small. Curry et al. investigated the effect of enteral erythromycin as a prokinetic agent on time taken to achieve full enteral feeds compared with placebo in a prospective randomised study comprising 62 infants with gastroschisis [47]. No benefit was observed in time taken to achieve full enteral feeds nor episodes of sepsis, duration of PN requirement or total hospital stay in infants receiving erythromycin.

72.7 Congenital Lung Lesions

Congenital cystic adenomatous malformation (CCAM) and bronchopulmonary sequestration are congenital lung lesions often detected on routine antenatal scanning. Whilst there is general consensus that symptomatic CCAMs should be surgically excised to allow symptomatic relief, controversy exists surrounding the optimal management of asymptomatic lesions. Justification for surgical excision of asymptomatic lesions is the avoidance of symptoms or other complications (e.g. malignant transformation) in the future. However such an approach is not without risk and involves exposing the child to potentially significant surgical complications [48]. Whilst there are no randomised studies comparing surgical excision with non-operative observation,

Stanton et al. have performed a meta-analysis of the postnatal management of antenatally diagnosed lung lesions [49]. They concluded that the risk of an asymptomatic lesion becoming symptomatic is extremely low and that a non-operative approach may be appropriate for small lesions. A more recent study confirmed that non-operative observation does appear to be an acceptable management strategy [50]. Further prospective studies are required to provide reliable data to guide clinicians and parents on the optimum management of asymptomatic lesions.

72.8 Hirschsprung Disease

Hirschsprung disease, characterised by an absence of ganglion cells in the nerve plexi of the large bowel, most commonly presents in the neonatal period with failure of passage of meconium within the first 48 h of birth and is often associated with abdominal distension, with or without vomiting. Diagnosis is based on rectal biopsy and following diagnosis, definitive surgery is planned to excise the affected colonic segment. There are a number of operative techniques, the main differences between them being the nature of the anastomosis between the 'pulled through' section of normal bowel, proximal to the excised aganglionic segment and the rectum. Evaluating and comparing these procedures is problematic for many reasons. Firstly, the main outcome measures of interest are long term and primarily relate to bowel function. As is the case following surgical correction of anorectal malformations, there are difficulties in quantifying bowel function in such a way that meaningful results can be achieved. In additional there is inter-patient variability in the severity of disease, length of affected intestine and susceptibility to enterocolitis, a well-established complication of Hirschsprung disease. Thus strong evidence in support of one operative technique over the others is lacking.

Despite this, significant advances in the management of neonates with Hirschsprung disease have been made in recent times. With the advent of laparoscopic surgery, many surgeons are performing a pull through procedure either with the assistance of the laparoscope [51] or in a completely minimally invasive fashion [52]. Early experience suggests that the traditional benefits of minimally invasive surgery can be achieved with functional outcome similar to that reported following open surgery. However, long term follow-up of these children is, at present, lacking.

The other recent advance is the use of the primary pull-through procedure in selected infants. The traditional approach to the infant with Hirschsprung disease has been to achieve intestinal decompression with a stoma, to perform a pull-through procedure with this covering stoma and then to close the stoma following successful healing of the pull-through. However it is now clear that selected infants can be successfully managed with a primary pull-through procedure with intestinal decompression achieved preoperatively with rectal washouts and avoiding the need for a stoma altogether. One potential disadvantage of this is a higher incidence of postoperative enterocolitis [53] but this is not a consistent finding across series [54] and it is evident that the primary pull-through is here to stay.

72.9 Inguinal Hernia

Inguinal herniotomy is the procedure of choice for neonates with an inguinal hernia (IH). Gross et al.'s report in 1953 of 3874 children who underwent inguinal herniotomy reported a recurrence rate of just 0.15% [55]. The standard approach to inguinal herniotomy was by an open groin incision but laparoscopic repair is now routinely practised with comparable outcomes [56]. In the neonatal population there are a number of issues which remain largely unanswered. These are: how the contralateral groin should be managed, whether laparoscopic repair confers any benefit over open repair in this age group and whether repair should be undertaken on an urgent or even emergent basis due to the perceived higher risk of incarceration in the neonatal population.

Despite being debated for over 50 years, management of the contralateral groin in infants with unilateral IH remains controversial. It is recog-

nised that a proportion of infants with IH will develop a metachronous contralateral hernia but identification of such infants has proved difficult. Some surgeons advocate routine contralateral open groin exploration at the time of repair of IH but this places the contralateral vas deferens and testicular vessels at potentially unnecessary risk. A systematic review estimated that the incidence of metachronous contralateral hernia in infants <6 months of age was 11% and that 9 contralateral groins would need to be routinely explored to prevent one metachronous contralateral hernia [57].

The introduction of laparoscopic IH repair has serendipitously provided a unique insight into this problem. Laparoscopy enables the surgeon to visualise both deep inguinal rings at the time of inguinal hernia repair and perform bilateral closure should the contralateral deep ring be open. Fundamental to the role of laparoscopic repair of IH repair in neonates must remain the efficacy of the procedure. Initial reports of laparoscopic repair of IH in children suggested a higher recurrence rate than could be achieved with open surgery [58, 59]. Recent RCTs comparing open and laparoscopic IH repair in children have reported similar recurrence rates with both techniques although none have focussed specifically on neonates [60–62]. The role of laparoscopy in the treatment of IH and prevention of metachronous IH in infants (<1 year) is currently being investigated in a prospective randomised study (www.marchtrial.org).

The optimal timing of IH repair in neonates is also unclear. The risk of incarceration of IH is believed to be higher in infants, in particular infants born pre-term, when compared with older children [63]. This has led to some surgeons repairing inguinal hernias on an urgent basis in infants, and for pre-term infants with an IH to have a hernia repair prior to discharge home. The precise risk of incarceration, however, is unknown as there are no observational studies where children known to have a hernia have been observed without planned elective surgery.

One important consideration in hernia repair in boys is future fertility, because of the possibility of damage to the vas or vessels, either during repair, or if a hernia becomes incarcerated. Very little is known about testicular size and fertility following herniotomy, but hopefully infants who have been recruited to RCTs will provide cohorts who will be followed up into puberty to answer this important question. This further demonstrates a significant problem for top-level evidence in neonatal surgery, that important outcomes may not be apparent for many years. This provides problems, particularly where populations are relatively mobile, as in the UK.

72.10 Necrotising Enterocolitis

The general principles of surgery for the infant with advanced necrotising enterocolitis (NEC) are to control intra-abdominal sepsis and remove ischaemic or irreversibly diseased intestine whilst preserving as much intestinal length as possible. A number of techniques have been proposed to achieve these aims, including resection of bowel with primary anastomosis, resection with stoma formation and the ‘clip and drop’ technique with subsequent ‘second look’ laparotomy [64–66]. None of these techniques has been subjected to a RCT to determine superiority over the others and they are all in common usage today with justification for their use coming from a number of series all reporting, in general terms, similar outcomes. However the landscape is beginning to change with an on-going trial of stoma versus primary anastomosis in infants with NEC requiring intestinal resection.

In addition to laparotomy, peritoneal drainage has been proposed as a useful intervention in the infant with perforated NEC. Initially described by Ein et al. [67] as a procedure for infants thought too unwell to tolerate laparotomy, it has subsequently been described as a stabilising manoeuvre [68, 69] in the smallest and sickest infants and even proposed as primary definitive treatment [70–72]. Recently, two RCTs have addressed the issue of whether primary peritoneal drainage or laparotomy is superior in the smallest infants with NEC. These are summarised in Table 72.1 [73, 74].

Post-operative treatment of infants who have had surgery for NEC is also open to debate. The

Table 72.1 RCTs comparing laparotomy with primary peritoneal drainage in infants with perforated necrotising enterocolitis

Study	Included infants (g)	Number	Main outcomes	Authors conclusion
Moss 2006 [73]	<1500	PPD 55 Lap 62	No difference in mortality or dependence on PN at 90 days or length of hospital admission	No effect of procedure on outcome
Rees 2008 [74]	<1000	PPD 35 Lap 34	No difference in survival, ventilator or PN dependence at 1 or 6 months or length of hospital admission. 74% of infants undergoing PPD required delayed laparotomy	Recommend early laparotomy

PPD primary peritoneal drain, *Lap* laparotomy, *PN* parenteral nutrition

Table 72.2 RCTs comparing open and laparoscopic pyloromyotomy in infants with pyloric stenosis

Study	Detail	Number	Recovery time	Complications	Other significant findings	Authors conclusion
Greason 1997 [79]	LP vs. UMB	LP 10 OP 10	LP < OP	Similar	-	Recommend LP
St Peter 2006 [77]	LP vs. Open[a]	LP 100 OP 100	Similar	Similar	Less pain and vomiting with LP	Recommend LP
Leclair 2007 [78]	LP vs. UMB	LP 50 OP 52	Similar	Similar	Less pain with LP	Recommend OP
Hall 2009 [76]	LP vs. UMB	LP 87 OP 93	LP < OP	Similar	Less analgesia with LP	Recommend LP

[a]Open in this study was either by supra-umbilical or transverse upper abdominal incision
Umb supraumbilical, *LP* laparoscopic pyloromyotomy, *OP* open pyloromyotomy, <, denotes shorter than

period of antibiotic usage, time to introduction of enteral feeds, and type of enteral feed are all areas where practise is based on weak evidence. Although there have been no RCTs, a retrospective cohort study suggested that an early re-introduction of enteral feeds is associated with benefit in terms of hospital stay and decreased incidence of central venous catheter-related sepsis, but apparently without increased risk of recurrent NEC [75].

72.11 Pyloric Stenosis

The standard surgical approach to the infant with pyloric stenosis is the pyloromyotomy based on the technique originally described by Ramstedt. A number of modifications to this procedure have been introduced over time. Whilst the underlying surgical procedure has remained constant, the approach to the pylorus has been modified in attempts to improve cosmetic outcome, shorten post-operative recovery and reduce post-operative pain. The pyloromyotomy may be performed via an open incision in the right upper quadrant (RUQ), an open supra-umbilical incision or via a laparoscopic approach.

Four RCTs have studied the effect of surgical approach to the pyloromyotomy on post-operative recovery all comparing laparoscopic pyloromyotomy (LP) with open pyloromyotomy (OP) [76–79]. These are summarised in Table 72.2. Whilst three of these studies recommend LP over OP on the basis of shorter post-operative recovery and/or less post-operative pain or vomiting, one study is notable in its recommendation of OP over LP [78]. Although the incidence of complications was similar in both

groups in this study, the authors felt that although there was not a statistically significant difference, the trend towards a higher incidence of incomplete pyloromyotomy following LP (LP 3/50 *vs.* OP 0/52; p = 0.11) precluded the use of this approach.

A meta-analysis [80] including the three large scale RCTs concluded that post-operative recovery was shorter following LP with a similar incidence in overall complications between the groups. However, there was a trend (p = 0.06) towards a higher incidence of incomplete pyloromyotomy following LP when compared with OP. A further meta-analysis, which included prospective cohort studies as well as the RCTs reached similar conclusions. The findings of a trend towards an increased rate of incomplete pyloromyotomy in both these meta-analyses highlight another problem in conducting RCTs and meta-analyses of RCTs in neonatal surgery. Major complications, such as incomplete pyloromyotomy, are rare such that individual RCTs are frequently not powered to detect them. Even when several RCTs are meta-analysed, rare complications are problematic as RCTs without any complications (e.g. the zero rate of incomplete pyloromyotomy in each arm one of the trials [77]) do not contribute to the overall effect sizes in the meta-analysis when odds ratios or relative risks are used. Thus the strong trend towards a higher rate of incomplete pyloromyotomy following LP is critically dependent on precisely how the meta-analysis is performed. A large multicentre retrospective study of incomplete pyloromyotomy following open and laparoscopic pyloromyotomy showed that although there was a significantly increased risk following laparoscopy, the risk difference was <1%. One could argue that although important, such complications are so rare that they do not pose a *clinically significant risk* on an individual patient basis.

In summary, it appears that duration of post-operative recovery and post-operative pain are shorter following a laparoscopic approach to the pyloromyotomy and that LP is a valid technique so long as due care and attention is paid to avoiding incomplete pyloromyotomy.

72.12 Commentary

Despite the well-established and accepted role for surgical intervention in the management of many conditions affecting the term and pre-term neonate, a quality evidence base supporting many of these interventions is lacking. Surgical approaches and techniques have largely evolved over time with outcomes being compared to history rather than being formally compared prospectively. There is a clear need for well designed, prospective, randomised studies in improving the outcomes of infants with surgical conditions as well as advancing our knowledge. Neonatal surgery is a difficult area in which to conduct randomised controlled trials because of the relatively small number of patients, and the perceived difficulty in getting surgeons to participate and parents to consent to randomisation. In addition, some outcomes are difficult to assess or compare.

There is now clear evidence that successful surgical randomised controlled trials can be achieved even in this patient population. Of note, however, only a few trials have randomised and studied the number of patients required by their power calculation. Due to the relative small number of surgical neonates in each hospital it is necessary to: (1) develop a collaboration among paediatric surgical units to foster multicentre RCTs; (2) change the attitude of clinicians, nurses and parents similarly to encompass the concept of widespread routine recruitment into RCTs; (3) appreciate the importance of protocol, equipoise and clinical relevance in the management of surgical neonates. Evidence based neonatal surgery is, quite rightly, here to stay; we must encompass it, develop it and excel in it for the future benefit of those in our care.

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3

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