Neonatal Surgery

Contemporary Strategies from Fetal Life to the First Year of Age

Mario Lima
Olivier Reinberg
Editors

Springer

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Introduction to Neonatal Surgery

1

Olivier Reinberg

In 1989, the British National Confidential Enquiry into Perioperative Deaths (NCEPOD) ruled "that pediatricians and general surgeons must recognize that small babies differ from other patients not only in size and stated that they pose quite separate problems of pathology and management" [1].

As pediatric surgeons, we are convinced that children are not just small adults. This is all the more true for neonates. Neonates have some unique problems that require very special knowledge, special surgical managements, and facilities specifically designed for them. Pediatric surgeons must understand their special needs and that of their relatives. They must learn team working with other specialists. They have to create the conditions to follow their patients from birth into adulthood as the treatments do not end with the healing of the problem but once the child has become an adult.

With the rapid advances in fetal diagnosis, babies are no longer referred at the time of birth, but when prenatal diagnosis is made even if termination of pregnancy is planned because of an expected poor prognosis. Direct contacts between the prenatal team, the neonatologists, and the pediatric surgeons are also highly recommended to ensure continuity in the messages delivered to the parents.

We live now in the era of evidence-based medicine (EBM), and best evidences are generated from prospective trials. Unfortunately, when compared with adult general surgeons who may operate hundreds of similar cases, pediatric surgeons perform a great variety of different procedures but few of each. Consequently, the indications for surgery and the type of procedure performed in neonates are rarely supported by randomized controlled trials, the majority being supported by retrospective studies and surgeon's preferences. Hall and Pierro have tried to summarize what was the EBM randomized controlled trial (RCT) (level I evidence) of some of the most common neonatal procedures (esophageal atresia, congenital diaphragmatic hernia (CDH), bowel atresia, anorectal malformations, anterior abdominal wall defects, congenital lung lesions, Hirschsprung's disease, inguinal hernia, necrotizing enterocolitis, pyloric stenosis). Their review highlights the fact that a quality evidence base supporting many of these interventions is lacking. Only a few randomized controlled trials have been done in neonatal diseases such as congenital diaphragmatic hernia, necrotizing enterocolitis, pyloric stenosis, and inguinal hernia. All of these trials have been based on collaboration between pediatric surgical units convinced by the importance of networks to promote multicenter prospective studies [2].

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In 1999, Hardin and Stylianos undertake to study the current state of the pediatric surgery literature and its value in determining best clinical practice. As of March 1, 1998, they found 9373 references provided through Medline. After review, only 34 studies (0.3%) were classified as prospective, randomized, controlled studies [3]. Twelve years later, Ostlie and St Peter have done a similar study in 2010, collecting all randomized controlled trials from January 1999 through December 2009 published in the English literature excluding transplant, oncology, and the other non-general subspecialties, to conclude that randomized controlled trials represent less than 0.05% of all publications involving pediatric surgery in the 26 journals with at least one trial (<1 trial for every 200 articles) [4]. It is concerning that they document a similar lack in the twenty-first century, despite the increased educational and public expectations placed on EBS.

In a recent lecture, Juan Tovar advocated to which extent pediatric surgery needs to base its therapeutic attitudes and operations on a solid research background [5]. This is particularly difficult on the field of clinical research because of the low prevalence of many of the conditions involved and also because of the fact that patients are minors that are not entitled to give informed consent by themselves for randomized studies. As regards laboratory research, this specialty is scarcely interesting for basic scientists. This situation can only be improved by prospective randomized studies performed in network collaboration with other hospitals/countries and by basic research conducted by pediatric surgeons and/or in association with other scientists [5].

Among the three particularly relevant recommendations that NCEPOD made in the report on perioperative pediatric deaths [1], the first one was: "surgeons and anesthetists should not undertake occasional pediatric practice". This was also a statement of the European Union of Medical Specialists (EUMS) in 1995: "Surgeons taking care of children should have adequate training in a pediatric surgical unit. They should also continue to have regular exposure to this type of patients." Neonatal surgery should only be carried out by surgeons and anesthetists whose pediatric workload is of adequate volume to maintain a high level of surgical competence and to allow the training of the residents. Congenital birth defects complicate 3–6% of pregnancies leading to live birth. As for example of the structural birth defects associated with significant mortality/morbidity, CDH is among one of the most common anomalies, occurring in about one per 2000–3000 live births. Consequently, the opportunity of training—and to keep his expertise—on a CDH is low. Added to these facts, the combination of a shortened training period and the "new deal" on junior doctors about the number of hours has serious implications for training.

This means that neonatal malformations need to be concentrated in some centers to allow sufficient case load. There are arguments for and against such large regional specialist pediatric centers. The benefits of centralization include concentration of expertise, more appropriate consultants on call, development of support services, and training. The disadvantages include children and their families far from their homes and the loss of expertise at a local level. The benefits of centralization far outweigh the adverse effects of having to take children to a regional pediatric intensive care center [6]. Unfortunately, in many places, politicians favor the multiplication of small regional centers to satisfy their voters who are poorly informed of the cold hard facts.

Nowadays, it is unacceptable to train on real patients. The new technologies, namely, minimal invasive surgery and simulators, have been of great help using simulation technology to reduce risks to both students and patients by allowing training, practice, and testing in a safe environment prior to real-world exposure. This is supported by interest in quality of care, restrictions on the use of animal models, limited number of cases, medicolegal pressures, and cost-effective performance. Many models are available. The usefulness of mechanical simulators with faithful models have been proven efficient: hypertrophic pyloric stenosis (Plymale, 2010), closure of patent peritoneo-vaginal tract (Breaud, 2014), pyeloplasty (Breaud, 2014), esophageal atresia (Maricic and Bailez, 2012; Barsness, 2014), and

CDH (Barsness, 2013). They have shift to realistic interactive models. Computerized modern technology with electronically assisted devices and virtual reality environment has provided new tools to the mechanical simulators.

We have now the tools to evaluate cognitive/clinical skills, technical skills, and social/interactive skills as we have seen how important this could be in neonatal surgery. Surgical simulators (mechanical, computerized, virtual) and models (animals and interactive) are the appropriate tools to learn, to train, to assess surgical skills, and to keep his expertise, in spite of the small number of cases.

Becoming a pediatric surgeon requires completion of one of the longest training programs among the medical systems and probably the widest as they have to learn a great variety of procedures but few of each. While specialization among adult surgeons usually focuses on a particular organ or region of the body, pediatric surgery deals with a defined age group. Pediatric surgeons are trained to operate anywhere on the body, and thus they appear to be probably the last general surgeons. They must ask their authorities to provide them modern tools to avoid training on real babies. Undoubtedly, this is expensive, but as said by Bok Derek at Harvard Law School, "If you think education is expensive, try ignorance!" They have to learn teamwork and multicenter collaboration. This will be the challenge of the new generation of pediatric surgeons to promote collaboration between pediatric surgical units and to create networks as to publish multicenter prospective studies with adequate sample sizes.

In spite of these daunting challenges, they remain some courageous volunteers as you probably are, you reader of this book. We need neonatal surgeons, motivated, well trained, wishing to transmit their skills and their knowledge to the future one.

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Part I

General

2 Anesthesiological Considerations: Stabilization of the Neonate, Fluid Administration, Electrolyte Balance, Vascular Access, ECMO, Bronchoscopy, and Pain in Neonates

Fabio Caramelli, Maria Teresa Cecini, Monica Fae, Elisa Iannella, and Maria Cristina Mondardini

2.1 Introduction

Despite progress in anesthesiology, neonatal anesthesia today still represents one of the most challenging areas in this field for the anatomical, physiopathological, and pharmacological features of newborn babies and requires not only highly specialist knowledge but also manual and technical skills, owing to the size and fragility of these patients.

The mortality rate linked to anesthesiological problems has fallen dramatically in neonates and infants from 1/10,000 in the 1960s to 1/100,000 (1/1,000,000 in healthy patients) today, but it is considerably higher than the equivalent rate in adults.

This proves the particular vulnerability of this patient group, mainly due to difficulties in airway management, the presence of congenital lesion or syndromes, coexisting pathologies, and, potentially, prematurity.

Furthermore, the developing brain seems to be susceptible to the damaging effects of the anesthetic drugs. Extensive literature from laboratory and animal studies [1, 2], as well as some epidemiological and cohort studies in humans [3–6], provide evidence of neurotoxic (apoptotic) effects of anesthetics during the synaptogenesis, which can induce long-term neurocognitive deficits.

On December 14, 2016, the Food and Drug Administration (FDA) issued a warning statement for the USA regarding the use of anesthesia or sedation in children less than 3 years of age [7]. Nevertheless, the hypothesis of anesthetic neurotoxicity has not been confirmed in humans, at least for a single and short-term anesthesia [8, 9]; therefore, the FDA warning is not shared by several Anesthesia European Societies [10].

At the same time, the focus is actually concentrating also on the need to ensure the newborn a safe conduct of general anesthesia and good perioperative clinical practice. The Safetots initiative (http://www.safetots.org/) highlights that there is a casual relationship between poor anesthetic conduct and risk of neuromorbidity.

In fact, several perioperative events may cause cerebral morbidity. The concept of 10-N has been proposed by the Safetots initiative to prevent neurological injury. The **10-N** principles provide a simple matrix of clinical goals: **N**o fear, **N**ormovolemia, **N**ormotension, **N**ormal heart rate, **N**ormoxemia, **N**ormocapnia, **N**ormonatremia, **N**ormoglycemia, **N**ormothermia, and **N**o postoperative discomfort [11]. It is recommended

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that the 10-N be applied to maintain physiological homeostasis.

The development of pharmacological knowledge, the availability of new smaller medical devices, the doubts related to the aforementioned safety of anesthetic agents, and, above all, the increased spread of ultrasound in the field of anesthesia have led to a progressive increase in the use of locoregional anesthesia techniques even in babies.

These safe and effective techniques can be easily used in selected cases, even without sedative drugs, employing non-pharmacological techniques of distraction, as demonstrated by preliminary report of the ongoing GAS trial [8].

In the following pages, only certain aspects of the anatomy and physiology of the newborn and their changing features over time will be touched on briefly within each individual topic, apart from those of fluid balance and body composition.

2.2 Surgical Emergencies and Stabilization

With the advances in care of the newborn over the last 20 years, most of the surgical pathologies that were emergencies in the past no longer require immediate surgery.

This change in the approach toward the surgical neonate was also born from the evidence that adequate stabilization time before the operation is able to improve outcomes, leading the patient to the surgery in the best possible conditions.

The stabilization of the patient is even more important if he has to be transferred, given that the transport is challenging for the physiologic reserve of the critically ill newborn.

In fact there is greater risk for babies requiring neonatal intensive care who are transferred ex utero than those transferred in utero [12].

Stabilization is optimization of clinical conditions and physiologic functions on the basis of the underlying pathology and its pathophysiology, targeting the therapy also on coexisting diseases (e.g., CHDs), as failure to do so may mean futile every other efforts.

The fundamental concepts of the stabilization are always the same in medical and surgical emergencies—detailed medical history, exhaustive physical exam, and management of ABCDE—such as maintaining correct body temperature, fighting respiratory insufficiency, optimizing blood volume, and cardiac output.

Monitoring, respiratory and cardiac support, fluid and electrolyte replacement, and optimal analgesia are the cornerstones of this process, and this strategy should be carried on also in the operating theater to avoid any clinical deterioration.

In fact, as already mentioned, maintenance of physiological homeostasis is key for the safe conduct of anesthesia. Experience is recommended to avoid or minimize complications and adverse events, especially in neonates, which are prone to hypotension, desaturation, and effects of anesthetics.

During the perioperative period, it is important to avoid not only hypotension, hypocapnia, and hypoxemia but also hyperoxemia and hyponatremia, especially in neonates. All these events can cause subclinical neuronal damage: hypotension and hypocapnia can lead to cerebral hypoperfusion; hypoxemia is tolerated only for a short time because neonates have higher oxygen demand and lower oxygen reserves [13].

Congenital diaphragmatic hernia (CDH) is prototype of this changed paradigm.

Approximately 1 in 3000 babies is born with a congenital diaphragmatic hernia [14].

The disorder is characterized by herniation of the abdominal viscera into the thoracic cavity and pulmonary hypoplasia. This one, with associated pulmonary hypertension and ventricular dysfunction/hypoplasia, is key factor which contributes to the morbidity and mortality associated with CDH (30–40%).

The current strategy to postpone surgery until the cardiorespiratory function is stabilized reflects the idea that surgery cannot correct these factors [15].

Firstly, after delivery, the infant should be intubated immediately without bag and mask ventilation, and a nasogastric tube should be positioned to avoid bowel distension that can limit the expansion of the lung [15].

Routine use of surfactant is not recommended [16], and conventional ventilation seems to offer better results in comparison with high-frequency oscillatory ventilation (HFOV) regarding time on

mechanical ventilation, need of extracorporeal membrane oxygenation (ECMO), inhaled nitric oxide (iNO), sildenafil, inotropes, and numbers of failed treatment, as shown by the recent VICI (Conventional mechanical ventilation versus high-frequency oscillatory ventilation for congenital diaphragmatic hernia: a randomized clinical trial (the VICI-trial)) [17].

These results probably suggest that minimizing lung injury is much more important than the used strategy to reach it.

However, ventilation is not the only way to improve blood oxygenation. Inotropes and pulmonary vasodilators are also needed to maintain better systemic/pulmonary blood pressure (BP) and to counteract right-to-left shunting across the ductus.

Extensive use of echocardiography can not only give several prognostic factors [18, 19] but also helps in clinical management, allowing for monitoring of pulmonary hypertension, diastolic function of the right ventricle, dysfunction/hypoplasia of the left ventricle, and response to the therapy.

iNO, the most frequently used pulmonary vasodilators [20], failed to improve survival or reduce the need for ECMO, but, in some cases, an increase in PaO_2 was observed [21].

Pulmonary hypertension may also be treated by several other agents (Milrinone, sildenafil, PGI_2, inhaled iloprost, bosentan) even if there is limited evidence of positive effects on primary outcomes [22–26].

However, the hemodynamics, the cardiac insufficiency, and the pulmonary hypertension should be managed simultaneously, as previously described, in order to progressively obtain the better oxygenation and perfusion with the lesser ventilatory insult during the stabilization phase.

From this point of view, prostaglandin-E $(PGE)_1$ can also be used to improve the hemodynamics, employing the ductus as a ventricular vent in case of severe pH and right ventricular dysfunction [27, 28].

There are no standard criteria to define physiologic stabilization, but also our group has proposed the trend and the value of five different respiratory and blood-gas-derived indices to guide the timing of surgery [29]. The reliability of these indices may probably be increased by the use of echocardiography [30, 31].

2.3 Fluid Administration and Electrolyte Balance in Neonate in the Perioperative Period

Fluid and electrolyte therapy is an essential component of the care of the neonatal surgical patient, and an accurate understanding of the changing requirements of growing is fundamental in appreciating the many important pharmacokinetic changes that occur from birth to childhood.

There are developmental considerations that anesthesiologists should consider.

Total body water (TBW) content changes remarkably from before birth until 1 year of age. At 24 weeks' gestational age, a baby's TBW content is close to 85% of total body weight (BW), which is due to a large extracellular fluid (ECF) volume of 40–50% of BW (in comparison with 20% in adults) [32]. This percentage decreases to 75% of total BW for a term newborn but small for gestational age (SGA); preterm infants have an even higher TBW content than appropriate for gestational age babies (AGA) [33].

After birth, the excess of TBW is mobilized and excreted, and the newborn may lose up to 10–15% of its weight (in preterm babies) in the first week of life. Then, the intracellular fluid (ICF) compartment progressively increases at the expense of the ECF compartment. This means that extracellular water content falls in parallel with TBW content, from 45% at term to 20–25% at 1 year of age. The ECF is further divided into plasma volume (intravascular fluid, equal to 4–5% of BW and proportionally similar at all ages) and the interstitial fluid.

There is a similarity in extracellular and intracellular electrolyte composition in children and adults, but, due to the higher ECF volume in infants, there is more sodium and chloride per kilogram and less potassium in infants than in adults.

Furthermore, newborns carry a lower liver mass (glycogen stores) and muscle mass (protein stores) and, therefore, are less able to maintain the normoglycemia during fasting through glycogenolysis and gluconeogenesis.

The postnatal shift in body fluid is principally mediated through the regulation of water and

sodium excretion by the kidneys (due to the increase in atrial natriuretic peptide (ANP) secretion and tubular insensitivity to aldosterone) [34, 35].

A term newborn's glomerular filtration rate is about 25% of that of an adult, and this impairs the ability to excrete a water load. Renal function is not completely developed, and, in particular, sodium clearance is limited. Therefore, the neonate's kidneys have limited capacity to excrete both concentrated and diluted urine so are unable to concentrate urine despite dehydration [36, 37].

Neonates also have large blood volume, high metabolism, and high fluid turnover rates relative to their body weight. These changes have important implications for drug therapy, fluid management, electrolyte needs, and glucose requirements in the perioperative period.

In particular, neonates undergoing major surgery are at greater risk of developing dehydration, hyponatremia, and alteration in blood glucose level [38].

Hyponatremia is the most frequent electrolyte disorder in the postoperative period [39]. Recent studies have shown that hyponatremia is due to the administration of hypotonic solutions and the presence of multiple non-osmotic stimuli for antidiuretic hormone (ADH) release [40]. Severe hyponatremia leads to cerebral edema, the main clinical signs being a decreasing level of consciousness, disorientation, and, in the most severe cases, seizure, permanent handicap, or death [41]. Therefore, avoiding infusion of hypotonic fluids, during surgery and in the early postoperative period, should prevent hyponatremia [42].

Fluid requirement can increase due to high liquid loss during the perioperative stage, caused by prolonged fasting, vomit, diarrhea, fever, and major tissue exposure occurring during abdominal and thoracic surgery. Therefore, fluid administration for the neonatal surgical patients must be aimed at supplying basal metabolism requirements (maintenance fluids), compensating preoperative fasting and fluid losses (deficit fluids) and replacing losses during surgery (replacement fluids).

Conceptually, this distinction between maintenance requirements, deficits, and replacement loss is helpful to plan any intraoperative fluid management. Although the pathophysiological bases are well-investigated, some aspects still remain controversial, mainly in newborn infants.

The goal of infusion therapy is to maintain or reestablish the neonate's normal physiological state in blood volume, tissue perfusion, metabolic function, electrolyte, and acid-base balance [43].

The optimal regimen of fluid management is still a matter of debate, and great concerns remain about the type of fluids, the ideal composition of solutions, and the amount of fluids that should be administered [44].

In any event, the neonatal anesthesiologist must bear in mind that the preoperative fasting times for patients should be as short as possible to prevent newborn dehydration, ketoacidosis, and discomfort [45].

In line with the European Consensus Statement Guidelines, recent literature recommends the use of low glucose (1–2.5%) isotonic balance solutions during neonatal surgery. These types of fluids have been shown to maintain acceptable glucose levels and prevent electrolyte imbalances in the perioperative period [46].

Due to the renal function immaturity, the majority of synthetic colloids should not be used. The colloid molecules are large and cannot be filtered by the kidneys; therefore, they remain in plasmatic volume for an unpredictable time.

Albumin 5% has been considered the gold standard for the maintenance of colloid osmotic pressure in neonates and continues to be the most frequently used fluid in volume replacement therapy.

The "right amount" of fluid administration still remains uncertain; however, a fluid infusion rate of approximately 10 mL/kg/h is required in neonates [47].

The most useful parameters that assess the efficacy of the intraoperative infusion therapy are mean arterial blood pressure, heart rate, capillary refill time, core-peripheral temperature gradients, base deficits, and blood glucose levels. Measurement of central venous pressure and diuresis do not predict the real fluid responsiveness.

In case of major surgery, regular (hourly) blood gas analyses should be performed to assess the acid-base status (base excess, lactate) and

blood glucose level. It is recommended to use a syringe pump or infusion pump in order to avoid accidental overload fluid infusions during neonatal intraoperative fluid therapy.

In the postoperative period, neonates on intravenous fluid therapy need to be evaluated regularly with daily weight measurements, fluid balance assessment, plasma electrolytes, and glucose concentrations.

2.4 Pharmacology

The pharmacokinetics and the pharmacodynamics in neonates are often difficult to predict; there are considerable interindividual differences and variability related to gestational age, postnatal age, coexisting diseases, and different genetic polymorphisms. Indeed, pharmacological data is often lacking and extrapolated from adults by allometric equations with corrective factors for the maturation of metabolic functions [48] (Box 2.1).

Not only is distribution volume increased in neonates but also metabolic/elimination ability is reduced at birth; this depends on postconceptional age and changes quite rapidly over time [49, 50].

Pharmacodynamics of anesthetics is also affected by rapid changes in neuronal connections, functional interrelationships, regional blood flow, and number of γ-aminobutyric acid type A ($GABA_A$) receptors in the developing human brain [51].

Often the use of drugs is off-label in neonates; only a minority (<5%) of the medications used in hospitalized neonates had been approved by the FDA, and no anesthetics had updated labeling for premature babies above 29 weeks of GA [52, 53].

Neonates have narrower margins of error in drug delivery and dilution as well as a higher incidence of drug substitution and drug dosage errors in comparison with adults, increasing the clinical risk of drugs with a low therapeutic index, like anesthetics [54].

Furthermore, adult monitoring systems of anesthesia levels are not validated for use in neonates, making the measurement of the pharmacodynamics anesthetic targets impossible [55].

Therefore, clinical evaluation maintains a pivotal role in the management of anesthesia.

In this setting, inhalation agents usually remain the preferred choice of neonatal anesthesiologists for their versatility, predictability, and singular pharmacokinetics, independent of the different organ functions.

2.5 Vascular Access in Neonates

Adequate vascular access is often challenging in neonates [56] but is fundamental in modern emergency and intensive care and plays a decisive role in stabilization of the patient.

Nowadays, the use of ultrasound (US) has greatly increased the percentage of success in gaining vascular access [57], but, given the size of neonatal structures, equipment with a small linear probe at high frequency (>10 MHz) is needed. Furthermore, it should include Doppler, which allows screening for occlusion and thrombosis, and zoom functions.

The vessel can be visualized in the short-axis view (SAX), where the probe is placed transversally to the direction of the vessel, which is seen in cross section, and in the longitudinal view or long-axis view (LAX), where the probe follows the direction of the vessel, which is seen in its length.

According to the chosen visualization approach, the progression of the needle will be placed in the US beam, so called in-plane (IP) or will cross it perpendicularly, so called out-of-plane (OOP).

Obviously, in the first case, the movement and position of the needle can be seen clearly, but it is not simple to keep the needle in the US beam.

2.5.1 Peripheral and Central Venous Catheterization

Several different approaches are possible, and the choice among these different options is made on gestational age, size, site availability, underlying pathology, and, above all, duration of and indication for vascular access.

They can be classified on the basis of site of access and tip position (umbilical, peripheral, central peripherally inserted, and central) and of expected length of use (short term, long term, and permanent).

2.5.1.1 Umbilical Catheters (UC)

The umbilical vein is the recommended emergency access for neonatal resuscitation, and catheters can easily be positioned in the first few days of life, sometimes up to the end of first week. It is to consider as any other central line but must be removed after 5–7 days [58].

Indications for positioning of UC are low GA (<29 weeks) or higher GA (>29 weeks) but needing mechanical ventilation (MV), total parenteral nutrition (TPN), hemodynamic support, or intravenous infusion in cases of difficult peripheral access [59].

The choice of size according to ultrasound measurement of the diameter of the inferior vena cava and ecographic evaluation of tip position are strongly recommended. A high position is optimal, where the catheter is advanced through the ductus venosus into the IVC. If a radiological check is carried out, the optimal response is the T6–T9 space, above the diaphragm. The tip of a UC in the heart may result in perforation, pericardial effusion with cardiac tamponade, potentially fatal arrhythmias, endocavitary thrombosis, or pleural effusion.

A UC placed in the portal system can lead to necrotizing enterocolitis, colonic perforation, necrosis and hepatic hematomas, hepatic cysts perforating vessels of the portal system, and portal hypertension. Future perspective is to follow the catheter under echographic vision along its progression up to the optimal point. UC migrations have been demonstrated in 50% of patients in the first 24–48 h.

2.5.1.2 Peripheral Venous Catheters (PC)

They are generally inserted at the level of superficial veins of the upper limbs, lower limbs or, in certain cases, at the level of the scalp. They are indicated in preterm births >31 weeks. GA or at term which should receive non-hyperosmolar fluid therapy for a short period of time (maximum 6 days).

In addition to needle cannulas, long cannulas (mini-midline) and long peripheral catheters (midline) may be used, and, in these cases with peripheral access, it is possible to advance and position the catheter up to a great vessel, which allows for it to be kept in place for a longer period of time and to be used for endovenous solutions with higher osmolarity.

Peripheral access can also be gained by using a surgical venous cutdown (the saphenous vein is the usual primary choice). This method, frequently used in the past, today has a limited role only in emergency situations when other peripheral, central, and intraosseous attempts fail.

Intraosseous Catheters

Intraosseous catheters still have a major role in life-threatening emergency situations when other access methods fail and when time is of the utmost importance.

In neonates, the preferred choice is the proximal tibia, but other sites are the distal tibia and distal femur [60].

The pediatric resuscitation guidelines from the American College of Surgeons Advanced Trauma Life Support (ATLS) manual recommend that intraosseous access should be established in the newborn in case of circulatory collapse if umbilical venous access cannot be rapidly achieved [61].

2.5.1.3 Peripherally Inserted Central Catheters (PICC)

In the same way, as described above for midline catheters, the tip can be placed in a central position (at the junction of the superior vena cava with the right atrium).

Usually, a suitable vein is selected under US guidance, and the skin is carefully cleaned and draped. The vein is cannulated using a removable needle, a peelable cannula, or semi-Seldinger technique. The catheter is then inserted into the vein and slowly advanced up to the desired length. Correct catheter tip location must be verified either radiologically or ultrasonographically or using intracavitary electrocardiography.

PICCs combine the advantages of peripheral catheters (less infection risk, fewer complications

during implant) with the advantages of central catheters (long-term use, high osmolarity of fluids infused).

Its main disadvantages are hazardous venous progression after initial cannulation and small-caliber catheters that may preclude blood sampling, transfusion, and rapid fluid rates. Thrombosis and catheter occlusion (10% risk) are the most frequent mechanical complications with PICCs, but even cases of rupture and embolization have been described.

However, a Cochrane review suggested that PICC use improves nutrition in newborns without any evidence of increased adverse events, including systemic infection [62].

2.5.1.4 Central-Inserted Central Catheter (CICC)

Central access (internal jugular, IJV; subclavian, SV; or femoral vein, FM) can be gained percutaneously through direct puncture with a landmark approach, but a US- guided technique has fewer risks of complications.

After the vein puncture, the catheter is placed into the vein using the Seldinger technique and an atraumatic guide wire with a J-tip. Unfortunately, in the smaller patient, the radius of curvature of the J-tip is close to, or larger than, the vein. This can produce difficulties when introducing the guide wire [63, 64].

The central way is chosen when the peripheral approach is not achievable, and the patient needs medium- or long-term infusion of TPN, drugs or inotropes, and hemodynamic monitoring (CVP).

Whatever the site of insertion, verifying the catheter tip position with X-rays is mandatory. For catheters placed in the superior vena cava (SVC), the tip should be [1] outside the pericardial sac to avoid perforation and tamponade and [2] parallel to the vessel wall to avoid perforation. For catheters in the inferior vena cava (IVC), the tip should be below the level of the renal veins so as not to obstaculate drainage.

In case of CVP monitoring, the tip should be placed in the upper part of the right atrium, but this increases the risk of dysrhythmias, thrombosis, and perforation.

Complications of Central Access

Perforation, infection, and thrombosis are the three major late complications of central venous access. The early complications are malposition, arterial puncture, hematoma or hemorrhage, and pneumothorax or hemothorax in the cases of IJV or SV.

A strict protocol of catheterization technique and management is needed to avoid infection. The use of maximal sterile barriers is recommended. Aseptic technique is mandatory as echographic guidance. Tunneling reduces the incidence of infection [65].

Two percent chlorhexidine is now recommended, especially in preterm infants, for disinfection. Over the last 10 years, several studies have shown its superiority to iodopovidone (harmful due to reabsorption of iodine), and it can be used even for continuous antisepsis at the exit point [66].

Any strategy stabilizing the catheter at the onset reduces risk of infection and thrombosis. For this reason, the use of "sutureless" devices for catheter stabilization and semipermeable transparent dressings is highly recommended, as well as the application of iso-acrylic glue at the exit point.

There is no great consensus on efficacy and safety of heparin for prevention of catheter-associated thrombosis and occlusion. In fact, prophylactic continuous heparin infusion does not seem to reduce the risk of thrombosis, but it may obstaculate catheter occlusion and prolong its life [67].

However, on the basis of a Cochrane review [68] and RCT [69], the Antithrombotic Therapy and Prevention of Thrombosis in Infants and Children Guidelines from the American College of Chest Physicians (ACCP) published in 2012 [70] recommend a UFH continuous infusion at 0.5 units/kg/h over no prophylaxis (Grade 1A) or intermittent local thrombolysis (Grade 2C) to maintain catheter patency.

2.5.2 Arterial Catheterization

Despite noninvasive monitoring techniques, indwelling arterial catheters are often required in the management of critically ill neonates or

neonates undergoing major surgery for continuous hemodynamic monitoring and blood sampling.

The umbilical, the radial, and femoral artery are the most frequently used. The humeral artery should be considered with caution (terminal artery, proximity of median nerve), even if one study shows the same complication rate as the radial artery [71]. The temporal artery should no longer be used for the risk of cerebral embolization when flushing the line. In neonates, the posterior tibial artery and the dorsalis pedis artery can easily be cannulated.

The major complications of arterial cannulation are nerve injury and ischemia. Ischemia may be related to [1] vasospasm, usually temporary [2], thrombosis, much more dangerous, but often blood flow resumes several weeks after removal and therapy [3], embolism.

The ACCP guidelines, previously mentioned, also recommend the prophylactic infusion of unfractionated heparin to prolong catheter patency and avoid thrombosis. The usual dose suggested is 0.5 U/mL/h at 1 mL/h, except for arterial UCs (0.25–1 U/mL, 25–200 U/kg/day) [70].

2.6 Neonatal Bronchoscopy

Airway problems in the neonatal population are often life-threatening and raise challenging issues in diagnosis and management.

The airway problems may result from congenital or acquired lesions and can be broadly classified into those causing obstruction or those due to an abnormal "communication" in the airway.

A high index of suspicion helps ensure an early diagnosis. Consider the possibility of an airway problem and check whether the following symptoms/signs are present:

- Recurrent stridor or wheeze
- Chronic cough
- Recurrent cyanotic episodes
- Life-threatening events
- Feeding difficulties with failure to thrive
- Repeated failed extubation attempts
- Associated congenital anomalies especially cardiac defects
- Signs of dysmorphism
- Recurrent aspiration pneumonia
- Persistent atelectasis or lobar hyperinflation on chest X-ray

Bronchoscopy is essential to determine the extent and severity of the airway problem and to plan treatment strategy [72].

This can be done using flexible bronchoscopes at the bedside or rigid bronchoscopes in the operating room.

2.6.1 Flexible Bronchoscopy (FB)

For the neonate with small airways, lung disease, and very little respiratory reserve, a bedside study with a flexible scope is possible, but a rigid bronchoscopy with general anesthesia is likely to be needed in the operating room.

2.6.1.1 Indications

FB enables us to obtain anatomical and dynamic information of the airways and to perform cytological and microbiological studies. Its indications arise with the need to respond to symptoms or radiological anomalies that cannot be explained by noninvasive methods or to obtain samples from the lower airways [73].

– Persistent Stridor
  Its main cause is the laryngomalacia tending to disappear within the first year and therefore does not usually require endoscopic revision; in case of atypical presentation in association with syndromes or malformations, a complete exploration is recommended as there may be anatomical, congenital, or acquired anomalies.
– Persistent/Recurring Atelectasis
  The most frequent findings are mucus plugging, foreign bodies, extrinsic compression in cases of congenital cardiopathy, and inflammatory granulation tissue.

– Therapeutic Procedures
  FB can be useful for resolving atelectasis due to the retention of secretions or mucus plugging. The percentage of radiological re-expansion is variable, generally not higher than 50%.
– Difficult and Selective Indications
  Bronchoscopy can act as a guideline for intubation in cases of craniofacial anomalies and polymalformative syndromes or in selective bronchial intubation.

2.6.1.2 Contraindications

The indication for FB should be individualized, evaluating the risk/benefit for each patient.

Some absolute contraindications impede performing bronchoscopy: severe refractory hypoxemia, hemodynamic instability, uncorrected hemorrhagic diathesis, or the lack of authorization for the procedure by the parent.

There are some relative contraindications determined by the team's experience or the hospital's level of critical care: very premature newborns, congenital cyanotic cardiopathies with an increase in bronchial collateral circulation, severe pulmonary hypertension, or coagulation alterations.

2.6.1.3 Complications

Neonatal FB is in general a safe procedure. Possible complications depend on the patient's risk factors, the type of procedure carried out, inadequate sedation/anesthesia, choice of instruments of an improper size, and the inexperience of the bronchoscopist.

2.6.2 Rigid Bronchoscopy (RB)

FB has slowly acquired a predominant role in pediatric bronchoscopy, and, although it has substituted RB in most centers, rigid bronchoscopy is still widely used. The basic reason is the high incidence of foreign bodies in children.

On the other hand, despite there being new ultrafine scopes for exploring newborns and infants, RB is still useful as a diagnostic or therapeutic tool when there is compromised ventilation, when extensive biopsies are necessary or when atelectasis should be resolved with the elimination of mucus plugging.

The majority of indications for RB are therapeutic: endoscopic treatment of localized airway obstruction, extraction of foreign bodies, and therapeutic instrumentation of the airway.

RB can be of use in the perioperative management of tracheoesophageal fistulas, both isolated and recurrent, as it allows for its identification and canalization, facilitating the surgical approach [74].

Pediatric RB is a procedure not regularly performed in most centers; therefore, learning this technique usually requires specific training, generally in a reference center [75].

2.6.2.1 Obstruction of the Central Airways

The larynx, trachea, and main bronchi are the bane of various surgical pathologies causing stenosis of the lumen, from tumor to inflammatory lesions. RB is the endoscopic best procedure when open surgery cannot be contemplated to treat these processes either with the application of laser, implantation of endoprosthesis, or other therapies.

In critical stenosis of the common airway with a reduction to 20% of the predicted lumen and the patient's life at risk due to asphyxia, RB can be a lifesaving procedure as it allows for the immediate restitution of the airway. It can dilate, opening the airway or progressively dilating the inflammatory stenosis.

This not only avoids the need for tracheotomy if the obstruction is laryngeal, but it is also the only option when the obstruction is located under the cervical trachea.

2.6.2.2 Extraction of Foreign Body

Rigid bronchoscopy is the best procedure for the safe and quick extraction of foreign bodies in children. Although there are publications endorsing the good performance of FB [76], it is usually a complicated procedure in small children. In these patients, RB is preferred as it offers the advantages of general anesthesia, assisted ventilation, larger instruments, and a greater variety of accessories.

The ideal procedure would start with FB, yielding greater reach in the exploration and the

identification of the foreign body, then extraction with RB, and finally a revision with FB in order to rule out a residual foreign body. In some cases in which the clinical and/or radiological information is conclusive, the procedure may be directly initiated with RB.

2.6.2.3 Complications

The complications of RB are due to the instrumentation with the bronchoscope itself, the medication used, the ventilation technique, the underlying pathology, the experience of the endoscopist, and the type of intervention.

2.7 Extracorporeal Life Support (ECLS or ECMO)

Extracorporeal life support (ECLS), also called ECMO, is a modified form of heart and lung bypass used on a temporary basis and as an alternative to conventional methods of life support. This compensates, when aggressive therapy and mechanical ventilation (MV) fail to maintain acceptable oxygenation and perfusion, for the deficit of cardiocirculatory and/or pulmonary functions until the body recovers and extracorporeal support is no longer needed. Therefore, ECLS is a rescue therapy for patients with a predicted mortality of 80–100%.

Indications for the use of neonatal ECMO are severe respiratory failure and/or major circulatory insufficiency, refractory to maximal medical management (INO, HFOV, and surfactant included) but a potentially reversible etiology.

With the introduction of membrane oxygenators in clinical practice, ECLS for prolonged periods of time became feasible, and so, in 1975, Bartlett and colleagues reported the first successful use of ECMO to treat severe respiratory distress in a newborn baby [77, 78].

After initial promising results, many prospective randomized trials and one uncontrolled trial demonstrated a better survival rate with ECMO than conventional therapy in the neonatal age. The same result was not confirmed by a similar RCT in adults [79–83].

The Extracorporeal Life Support Organization (ELSO) was founded in 1989, and, after 10 years, the data from its registry showed an approximate 80% survival rate in 12,175 patients, treated with ECMO from 1988 to 1998, with neonatal respiratory failure with a predicted mortality rate of approximately 80% [84].

In spite of these results and the improvement in the technology of ECLS systems (centrifugal pump with levitation technology, heparin-bonded circuits, miniaturization of cannula and pumps, dual-lumen catheters, etc.), nowadays, the use of neonatal ECMO is reducing, as shown by the ELSO registry and by many randomized studies; this is probably because the introduction of inhaled NO, HFOV, and surfactant into clinical practice has progressively reduced the need for its use [85].

Eighty percent of cases have a primary respiratory diagnosis, the others have a primary cardiac diagnosis; 4% of ECMO runs are cases of extracorporeal cardiopulmonary resuscitation (eCPR) [85].

This implies that the usual ECMO patient is now much more complex, unstable, with lower GA or weight and requiring a longer period of support than in the past.

Therefore, in comparison with the previous era, complications and mortality rates are a little higher.

Respiratory ECMO in newborn babies concerns two conditions—primary diagnoses associated with primary pulmonary hypertension of the newborn (PPHN) (idiopathic PPHN, meconium aspiration syndrome, neonatal acute respiratory distress syndrome, group B streptococcal sepsis, and asphyxia) and congenital diaphragmatic hernia (CDH)—but the outcome can be very different depending on the etiology (better in case of meconium aspiration syndrome, worse in CDH) and the GA at time of cannulation.

CDH remains an indication to ECMO, but systematic reviews do not demonstrate a substantial benefit [86–88]. This is probably related to the difficulty of predicting the reversibility of the PPHM and the related lung hypoplasia, because the ECMO efficacy depends on it. ECMO is a support, not a therapy.

Observed-to-expected lung-to-head ratios (O/E LHR) and MRI total lung volume (TLV)

can predict the need of ECMO and mortality [89, 90] but have not yet been strongly correlated with morbidity or PPHN [91].

However, not only the overall survival rate should be considered but also the survival rate stratified according to the differences in referral pattern, as suggested by Zalla and coworkers in 2015 [92].

At present, there is no single test or index available to predict this reversibility nor strong RCTs to assist in all issues of ECMO management in CDH, although many authors and institutions have proposed similar referral criteria to ECMO in this setting [93–95].

Even if these criteria may help the decision regarding ECMO runs, survival benefit of ECMO in CDH could not be established with the referral criteria used at that time, as suggested also by one large review in the UK [86].

However, the absence of an initial response to resuscitation with preductal saturation >85% and a PCO_2 <65 mmHg are strongly associated with worse prognosis and constitute relative exclusion criteria for ECMO in some centers [96].

The ideal length of time on ECMO in patients with CDH is difficult to establish; it may be identified within 3–4 weeks, but a higher time on ECMO can be needed even with satisfactory pulmonary outcome [97].

Selection criteria for ECMO in neonates [98] are gestational age of 34 weeks or more, birth weight of 2000 g or higher, no significant coagulopathy or uncontrolled bleeding, no major intracranial hemorrhage (grade 1 intracranial hemorrhage), mechanical ventilation for 10–14 days or less, reversible lung injury, no lethal malformations, no major untreatable cardiac malformation, and failure of maximal medical therapy.

The decision to respiratory ECMO runs is guided by the ratio between the degree of ventilatory injury and the effects of ventilator support; therefore, usual referral criteria are peak inspiratory pressure >35 cm H_2O, the alveolar-arterial (A-a) gradient >600–624 mmHg for 4–12 h, and, above all, the oxygenation index (OI) >40 in 3 of 5 post ductal gas determinations obtained 30–60 min apart.

ECMO may be indicated also in failure to wean from 100% oxygen despite prolonged (>48 h) maximal medical therapy or persistent episodes of decompensation, severe hypoxic respiratory failure with acute decompensation (PaO_2 < 40) unresponsive to intervention, severe pulmonary hypertension with evidence of right ventricular dysfunction and/or left ventricular dysfunction, and pressor-resistant hypotension [98].

Contraindications are related to the specific benefit risk/ratio. According to the ELSO guidelines, these can be divided into absolute and relative, as shown in Table 2.1.

The extracorporeal circuit is usually applied in two different modes: (1) veno-venous bypass, where the blood is withdrawn from a central vein, pumped into the system, oxygenated, and reinjected always in a central vein at the same level or in another place, and (2) venoarterial bypass, where the blood is returned to the body through a cannula placed not in a central vein but through the right common carotid artery into the aortic arch.

The first method allows only respiratory support, leading to an improvement of hemodynamics only by an increase in tissue oxygenation.

The second also provides circulatory assistance, increasing cardiac output through the flow of the pump (but with an increase in the LV afterload that can sometimes worsen an underlying heart failure).

Additionally, in postcardiotomy shock, direct cannulation of the right (±left) atrium and aorta is preferred, like in adults [99], but, in this case, a sternotomy is necessary with the associated higher risk of infection.

Table 2.1 Absolute and relative ECMO controindications

Absolute	Relative
Lethal chromosomal disorder (includes trisomy 13, 18 but not 21) or other lethal anomaly	Irreversible organ damage (unless considered for organ transplant)
Irreversible brain damage	<2 kg
Uncontrolled bleeding	<34 weeks post-menstrual age (increased incidence of increased intracranial hemorrhage)
Grade III or greater intraventricular hemorrhage	Mechanical ventilation greater than 10–14 days

Even if one method has specific advantages/disadvantages over the other, the choice of cannulation technique is more often dictated firstly by vessel size and anatomy, as well as the presence of hemodynamic instability.

VA (Vascular Access) cannulation ensures cardiocirculatory support, as previously described, but supplies less oxygenated blood to the myocardium and is burdened by more risks of systemic embolization with more intracranial bleeds and seizure; VV cannulation helps to decrease pulmonary artery pressure, pumping oxygenated blood directly into the pulmonary artery, but needs higher pump flow, neonate weight >2.5 kg, and strict control of positioning to avoid recirculation.

Some studies, which were not randomized and controlled, reported better outcomes for VV ECMO (except in the cardiac patient), but probably this data reflects a selection bias for the aforementioned reasons [100, 101].

In fact, despite the potential benefits of VV mode, the most frequently used approach remains VA ECLS with surgical cannulation and ligation of the internal jugular vein and the carotid artery (72% according to the ELSO registry).

This probably testifies to the greater hemodynamic instability of today's respiratory ECMO patient. However, the use of new dual-lumen cannula is becoming more popular because it enables a veno-venous bypass with only one cannulation, usually through the IJV.

Before ECMO starts, the patient must be anticoagulated, and, at the beginning, the usual rapid correction of oxygenation and carbon dioxide level makes strict control of hyperoxia, hypocapnia, and their dangerous effects mandatory.

During the stabilization phase, ventilation must be reduced and positive inspiratory pressure (PIP) lowered. Fluid overload is common and must be treated aggressively, eventually using continuous renal replacement therapy (CRRT) on the circuit [102].

Given the high risk of neurological complication, careful neuro-monitoring should be routinely performed by cranial ultrasound, and cerebral oxygenation should be continuously evaluated by NIRS (near-infrared spectrometry).

ECMO strategy remains a procedure with very high risk of complications, so that its use is justified only by the highest risk of mortality without this extracorporeal support.

The major complications are related to the difficulty of managing the delicate balance between thrombosis and hemorrhage (due to the foreign surfaces of the system and the underlying conditions) and to the high risk of infection, also linked to the immunosuppressive effect of the ECLS.

However, after more than 40 years since its first successful use and despite improvements in the medical and surgical management of severe respiratory/cardiac insufficiency of the newborn, neonatal ECMO continues to be the only evidence-based ECLS strategy and maintains its own role in the management of very critically ill patients.

2.8 Pain in the Newborn

The important metabolic and hormonal response of newborns undergoing invasive procedures, performed without antalgic coverage, was the main element that led research to the demonstration of the capacity to perceive and manifest pain in neonates [103].

These studies emphasized that at every age (fetus, premature, in-term newborn, infant, baby), there is a definite perception and response to pain; the individual is born with an anatomically structured and functionally active nociceptive system [104].

The state of immaturity makes the newborn far more vulnerable to pain stimulus. In fact, the conduction pathways of the inhibitory system are not yet completely myelinated, and the discriminating capacity between sensory stimulus and harmful stimulus is low.

As the newborn develops, the ability to differentiate stimuli will mature as will the capacity to process information through cognitive ability, adaptation, memory, and affective and emotional influences.

At birth, the central nervous system (CNS) is not completely developed; the synaptogenesis starts from the 24th week of gestational age, with the development of the synaptic connection network.

The "brain growth spurt period" in humans commences in the last trimester of pregnancy and continues at least until the second year of life.

During this period, alongside the differentiation, maturation, and neuronal migration, a genetically determined cellular suicide process is observed. Redundant neurons and those that have failed to connect to targets are eliminated by apoptosis. Only neurons that receive adequate trophic factors are able to survive.

Neurotransmitters are the trophic factors involved in neuronal survival: the glutamate, excitatory neurotransmitter, and the GABA, inhibitory neurotransmitter.

Synaptogenesis is an activity-dependent process, and an excessive depression of neuronal activity may constitute a signal that induces apoptosis.

Sedative anesthetic drugs reduce neuronal activity through an NMDA (N-Methyl-D-aspartate receptor) receptor antagonist or GABA-A receptor agonist mechanism.

In theory, the exposure of developing neurons to these agents could alter homeostasis, transforming apoptosis from a biological phenomenon into a pathological phenomenon, with short- and long-term sequelae on neurocognitive development.

This phenomenon has been demonstrated in the brains of guinea pigs and nonhuman primates, in preclinical studies, but it has not been confirmed in humans, at least for single exposure to anesthetics [8, 9].

There is a lack of data on repeated or prolonged administration, as sometimes needed in critically sick newborns in intensive care, and there is no evidence of safety in the use of analgesics [105, 106].

However, it has been shown that the newborn that has experienced early, recurring, and prolonged pain has a high risk of developing sequelae in neurocognitive development and altered pain response. The longer the exposure to stimulation, the less the newborn will be able to modulate and modify the reinforcement of frequently activated neuronal circuits and will have a greater risk of developing pain memory.

This supports the importance of paying close attention to the treatment and the prevention of pain in the newborn who has to undergo invasive procedures.

Taking care of pain means, first of all, evaluating it.

The assessment of acute pain at the neonatal age makes use of algometric instruments, some validated also for premature birth as the Premature Infant Pain Profile (PIPP) scale. It is a simple-to-use observational scale that analyzes the variation of physiological parameters ($SatO_2$, heart rate) together with the observation of the most typical pain behavior in the newborn—crying and facial expressions.

Management of acute neonatal pain must rely on pharmacological strategies, complemented by specific non-pharmacological techniques such as sensory saturation that includes three types of stimulation—oral, tactile, and auditory [107].

In neonates, pharmacokinetics and pharmacodynamics of analgesics, as well as other drugs, differ from that of adults due to different degrees of functional organ maturity. Metabolism is slowed by enzymatic immaturity, and renal excretion is reduced, potentially resulting in accumulation of drugs and active metabolites. Genetic polymorphism also influences pharmacokinetics inducing different enzymatic patterns with different enzymatic activity.

For that reason, there are both slow and ultrafast metabolizers of some specific drugs. This results in a great interindividual variability of drug response: for some, the ineffectiveness and, for others, a greater risk of toxicity.

This phenomenon has been demonstrated for codeine and is suspected for tramadol, hydrocodone, and oxycodone [108].

In the case of morphine, the active metabolite, morphine-6-glucuronide (M6G), is primarily responsible for the analgesic effect, but the enzymes of glucuronidation are immature at the neonatal age, and the amount of M6G produced is uncertain.

Genetic differences also influence the pharmacodynamics determining morphological variations of the binding receptors.

Extreme variability of effect supports a cautious approach, using small doses titrated on clinical response.

Research into drugs without kinetics dependent on hepatic and renal function led to remifentanil, a drug metabolized by tissue esterases, already present and functioning at birth. However, the rapid offset of remifentanil opens the problem of treatment discontinuation and suspension. Furthermore, the hemodynamic response and the risk of thoracic rigidity are two major adverse effects.

Regional neuraxial anesthesia and peripheral nerve blocks represent a valid strategy in intra- and postoperative pain management, especially nowadays, given the improvement of equipment specifically designed for neonatals, the use of eco-guided techniques, and new safer local anesthetics.

Regional anesthesia, however, is a challenging technique and, especially in the newborn baby, requires expertise and experience. Careful analysis of the risk/benefit balance and a meticulous technique are always recommended [109, 110].

Non-opioid analgesics usually have an opioid-sparing effect but can substitute them in case of slight pain. NSAIDs are not indicated in neonates due to the risk of adverse effects on renal perfusion, thrombophilic profile, platelet dysfunction, and damage of gastric mucosa.

Paracetamol represents the most non-opioid analgesic used at the neonatal age.

The risk of hepatic overdose and accumulation of the metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI) are very low due to the functional immaturity of the CYP2E1 enzyme and the resulting low concentration of the toxic metabolite. For the most recent intravenous formulation, Allegaert in 2011 [111] studied pharmacokinetic variables of paracetamol, such as clearance, volume of distribution, and half-life and found 10 mg/kg every 6 h to be an optimal dose for neonates of >32 weeks GA.

A previous study had suggested even higher doses of 15 mg/kg every 6 h for the full-term newborn, advising a reduction in the case of hyperbilirubinemia [112].

In light of the above, the optimal therapy of acute pain in newborns must provide a multimodal regimen in order to minimize adverse effects, enhance synergies, and achieve maximum effectiveness.

2.9 Summary

Even with the improvement in knowledge and availability of new dedicated medical devices, the particular vulnerability of newborns still makes neonatal anesthesia and intensive care challenging.

There are still many unanswered questions and topics for discussion. Evidence-based data is lacking, and many decisions are made even today on the basis of pathophysiological deductions and good clinical "common sense."

Further studies and research should be carried out in order to obtain better evidence-based data, as is available for adults, and to improve to a greater extent the outcomes in neonatal anesthesia and perioperative intensive care.

Box 2.1 Allometric equation and corrective factors of Hill model

$$y = a \times \text{BodyMass}^{\text{PWR}}$$

y is the variable of interest (e.g. Clearance)
a is the allometric coefficient
PWR is the allometric exponent

Allometry alone is insufficient to predict the clearance of drugs in neonates and infants from adult estimates. The Hill model describes maturation introducing the maturation factors (MF)

$$\text{MF} = \left(\text{PMA}\right)^{\text{Hill}} / \left(\text{TM}_{50}^{\text{Hill}} + \text{PMA}^{\text{Hill}}\right)$$

TM_{50} = maturation half-time
The Hill coefficient relates to the slope of this maturation profile

$$P = P_{\text{std}} \times F_{\text{size}} \times \text{MF} \times \text{OF}$$

P = Pharmacokinetic parameter
P_{std} = value in a standard size healthy adult
$F_{\text{size}} = (W/70)^{\text{PWR}}$
OF = organ function

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Imaging in Neonates

3

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The study of neonatal surgical diseases, both thoracic and abdominal, involves the use of different diagnostic techniques, sometimes complementary, each with specific characteristics.

The most neonatal pathologies currently have prenatal diagnosis, generally ultrasonography, when deemed necessary confirmed by studies of fetal magnetic resonance.

Postnatally, the first-level examinations are ultrasonography and conventional radiology, both plain radiographs and contrast studies, the latter for the gastroenteric and urinary tract.

MRI is part of the second-level diagnostic techniques, which has among its great perks the lack of ionizing radiation, multiplanar and multiparametric capabilities, and the high contrast resolution; its limitation is instead the relative length of the sequences with consequent need to perform the sedation/anesthesia investigation.

Although it is a very reliable diagnostic test, thanks to the high spatial resolution, the CT has limited indications in neonatal age, due to the high radiation dose, used only in a very few selected thoracic diseases.

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In the following paragraphs, we will discuss individually the surgical thoracic, gastrointestinal, and urogenital disease as observed in neonatal age, emphasizing for each district the indication of the different imaging techniques and the relationship between them, in order to define optimal diagnostic and reproducible algorithms.

3.1 Neonatal Chest Imaging

The study of neonatal chest takes advantage of different diagnostic techniques, each one with its own features, suitable to answer specific clinical questions.

As for other systems and apparatuses, diagnosis of neonatal surgical pathologies is often prenatal, thanks to fetal ultrasonography and fetal magnetic resonance imaging (fetal MRI), especially in very complex conditions (such as congenital diaphragmatic hernia and high airway obstruction) that require a planned delivery in a third-level center and specific obstetric techniques (e.g., EXIT). In particular, in case of congenital diaphragmatic hernia, fetal MRI gives information about localization (left or right), herniated organs, lung volumes and degree of maturation, mediastinal shift, polyhydramnios, and associated pathologies [1].

All the major diagnostic studies are useful for the diagnosis of neonatal thoracic pathologies, starting from chest X-ray and ultrasonography; second-level examination is magnetic resonance

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imaging (MRI), while computed tomography (CT) is reserved to large lung/mediastinal expansive lesions, pre-surgical planning of congenital pulmonary dysplasias, and severe respiratory distress from unrecognized cause.

3.1.1 Radiography

After birth, the first-level examination for the newborn remains the chest radiograph (be it digital or analogue). This exam is relatively cheap, easy to execute, and widespread; the information it gives are rapidly available, and, in expert hands, the radiation dose is very low.

The radiograph is routinely executed in a single, anteroposterior view with patient laying in supine position. Additional views, such as translateral and lateral decubitus with horizontal beam, can be useful for diagnosis. The collimation of the X-ray beam should be as narrow as possible to avoid exposure of other organs and systems.

Chest X-ray allows to easily differentiate medical from surgical causes of respiratory distress in newborns; in many cases, it confirms prenatal suspects of several pathologies. With chest radiograph it is possible to evaluate lung expansion and radiolucency, heart size and mediastinal silhouette, and position of catheters, endotracheal tubes, and thoracic drainages. A hyperlucency of a hemithorax and a shift of the mediastinal silhouette allow the diagnosis of pneumothorax (Fig. 3.1); if the hyperlucency is limited to a localized area of parenchyma, cystic dysplasia (Fig. 3.2), congenital lobar overinflation, or bronchial atresia is the most likely diagnosis, which must be confirmed with second-level examinations.

On the other hand, a pulmonary opacification can be caused by a pleural effusion or an expansive mass, bronchogenic cysts, pulmonary sequestration, or cystic dysplasia in a very early stage, when cysts are still filled with fluid.

Furthermore, chest X-ray can show a widening of the mediastinal silhouette in the rare expansive pathology of this district, such as lymphangiomas, thymic neoplastic diseases,

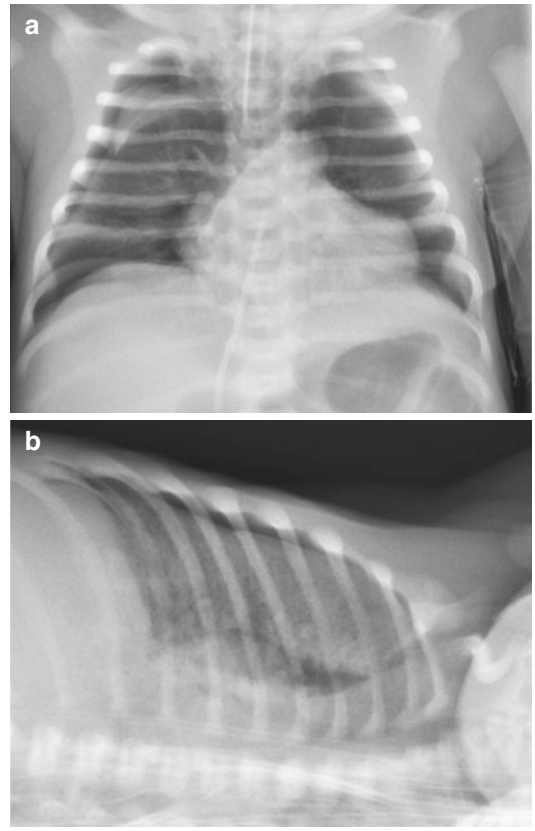

Fig. 3.1 Anteroposterior chest radiograph of a newborn showing bilateral pneumothorax and pneumomediastinum (**a**) and left lateral decubitus confirming right pneumothorax (**b**)

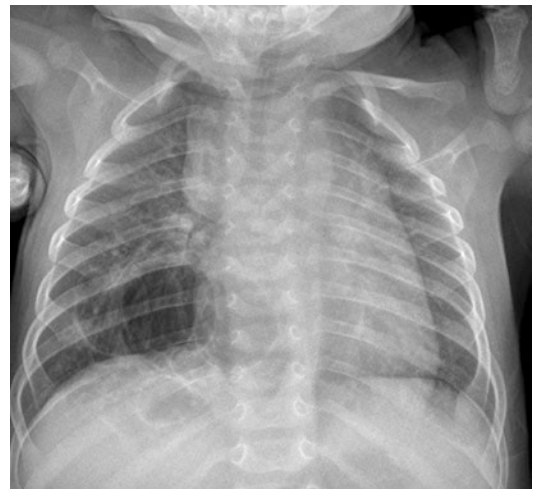

Fig. 3.2 Chest radiograph of a newborn showing multiple air-filled cysts in the inferior part of the right lobe

and paravertebral neoplasias (neuroblastoma, ganglioneuroblastoma, and ganglioneuroma). A peculiar appearance is represented by congenital diaphragmatic hernias, both posterior (Bochdalek) and anterior (Morgagni) and by the rarest cases of eventration of the diaphragm.

3.1.2 Ultrasonography (US)

Ultrasonography (US) of the chest is performed with high-resolution multifrequency transducers, convex or linear [2]. It does not use ionizing radiations and does not require sedation, characteristics that make it a very useful tool in neonatal imaging. Adding to this, low mineralization of the bones allows other approaches than in adults. It is operator dependent and this remains its main limit.

US is especially useful in pleural effusion identification and quantification and can be a guiding tool for thoracentesis. US is the most reliable technique to evaluate pleural effusions, allowing to discriminate between homogeneous, anechoic fluid effusion and complicated ones, when features such as echogenic debris, mobile fibrin strands, septations, or a honeycombing appearance are present [3].

Its use is nowadays extended to parenchymal and mediastinal examination: it allows to evaluate diaphragmatic profiles, to analyze which abdominal organs are herniated into the thorax in case of diaphragmatic hernia, and to identify solid pulmonary lesions, mediastinal masses, and congenital pulmonary malformations (e.g., pulmonary sequestration). Thanks to color Doppler techniques, US evaluates blood vessels without endovascular contrast medium.

Finally, it is of paramount importance in those pathologies which can involve also the neck, such as lymphangiomas and anomalies of branchial apparatuses: on the base of the different echogenicity, it can diagnose bleedings that can cause sudden growth in size of the lesions, with subsequent airway compression or dislocation. These complications are suspected when the usual homogeneous fluid content becomes corpusculated, with contextual levels.

3.1.3 Magnetic Resonance Imaging (MRI)

For many years magnetic resonance imaging (MRI) has been considered an experimental study technique for pulmonary parenchyma examination. This assumption was based on the poor quality of images, due to movement artifacts resulting from breathing and heartbeat.

Nevertheless, over the years, the development of faster sequences (e.g., turbo spin-echo T2-weighted) with movement artifact reduction techniques (multi-vane) and the use of triggers have extended the indications for MRI in the study of the chest.

MRI does not use ionizing radiations; thus it plays an important role in the postnatal confirmation of congenital pulmonary malformations, both air malformative diseases such as congenital pulmonary airway malformations (CPAM) and vascular ones, such as pulmonary sequestration. For example, CPAM is characterized by round, hyperintense areas in T2-weighted sequences; pulmonary sequestration is seen as an area of the lung with different signal intensity, higher than the surrounding healthy parenchyma, and with associated intralesional flow void images. It is also possible to identify the afferent arterial vessel, usually originating from supra- or infradiaphragmatic aorta, thanks to "black-blood" angiographic sequences, without the need of intravenous contrast medium injection (Fig. 3.3).

It is possible to perform this examination either in sedation or during natural sleep, without the need of anesthesia, making it feasible already in the first days of neonatal life, delaying the execution of CT for the surgical planning to the following months, just before the surgery.

One of the most important fields of application of the chest MRI is the examination of mediastinal masses (e.g., thymic cystic teratomas, mediastinal lymphangiomas, pleuropericardic cysts,

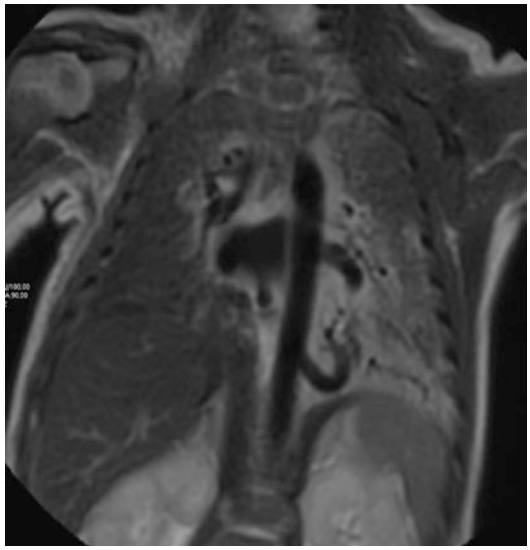

Fig. 3.3 Postnatal MRI of a 3-day-old newborn, showing a pulmonary sequestration, in the lower left lobe: the afferent arterial vessel and venous drainage are identified by intralesional flow void images

esophageal cystic duplications), especially of the posterior mediastinum (e.g., neuroblastoma).

3.1.4 Computed Tomography (CT)

Computed tomography (CT) is the gold standard technique for the study of the chest [4]; in the newborn, due to the high radiation dose, this diagnostic procedure has a very limited use and is dedicated to a few clinical indications.

It is possible to acquire large volumes in a short time, and ever-thinner slices allow multiplanar reconstructions from raw data. Thus, CT is able to study the airways and create 3D reconstructions for virtual endoscopy, to identify blood vessels (especially when there is a suspect of vascular anomalies such as vascular rings and a pulmonary artery sling) and, most of all, to evaluate pulmonary parenchyma and its pathologies (e.g., cystic parenchymal malformations, bronchogenic cysts, pulmonary sequestration, lobar overinflation, or bronchial atresia) [5].

As already indicated above, CT (with intravenous contrast medium injection) is a second-level investigation for the study of congenital pulmonary dysplasias, both for those which need a precocious surgical operation and for the "programmable" ones, which anyway need a pre-surgical planning. The former include those malformations which cause a mediastinal shift, such as congenital lobar overinflation and large congenital pulmonary airway malformations [5, 6].

Congenital lobar overinflation (also known as congenital lobar emphysema) is characterized by an expanded hemithorax, a hyperinflated low-attenuation lobe with pulmonary vascular pruning, variable degrees of atelectasis of ipsilateral adjacent lobes, and mediastinal shift into the opposite hemithorax. Measurements of lung attenuation value of the affected lobe are not needed for diagnosis, because visual assessment usually suffices to identify hyperinflation. In the immediate postnatal period, the attenuation value may be increased, closer to that of soft tissue due to impaired clearance of retained lung fluid; as fluid is resorbed, the attenuation value of the lobe decreases.

The appearance of congenital pulmonary airway malformations (CPAM) on CT depends on the relative presence of cystic and solid components and whether there is superimposed infection. CPAM is seen as multiple thin- or thick-walled, air- or fluid-filled cysts of variable size, expanding the affected lobe or lobes and displacing the mediastinum to the opposite hemithorax. Type III, which is very rare, appears as a solid mass. A higher attenuation equal to soft tissue or thick walls may be seen when the cyst contents are infected or hemorrhagic. Air-fluid levels can be seen occasionally, but they do not necessarily indicate infection.

Large CPAM may mimic cystic pleuropulmonary blastoma (Fig. 3.4): the latter appears at CT examination as a solid, cystic, or mixed attenuation mass in the lung periphery often adjacent to the pleura in the lower zones; associated findings include pleural effusion and contralateral mediastinal shift. The solid components of the mass lesion are seen to enhance with intravenous contrast administration. Cross-sectional imaging should include the mediastinum as hilar metastases can occur.

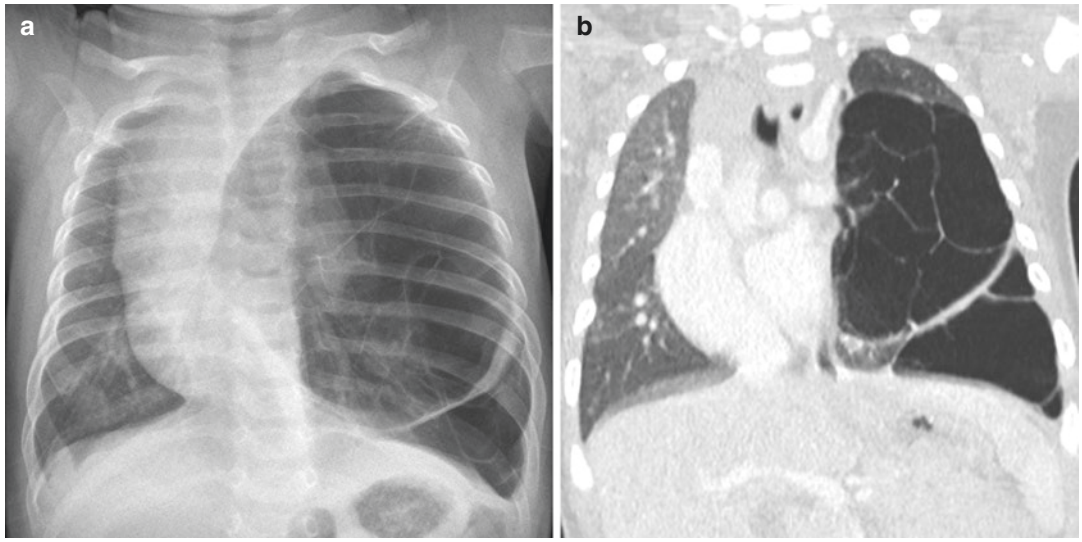

Fig. 3.4 Pleuropulmonary blastoma. Chest radiograph (**a**) and CT coronal reconstruction (**b**) show multiple cysts occupying the left hemithorax, crossing the midline, and displacing the mediastinum to the right

In the other cases, when there are no urgency conditions, CT execution is postponed to the third–sixth month of life of the infant. This is the case of bronchial atresia, pulmonary sequestration, noncomplicated congenital pulmonary airway malformations, and hybrid lesions [5–7].

In bronchial atresia, air enters the affected segment via collateral channels, producing overinflation and air trapping, while mucus secretions generated in the affected bronchus accumulate originating mucus impaction (mucocele): CT is diagnostic because it shows the segmental overinflation and mucous impaction with great precision. In some cases, a cystic lesion containing gas and fluid corresponding to a severely dilated bronchus just distal to segmental bronchial atresia can also be seen.

Pulmonary sequestration can be intralobar or extralobar [8, 9]. CT findings of intralobar sequestration include a homogeneous or inhomogeneous solid mass, with or without definable cystic changes; it can also appear as an aggregate of multiple small cystic lesions with air or fluid content, a well-defined cystic mass, or a large cavitary lesion with air-fluid level; adjacent emphysematous changes are common. Contrast medium intravenous injection is necessary to show systemic arterial supply, most commonly from the distal thoracic aorta, and venous drainage via the pulmonary veins into the left atrium. In extralobar sequestration, CT shows a homogeneous, well-delimited, round, ovoid, or triangular mass, sometimes with internal cystic areas; arterial supply is always systemic (upper abdominal or lower thoracic aorta), while venous drainage is usually to the inferior vena cava or the azygos system and occasionally the coronary artery or portal veins. The cysts of CPAM communicate with the airways, and their vascular supply comes from pulmonary circulation; however, there are many examples of CPAM fed by systemic blood vessels, and in these cases it is extremely difficult to differentiate CPAM from pulmonary sequestration, as they correspond to overlapping malformations (hybrid lesions) (Fig. 3.5): from the radiological viewpoint, the differentiation between CPAM with systemic supply and pulmonary sequestration is impossible.

Finally, CT is used to study mediastinal and thoracic masses, specifically in poorly explorable areas (e.g., pulmonary apex, near the diaphragm, adjacent the chest wall or central airways), and to evaluate soft tissues, vessels, and airway infiltration; in these cases, nevertheless, it is preferable to use MRI, which is analogously diagnostic but not radiative.

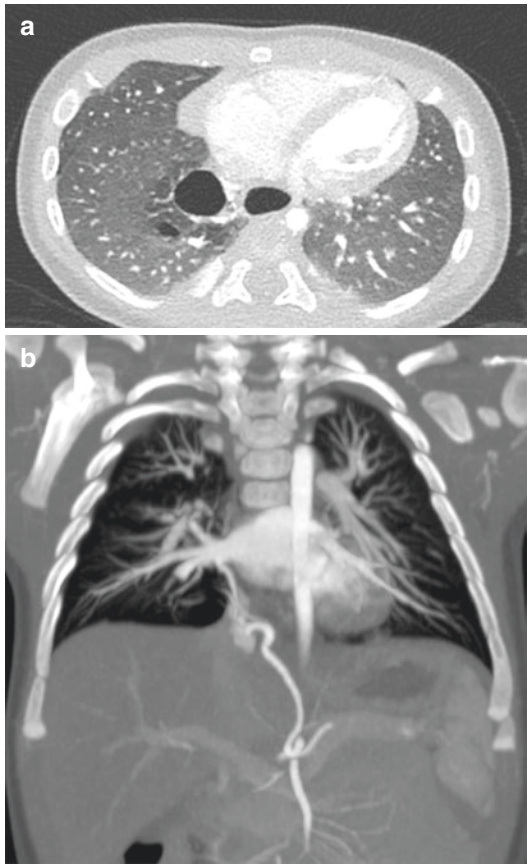

Fig. 3.5 Axial (**a**) and coronal MIP reconstruction (**b**) CT show a cystic lesion and a systemic arterial supply in a hybrid lesion

3.2 Gastrointestinal Neonatal Imaging

The most important diagnostic techniques for the digestive system in neonatal age are still today plain abdominal radiographs and conventional contrast studies [10, 11].

In recent years, ultrasound has been added to these techniques with an increasingly important role, so much so as to be considered an extension of clinical evaluation, both in terms of urgency and in elective studies.

Magnetic resonance is reserved for selected cases, especially in the evaluation of complex malformation patterns or in the presence of expansive diseases, while the computerized tomography, whose use is almost exceptional, does not find significant indications [12, 13].

It must be remembered that many gastrointestinal tract abnormalities have a prenatal diagnosis, and this often changes and influences postnatal diagnostic strategies.

3.2.1 Radiography

The air present in the digestive system is a natural contrast agent, which is positively used in conventional radiographs performed during neonatal age [10–14].

After birth, the normal progression of the air along the whole alimentary canal occurs within a few hours; the air is visible in the stomach within a few minutes, and then it progresses in about 3 h toward the loops of the small intestine and finally becomes visible in the sigmoid rectum after about 6–8 h.

Neonatal obstructions occur when the air progression is interrupted, generally due to the presence of an atresic trait but also in cases of meconium ileus or peritonitis, Hirschsprung disease, and functional immaturity of the colon; all these conditions can be effectively diagnosed with exclusive use of conventional radiology (Fig. 3.6); even in doubtful cases, plain abdominal radiographs can be useful to indicate subsequent diagnostic procedures.

The obstructions may be incomplete, for example, due to the presence of stenotic traits, webs, duplications, intestinal malrotation, peritoneal bands, and aganglionosis; these pathological conditions may occur later, and other diagnostic procedures are generally necessary for diagnosis.

The abdominal radiograph in the neonatal age is exclusively performed with supine anteroposterior view; only in some cases the translateral view with horizontal beam is added, which allows the recognition of air-fluid levels and facilitates the visualization of pneumoperitoneum; in the latter condition, an additional view in left lateral decubitus with horizontal beam can be performed.

All cases of pneumoperitoneum, however determined, have an exclusive radiographic diagnosis as well as the high-obstructive conditions,

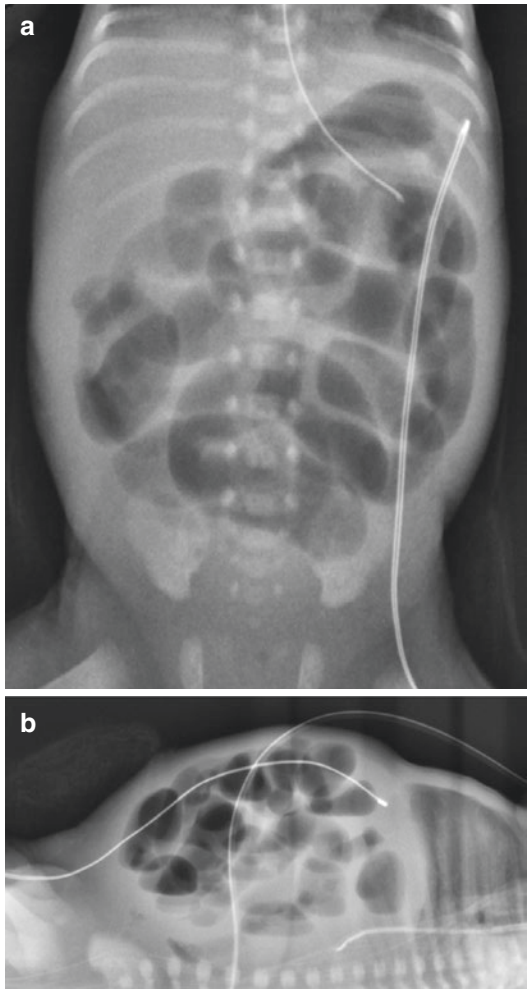

Fig. 3.6 Plain abdominal radiographs. Supine anteroposterior view (**a**) and translateral view (**b**) show the presence of many dilated intestinal loops with air-fluid levels in low intestinal obstruction

between those duodenal atresia with the sign of the double bubble and the less frequent pyloric atresia with the sign of the single bubble and jejunal atresia, with a few loops dilated upstream obstruction and complete meteoric silence downstream.

Usually all these conditions do not require further radiologic evaluation after radiography: complementary procedures are not usually helpful and contrast studies are contraindicated.

The esophageal atresia has a diagnostic role in the plain abdominal radiograph combined with the chest radiograph; at prenatal US this disease is suspected due to the presence of polyhydramnios, lower intraluminal liquid in fetal gut, and inability to detect the fetal stomach.

On anteroposterior and lateral chest radiograph, the radiological findings are a blind pouch of the proximal esophagus, distended with air.

Radiographic evaluation always should include the abdomen to assess the presence or the absence of gastrointestinal air due to the existence or not of the fistula, allowing the tracheoesophageal atresia classification [15]. A complete absence of air in the stomach and bowel is observed in the I and II types, while the air is commonly present in III and IV types.

The necrotizing enterocolitis (NEC) is one of the most common acquired, life-threatening gastrointestinal diseases in the newborn, especially in premature infants of extremely low birth weight [11, 14–16]. In NEC bowel dilatation is a nonspecific, early sand commonest finding, best appreciated on the plain abdominal radiograph, and may be the only sign present in many patients with either mild or severe forms of the disease. The dilatation is usually due to an ileus and may be generalized or focal, depending on the extent of bowel involvement. Furthermore, the degree of dilatation usually correlates well with the clinical severity of the disease, and the distribution of the dilated loops in serial examinations is related to clinical progression. An ominous sign is the change from generalized dilatation to an asymmetric distribution where dilatation is confined to a more localized area of the abdomen. It is even more worrisome if the asymmetric pattern persists and the dilated loops maintain the same appearance as fixed loops on follow-up plain abdominal radiographs. This suggests the development of full-thickness necrosis and may precede clinical deterioration including signs of peritonitis. For these reasons, the degree and pattern of bowel dilatation are the most important signs for early diagnosis and for follow-up.

Intramural gas is also an early sign that may precede clinical signs. Although intramural gas may be present in other neonatal conditions, it is most commonly seen in NEC and thus has been considered a virtually pathognomonic sign of NEC. However, intramural gas is not present in

all cases of NEC; it is more commonly present in the distal small bowel and large bowel and is therefore most commonly seen in the right lower quadrant.

The amount of intramural gas present does not always relate to the clinical severity of NEC in any particular patient, and disappearance of intramural gas does not always correlate with clinical improvement. On plain abdominal radiographs, intramural gas may be diffused or localized and appears as linear or rounded radiolucencies; the rounded lucencies represent intramural gas in the submucosa, and when extensive they may have a bubbly appearance; the linear lucencies, often curvilinear, represent intramural gas in the subserosa (Fig. 3.7).

In NEC, portal venous gas is an extension of intramural gas that enters the veins of the bowel wall and passes into the portal venous system; it's not always associated with a fatal outcome. However, like intramural gas, portal venous gas may appear and disappear rapidly. Its disappearance is not always associated with clinical improvement. On a supine plain abdominal radiograph, portal venous gas appears as branching, linear, radiolucent vessels that may extend from the region of the main portal vein toward the periphery of both hepatic lobes, and the extent depends on the amount of portal venous gas present.

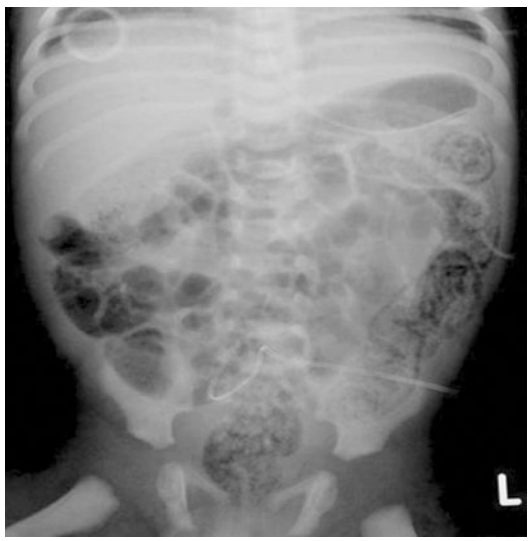

Fig. 3.7 Plain abdominal radiographs. Massive submucosal and subserosal pneumatosis of the left colonic wall in NEC

Plain abdominal radiograph has a role in anorectal malformations studies, when you need to perform plain abdominal radiograph in translateral prone view for the evaluation of the rectal cul-de-sac and its distance from the perineum [11–13]. Furthermore this study allows to detect sacrococcygeal anomalies often found in caudal regression syndrome or other skeletal abnormalities in different syndromes (VACTERL association).

3.2.2 Contrast Studies

The contrast studies are still useful for the assessment of some congenital gastrointestinal diseases; for neonatal conditions they are basically upper gastrointestinal (UGI) series, small bowel follow-through (SBFT), water-soluble contrast enema, and, less frequently, the barium enema [10–15].

Loopograms have an important role in children who have a stoma.

The aim of the modern pediatric radiologist is to work in close collaboration with the surgeon to perform contrast studies only in selected patients, using correct technique, at the lowest dose possible to meet specific diagnostic questions.

The continuous fluoroscopy technique with the last image capture technique or the pulsed fluoroscopy with capture of the acquired series is now commonly used. High-dose standard full exposures are reserved for cases of difficult diagnosis or when a more definite anatomical detail is essential (e.g., thin fistulas tracheoesophageal).

Barium formulations are not preferentially used. In neonates, especially in premature babies, and in circumstances where aspiration is a risk or a perforation is suspected, a low-osmolality water-soluble non-ionic contrast media is preferentially used.

The high-osmolality water-soluble iodinated contrast media should never be used in the UGI for the aspiration risk and the consequent possible serious complication, as acute pulmonary edema. It is instead preferred for the enema in neonates

with suspected meconium ileus or meconium plug syndrome for its therapeutic effect.

With regard to the proximal digestive tracts, the main neonatal surgical conditions in which contrast studies are currently applied as tracheoesophageal fistulas and partially high obstructive conditions, such as duodenal webs, annular pancreas, duodenal and jejunal stenosis, and congenital bands in the intestinal malrotation; the contrast studies are instead obsolete in midgut volvulus, whose diagnosis is today determined by sonography.

In neonates with tracheoesophageal fistula, the tube esophagram (as part of an UGI series) is the gold standard examination for H-type tracheoesophageal fistula, mostly in those neonates known to have aspiration or being ventilated at the time of the study.

It is worth noting that even a high-quality tube esophagram does not always demonstrate an occult fistula, and in occasional cases bronchoscopy may also have to be performed. Similarly bronchoscopy may miss a fistula revealed by a contrast study. The tests are therefore complementary.

In neonates and infants with suspected gastroesophageal reflux disease (GERD), the 24 h pH probe is now the mainstay for making or confirming the diagnosis of reflux in children; however, the UGI is still used in many centers to confirm that the underlying GI anatomy is normal.

Although in precipitous decline, the SBFT may still be performed in preparation for elective gut resection and for surgical planning when information regarding small bowel transit is required and in suspected subacute obstruction or obstruction.

The first part of the study is for an upper GI series; the serial images are then acquired at appropriate intervals to answer the specific clinical question.

Contrast studies of the lower GI tract have not changed substantially over recent years, and the water-soluble contrast enema and, more rarely, the barium enema remain the mainstay of imaging. The enema studies are indicated in the bowel obstruction, especially lower obstruction.

The generic diagnosis of high intestinal obstruction is usually straightforward at radiography, which demonstrates a few dilated bowel loops, which are more than would be seen in duodenal atresia and fewer than in ileal atresia or other causes of low bowel obstruction. There is no gas in the lower portion of the abdomen. The patient usually requires no further radiologic investigation, although barium enema examinations are still performed in attempts to exclude second and third areas of atresia lower in the bowel. In isolated proximal atresia of the jejunum, the colon is normal in size because the remaining small bowel distal to the atresia produces sufficient intestinal secretions to produce a normal-caliber colon.

Neonatal low intestinal obstruction is defined as an obstruction that occurs in the distal ileum or colon; the clinical signs include vomiting, abdominal distention, and failure to pass meconium. Ileal and colonic atresia, meconium ileus or peritonitis, Hirschsprung disease, and functional immaturity of the colon can determine the obstruction. Anorectal malformations are also an important cause of low intestinal obstruction but are almost always evident at physical examination.

The diagnosis of low obstruction is usually apparent at abdominal radiography because of the presence of many dilated intestinal loops, but the differentiation between ileal and colonic obstruction is difficult if not impossible. This distinction can readily be made with a barium enema study, which helps determine the presence of functional microcolon (Fig. 3.8), indicates the position of the cecum with regard to possible malrotation, and shows the level of the obstruction in colonic atresia. In ileal atresia the colon has a normal location but a minute caliber.

The colonic atresia is often indistinguishable from obstruction of the distal ileum, especially when the atresia is located in the ascending colon. Barium enema examination usually reveals a distal microcolon with obstruction to the retrograde flow of barium at the site of the atresia.

Meconium ileus is the result of intraluminal obstruction of the colon and lower small bowel due to impaction of meconium and represents the earliest clinical manifestation of cystic fibrosis. Contrast enema shows a functional microcolon,

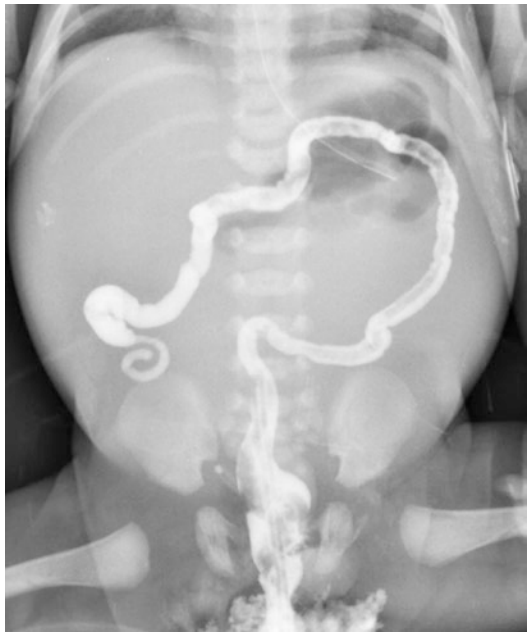

Fig. 3.8 Barium enema study shows a severe functional microcolon in newborn with ileal atresia

involving the entire large bowel and impacted meconium pellets particularly in the right colon or in the distal ileum caused by retained meconium. Meconium ileus is among the few pediatric conditions in which the enema is performed with high-osmolality water-soluble iodinated contrast due to therapeutic effects. Advantage is taken of the high osmotic pressure of the contrast medium: the surrounding tissue is forced to release considerable amounts of fluid, which then flows into the gut and dissolves the inspissated meconium. Therefore, the enema is both diagnostic and therapeutic and can be followed by expulsion of meconium during or after the procedure.

Meconium peritonitis, chemical peritonitis resulting from intrauterine bowel perforation, is often associated with underlying disorders as small bowel atresia, meconium ileus, volvulus, and intussusception, although some cases are idiopathic [17]. The extruded bowel contents provoke an intense peritoneal inflammatory reaction, leading to the formation of dense fibrotic tissue. This tissue often calcifies, resulting in the characteristic intraperitoneal calcifications identified prior to birth with US and after birth with abdominal radiography and US. The calcifications of meconium peritonitis may extend into the scrotum through a patent vaginal process to produce a calcified mass in the scrotum.

Hirschsprung disease is a form of low intestinal obstruction caused by the absence of normal myenteric ganglion cells in a segment of the colon [11–13]. The aganglionosis extends proximally from the anal canal, and the rectosigmoid area is involved in most cases. Ultrashort segment disease (aganglionosis limited to the region of the internal sphincter) is very rare, as well as aganglionosis of the entire alimentary tract. In newborn with Hirschsprung disease, the peristaltic waves do not pass through the aganglionic segment, leading to functional obstruction within a few days after birth.

Radiography performed in children with Hirschsprung disease yields findings similar to those in other forms of low small bowel obstruction: variable gaseous distention of the colon and small bowel, often with air-fluid levels. The colon is usually difficult to identify accurately, and gas is usually absent in the rectum. Barium enema studies demonstrate patency of the colon, which is short but usually normal in caliber. A transition zone between the narrow and dilated portions of the colon in the shape of an inverted cone is the most characteristic radiologic finding (Fig. 3.9).

A common cause of neonatal obstruction is the functional immaturity of the colon, particularly in premature neonates and in those whose mothers were treated during labor with magnesium preparations and sedatives and in those with diabetic mothers. It comprises several entities, most notably small left colon syndrome and meconium plug syndrome. Affected patients have abdominal distention, difficulty in initiating evacuation, and sometimes vomiting; typically the bowel distention is less severe than with an organic obstruction. The condition is both diagnosed and treated with a contrast enema; typically, there is clinical improvement following the enema, and over the course of hours to days, the radiographic and clinical signs of obstruction subside. In meconium plug syndrome, contrast enema is performed with high-osmolality water-soluble contrast.

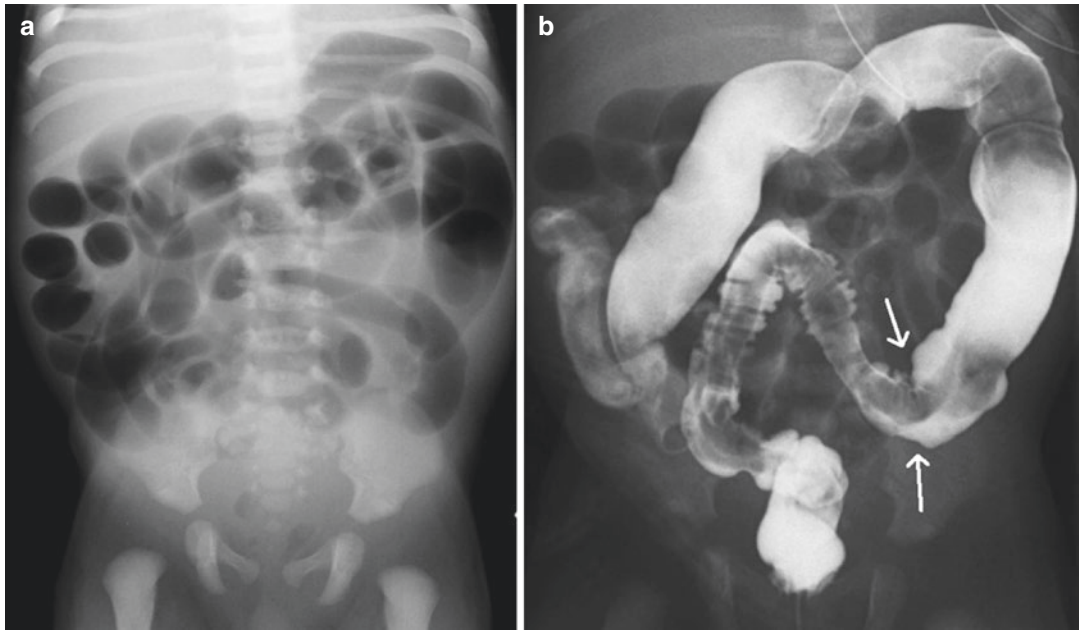

Fig. 3.9 Plain abdominal radiographs (**a**) and barium enema (**b**) in Hirschsprung disease: note in (b) the transition zone (white arrows) between the narrow and dilated portions of the colon

3.2.3 Ultrasonography (US)

Sonography is an excellent imaging modality for the evaluation of the gastrointestinal tract in neonatal patients, so as to be now considered extension of the clinical evaluation, both in emergency conditions for elective studies [18, 19].

The well-known advantages of sonography are its lack of ionizing radiation and the easy availability, while major drawbacks include its operator dependency and reproducibility. Moreover it is an excellent bedside high-yield imaging tool in intensive care units, and it can also be used to guide therapeutic maneuvers like in enema for meconium ileus.

In the last decades, advances in US technology, particularly improvement in high-resolution linear probes, have greatly improved the quality of GI sonographic imaging with a consequent positive impact on its diagnostic yield. Likewise, progress in Doppler techniques allows better depiction and quantification of even slow flow of small vessels within the normal and pathological GI structures.

In addition to the conventional transabdominal approach, other less common types of approaches might be necessary and should be included in the specific disease conditions, such as the suprasternal and mediastinal US approach to visualize the upper esophagus in tracheoesophageal atresia or the perineal US approach to evaluate the anal canal or the distal rectal pouch location and its distance to the skin surface in anorectal or in cloacal malformations.

3.2.3.1 Upper GI Tract

In neonates esophageal atresia is usually diagnosed with frontal and lateral radiograms, but sonography can give additional precious information to the surgeon. Besides the role of abdominal and cardiac sonography to search for associated abnormalities, mediastinal sonography allows the characterization of the length, morphology, and structure of the wall of the blind upper esophageal pouch which can be improved by the administration of small amount of saline fluid through the esophageal tube; rarely even a tracheoesophageal fistula may be recognized by sonography.

With a superior abdominal US approach, the cardia and the adjacent distal esophagus are often

easily depicted, although visualization of the entire distal esophageal length behind the heart is difficult and restricted.

In neonates and infants with suspected gastroesophageal reflux disease (GERD), sonography is a widely available, noninvasive, and sensitive method that can provide both useful anatomical and functional information, although its role is still controversial and debated. The complex issue of GER and GERD is related to many factors, including the difficult distinction between physiological and pathological GER and the impasse to establish a cause-effect relationship between GER and symptoms or complications related to GERD.

US is generally considered the modality of choice to confirm or exclude the diagnosis of hypertrophic pyloric stenosis as both the lumen and the surrounding musculature are directly visualized [20]. The diagnosis of HPS is based on sonographic morphological and dynamic findings: the most significant criteria are a thickened pyloric muscle (greater than 3 mm), a pyloric length greater than 18 mm, and the lack of luminal opening of the pyloric channel (Fig. 3.10).

The gastric duplication cysts are usually easily recognized when they have the classic sonographic appearance of localized fluid formations with a thick layered wall. The gastric emptying may be used to highlight the close relationship of the cyst with the gastric wall.

After ultrasound evaluation of esophageal-gastric junction, stomach and pylorus, the next step is to follow the duodenum to check the D3 position, normally passing between the abdominal aorta and the superior mesenteric artery; the normal position of duodenojejunal junction can also be identified, on the left side of the aorta.

3.2.3.2 Small and Large Bowel

The ultrasound can be used to recognize the intestinal malrotations [21, 22]. In the past years, barium enema and radiographic study of the upper gastrointestinal tract were used to evaluate duodenum morphology, duodenal-jejunum junction position, and cecum position, and it is still considered the criterion standard [21–23]. Actually, in addition to these invasive examinations that use X-rays, sonography with color Doppler is used to identify intestinal anomalies of rotation and fixation. The best known sonography finding is an abnormal relationship between the superior mesenteric artery (SMA) and the superior mesenteric vein (SMV), although a normal position does not exclude the presence of abnormal midgut rotation. In addition the normal position of the third duodenal portion is believed to be a more reliable mark to exclude the intestinal malrotation in respect to the position of the mesenteric vessel.

Midgut volvulus is the most frequent cause of acute abdomen in newborns, and it is a common consequence of intestinal malrotation. It's a life-threatening emergency; early diagnosis is important in this disease, to avoid the risk of intestinal infarct and necrosis. If not promptly diagnosed and treated, it leads to death or a lifelong dependence on total parenteral nutrition in survivors with short bowel syndrome.

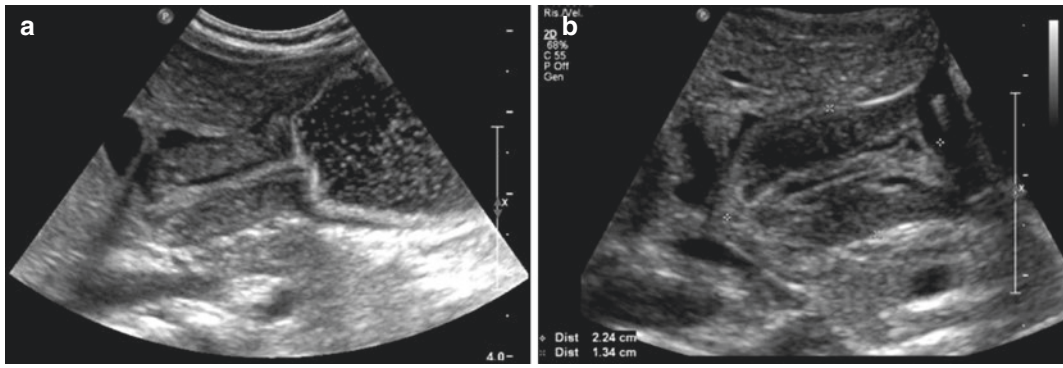

Fig. 3.10 US study (**a**, **b**) shows a thickened pyloric muscle without luminal opening in hypertrophic pyloric stenosis

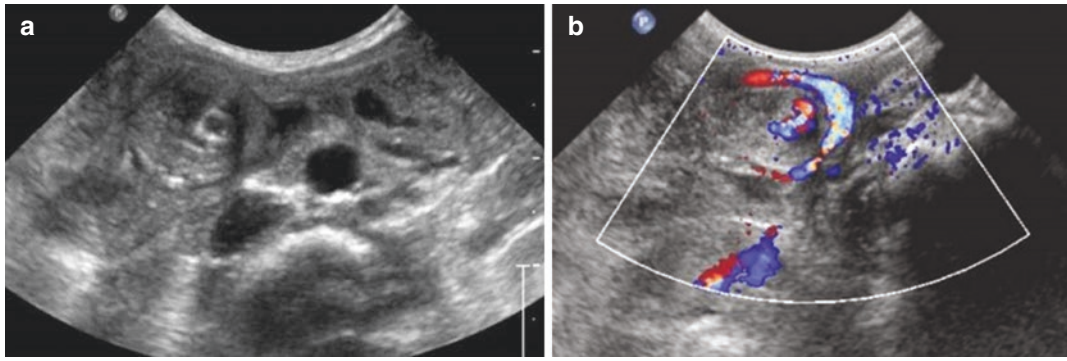

Fig. 3.11 US study (**a**) and color Doppler (**b**) show the whirlpool sign, with the superior mesenteric vein and mesentery wrapped around the superior mesenteric artery in a clockwise direction

Therefore learning to recognize the US findings of midgut volvulus is imperative: the volvulus is responsible for the whirlpool-like appearance on cross-sectional images, created when the superior mesenteric vein (SMV) and the mesentery wrap around the superior mesenteric artery (SMA) in a clockwise direction. Visualization is enhanced by the vascular signal at color Doppler flow sonography (Fig. 3.11).

For the neonate with the classic appearance of a whirlpool sign, additional imaging investigation is often unnecessary, and the surgeon should be alerted to plan for emergency surgery. The advantages of sonography for this age group are apparent, since it can be performed at the bedside in intensive care units and lacks the adverse effects of ionizing radiation.

The diagnosis of neonatal bowel obstruction or the confirmation of the prenatal diagnosis of these conditions is based on clinical and radiologic signs on abdominal plain radiograph, occurring with delay of 12–24 h; in very distal obstruction, it may appear even later.

Sonography can contribute with important additional information [10–14]; first of all it can document the obstruction, showing severe distension of the proximal bowel loops (diameter from 16 to 40 mm) with thin walls and increased peristalsis, filled with fluid and punctuated with echodense particles of gas. The distal bowel is small in size (3–4 mm) with echodense or target-like meconial content.

Furthermore sonography allows assessment of the colon size and its content, a main marker to assume the probable location of the obstruction thus indicating the need to perform a contrast enema in case of lower bowel obstruction. The colon is of normal caliber (9–14 mm) in very proximal small bowel atresia, while the microcolon (3–5 mm) is easily recognized in distal small bowel atresia and in meconium ileus. The last severe microcolon is present, but the small bowel is less dilated and less peristaltic. The most important finding is the characteristic appearance of the dilated bowel loops, which contain abnormal meconium: the thick meconium sticks on the bowel walls resulting in a pseudo-thickening. The distal bowel loops, in the right lower quadrant, are small (3–4 mm), with target-like appearance due to the impacted meconial pellets.

Hydrocolon is present in meconium plug syndrome and small left colon syndrome.

Besides small bowel obstruction, hepatic, splenic, scrotal, and peritoneal calcifications are observed in the meconium peritonitis with single or multiple meconium pseudocysts and free intraperitoneal fluid [17].

Occasionally sonography study highlights the cause of obstruction, either intrinsic (e.g., duodenal web) or extrinsic (e.g., GI duplication cyst or annular pancreas) [24].

In the anorectal malformations, the distance between the rectal cul-de-sac and the perineum can be reliably measured with perineal sonography [25]. Furthermore, sonography can be performed in patients whit associated genitourinary tract and dysraphic abnormalities; therefore all patients with congenital anorectal malformations

should have a genito-renal tract and spinal US examination as a screening test in the early newborn period.

Sonography is still not routinely used for diagnosis and follow-up of NEC, but it can provide information that is not provided by plain abdominal radiography and that may affect the management of NEC [16, 26]. Like radiography, sonography can depict intramural gas, portal venous gas, and free intraperitoneal gas; however, the main advantage of abdominal sonography over plain abdominal radiography, including color Doppler sonography, is that it can show intraabdominal fluid, bowel wall thickness, and bowel wall perfusion [27].

The ability to depict abdominal fluid is the first major advantage of sonography study over plain abdominal radiography, whether this is intraluminal or extraluminal and whether it is free in the peritoneal cavity or a more localized fluid collection.

The second major advantage of abdominal US in NEC is its ability to visualize the bowel wall directly and to assess bowel wall thickness, echogenicity, and peristalsis.

With both bowel wall thickening and thinning, the normal echogenicity of the wall (so-called gut signature) is lost, and it may be difficult to resolve the bowel wall from echogenic intraluminal content in severely affected loops. Bowel wall thickening is accompanied by an increased echogenicity of the full wall thickness; however, it is a non-specific sign, as it is also seen in other causes of diffuse edema in the absence of inflammation or ischemia.

The third major advantage of abdominal US including color Doppler is the ability to directly assess arterial perfusion of the bowel wall, to infer the viability of individual loops.

Three categories of flow were recognized at color Doppler: normal, increased, and absent. The hyperemia is the result of vasodilatation of mural and mesenteric vessel secondary to intestinal inflammation, with specific flow pattern ("zebra" pattern, "Y" pattern, and "ring" pattern) (Fig. 3.12).

Flow is absent when no color Doppler signals were identified in the bowel wall.

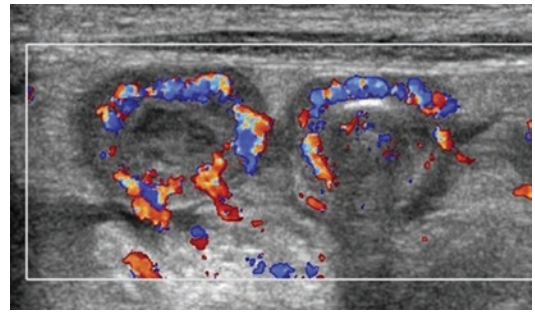

Fig. 3.12 Color Doppler sonography shows two loops with a thickened wall and ring pattern with increased perfusion

Thinning of bowel wall and lack of perfusion are instead highly suggestive of nonviable bowel and may be seen before visualization of pneumoperitoneum at plain abdominal radiography. As the mortality is higher after perforation, earlier detection of severely ischemic or necrotic loops, before perforation occurs, could improve the morbidity and mortality in NEC.

3.2.3.3 Other Diseases

Sonography is the imaging modality of choice to initially evaluate neonates with persistent jaundice. In biliary atresia, one of the most common findings is an absent or small (<1.5 cm) or empty gallbladder, after fasting for several hours. Absence of the gallbladder is present in approximately two thirds of neonates with biliary atresia. The triangular cord sign (defined as a triangular or tube-shaped echogenic focus at the porta hepatis that follows the portal veins and measures more than 4 mm in thickness) is another characteristic finding. However, it may be difficult to distinguish this sign from diffuse periportal echogenicity due to inflammation or cirrhosis. Other signs that have been described in the diagnosis of biliary atresia include an absent common bile duct, a hypertrophic hepatic artery (reported diameter 2.2 ± 0.59 mm), and an increased hepatic subcapsular flow on color Doppler sonography (CDS).

Choledochal cysts are very rare congenital saccular or fusiform dilatations of the biliary tree, usually classified according to Todani in

five types. Type I choledochal cysts are the most common, occurring in up to 80–90% of cases. Choledochal cysts usually present with cholestatic jaundice, but abdominal pain and fever may also be present. As choledochal cysts are often associated with an abnormal junction of the common bile duct and pancreatic duct, an ascending cholangitis and/or pancreatitis belongs to the most frequent complications, caused by reflux of pancreatic secretions in the bile ducts.

Other complications include liver cirrhosis, portal hypertension, and spontaneous cyst rupture.

Imaging plays an essential role in defining the extent of disease and guiding the surgical approach, as complete excision of the cysts is usually the treatment of choice. On US, the localization and degree of bile duct dilatation can be easily identified. Due to bile stasis in the dilated bile ducts, sludge or bile stones may be identified. As type 5 choledochal cysts (Caroli disease) are associated with autosomal recessive polycystic kidney disease, the kidneys should be examined as well.

Sonography may finally disclose other pathologic conditions such as hernias, duplication and mesenteric cysts, and tumor and tumor-like conditions.

3.2.4 Magnetic Resonance Imaging (MRI)

The main peculiarity of MRI is to provide multiplanar images with high resolution of tissue contrast, without the use of ionizing radiation; the duration of the investigation is still likely to require sedation.

In neonatal age, magnetic resonance imaging was the second-level investigation for the study of benign expansive lesions, already diagnosed by ultrasonography and sometimes known since the prenatal age. The most frequent lesions are mesenteric cysts, intestinal duplication cysts, and lymphangiomas, which the magnetic resonance can confirm, providing precious and more detailed pre-surgical anatomical information [24] (Fig. 3.13).

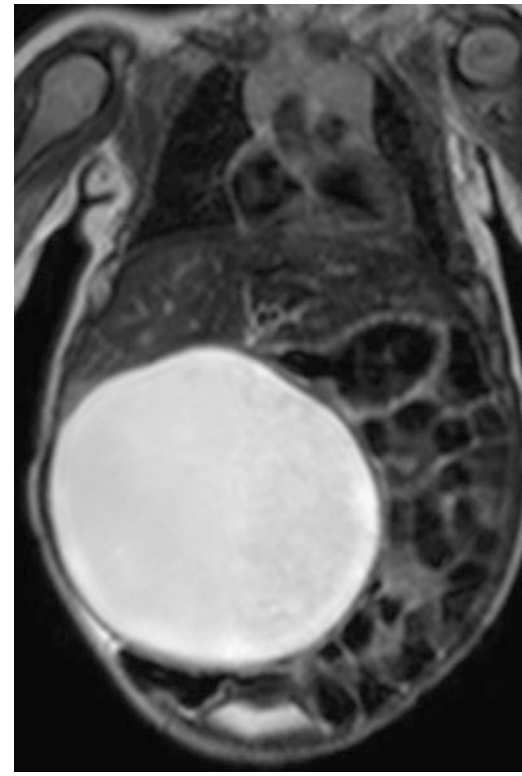

Fig. 3.13 Coronal MRI: T2-weighted image shows a large fluid mesenteric cist in the right abdomen

Although it is a rare occurrence, the onset of oncological pathologies, such as hepatoblastoma, ganglioneuromas, and neuroblastomas, is possible in the neonatal period; in these cases the MRI, in addition to being useful in preoperative planning, is used for staging.

Very important is the use of MRI in the congenital malformations of the biliary tree, from the atresia to the choledochal cysts, thanks in particular to the cholangiographic sequences (MRCP) that allow the evaluation of the biliary tree, without using contrast medium (Fig. 3.14).

In biliary atresia hepatobiliary scintigraphy (HBS) and magnetic resonance cholangiopancreatography (MRCP) may play a role, the latter only utilized as a problem-solving technique provided that the biliary tree is dilated. In choledochal cysts, MRI (including MRCP) is currently the most accurate preoperative imaging modality to demonstrate the extent of disease and the relationship of the cysts to the surrounding tissues.

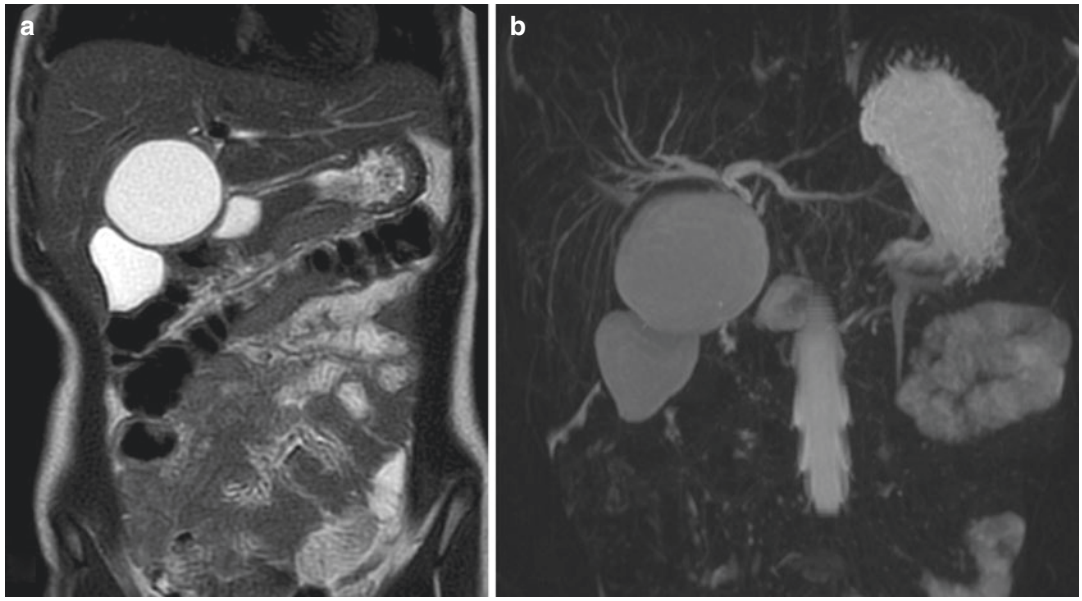

Fig. 3.14 Coronal MRI T2-weighted image (**a**) and MRCP (**b**) in a rare case of common bile duct diverticulum

Finally, the MRI is very helpful in the study of anorectal abnormalities, particularly in the preoperative evaluation of the newborn or infant prior to definitive pull-through repair surgery and in postoperative course pediatric patients with continuing problems [28]. Examination during sedation may give them to more accurate estimation of the true level of the elevator sling with multiplanar direct visualization of the distal rectum and related musculature (levator ani muscle, puborectalis muscle, external sphincter).

When the radiographic or sonographic examination is abnormal, then MRI can be used to accurately depict the likely associated intraspinal pathology such as tethered cord, caudal regression syndrome, hydromyelia, or a lipoma of the terminal filum. Associated lesions such as sacrococcygeal hypoplasia, lumbar spine, or renal anomalies can also be evaluated.

3.2.5 Computed Tomography (CT)

CT is a highly radiant investigation and therefore a level II diagnostic technique, which does not have significant applications in neonatal age. The only very rare exceptions are those in which a perfect assessment of thoracic and abdominal vascular anatomy is required.

3.3 Urogenital Neonatal Imaging

Like in other body parts, urogenital system examination starts with a prenatal ultrasonography, which usually is the first to underline renal, urinary tract, and genital malformations that altogether amount to more than a third of congenital anomalies in newborns.

Usually second-level prenatal ultrasound exam, in association with color Doppler imaging, is able to evaluate the malformation's type and seriousness.

However, in some complex cases or with poly-malformative syndromes, or when oligo-anhydramnios is present, fetal MRI might be needed to reach a more correct analysis and improve the postnatal clinical-therapeutic management.

Among the surgical diseases, the MRI finds use in multicystic kidneys, posterior urethral valves (hydro-ureteronephrosis evaluation and the frequently associated renal dysplasia), renal masses, neurological bladder and its associated

pathology (myelomeningocele), megabladder-microcolon (prune belly syndrome with abdominal wall study), cloacal exstrophy, urogenital sinus diseases and expansive diseases, and most common ovarian masses.

3.3.1 Ultrasonography (US)

After birth, ultrasound imaging is often the only exam needed to a definitive diagnosis and the key to indicate subsequent diagnostic algorithms, significantly reducing the need for other exams [29–34].

It is a real-time, operator-dependent exam that requires highly experienced examiner, trained in pediatric radiology.

It requires high-resolution, multifrequency (3–18 MHz) probes, with which can be meticulously examined both the urinary and the genital system.

3.3.1.1 Urinary System

Regarding the urinary tract, it's essential that the operator is experienced with the appearance variations of the growing kidney. In the prenatal age, kidneys keep their typical fetal lobulation, showing notches or wave profile. Renal cortex during this time is relatively hyperechoic compared to the liver, especially in premature newborns, with increase of normal corticomedullary differentiation. Medullary pyramids are relatively hypoechoic compared to cortex, while the renal sinus is not represented due to absence or paucity of fat. Pyelocaliceal cavities and ureters are visible only when dilated and appeared anechoic. The bladder needs to be evaluated in size and morphology, its wall thickness must be measured, and every endoluminal growth needs to be examined.

In addition to typical uses, there are newer ones that have great relevance in urinary system study; the use of high-frequency linear probes with transperineal approach to assess male's urethra, female's vagina, and surrounding structures should be remembered.

Very important are also color Doppler studies that allow a fast and comprehensive overview of vascular anatomy, as well as an assessment of the flow speed and direction. Color Doppler studies can also give information and directly visualize urethral jet.

Doppler sonography gives detailed information on flow profiles; in newborns it is characterized by a physiological low flow speed, a higher resistivity index, and peak diastolic seed a little lower.

Doppler study is also very useful in perfusion alteration indirect sign evaluation, as is verified in renal vein neonatal thrombosis (that involves a higher resistivity index of the affected kidney), renal arteries stenosis, or flow variations in kidney failure.

Power Doppler studies show the blood flow volume instead of its speed, particularly useful in peripheral renal vascularization evaluation.

Its use allows focal perfusion defect (renal infarction, segmental pyelonephritis) diagnosis or cortical perfusion diffuse reduction.

Ultrasonography recognizes several congenital diseases, first of all anomalies of number (renal agenesis), position (simple ectopia), and fusion (horseshoe kidney, crossed fused ectopia, and renal duplications); those malformations have anyway no surgical interest.

On the other hand, antenatally diagnosed hydronephrosis represents one of the more frequent indications to neonatal US; congenital hydronephrosis can be secondary to mechanical or functional causes (Fig. 3.15). Obstruction's mechanical causes include ureteropelvic junction obstruction (UPJO), ureterovesical junction obstruction (UVJ), simple ureterocele, and posterior urethral valves.

Functional causes include the prune belly syndrome and the vesicoureteral reflux.

In newborns with prenatal diagnosis of severe bilateral hydronephrosis, ultrasound imaging is required on the first day of life, especially in case of hydro-ureteronephrosis and/or suspected bladder anomalies or urethral valves.

Instead, in case of moderate bilateral hydronephrosis or unilateral hydronephrosis (with or without ureteral dilatation) prenatal diagnosis, ultrasound examination can be delayed until the first week of life, due to the urinary system immaturity and the risk to underestimate pathological findings presence and seriousness.

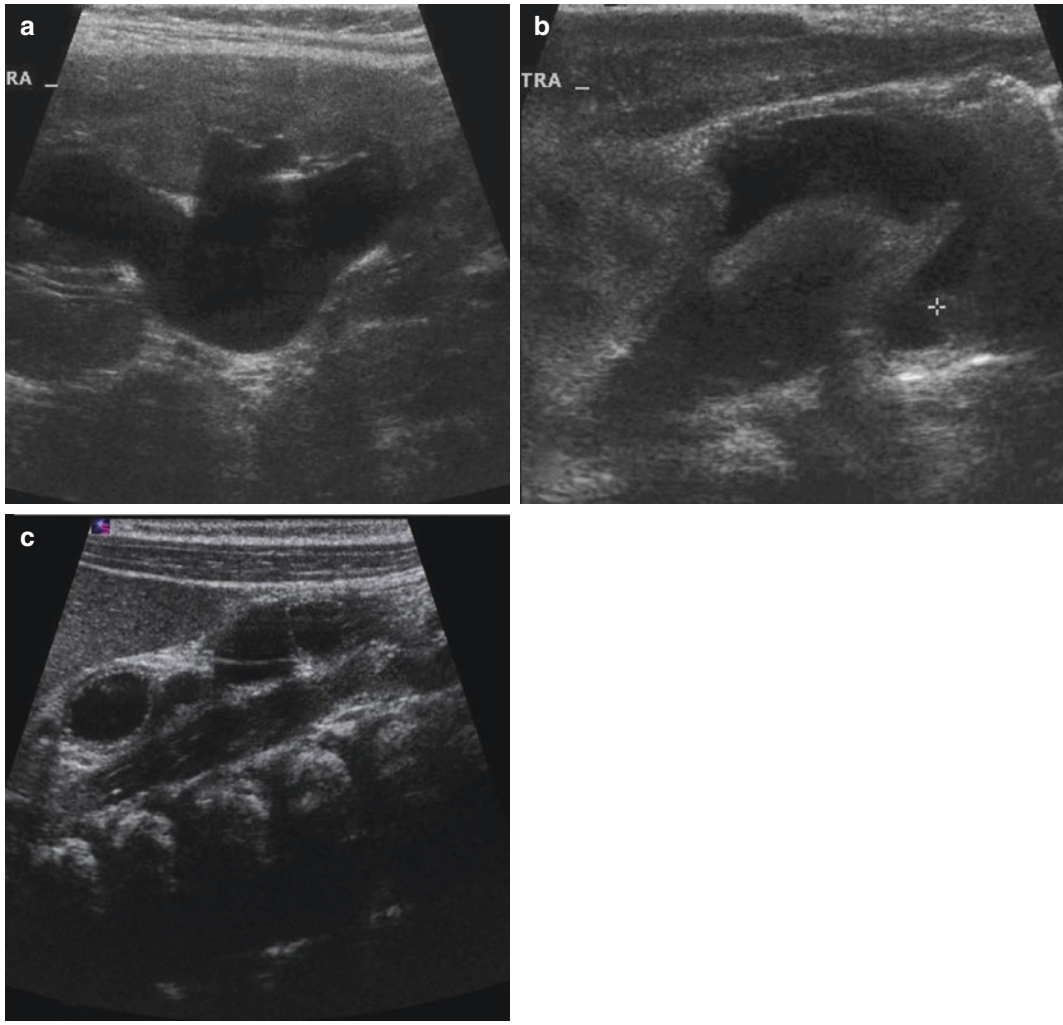

Fig. 3.15 Sonography at birth. Important hydro-ureteronephrosis (**a**, **b**, **c**): the thickening of mucus lining is strongly suggestive of vesiccoureteral reflux

US alone isn't able to discriminate between obstructive uropathy and reflux diseases, so definitive diagnosis requires subsequent imaging investigations.

Only in some cases can ultrasound imaging strongly direct toward an obstructive condition, as is seen in cases of serious pelvic balloon-like dilatation, without corresponding ureter size alteration: those cases are strongly suggestive of UPJO. On the other hand, presence of hydro-ureteronephrosis with thickening of mucous lining is strongly suggestive of vesicoureteral reflux.

Among the renal cystic diseases can be of surgical interest the multicystic dysplastic kidney, a non-hereditary developmental anomaly that is believed to be the consequence of early in utero urinary tract obstruction.

Expansive diseases diagnosis is also echographic; in neonates, those diseases, although rare, involve more often the kidney (mesoblastic nephroma, nephroblastomatosis).

3.3.1.2 Genital System

The internal female genitalia are prominent at birth due to maternal and placental hormonal

stimulation. After 2–3 months, the uterus is small and malformations are easily missed. Therefore, in suspected malformations of the female genitalia, the investigations should be performed shortly after birth.

Congenital anomalies of the female genital tract result from developmental anomalies of the Müllerian duct with or without combined abnormalities of the urogenital sinus or cloaca.

There is a developmental relationship between the genital and the urinary tracts; hence anomalies in both systems are often coexisting. Comprehensive US examination of the internal genitalia should be performed in all female neonates with multicystic dysplastic kidney (MCDK), unilateral renal dysplasia, or single kidney due to the high risk for associated genital malformation, as well as in individuals with suspected or obvious genital or cloacal malformations or congenital adrenal hyperplasia. Both curved array transducers of adequate size and high-resolution linear transducers must be applied using both abdominal and perineal approach. In neonates the filling of the vagina, and sometimes also the rectum (called sonogenitography), will facilitate accurate depiction of anatomy, particularly in more complex malformations.

The size, morphology, and position of the vagina, cervix, and uterus, including signs of uterine duplications and cervical or vaginal obstruction, should be described, both during filling and before and after voiding. If there are signs of obstruction, the distance from the site of obstruction to the perineal orifice should be assessed.

Malformations of the female genitourinary system may be isolated or part of a syndrome with other associated anomalies, particularly spinal or skeletal malformations. In complex malformations such as intersex conditions, urogenital sinus, or cloacal malformations, the child should always be referred to a dedicated pediatric center for further workup and treatment.

In healthy female neonates, the small, anechoic follicular cysts up to 10 mm in diameter in the ovaries are a normal finding, and they generally do not have a pathological significance.

In the neonatal period, even large ovarian cysts may be seen, and they may be incidental findings on prenatal or postnatal US, but they may present postnatally as pelvic or abdominal-pelvic mass. Normally these cysts resolve within a few weeks after birth and cause no complications. Complications from larger ovarian cysts include bleeding into the cyst, ovarian torsion, and occasionally ovarian strangulation in an inguinal hernia.

The US appearances of a simple, uncomplicated cyst are the anechoic content, a thin wall, without intralesional septa; another finding is the daughter cyst sign.

Hemorrhagic cysts and cysts associated with adnexal torsion appear as complex masses containing multiple septations, low-level echoes, clotted blood, and/or fluid-debris level; other findings of torsion include thick, echogenic walls, and a twisted vascular pedicle.

Occasionally a specific diagnosis of ovarian teratoma can be made when highly echogenic foci with shadowing are demonstrated within a complex adnexal mass.

Indirect sliding inguinal hernias containing the ovary and fallopian tube are not uncommon in neonates, with an increased risk of vascular compromise. Ultrasound is an accurate method to determine the content of inguinal hernias and will help determine further management.

In male newborns, US plays an important role in extravaginal torsion (Fig. 3.16). It usually occurs at a level of spermatic cord in utero, and all of the scrotal contents on the affected side are strangulated. Affected neonates present with a swollen red scrotum with a firm enlarged testis. While it is most commonly unilateral, bilateral extravaginal perinatal torsion does occur. The testis is usually necrotic at birth so that surgical salvage is unlikely. In contrast, when extravaginal torsion occurs after birth or produces only partial ischemia, the testis may be viable and hence salvageable with surgery.

US findings of extravaginal torsion vary depending on the duration of torsion. Findings in more recent torsion include an enlarged heterogeneous testis with hypoechoic and hyperechoic areas. More chronic torsion demonstrates a minimally enlarged or normal size hypoechoic testis with peripheral echogenicity corresponding

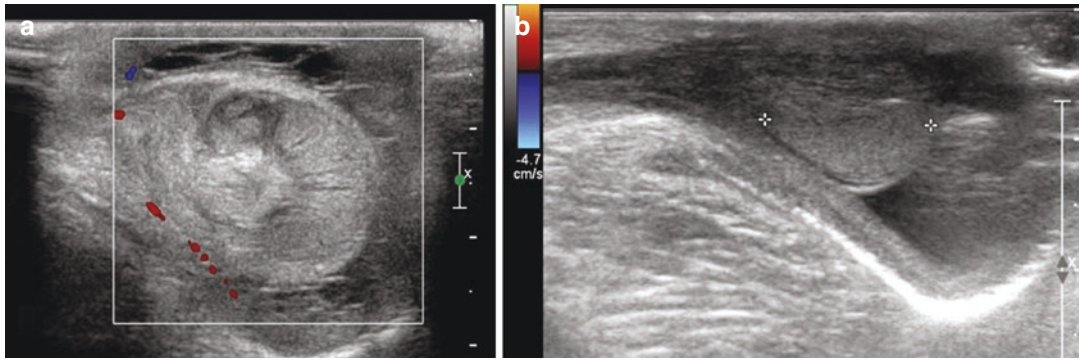

Fig. 3.16 Scrotal sonography in newborn: color Doppler evaluation (**a**) shows an enlarged heterogeneous testis with hypoechoic and hyperechoic areas, without vascular signal; (**b**) normal finding of the contralateral testis

to calcifications in the tunica albuginea. Scrotal skin thickening and hydroceles with debris and/or septations are common associated findings. Doppler signals are often absent in the testis and in the spermatic cord, although some flow may be seen with power Doppler imaging. The contralateral testis may demonstrate compensatory hypertrophy, a finding seen in other cases of congenital monorchism.

US is also used in neonates and infants with hydrocele, associated with a patent vaginalis process, which allows peritoneal fluid to enter the scrotal sac. Hydroceles can present as loculated or encysted around the spermatic cord if the vaginalis process closes above the testis and below internal inguinal ring.

Scrotal extratesticular calcifications may be observed at ultrasonography in meconium peritonitis, usually between the layers of the tunica vaginalis, as hyperechoic foci with acoustic shadowing.

US can be requested in cryptorchidism, at birth most frequently found in premature male infants. Testicular migration can arrest anywhere along the course of descent from the retroperitoneum into the scrotum; in most cases the undescended testes are located in the inguinal canal, or just proximal to the internal inguinal ring, while rarely are located in the abdomen. Hypo-atrophy of the undescended testis is common, and at US the testis is smaller and more hypoechoic than the contralateral normally located testis.

Furthermore US can aid in establishing a diagnosis of an inguinal hernia, more frequent in premature, by demonstrating peristalsing fluid or air-filled loops of bowel in the scrotum and a normal testis and epididymis. Identification of peristalsis favors viable bowel, while absence of peristalsis and blood flow in the herniated bowel suggests ischemic changes. When omentum also extends into the inguinal canal, the hernia will appear as a complex echogenic mass.

3.3.2 Contrast Studies

The contrast studies are voiding cystourethrography (VCUG) and voiding urosonography (VUS) [35–39].

Voiding cystourethrography (*VCUG*) is still today the first-choice exam for vesicoureteral reflux diagnosis and male urethra diseases (Fig. 3.17). The exam requires positioning a bladder catheter without balloon and then highly concentrated, radiopaque contrast medium bladder injection, until complete bladder filling. The field of view must include all the urinary system, from the kidneys to the urethra, to evaluate male urethra, which is a fundamental lateral projection acquired during the urination and after the catheter removal.

It's important to remember that it is a radiant technique, moreover without the possibility to shield the gonads: for this reason VCUG must be executed exclusively with a pulsed fluoroscopic technique, ideally with the lowest pulse setting, with a notable dose reduction.

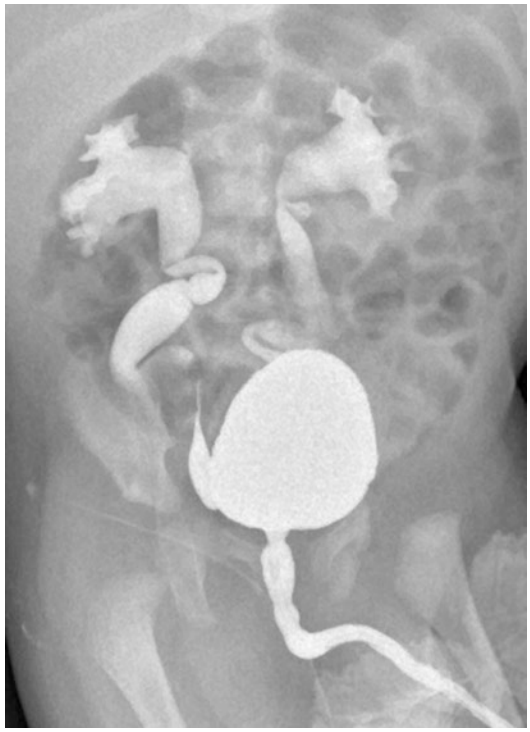

Fig. 3.17 VCUG demonstrates severe bilateral reflux and normal urethra in a male neonate

For the same reasons of radioprotection, is the use of voiding urosonography (VUS) is more and more widespread, possibly thanks to the introduction of second-generation echographic contrast agents injected in the bladder after catheterization, similarly to what already said for VCUG. Those produce a high enhancement and a strong harmonic response, but most of all they have a higher resistance to the ultrasound beam mechanical impact, allowing a longer study time, needed to possible reflux detection (Fig. 3.18).

3.3.3 Magnetic Resonance Imaging (MRI)

In newborn, MRI has very peculiar indications, usually required as second-level exam to evaluate complex urinary and genital system malformation conditions (bladder exstrophy, cloaca, urogenital sinus anomalies, genital congenital anomalies) or more often as a functional study in obstructive uropathy [40–48]. For the latter today, it can be considered the only diagnostic technique that detailed anatomical and functional information of the urinary system, without using ionizing radiation.

It must be considered, anyway, that the MRI is a second-level exam, usually executed on infants only in a limited number of selected cases, due

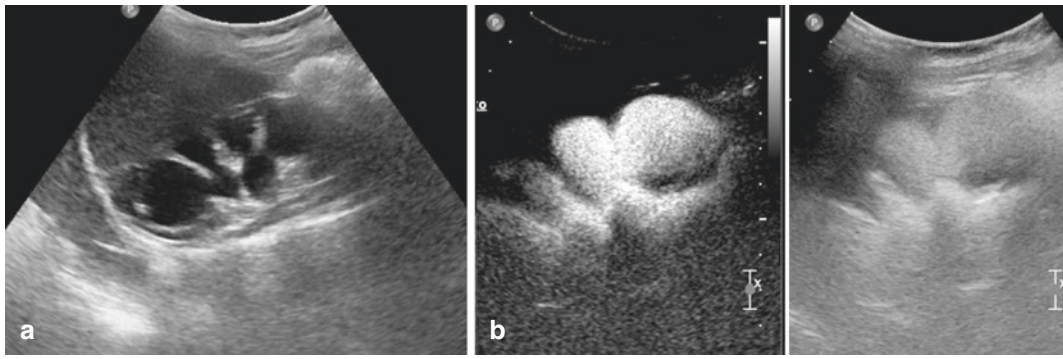

Fig. 3.18 Voiding urosonography (VUS): pre-contrastographic US study (**a**) and post-contrastographic US study (**b**) with optimal VUR visualization

to its needing sedation/anesthesia and the use of intravenous contrast medium.

The knowledge of the relationship between the administration of paramagnetic contrast agent and nephrogenic systemic fibrosis requires great caution in its use in pediatric age, particularly in neonatal and infant age, and full compliance with all precautionary measures.

Functional uro-MRI requires an initial patient's preparation phase (hydratation and furosemide injection), followed by pre- and post-contrast sequence acquisition. Pre-contrast imaging is the most important phase for the anatomic evaluation of the urinary tract. It is performed with TSE T2-w and 3D T2-w sequences; the latter are used to generate MIP and VR images, which allow the best visualization of the pelvicalyceal system and ureters.

The resulting images are very useful for the evaluation of obstructed collecting system, duplex systems and complex anatomical variants, and bladder abnormalities, including ureteroceles and ectopic ureteral insertion. Same sequences are also fundamental in poorly functioning system or in functionally excluded kidneys, which obviously have little or no displayed in contrastographic phase, similarly to what occurs with scintigraphic studies.

The following post-contrastographic phase, vascular and excretory, allows to dynamically study the urinary system. Typically after the contrast administration, continuous dynamic images are acquired, until the complete enhancement of the excretory system. The high-resolution images obtained are excellent for 3D VR reconstructions with the optimal visualization of the renal cortex, the medulla, the pelvicalyceal system, and the ureter course into the bladder.

The post-processing phase can be measured in various parameters of renal function and particularly the renal transit time, the calyceal transit time, the time-intensity curves, the differential renal function, and the glomerular filtration rate (GFR). These are very important parameters, similar to those used in scintigraphic studies.

Finally the MRI is used in newborn and infants for a better evaluation of the masses, frequently kidney's masses, diagnosed with ultrasonography (Fig. 3.19).

3.3.4 Other Diagnostic Techniques

Plain film and intravenous urography virtually disappeared from pediatric radiology, because anatomical and functional information can be acquired with the same or higher level of detail with ultrasound or MRI and nuclear medicine studies.

CT has instead as major drawback the high radiation dose and, according to the ALARA principle, should be used in children only in the rare cases in which the same diagnostic information cannot be obtained with other, less or no radiating, imaging techniques.

That is the reason why CT does not find significant indications in neonates and infants.

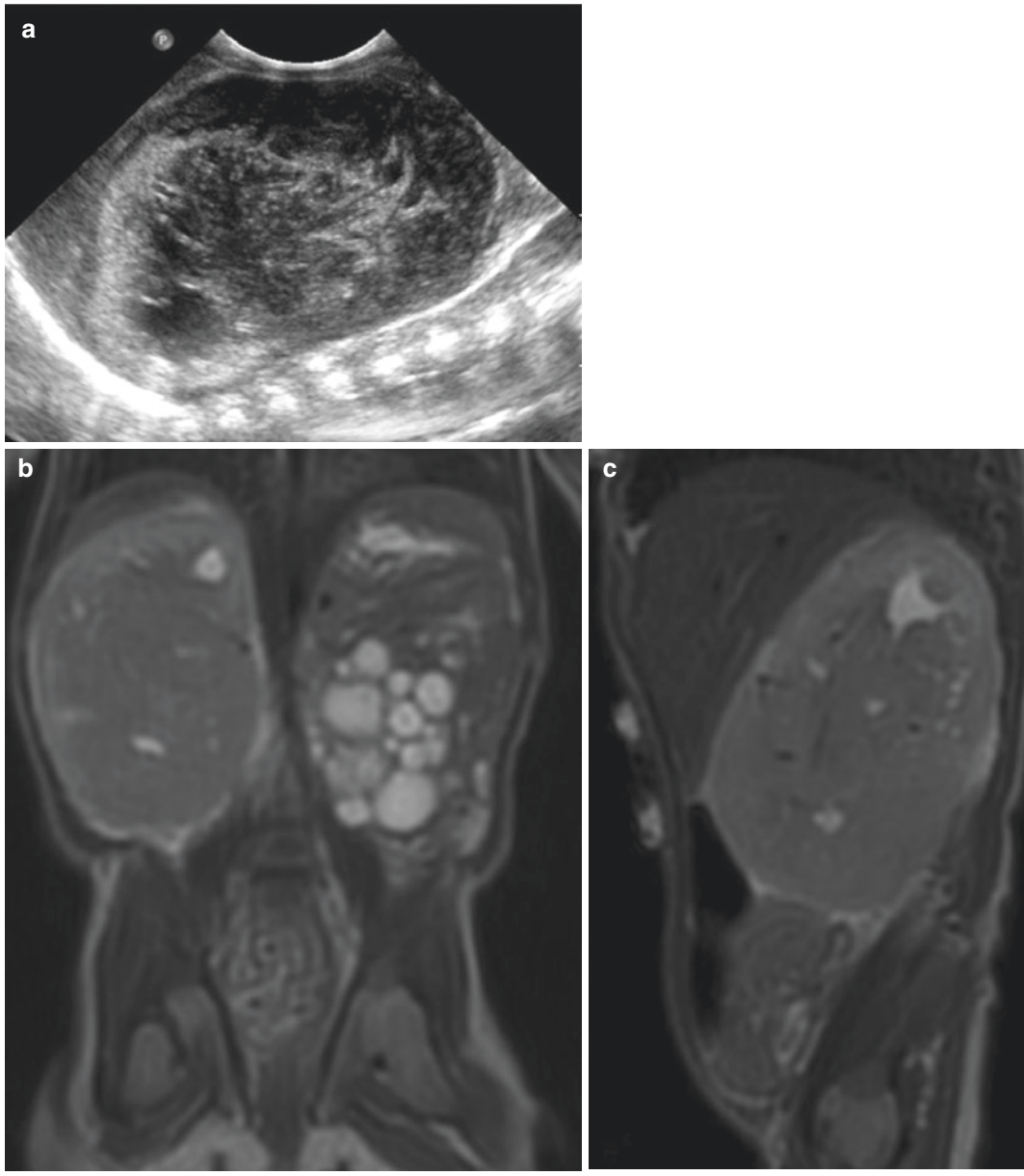

Fig. 3.19 US (**a**) and MRI (**b**, **c**) show large right kidney masses (nephroblastoma). Note in (b) the contralateral multicystic kidney

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4 Neonatal Surgical Education in Minimally Invasive Surgery Based on Simulation

Maximiliano Maricic and María Marcela Bailez

4.1 Introduction

Neonatal minimally invasive surgery (NMIS) requires a high level of training in both neonatal and MIS disciplines. It requires a progressive goal-oriented curricula content specific to each surgical neonatal pathology. Evaluation of the theoretical and practical contents at each stage of training is mandatory. Surgical skills training has been classically done in the operating room under the supervision of the senior surgeon and in animal models, when available. The difficult learning curve combined with the few cases per year for each surgeon is a critical factor against the spread of these procedures that are feasible and effective in experts' hands.

Simulation is used as a complementary learning tool in minimally invasive surgery (MIS). It allows training in a safe, standardized, and controlled environment, without compromising the safety of the patient. The goal of simulation is to transfer the acquired skills to the operating room, improving patients' outcome.

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Even though there is not an evidence-based research result of this ultimate goal in this topic, with the aim of improving the learning curve for NMIS, the senior author decided to include simulation in a regular basis in the curricula of our pediatric surgical residents and created an MIS education fellowship, starting in 2013.

We use a spiral education method, where we increase the complexity of the procedures in a progressive way, but we reinforce the basic concepts of MIS in all the stages of the training and incorporate suture skills from the beginning.

4.2 NMIS Curricula Including Simulation in Pediatric Surgery Training Programs

Neonatal/infant MIS procedures should be addressed as very advanced ones at the time of planning the content of a curricula. The concept of progressive training should not be underestimated and rigorous basic and intermediate levels of MIS training courses including simulation should be done before a NMIS course. We understand this may change in relation to every region needs or program, for example a previous general surgery residency as a requirement to enter a pediatric surgery program or not.

An efficient training program is one in which skills are trained in a programmed, progressive, specific way. An adequate evaluation system of the results and progress of the student with

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debriefing at each stage is mandatory. A suitable program allows performing tasks with progressive complexity and precision.

The first approach to endosurgery should include every professional aspect of MIS like knowledge of equipment and instruments, electrosurgery, ergonomy, and the art of MIS suturing.

With this in mind we developed different levels of simulation courses and not only include them in the curricula of different residency programs but also offered them to pediatric surgeons in need of MIS training for different reasons.

We designed three levels of in situ courses with progressive complexity and created our own low-cost inanimate and hybrid basic, intermediate, and specific neonatal models, some of them already published and validated.

4.3 Course Contents

Each course has a cognitive and a simulation-based skill content. The cognitive aspect is shared virtually and discussion is promoted before starting with the skills simulation stations. Depending on the stage of the training we are in, we use different types of endotrainers, such as adult-sized devices with an 8-L working area (Fig. 4.1), advanced devices of 500–800 mL like Pediatric Toronto model [1] (Fig. 4.2), and neonatal models that are specifically developed and validated with working areas between 100 and 40 mL [2] (Fig. 4.3).

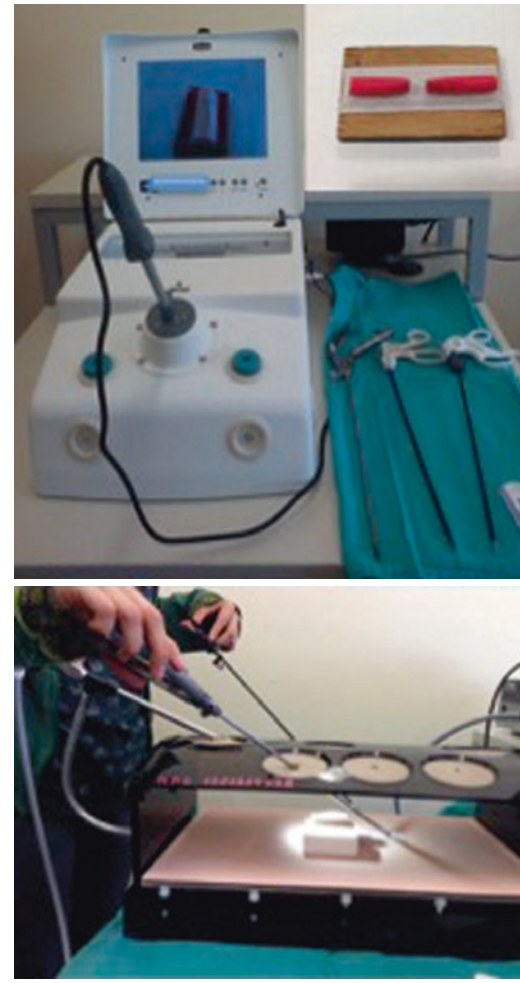

Fig. 4.1 Initial box trainers 8 L

4.3.1 Level 1: Basic or Essential Skills Course

It includes principles of ergonomy, electrosurgery, equipment and instruments, art of intracorporeal and extracorporeal suturing, port placement, strategy for common procedures, and team working.

The goals include the use of both hands for exposing and dissection, correct use of energy, lens and tissue handling, needle grabbing, and Roeder extracorporeal and square intracorporeal knot techniques.

The participants change stations every hour with 32 h distributed in 3 days. A personalized supervision avoiding the development of inadequate maneuvers and teaching the professional ways and tricks to shorten the learning curve is undertaken and data is obtained for debriefing to guaranty that the objectives are reached.

A personalized supervision avoids inadequate maneuvers, provides the opportunity of sharing tips and tricks in order to have a shorter learning curve, and ensures reaching the pre-established objectives. We usually use virtual trainer devices in this stage of training (Fig. 4.4) and plan workshops to acquire the practical concepts of the cognitive content about electrosurgery, instruments, and equipment.

Fig. 4.2 Advanced box trainers. Own development and Toronto model (below) Working area: 500–800 mL

4.3.2 MIS Suture and Knots

We consider the art of endosuture and vessels dissection with either sealing or ligature as the fundamental skills to assess before starting with the specific models. Multiple knots have been described. We decided to standardize some of them for an educational purpose.

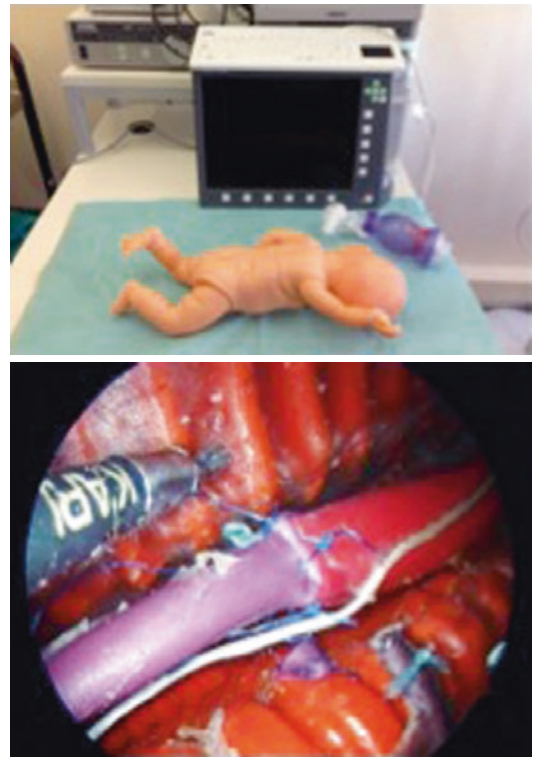

Fig. 4.3 Neonatal advanced trainer. Own development. Working space 100–500 mL

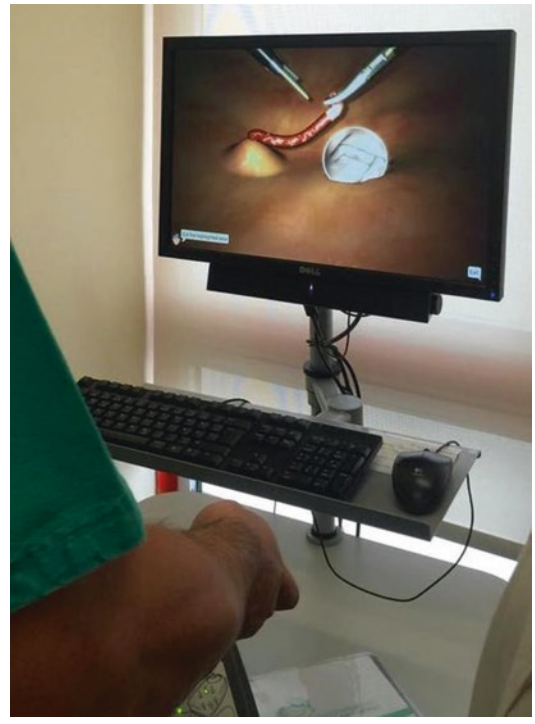

Fig. 4.4 Virtual devices

Extracorporeal knots: These allow solving a great number of situations, are very versatile, and require adequate coordination, precision, and care of the tissues. We teach how to avoid the use of specific instruments like knot pusher and slide it with a Maryland dissector or the needle holder. They may be used for example in a diaphragmatic plication or rectourinary fistula during a rectal pullthrough.

Square knot or surgeon knot is the main intracorporeal knot that we use for training and its practice develops coordination and precision skills.

Intracorporeal slide knot: This knot has the benefits of intracorporeal and extracorporeal suturing. It is designed for tissues under traction that needs to be put together gradually (for example esophageal atresia (EA)). Most of the expert MIS neonatal surgeons use this knot. We include it in level 2 and 3 courses.

Initially we teach each of these knots separately, but the final objective is to provide the student a number of tools that allow choosing the best knot for each moment and tissue.

4.3.3 Level 2: Advanced Course

We start doing an assessment of suturing (square knot technique) in a tubular silicon structure (Fig. 4.5) and dissection and vessel sealing in live tissue (pig or cow kidney or lung into a trainer) using a vessel filling technique.

Cognitive content includes innovation, advanced technology, thoracoscopy, and other intracorporeal suturing techniques like running sutures and intracorporeal sliding knots.

We use plastic mannequins opened in the abdominal area to introduce a block of animal viscera to simulate a Nissen procedure, colonic biopsies or resections and cholecystectomy. These models are also used to simulate safe trocar insertion technique in level 1 courses (Fig. 4.6).

Only after a basic and advanced period of training we recommend the introduction of animal models into the curriculum to perform guided procedures (cholecystectomy, salpingectomy, Nissen, nephrectomy, and diaphragmatic suturing). We use 10 kg piglets under anesthesia following the rules of the bioethics committee in relation to the use of experimental animals. During the last 2 years we have replaced experimental animals by blocks of live tissue from farm animals acquired in butcher shops, making hybrid models (Fig. 4.6). This reduces costs and clears the ethical problems involved in working with live animals.

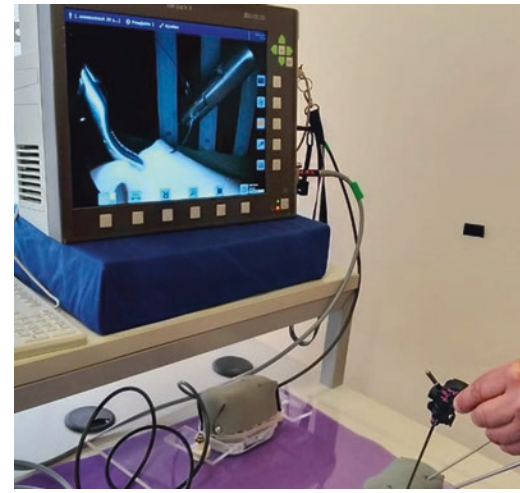

Fig. 4.5 Suture assessment

4.3.4 Level 3: Neonatal Advanced Course

It is a pure neonatal/infant MIS training course and includes not only skills, but also team behavior simulation and appropriate care, of the fragile ergonomic instruments essential to acquire speed and effective actions in a safe environment. During the course instructors will support participants to care instruments and ergonomics, and to acquire speedy, effective, and safe actions and movements taking care of the simulation models as if they were real patients.

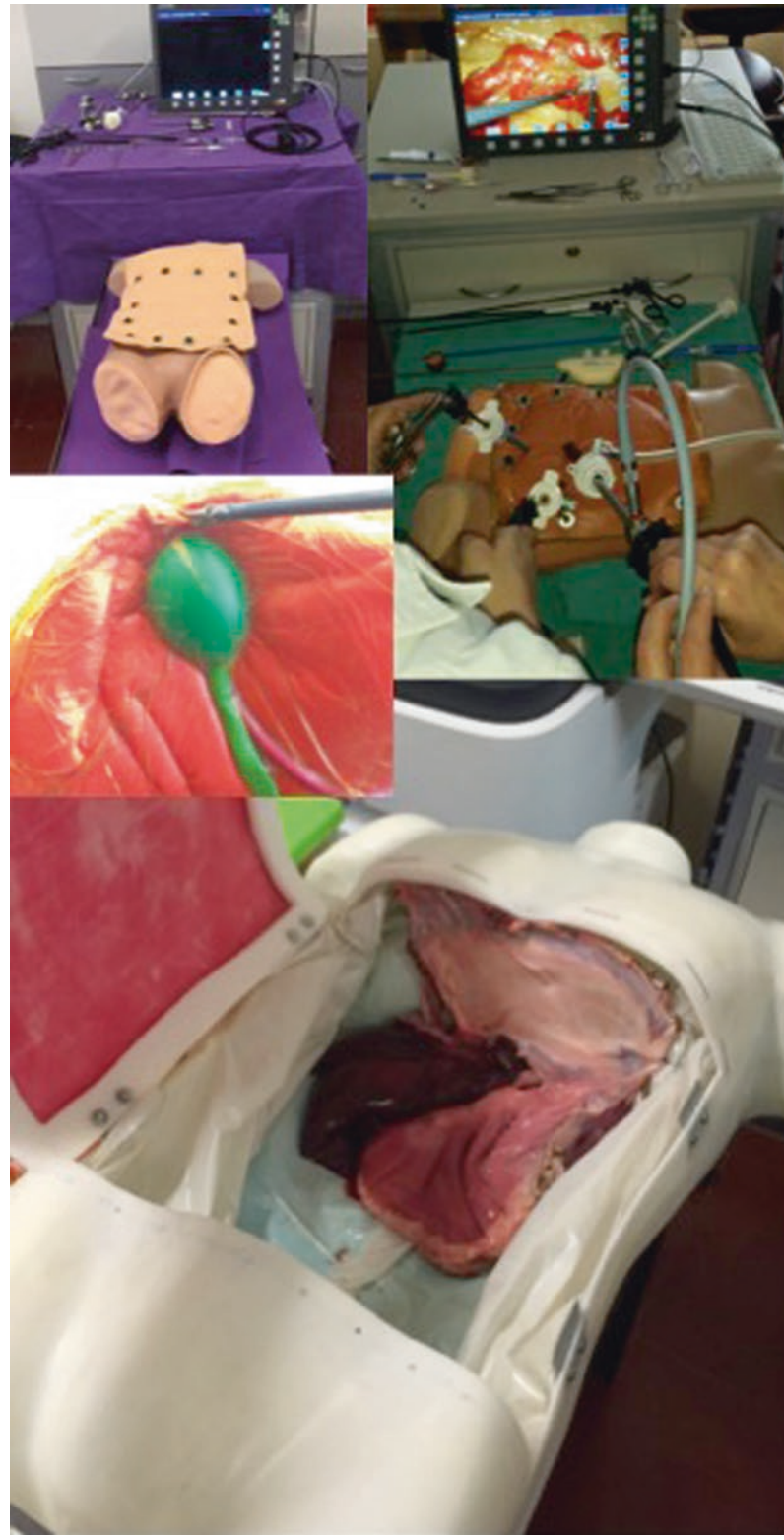

Fig. 4.6 Hybrid model 1

It is mandatory to achieve level 1 and 2 to achieve level 3. Sophisticated courses with many stations and technology using either inanimate or live models are not worth planning with participants that should have practiced or even attended a suturing course before being exposed to these models. They are not cost-effective and may cause frustration in the learning process.

Small volume trainers simulating an infant or neonate abdomen or thorax are used only after an assessment of basic suturing in regular trainers is done. Exercises include transference, cutting precision, extracorporeal and intracorporeal suture with fine needles and threads, for example the Toronto model [1] with a working area of about 800 mL. This is a webcam trainer to practice transference, precise cutting, and suturing using extracorporeal and intracorporeal suturing techniques inspired in the FLS.

The first neonatal MIS model used in our institution was the one developed by Karen Diefenbach when she was a pediatric surgical fellow in Yale (Fig. 4.5). This model is now part of an educational project shared with IPEG.

We have found a shortage of training models available for level 3 courses. Therefore we have developed our own models of neonatal training with a small working area between 40 and 400 mL and inspired in the expertise in NMIS.

Inspired by his daughters' toys, our first MIS trainee-fellow modified the plastic handbags of their dolls and with the help of the scrub nurses they developed simple neonatal trainers to practice handling and suturing in small spaces.

Until now we have developed trainers for specific surgical procedures in newborns and infants: esophageal atresia with tracheoesophageal fistula (TEF/EA), duodenal atresia (DA), congenital diaphragmatic hernia repair (CDH), lobectomies, hepaticojejunostomy after choledochal cyst resection (Figs. 4.7–4.11).

They challenge the tasks of working with delicate tissues, suture in extremely small spaces (e.g., less than 50 mL) in an environment of high anatomical similarity, resembling specific pathologies of the newborn.

Two participants are assigned to work together per model. This strengthens the skills of team coordination and the understanding of the value of being in charge of a 30-degree mini endocamera. Ergonomic short 3 mm instruments are used. The instructor provides tricks and technical tips, as well as a discussion of the clinical aspects of the disease. Debriefing and evaluation of the results are carried out through exams and performance evaluation forms.

4.4 NMIS Instructors, Models, and Knots

4.4.1 Instructors

The fundamental bases for effective training are an adequate program, trained instructors, and specific models for each stage of training.

In our training curriculum one of the strengths is the training of instructors, who are pediatric surgeons who operate NMIS. All of them must complete the curriculum and pedagogical training. At the same time, they will be the ones who train other instructors in the future.

As mentioned above, the role of the instructor is very clear:

It accompanies the educational process in all its stages, reinforcing the concepts of patient care, ergonomics, specific techniques, and teamwork, and making continuous feedback to students.

4.4.2 Models

The high fidelity of the models is recommended to improve expertise. However they are expensive. Most of our models are cheap. They were all inspired by our experience in neonatal MIS and we have validated the first specific model we developed [2].

The combination of ex vivo animal tissue and the use of 3D printed thoracic cages like in our last model (CDH) have been incorporated to improve fidelity (Fig. 4.9).

The use of live tissue enables the practice of energy devices and increases tactile sensation.

Fig. 4.7 Esophageal atresia with tracheoesophageal fistula (TEF/EA) model

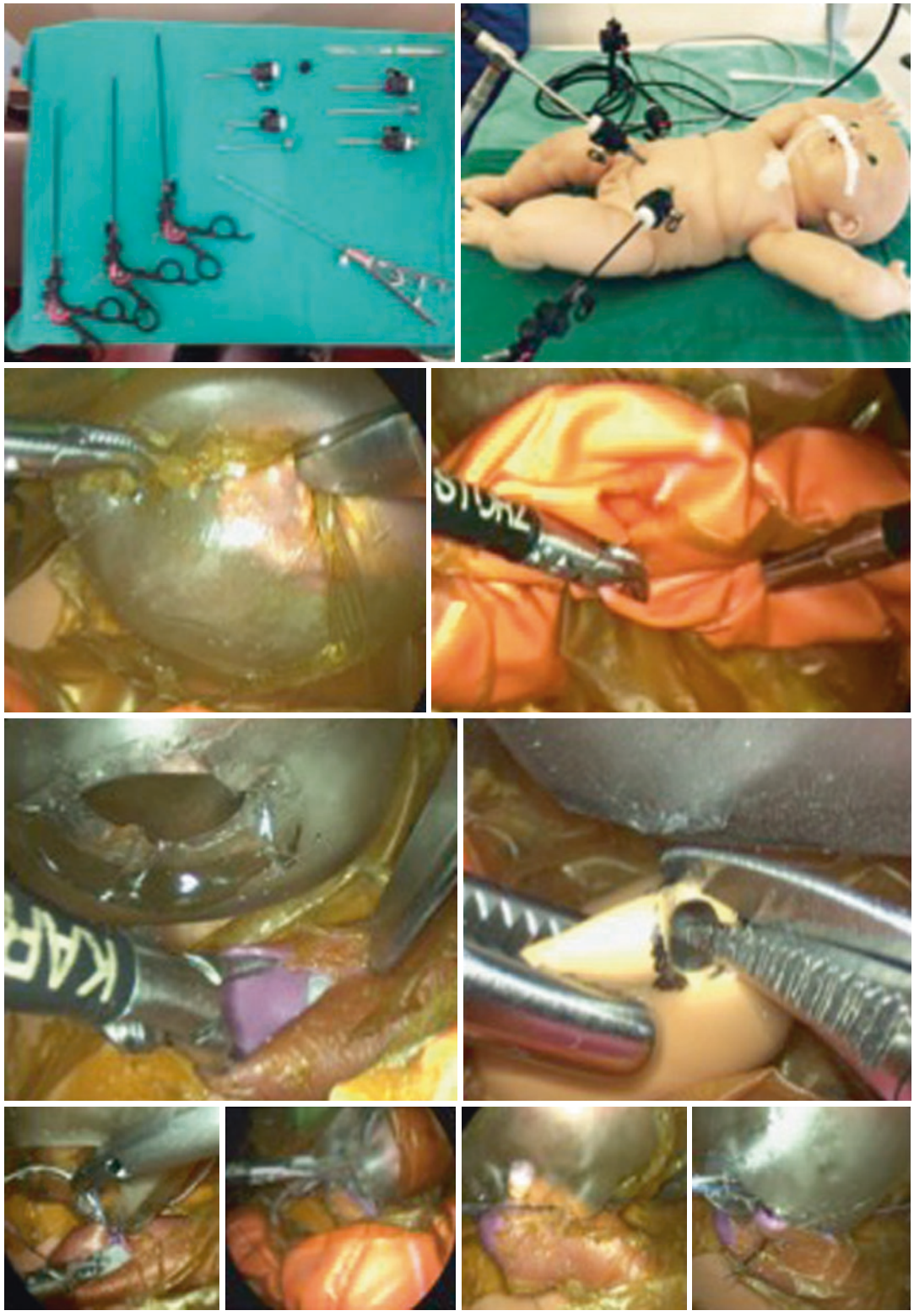

Fig. 4.8 Duodenal atresia model

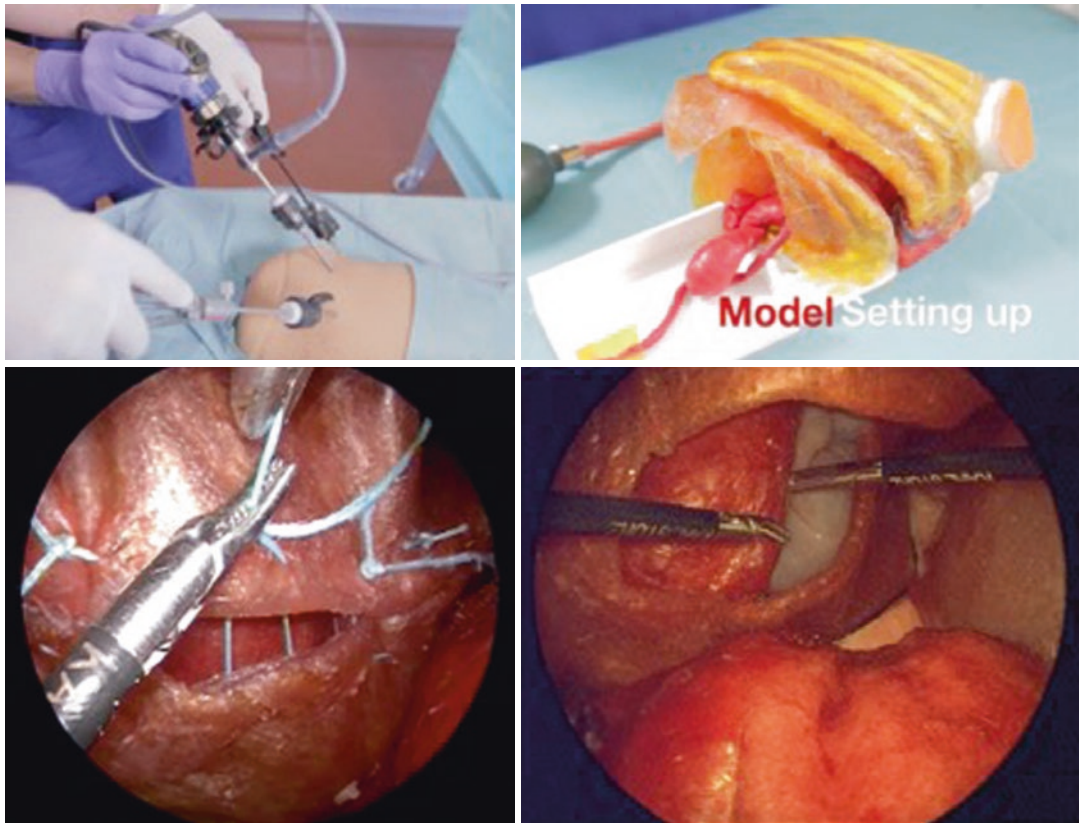

Fig. 4.9 Congenital diaphragmatic hernia repair (CDH) model

4.4.2.1 Esophageal Atresia with Tracheoesophageal Fistula (TEF/EA) [2] (Fig. 4.7)

The model consists of a doll representing a 3500 and 2000 g newborn and a spare part that resembles the right hemithorax and mediastinum with the trachea, ribs, upper and lower esophagus with a TEF, pneumogastric nerve, azygos vein, and mediastinal pleura. The simulated lung can be inflated either with a resuscitation bag or connected to a ventilator to simulate lung movements during surgery.

This is a low-cost model completely inanimate and made of latex silicone and plastic. All the steps of the repair of esophageal atresia are reproduced in this model:

- Working port placement
- Dissection and ligature of the azygos vein
- Dissection and ligature of the TEF
- Dissection and section of the upper esophageal pouch
- End-to-end esophageal anastomosis (muscle and mucosa are represented)
- Placement of transanastomotic probe
- Debriefing and endoscopic evaluation of the anastomosis

4.4.2.2 Duodenal Atresia (DA) [3] (Fig. 4.8)

The model consists of a dummy that represents a 4500 g baby in which a simulated type III duodenal atresia, made with silicon and latex, is placed in anatomical position. The steps that are trained in this model are:

- Working port placement
- Dissection of the proximal duodenal pouch
- Dissection of the distal duodenal pouch
- End-to-lateral anastomosis
- Debriefing and endoscopic evaluation of the anastomosis

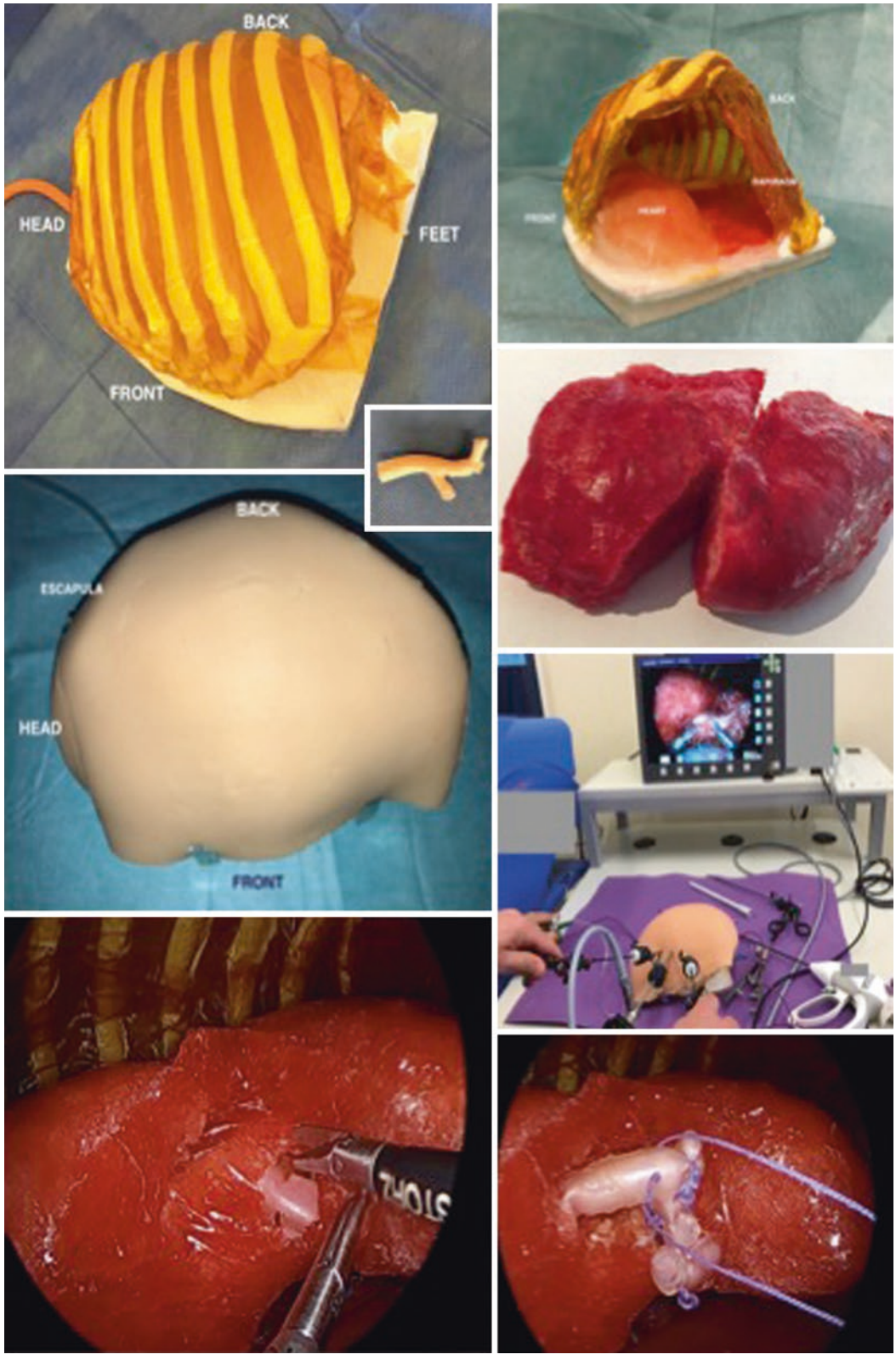

Fig. 4.10 Lobectomy model

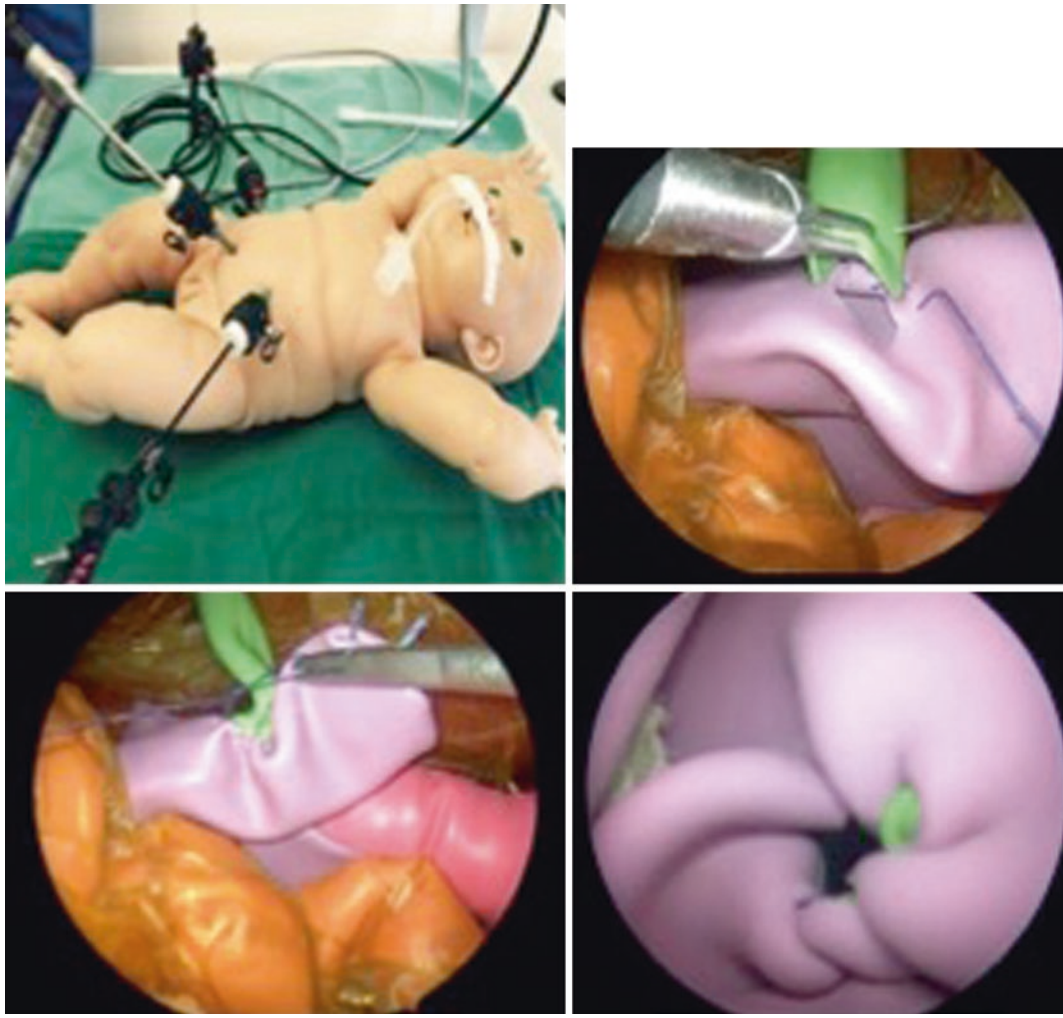

Fig. 4.11 Hepaticojejunostomy model

This model can be hybridized using live tissue from farm animals that can be previously modified to resemble the anomaly.

4.4.2.3 Congenital Diaphragmatic Hernia Repair (CDH) [4] (Fig. 4.9)

This is an inanimate model for training thoracoscopic repair of left congenital diaphragmatic hernia. Right defects can also be simulated. It is easily portable and a low-cost model made of synthetic materials such as polylactide (PLA), silicon, fabric, and latex.

The base of the model is a 3D printed left hemithorax, extracted from a CT scan of a 4 kg baby. A spare part includes the last three ribs and a base added that simulates the upper abdomen.

Heart, lung, and mediastinal structures are located resembling their anatomical position. The diaphragm with the chosen defect is placed on the spare part. Abdominal ex vivo viscera is placed at the base and passed through the defect to the thoracic cavity. Both parts are assembled and covered by a layer of silicone. All kinds of diaphragmatic defects can be simulated (different positions and sizes), with or without sac. Patch placement can also be trained. This model can also be hybridized and the diaphragm can be simulated with tissue.

4.4.2.4 Lobectomies (Fig. 4.10)

This model is completely inanimate and allows training of different types of lobectomies. Vascular and bronchial structures are anatomically located according to the type of lobectomy. As the materials are synthetic, they do not allow the use of energy; therefore we promote training in dissection, suture, or stapler. Depending on the side we use a right or left 3D printed hemithorax extracted from a 6 kg baby CT scan. This model can also be hybridized by including live tissue from farm animals as described by Kathy Barsness [6] with the disadvantage that the anatomy is very difficult to emulate.

4.4.2.5 Hepaticojejunostomy (Choledochal Cyst) (Fig. 4.11)

Similar to the duodenal atresia model, this is essentially a suturing model for a tiny end-to-side anastomosis resembling a hepaticojejunostomy after a cyst resection where the Y-roux is already made. The learner is meant to locate the loop through the mesocolon and perform the anastomosis either with running or interrupted sutures. We start with silicon or rubber tubes and then with live tissue. Endoscopic evaluation of the anastomosis is mandatory.

4.4.3 Knots

Multiple endoscopic knots have been described in literature. We decided to standardize some of them for an educational purpose. We believe that it is necessary for the surgeon to master different types of knots; this will allow a better resolution of the technical problems during the surgery in terms of suture.

Extracorporeal sliding knots: These allow solving a great number of situations, are very versatile, and require adequate coordination, precision, and care of the tissues.

Square knot or surgeon knot: It is the initial and main intracorporeal knot that we use for training and that serves to center the bases of coordination and precision, and also allows us to exercise a lot of tricks that allow the knot to be adequate and with effective movements. Again we move from large to small endotrainers.

Gladiator concept: This type of knot is a modification of the square knot that allows using the same hand to perform the knot.

Intracorporeal sliding knot: This knot is extremely useful and a key tool to solve a great amount of pathologies, including neonatal.

Initially, and for academic reasons, we teach each of these knots separately, but the final objective is to provide the student with a number of tools that allow choosing the best knot for each tissue and can combine them depending on the moment of the surgery.

4.5 Conclusion

Training in neonatal endosurgery (NMIS) is a challenge. Simulation tools must be included in the curricula to compensate the small number of patients required to improve the learning curve.

We acknowledge tools available from different groups around the world emphasizing those developed by work groups that are dedicated to training in MIS [5–8]. We continued developing our own neonatal specific training models, which allow us not only to improve skills but also to advance in new techniques or tricks. Data about clinical outcome is needed. As we have emphasized in this chapter the initial stages of skill training should include the use of large-volume endotrainers (as FLS-SAGES) and virtual trainers that develops bimanual dexterity and hand-eye coordination as well as tactile sensitivity or feedback of the instruments and practice of endosuture. Advanced MIS suturing is required before introducing any learner to a neonatal model.

Regarding the quality of the tools, we started with low-cost models to acquire basic skills and after assessment of performance we progress to models with 3D printed structures and live tissue. According to our training program, no student moves to practice in animal models until they have acquired advanced bimanual and suturing skills in inanimate models.

During the last 2 years we have replaced animal models by hybrid ex vivo trainers. A team of

motivated mentors helped to fulfill the specific goals required in the curricula. Scrub nurses involved in this team have been an unexpected source of success not only in relation to arranging stations but also in the manufacture of the models and the education of their peers.

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Part II

Head and Neck

Congenital Choanal Atresia

5

Pedro Saraiva Teiga, Kishore Sandu, and Lluís Nisa

5.1 Introduction

Congenital choanal atresia (CA) is a condition characterized by a non-permeable posterior nasal aperture, also known as choana (from Greek *funnel*). For incomplete forms, the term choanal stenosis should be used. For the sake of simplicity, only CA is used in the present text. The bony frame of the choana is formed by the sphenoid body cranially, the horizontal portion of the palatal bone caudally, the vomer medially, and the medial pterygoid lamina laterally.

CA is unilateral in 60–70% of the cases and preferentially affects the right side, usually with an accompanying ipsilateral septum deviation. Unlike previously thought, most CAs have a mixed bony-membranous composition, with approximately only one third being purely bony CAs. The estimated incidence of CA is estimated to be around 1:5000–1:7000 live births and having the female-male ratio of 2:1 [1–3].

Classically four embryological models of CA have been described: (1) persistence of the nasobuccal membrane; (2) persistence of the buccopharyngeal membrane; (3) abnormal mesodermal adhesions in the nasal choanae; and (4) misdirection and migration of neural crest elements [4, 5]. While the exact embryological mechanisms remain to be fully elucidated, the fact that patients with neural crest pathologies such as CHARGE syndrome or Treacher Collins syndrome (TCS) often present CA supports the neural crest embryological theory. Both of these syndromes feature hypoplasia of the facial bones, cleft palate, and middle and external ear defects, most of which can be explained by aberrant migration of neural crest elements. The derivatives of the neural crest include among others bone and cartilage [6]. From an embryologic perspective, facial structures develop within the first 12 weeks of development. The neural crest cells migrate between the 3rd and 4th weeks of development and play an essential role in the formation of the face. With time, the nasobuccal membrane will separate the primitive mouth (stomodeum) and the nasal cavity. The nasobuccal membrane usually divides in order to create the posterior opening of the nasal cavity (i.e., the primitive choana). Subsequently, craniofacial development leads to a posterior displacement of the choana. It is thought that aberrant migration of the neural crest cells may indeed be the cause of a wide spectrum of malformations. The heterogeneity of clinical manifestations of patients with neural crest disorders remains unclear from an embryological, molecular, and genetic perspective [7, 8].

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Diagnosis of CA relies on nasal endoscopy and CT scan.

CA is associated with other congenital malformations in approximately 50% of cases [3, 9].

5.2 Diagnostic Approach

5.2.1 Clinical Presentation

The manifestations of CA depend on the unilateral vs. bilateral presentation. Bilateral CA can dramatically present with *asphyxia neonatorum*, or milder respiratory distress with intermittent cyanosis, usually relieved by crying. This is due to the fact that newborns are obligate nasal breathers during the first 4–6 weeks of life, given the superior and vertical position of the epiglottis and the thorough contact of the tongue with the palate. Respiratory distress can in some cases present in the context of feeding, and feeding difficulties may lead to choking during feeding or dis-coordinate breathing and swallowing. In children intubated orally immediately after birth, bilateral CA can be first discovered within the frame of a failed extubation.

In contrast, unilateral CA is most often asymptomatic at birth, as it does not usually present with respiratory signs. Unilateral CA indeed needs a high suspicion index in patients with persistent unilateral nasal obstruction, unilateral rhinorrhea, or chronic/recurrent sinusitis. Diagnosis of unilateral CA is in some cases late in life.

5.2.2 Associated Comorbidities

CA is commonly associated with other congenital malformations, whether or not within a syndromic context. More particularly, approximately one third of patients with CA present laryngomalacia, tracheomalacia, and/or subglottic stenosis. CA is encountered in the frame of a polymalformative syndrome in around 20% of patients. It is therefore essential approaching children with CA in a multidisciplinary manner.

5.2.2.1 CHARGE Syndrome

The acronym CHARGE stands for *c*oloboma, *h*eart defect, *a*tresia choanae, *r*etarded growth and development, *g*enital hypoplasia, and *e*ar anomalies. Also known as Hall-Hittner syndrome, CHARGE syndrome can occur both as an autosomal dominant and a spontaneous congenital disease, with an estimated incidence of 1 in 12,000–15,000 live births. Around two thirds of patients feature mutations of the CHD7 gene, which encodes a chromatin remodeling protein. Neonates with CHARGE syndrome often present cyanosis at birth due to CA and a cyanotic heart defect. The only therapeutic possibilities are surgical repair of affected organs. Patients with CHARGE syndrome have a high rate of mortality during the first year of life, and the overall prognosis depends on synchronous presence of CA, heart defects, and tracheoesophageal fistula [10, 11].

5.2.2.2 Treacher Collins Syndrome (TCS)

TCS or Franceschetti-Klein syndrome is an autosomal dominant disorder with an estimated incidence of 1 in 10,000–50,000 live births, primarily due to TCOF1 mutations. TCS features hypoplasia of the facial bones, uni- or bilateral CA, external ear abnormalities, coloboma, and in some cases middle ear malformations resulting in conductive hearing loss. Patients with TCS have a normal intelligence [6].

5.2.3 Diagnostic Methods

The diagnosis of CA is primarily clinical. A high suspicion index in neonates with respiratory distress should prompt systematic endoscopic evaluation of the airway. CA can be diagnosed by means of flexible or rigid transnasal endoscopy or by passing a 120° telescope transorally. CT scan is an important adjuvant diagnostic method in order to precisely locate the stenosis and its extent and to rule out differential diagnosis of nasal obstruction in the newborn. CT scan is best performed after appropriate nasal decongestion and aspiration of stagnated secretions, and this is

even helpful for operation planning and perioperative guidance [2, 12].

Important differential diagnoses of congenital CA include pyriform aperture stenosis, encephalocele, and neoplasms such as dermoid cysts, chordomas, and rhabdomyosarcomas, among other entities [12, 13].

5.3 Management

The first step in the management approach of newborns with CA is airway management. CA (especially bilateral) can present with airway distress at birth. In such a context, some newborns will be immediately intubated orally. This approach is however suboptimal, since definitive management of CA requires its surgical correction at the earliest. Since CA requires a high suspicion index and some studies suggest that early surgery is rarely successful, intubation of newborns with CA could lead to prolonged intubation. If identified early, an alternative to intubation is the so-called McGovern nipple, which consists of an adapted nipple with a large opening fixed in the newborn's mouth. Newborns can be feed by means of a feeding tube passed through the McGovern nipple. Therefore, the optimal timing of surgery should ideally avoid both excessively early surgery (before 7–10 days of age because surgical manipulation in very narrow nasal passages is difficult and cause increased iatrogenic mucosal trauma) and prolonged intubation. Tracheotomy should only be considered if early surgical management fails or in children with underlying comorbidities, especially those with CHARGE syndrome [14]. Unilateral CA is better managed later in life (>3 years) when the surgery is comparatively easy in the larger nasal passage.

There are a number of surgical procedures to definitively manage CA, including transnasal closed and open techniques and transoral techniques. The choice of technique depends on patient factors and surgeon's considerations.

The earliest surgical method was transnasal puncture followed by dilation. Puncture is suitable for predominantly membranous forms of CA and can be guided with an endoscope. Postoperative stenting following puncture is often performed, though restenosis rates are relatively high. Fiber-delivered CO_2/KTP or diode laser can be an option in membranous stenosis. Puncture is obviously not suitable for purely or predominantly bony forms of CA [15] (Fig. 5.1).

A transpalatal approach is equally possible and carries a high success rate (almost 90%). However, the associated morbidity, including dental cross bite, oro-nasal fistula, and velopharyngeal insufficiency, has resulted in a reduction of proponents of transpalatal approaches. Moreover, this approach is not suitable for young children with small oral morphology and growing facial bones [12, 15].

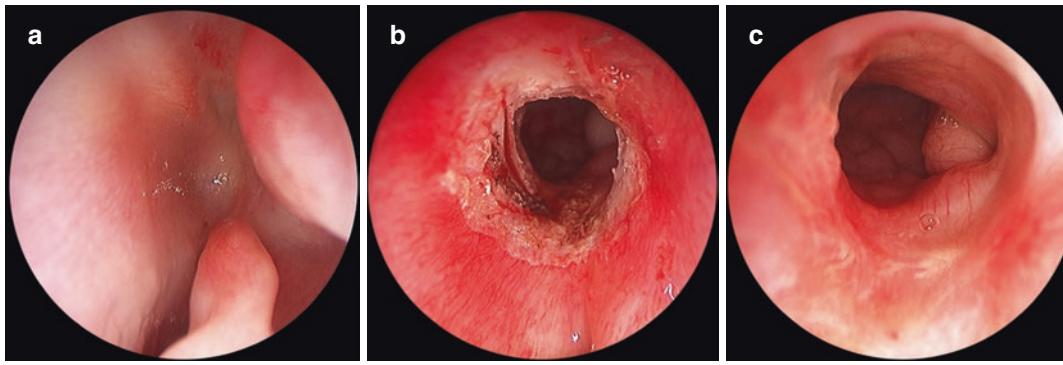

Fig. 5.1 (**a**) Complete unilateral choanal atresia; (**b**) treatment using CO_2 fiber and 0° telescope; (**c**) rhinoscopy of the patient 6 months later

Endoscopic repair progressively has become the standard method of treatment. Following nasal decongestion, a 2.9 mm rigid endoscope can guide the instruments to the choana. Otology set instruments used for ear surgeries work best in narrow access interventions as in CA. Simultaneous passing of the telescope and micro-ear cold instruments requires adequate degree of expertise. A lateral mucosal flap is raised in order to expose and remove the bony plate of the atresia. In case of bilateral CA, a part of the posterior vomer is equally removed using either a microdrill or a backbiting forceps, in order to create a *common single* posterior choanal opening or a *neochoana* [14–17] (Fig. 5.2).

Success rates following surgery, range between 67% and 88% [18]. Only a limited number of rather inconsistent prognostic factors following repair of CA have been identified. A retrospective study [19] interestingly addressed the prognosis of 46 children with CA following repair. Of these children, 28 had bilateral and 18 unilateral CA and were associated in 40% of the cases with other anomalies (primarily CHARGE syndrome). In spite of the limited number of patients included, the authors identified weight >2.3 kg at initial surgery, stent size >3.5 mm and duration longer than 12 weeks for primary surgery, as well as no associated facial anomalies as favorable outcome predictors. Other predictive factors may include presence of gastroesophageal reflux, age younger than 7–10 days at the time of initial surgery, and lack of postoperative follow-up [20].

The use of stents, the duration of stenting, and the kind of stents remain controversial issues. Soft silicon tubes (endotracheal tubes) can be used in each nostril and must be fixed to the anterior septal cartilage to avoid dislodgement. During the period of stent in place, the child does have a rough period and requires adequate nursing care. Typically, stents are left in place for 2–3 weeks. Several studies have shown no difference in terms of restenosis rates whether postoperative stenting is performed or not [18, 21, 22]. Similar controversies apply to application of mitomycin C. So far, no study has been properly conducted to demonstrate its benefit [3].

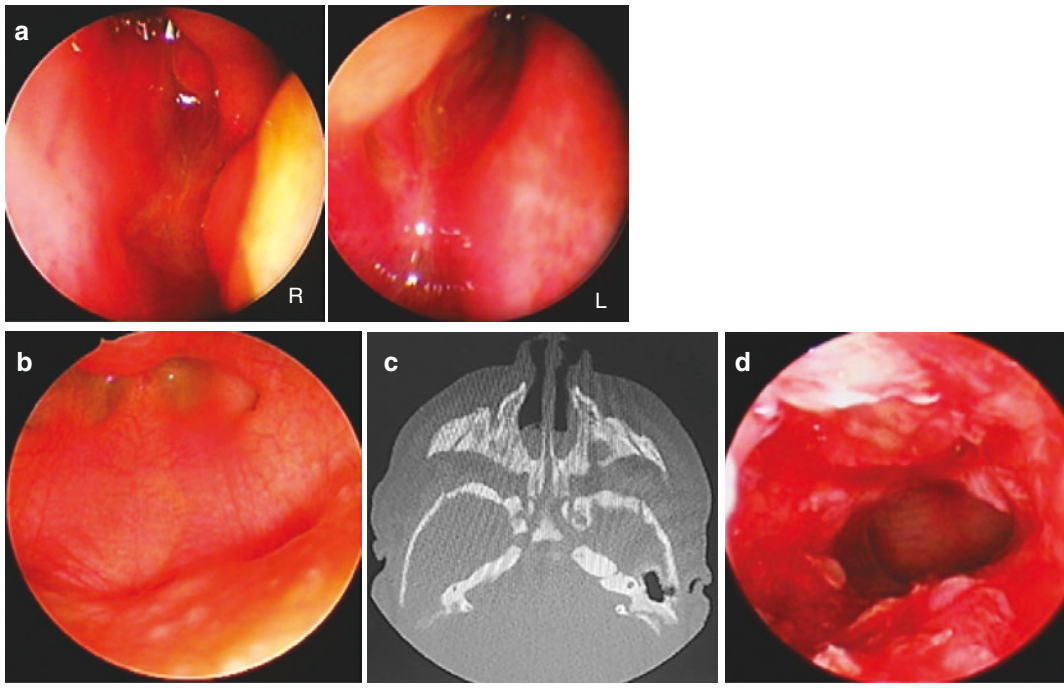

Fig. 5.2 Four days-old-premature girl, 2 Kg. (**a**) Anterior rhinoscopy with 0° endoscope; (**b**) Transoral retrograde view of the choanae using 120° endoscope; (**c**) Axial CT scan showing bilateral bony atresia; (**d**) After posterior septectomy showing a common *neochoane*

In spite of controversy, there is a general agreement that postoperative care with saline irrigations, close clinical follow-up, and crust removal are key to achieve optimal results [20]. These procedures are best done in operating rooms, under general anesthesia, and with appropriate endoscopy material. Following the surgical correction of choanae, majority of patients will require several additional dilation procedures. The authors use regular angioplasty balloons or cold urology dilators for such dilations. Injury to the skull base, posterior rhinopharynx, cranio-vertebral junction, and septum and nasal turbinates must be avoided during such a dilation. Progressive sizes of metal urethral bougies are passed nasally under endoscopic guidance using a 120° telescope passed transorally. We find the choanal dilation done in this manner very effective and safe. In our unpublished data—following primary corrective surgery—all patients required 2–10 dilation procedures to achieve an age-appropriate and symptom-free choanal size (Figs. 5.3 and 5.4).

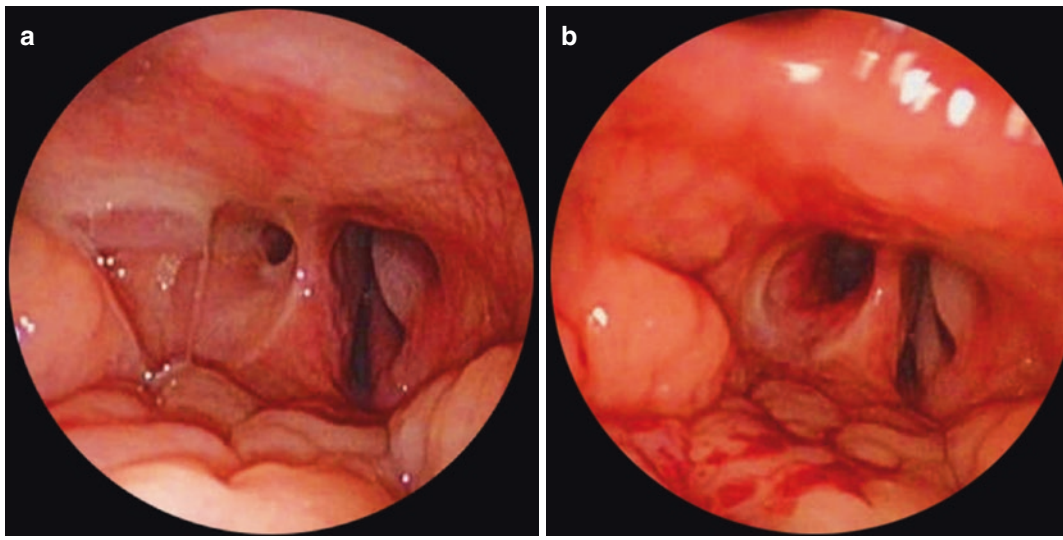

Fig. 5.3 (**a**) Unilateral choanal stenosis; (**b**) dilatation with urethral bougies and visualization using 120° telescope passed transorally

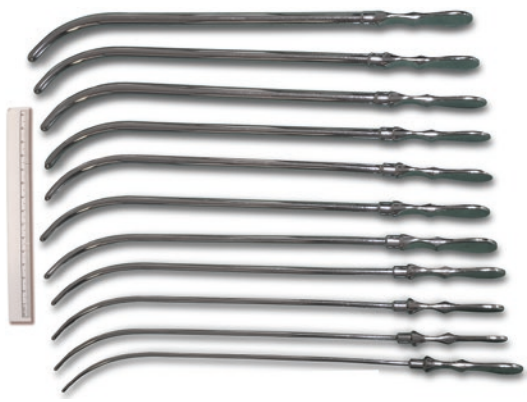

Fig. 5.4 Urethral bougies

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6 Facial Cleft and Pierre Robin Sequence

Anthony S. de Buys Roessingh, Oumama El Ezzi, Georges Herzog, and Martin Broome

6.1 Embryology, Epidemiology, and Genetics

The primary palate is the region of the upper lip and the alveolar process, the part of the gum region of the upper jaw which holds the teeth. The primary palate is formed first, already around the seventh week of intrauterine life [2, 6]. A malformation can lead to partial cleft lip, complete cleft lip, and alveolar cleft. The secondary palate is the true palate, consisting of an anterior bony part and a soft posterior part. Many varieties of clefts can occur, depending on the region involved, for instance, bifid uvula, cleft of the soft palate, cleft palate (CP), and Pierre Robin sequence (PRS) (Sect. 6.4). Clefts due to primary and secondary palate malformation can be unilateral or bilateral. A subcutaneous cleft palate is a special case which involves both the muscular soft palate and the hard palate and may be associated with bifid uvula. The muscles of the soft palate do not function normally, and the patient may have problems with speech, swallowing, and even the middle ear [7] (Figs. 6.1, 6.2, 6.3, and 6.4).

Facial cleft is present in 1 of 750 births, and its prevalence seems to vary between different ethnic groups. The causes of facial cleft are far from being understood and may be multiple. But the majority of clefts seem to be caused by genetic and environmental factors [6]. There are isolated clefts, clefts as part of a syndrome, clefts associated with a link to a specific illness, and clefts linked to chromosomal anomalies such as trisomy. For non-syndromic unilateral and bilateral cleft lip and palate (respectively, UCLP and BCLP), different kinds of causes are implicated, such as smoking, alcohol, and antiseizure drugs such as phenytoin and valproic acid [8, 9]. In other cases, a cleft can be caused by teratogenic agents such as rubella virus, thalidomide, cortisone, and antiepileptic drugs which perturb the development of the embryo [9]. Research on animals has demonstrated the teratogenic effect of substances such as corticosteroids. Dietary deficiencies resulting in lack or excess of vitamin A have been associated with clefting in animals, especially clefting of the palate. Folic acid appears to play an important role in preventing various types of malformation, including clefts [10].

UCLP is the most common and represents 37–50% of all cases of clefts [11]. CP is present in 25–40% of cases and cleft lip in 20% of cases. Clefts are twice as frequent in Asia as in Europe and half as frequent among the black population. CP is twice as frequent in girls and UCLP twice as frequent in boys. Their incidence seems to be higher in poor social conditions [12].

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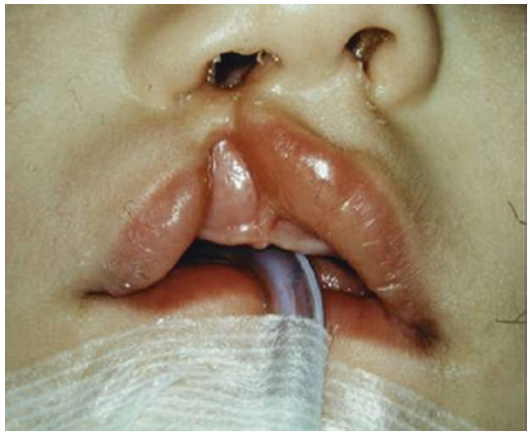

Fig. 6.1 A labial or labio-maxillary cleft

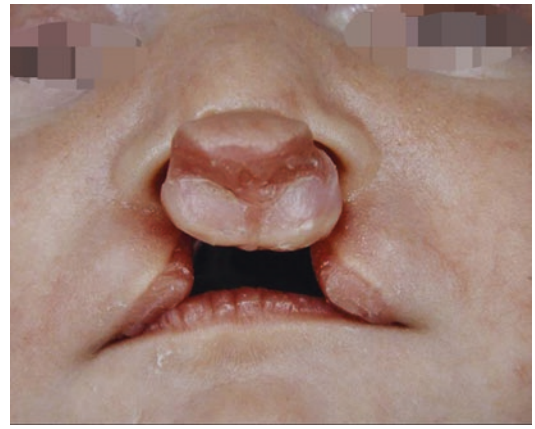

Fig. 6.3 A bilateral labio-maxillary-palatal cleft

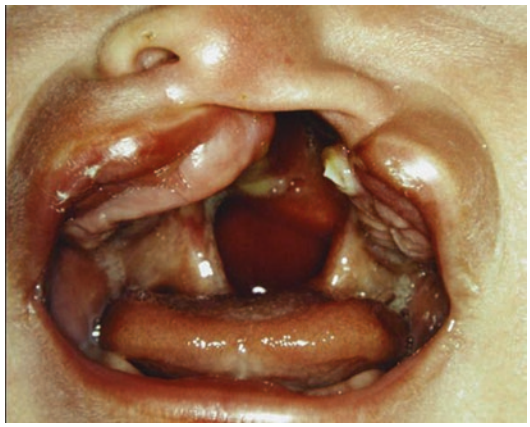

Fig. 6.2 A unilateral labio-maxillary-palatal cleft

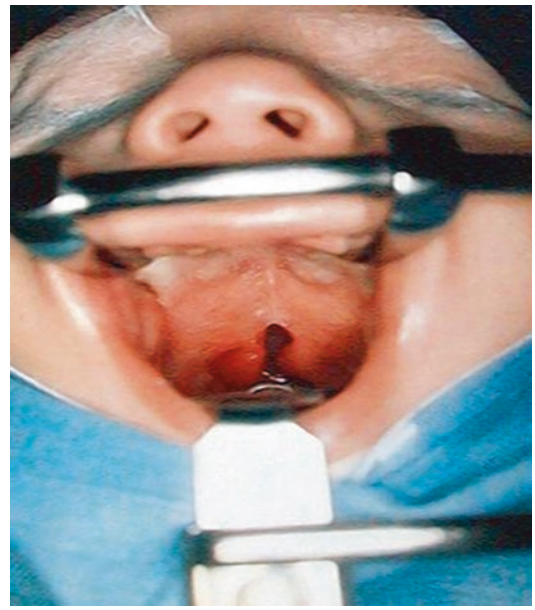

Fig. 6.4 A palatal cleft with bifid uvulae

UCLP has a 22% risk of associated malformations and CP 33%. In monozygote twins, the risk of having a cleft is 25–45%. In dizygote twins, the risk of having a cleft is 5%. The risk of having a child with a cleft without genetic family history is 3–5%. Among cases of UCLP, 70% are isolated, 5–8% show chromosomal abnormalities (especially the bilateral cases, BCLP), and 22% are accompanied by other abnormalities [13]. The risk of having a child with a cleft in autosomic dominant cases is 50% and 25% in autosomic recessive cases [14].

For the syndromic cleft lip and/or palate, the more frequent syndromes are the Stickler (autosomic dominant, palatal cleft), the Franceschetti (autosomic dominant), the Opitz (related to the X chromosome, hypertelorism, hypospadias), the cleft lip-ectodermal dysplasia (EEC, ectrodactyly, ectodermal dysplasia, cleft lip), the OFD1 (cleft palate, hamartoma, malformation of the tongue, malformation of the face and of the extremities), and the branchio-oculo-facial (BOF with a cleft lip) with different mutations such as PVRL1, MSX1 (4p16), FGFR1, TBX22 (cleft and ankyloglossia), and IRF6 (Van der Woude, 80% fistula lower lip). Chromosomal disorders

leading to a cleft also include the Down syndrome, the trisomies 13 and 18, the deletion 4p (with hypertelorism, short philtrum, scalp defect, ear pit), and the deletion 22q11.22 named also velocardiofacial syndrome (orofacial cleft, DiGeorge syndrome) with cleft palate, short palpebral fissures, small ears, alar hypoplasia, and conotruncal cardiac defect (Sect. 6.4). A single-gene disorder is present in the CHARGE association (ocular coloboma, choanal atresia, micropenis, cardiac defect), EEC syndrome, Fryns syndrome (diaphragmatic hernia, coarse face, digital hypoplasia), Opitz syndrome, popliteal pterygium syndrome (lip pits, popliteal web, genital anomalies), and the Van der Woude syndrome.

6.2 Antenatal Diagnosis

Antenatal diagnosis helps to prepare the parents. Ultrasonography is quite reliable, but images are not photos, and even 3-D images have to be carefully interpreted, as palatal clefts are not so easy to find. Nevertheless, due to its high prevalence, it is important to exclude the possibility of a cleft by means of a prenatal investigation. A diagnosis of facial cleft may be established as early as the 12th week of gestation, but it is usually done at 20 weeks. In numerous cases, an antenatal diagnosis of cleft lip and palate enables many future parents to better prepare themselves to confront and accept the facial malformation of the baby they are expecting [15]. The severity of the malformation should not be minimized, and its recognition allows the team to establish a contact with the future parents in order to offer them information and early support. Valuable psychological aid can be provided before birth, if necessary and required.

Micro-/retrognathia can also be diagnosed by prenatal ultrasonography. This early diagnosis allows the physicians to consider the possibility of PRS (Sect. 6.4). Parents should be prepared to face possible respiratory and/or feeding problems.

Amniocentesis, followed by cytogenetic analysis, is recommended for bilateral clefts or when associated malformations are suspected. The aim is to exclude the most frequent genetic disorders associated with a cleft.

After confirmation of the diagnosis, a first discussion must take place between the surgeon and/or the team and the parents, in order to prepare the latter. At that time, the various causes of the cleft, the schedule of the surgical repair, and the follow-up, especially concerning speech disorder and orthodontic problems, must be discussed. If deemed necessary, monthly discussions with the parents can be arranged. A dialogue can be set up between a representative of the team and the parents. Confidence can be built, thanks to this dialogue and the team's availability. It is the beginning of a long road for the family and the team. Information on parent support groups can also be offered [16].

At the time of birth, one should ensure that the midwives have been informed of the prenatal diagnosis and that a positive atmosphere reigns in the delivery room. As the parents have usually been previously informed of the expected malformation, the delivery can take place in a calm atmosphere. Any separation of the mother and the child must be avoided.

6.3 Feeding the Baby

The baby's feeding difficulties depend on the type and the severity of the malformation. They also depend on the weight of the baby and his resources and on whether he has the energy to suck.

At birth, a baby with a cleft lip may be fed normally by breast or bottle. But for babies with a CP, breast-feeding is anatomically impossible because the lack of palatal muscle entails a lack of the strength for suction [17]. Even if the baby is strong and heavy at birth, it may be exhausted after a few days, unable to suck and consequently losing weight. This is particularly true for babies born with a PRS, because of respiratory difficulties [18].

If feeding problems persist, a palatal plate or feeding plate may help. A palatal plate requires the making of an impression by the orthodontist, usually at the hospital as soon as possible after birth, so that its shape will perfectly match that of the palate. The baby adapts to it within a few

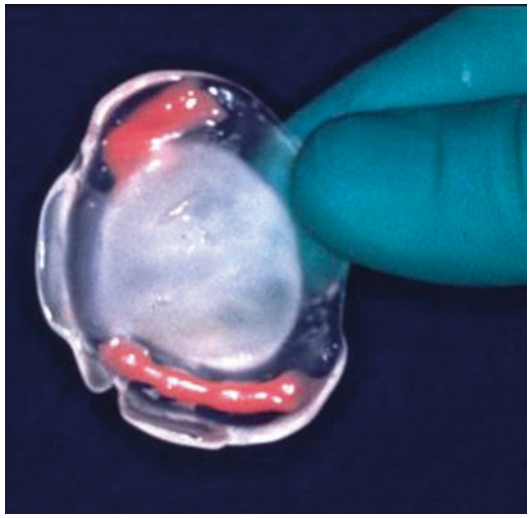

Fig. 6.5 Palatal plaque with absorbable glue along the borders

hours or days. The plate is made of acrylic resin, with a rigid outer part and a softer and more flexible inner layer that is in contact with the mucosa (Fig. 6.5). A feeding plate may have several advantages, even if not all proved: it facilitates bottle feeding but not breast-feeding, maintains the tongue in a normal position, allows the full growth potential of the maxilla by preventing the tongue from getting into the cleft, protects the sutures that closed the palatal cleft after surgery, and gives confidence to the parents [19].

Patients with feeding difficulties were defined by their inability to gain weight, prolonged feeding time (lasting more than 45 min), and need for nutritional support with a feeding catheter. Criteria for feeding difficulties were classified in two categories: grade I, when bottle feeding with prosthesis and open nipple is possible (<45 min), and grade II, with partial bottle feeding with prosthesis associated with nasogastric tube [20].

6.4 Pierre Robin Sequence and Syndrome

In 1923, the French stomatologist Pierre Robin described a group of patients who suffered from obstruction of the oropharynx due to the tongue being situated in the back of the oropharynx (glossoptosis). These patients also had a CP and micro-/retrognathia. The recognition of these three features constitutes the primary diagnostic criteria of PRS. Mandibular hypoplasia (micrognathia) seems to be a trigger for a cascade of events leading to tongue displacement, cleft palate, and respiratory distress, hence the term "sequence" (Fig. 6.6). The etiology of this type of PRS is supposed to be the presence of oligohydramnios or of an amniotic band which leads to compression of the chin and creates retrognathia [21]. The term "syndrome" refers to a number of abnormalities that often vary in degree and pattern of expression [22]. PRS occurs in 1 of 8500 births [21].

Glossoptosis is generally responsible for pharyngeal obstruction [23]. Due to this anatomical anomaly, these children are at high risk of severe respiratory insufficiency and prolonged hypoxia [24]. The physiopathology of airway obstruction is explained on the one hand by brainstem immaturity [23] and on the other hand by anatomical anomalies that provoke breathing difficulties: in particular, posterior retraction of a normal-sized tongue with interposition of the velum, neuromuscular impairment of the genioglossus muscle and other parapharyngeal muscles, prolapse of the medial walls of the pharynx, and medial movement of the lateral pharyngeal wall [24]. During growth, the airway obstruction will decrease as the mandibula grows, and the coordination of the parapharyngeal muscles improves in conjunction with voluntary tongue control. After a few months, mandibular catch-up growth improves the prognosis for these children.

Two types of PRS are generally observed: "deformational PRS" and "malformational PRS." Deformational PRS represents 40% of cases and is characterized by an isolated form of the three anatomic abnormalities without any other significant findings. Malformational PRS represents 60% of cases and is associated with the presence of other abnormalities such as various syndromes, chromosomal anomalies, teratogenic products, or neuromuscular disease [23]. This type of PRS has a less favorable prognosis. There is a third type of PRS, associated with connective tissue dysplasia [24].

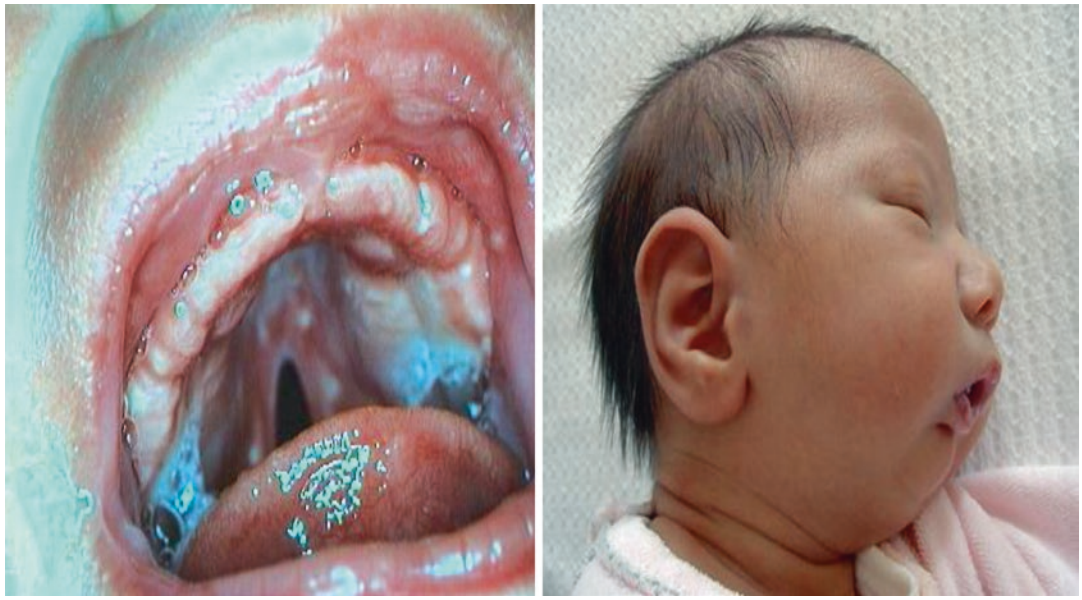

Fig. 6.6 Pierre Robin syndrome (PRS)

Pharyngeal obstruction must be anticipated at birth in order to avoid a catastrophic delivery, as the tongue may block the upper airways in the oropharynx and so interfere with breathing. The severity of airway obstruction varies considerably in PRS children. The main key of success of airway management is an accurate monitoring and treatment by a multidisciplinary team. The goal of the initial treatment is to minimize any airway obstruction in order to prevent hypoxia and promote normal neurological development [22, 25, 26].

Treatment of respiratory obstruction can be conservative or surgical. The different ways that we describe to treat these children reflect local practices and experiences. When upper airway obstruction is mild, children can be handled conservatively, by being placed in prone position. This positioning of the baby can be effective, as it prevents the tongue from falling into the hypopharynx. It can help PRS babies with mild to moderate respiratory obstruction, but it is certainly not sufficient in severe cases [27].

An accurate assessment of the problem rests on a combination of clinical observation, monitoring, and control of blood gases. Clinical criteria for respiratory distress are agitation, dyspnea, tachypnea, intercostal recession, tracheal tug, stridor, and position-dependent airway obstruction. Children with respiratory complications are assessed for oxygen saturation. Oxygen saturation is monitored continuously by pulse oximetry. Normal venous blood gas values are pH 7.4, $PaCO_2$ 40 mmHg, PaO_2 100 mmHg, and HCO_3 24 mmol/L. Polysomnography can be organized if the monitoring gives bad results. A full endoscopy evaluation of the upper aerodigestive system can be carried out to exclude other potentially treatable causes of airway obstruction [25]. But the risk of anesthesia for a child with respiratory difficulties must be taken into account. Close follow-up is mandatory to prevent neurological sequelae after prolonged or chronic hypoxia [27]. Gastroesophageal reflux (GER) is common in babies, but even more common in children with neurodevelopmental problems. A PH probe may be placed during polysomnography to objectivize the GER before starting medication.

Other conservative techniques are a continuous positive airway pressure (CPAP) and the use of a pharyngeal tube (PT) or of a laryngeal mask airway (LMA) [27, 28]. CPAP is generally used first, followed by PT if it proves not sufficient. PT is a safe treatment, even over a long period, insofar as the tube has been correctly placed (Fig. 6.7).

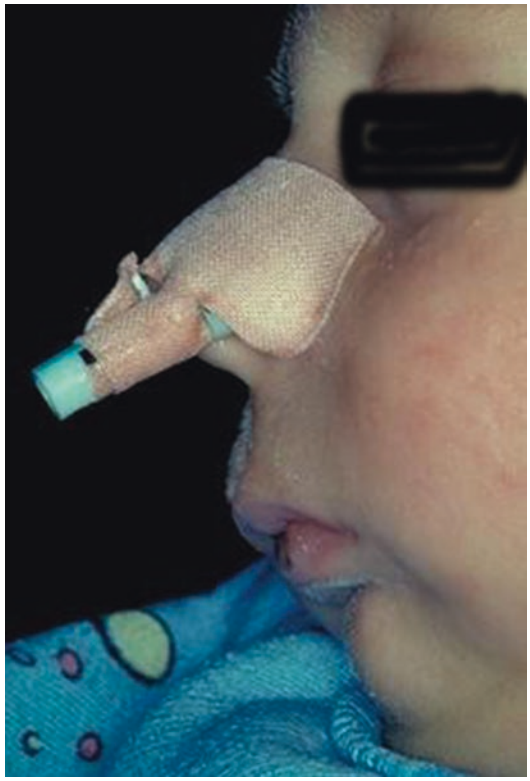

Fig. 6.7 Pharyngeal tube (PT) for a PRS

The nasopharyngeal tube is inserted under lateral X-ray control to ensure that it is cut at the correct length. It is then taped to the face. The diameter of the tube is chosen so as to avoid nostril stenosis. This treatment normally requires hospitalization at first, but can be continued at home depending on the parents and on the child's status. A relatively long-term use of a nasopharyngeal airway may be appropriate, while the child matures, i.e., gains weight in order to improve muscle tone and neurologic maturation. LMA is a method of ventilation support for respiratory obstruction. It can be used for long-term management of prolonged airway obstruction [29]. LMA has the advantage of being easily inserted, without a laryngoscope. It is less aggressive than endotracheal intubation. It avoids vocal cord edema and subglottic stenosis due to prolonged intubation. It allows the patient to swallow and to strengthen the genioglossus and parapharyngeal muscles. It does carry the risk of laryngospasm and coughing.

Tracheal intubation can be very difficult and complicated, with a possible consequence of pneumothorax, subcutaneous emphysema, or death. Endotracheal intubation should be avoided as it is very difficult to extubate these patients. Nevertheless, this treatment can save a newborn with severe respiratory distress.

Surgical methods include glossopexy [30], tongue-lip adhesion (TLA) [31], tracheotomy, or mandibular traction [32]. Surgical interventions such as glossopexy, TLA, or tracheotomy have been recommended for patients when airway obstruction could not be relieved by conservative management. Glossopexy could only relieve the airway obstruction caused by the posterior displacement of the tongue, but had little effect in patients with airway obstruction caused by other mechanisms. Glossopexy [30] is particularly non-physiological and creates feeding difficulties. It combines the difficulty to suture the button in the right place, the risk of pulling the tongue too far, the risk of wound infection and injuries to the Wharton duct and of deformation of the lip and chin and scarring of the chin and the mouth, and the risk of dental deterioration. Mandibular traction [32] with an outrigger bar allows the child to move his head laterally. Pain and tension are caused by hypertension of the neck. This method forces the child to remain in bed, and feeding is not simple. Ensuing disorders of facial growth are not known.

Difficulty in feeding is a direct consequence of airway obstruction and immaturity of deglutition. But even if respiratory problems are resolved, feeding problems can endure, as the palate is open and suction difficult. These problems are generally not permanent and disappear with catch-up growth. Several therapeutic options are possible, such as prone positioning or nasogastric tube feeding [20]. Palatal plaque can help these children to feed. But normal feeding with a palatal plaque can only be attempted after the resolution of the respiratory problems. Caouette and Laberge [20] classified three categories of PRS patient, according to their specific respiratory and feeding problems: adequate respiration in prone position and bottle feeding (category 1), adequate respiration in prone position but feeding difficulties requiring gavage (category 2), and

respiratory distress with endotracheal intubation and gavage (category 3). The mortality rate is, respectively, 1.8%, 10%, and 41%. Caouette-Laberge found mortality rates of 22.8% in children with PRS syndrome and 5.9% in children with PRS sequence (b).

Children born with a velocardiofacial syndrome (VCFS, DiGeorge, Shprintzen) have a 22q/11.22 microdeletion, i.e., a deletion of band 11 of the long arm of chromosome 22, a genetic disorder with a prevalence of 1/1800–1/5000, 80% being sporadic. It is used to be known as the CATCH 22 association: *c*ardiac malformation, *a*bnormal face, *t*hymus anomaly, *c*left palate, and *h*ypocalcemia [33]. These children have a 70% risk of cleft palate along with congenital cardiac malformation, facial anomalies, dental anomalies, ocular malformation, and psychomotor and learning disabilities, with velar insufficiency related to the cleft, scoliosis, and polydactyly. It is very important to diagnose this syndrome early in order to offer the patient and the family adequate medical and psychological support. The prognosis for development is quite good if the child is helped in the first years of life already.

6.5 Primary Surgery

6.5.1 Historical Elements

The first cleft lip operation is thought to have been performed in the year 390 AD. Jehan Yperman (1295–1351) was the first to describe cleft lip repair. The term "bec-de-lièvre" (harelip) was used in France by Ambroise Paré, the famous surgeon of four Kings (François I, Henry II, François II and Charles IX). The eighteenth century saw the elaboration of new techniques concerning the soft palate, suture of the split velum, and primary closure of the soft palate before cheiloplasty (Dessault, 1798). In the nineteenth century, surgery of the palate was developed by several surgeons: Collis (1868) was the first to describe a double lip plasty. In the 1930s of the twentieth century, improvements in anesthesiology allowed the development of new techniques, of which Victor Veau was one of the pioneers [34].

6.5.2 Age of Surgery

The ideal age for simple cleft repair is still a subject of debate. Thanks to the progress in pediatric anesthesia, surgery can be performed at a very early age. Anesthesia is best performed after the age of 3 months, when breathing reflexes are normal and tissues more developed and sturdier. For both anesthetic and surgical reasons, this period seems to be the right and safe time for surgery. Surgery is performed under general anesthesia, and a tracheal tube is normally used. Intubation helps to prevent liquid from seeping into the trachea. The tube is inserted orally in the direction of the feet (ray tube) and securely taped to the lower lip. This position allows the use of mouth gags in palatal surgery and makes it possible for the surgeon to check the symmetry of the lip repair.

The sequence of operations on children born with a total cleft may vary largely, depending on the local school of surgery and historical teaching. It may be complete surgical repair in one go at 4 months of age or lip repair first at 5–6 months and palate repair at 1 year of age. The Malek procedure [2] is soft palate repair at 3 months and anterior hard palate and lip closure at 5 months and, in cases of BCLP, soft palate repair at 3 months and anterior hard palate and lip closure on one side at 5 months and on the other side at 7 months. In children born with CP, closure is performed at 4–6 months. For UCLP and BCLP, a vomer flap may be used to reconstruct the nasal layer of the velum. All procedures have been described, and they can all be performed, as long as the surgeon keeps a good record of events.

6.5.3 Preparation for the Surgery

The child is installed at one end of the table. The head rests on an adjustable support with a hyperextension position. A pad placed under the shoulders keeps the neck extended. The surgeon stands at the end of the table, with the assistant on the right side of the table and the anesthesiologist on the left side. The infant's eyes are taped shut with sterile strips with a drop of Vaseline. Surgery

starts with the drawing of the lip repair. Then the tissues are usually infiltrated with bupivacaine hydrochloride-adrenaline in order to facilitate the mucoperiosteal undermining for a lip repair and to reduce bleeding thanks to the temporary hemostatic effect of the vasoconstrictor. The surgical equipment includes the specific instruments required for palate surgery, in particular the adjustable Veau mouth gag, the Trélat's blunt hook for the dissection and fracturing of the hamulus, the angulated Adson forceps, and the Veau elevators. For palatal surgery, we use absorber sutures 4-0 and 5-0 and, for labial surgery, absorber monofilament sutures and bipolar coagulation [2, 34].

6.5.4 Principles

The principal aim of modern surgery is to correct the obvious shortening of the lip. Since the 1950s, the flap technique is the most widely used method of repair. Earlier, in 1848, Mirault worked on a flap in the area of the Vermilion; then Jalaguier (1910) and Veau [34], his pupils, worked on reducing excessive scarring. In 1945, Le Mesurier [35] of Toronto described a quadrilateral flap procedure which represents a modified version of the technique originally described by Hagedorn. In 1952, Tennison [36] introduced a triangular flap method in order to preserve the Cupid's bow; in 1985, Millard presented another version of flaps based on a lateral triangular flap for a unilateral cleft in order to preserve the Cupid's bow and the symmetry [4].

One of the surgeons' concerns must be the symmetry of the height of the lip on the cleft side and the normal lip, and surgical procedures based on the principal of Z-plasty are normally used (Fig. 6.8). The exact symmetry between the two sides must be calculated with mathematical precision. The skin without muscle must be eliminated. The muscle for both sides has to be sutured together knowing that the orientation of the muscle fibers depends on the outlines of the incision, since the cutaneous-muscular flaps are used with a certain degree of rotation. The incision must take into account the final direction of the muscle fibers which will be reinserted [37, 38].

In bilateral clefts, the Cupid's bow is virtually nonexistent and must be created. Lip closure can be performed in one or two stages. If performed in one single stage, with incisions on both sides, the extensive denuding of tissue might impair the vascular supply to the bone structure and the soft tissue. It might create insufficient blood supply to the lower and medial portion of the lip, leading to necrosis. Lip closure should therefore be performed in two stages, at an interval of about 2 months [37, 38]. An abnormally short columella is one of the hallmarks of these malformations. Since it is difficult to include the correction of the

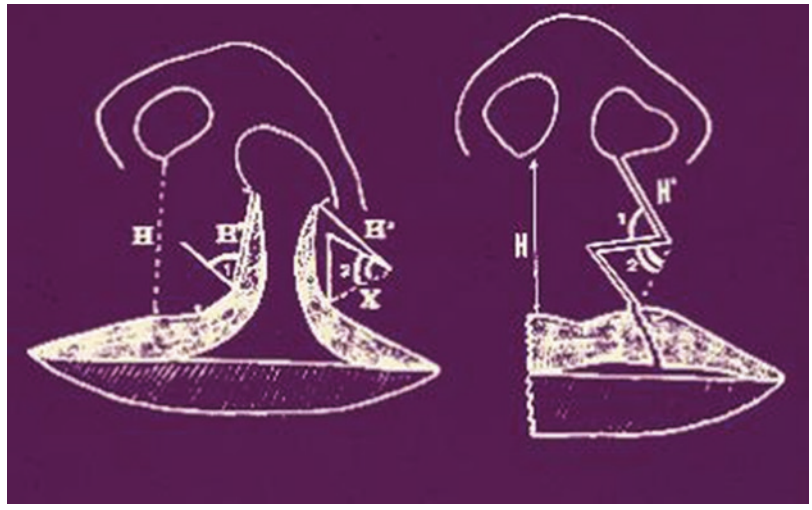

Fig. 6.8 Z-plasty following the Malek procedure

short columella in either phase of a two-stage cheiloplasty, it seems advisable to postpone this until later. The labial vestibule is virtually nonexistent and must be constructed from scratch by extending the outer mucosal tissue during the two-stage plasty [39].

6.5.5 Labioplasty

Plotting the reference points represents an essential step in the operation. Measurements are taken in order to help the surgeon calculate the precise dimensions of the plasty needed to obtain satisfactory lip height. Errors made in the initial preparation can seriously impair the final result. The height of the normal lip must be calculated. This calculation is relatively simple for unilateral clefts but more difficult for bilateral clefts. The precise position of the Cupid's bow must be determined if a triangular flap plasty is programmed, so that the top edge of the lip and the lateral superior points of the Cupid's bow are aligned with the middle reference point set by the nostrils and that the distance from the nose to the lip is satisfactory. In cases of bilateral clefts, this normal reference does not exist. The height of the lip must be therefore invented during the first operation and determined during the second operation by using a caliper to measure the height of the outer border on the vertical line from the outer alar base. In the Malek technique, this procedure is based on the principle of a Z-plasty (Fig. 6.9) Additional length is gained between two points thanks to the dissection of two triangular flaps that share a common side. The apices of the triangles are situated at each end of the joined triangular flaps. After the incision, inversion of the flaps results in inversion of the diagonals on the parallelogram initially traced. The long diagonal replaces the short and vice versa, so that the desired additional length is obtained [37, 38].

In the Le Mesurier [35] technique, the term "quadrangular flap plasty" given to this procedure has confused the issue. Actually, the inferior flap described by Le Mesurier is also a triangular flap characterized by a 90° angle at its apex. However this procedure is no longer used because it did not preserve the Cupid's bow.

In the Millard [4] procedure, there is also a Z-plasty. A small triangular flap with superior base is traced on the inner border by a curved incision, and a large triangular flap with a superior apex involves virtually the entire outer border.

In the Tennison [36] procedure, the dissection of a triangular flap from the outer border is destined to be fitted into an incision on the inner border. The major problem of this technique is the

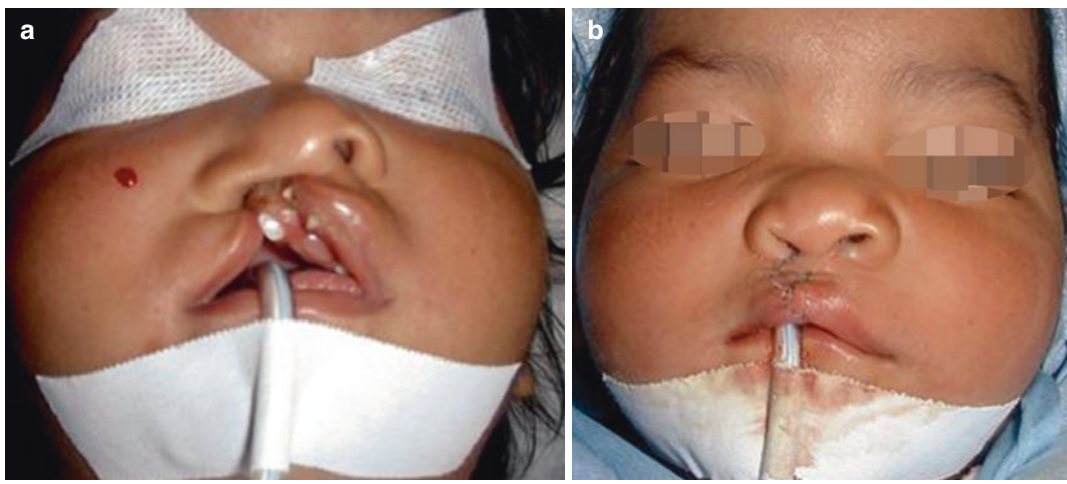

Fig. 6.9 Example of a labio-maxillary cleft before (**a**) and after (**b**) the surgery

adequate measurement of the dimensions of the triangle and the inner incision so that the desired gain in lip height on the cleft side corresponds to the height of the normal side. In this procedure, there is no calculation involved and the procedure is purely intuitive.

In the inferior triangle flap technique with incisions in both borders according to the Malek procedure [40], the essential angles are A and B, and the shape is an isosceles triangle. The mathematical precision of this method, based on an equilateral triangle flap, allows some variation, such as the inverted triangle plasty or the double Z-plasty, which may be used when the degree of hypoplasia is high. For the inverted Z-plasty, inclusion in the inner incision permits a good reinsertion of the alar wing. The triangular flap adds tissue to the upper portion of the lip, which is often rather thin on the inner border at this level. For the double Z-plasty, when hypoplasia is severe, the measurements give an equilateral triangle of considerable size.

6.5.6 Palatal Repair: Veloplasty and Staphylorraphy

Surgery on the palatal cleft must be done before 18 months of age to facilitate language acquisition. The most widely used technique over many years was introduced by Veau and is called the Wardill palatoplasty [34]. Two thick mucoperiosteum flaps are used in their entirety to close the cleft in the hard palate. This surgery is based on the elevation of the fibro-mucosae and produces major iatrogenic consequences, especially in the case of complete labio-palatal clefts. Scars induce retrognathia and endognathia due to the devascularization of the bone structure through detachment of the mucoperiosteum and creation of fibrotic scar tissue. This is even more obvious when surgery is performed in the first months of life [34, 41]. Palatal cleft may be very short, very long U-shaped, or V-shaped or present as a bifid uvula with open bone covered by mucosa, known as submucosa cleft (Figs. 6.10, 6.11, and 6.12).

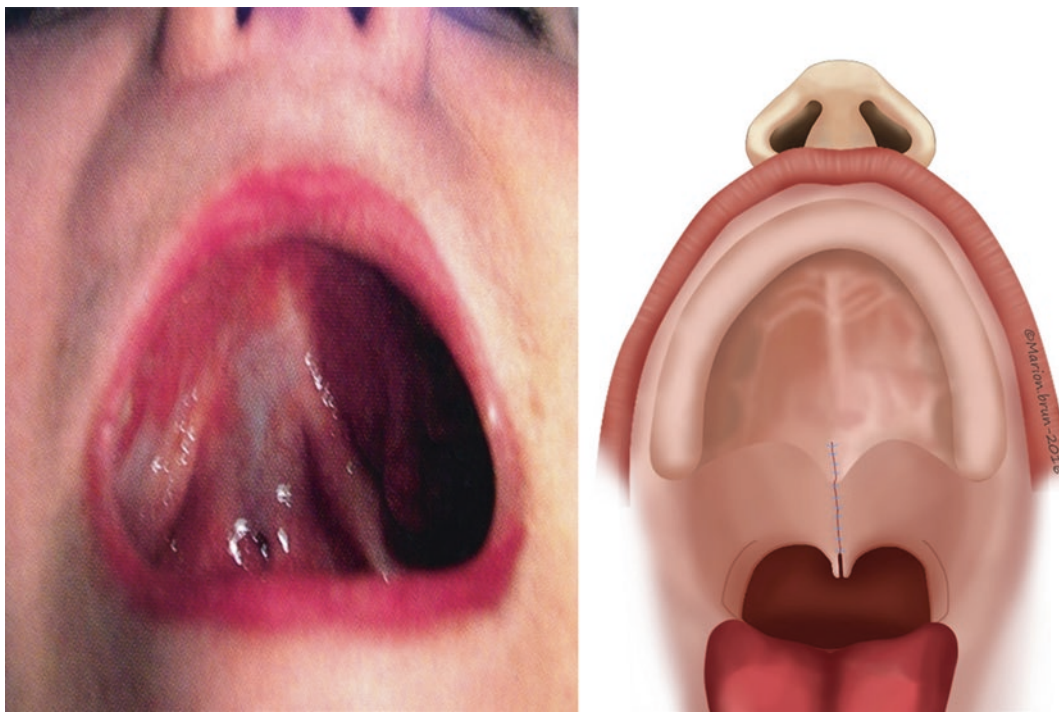

Fig. 6.10 Submucosal cleft palate with bifid uvula

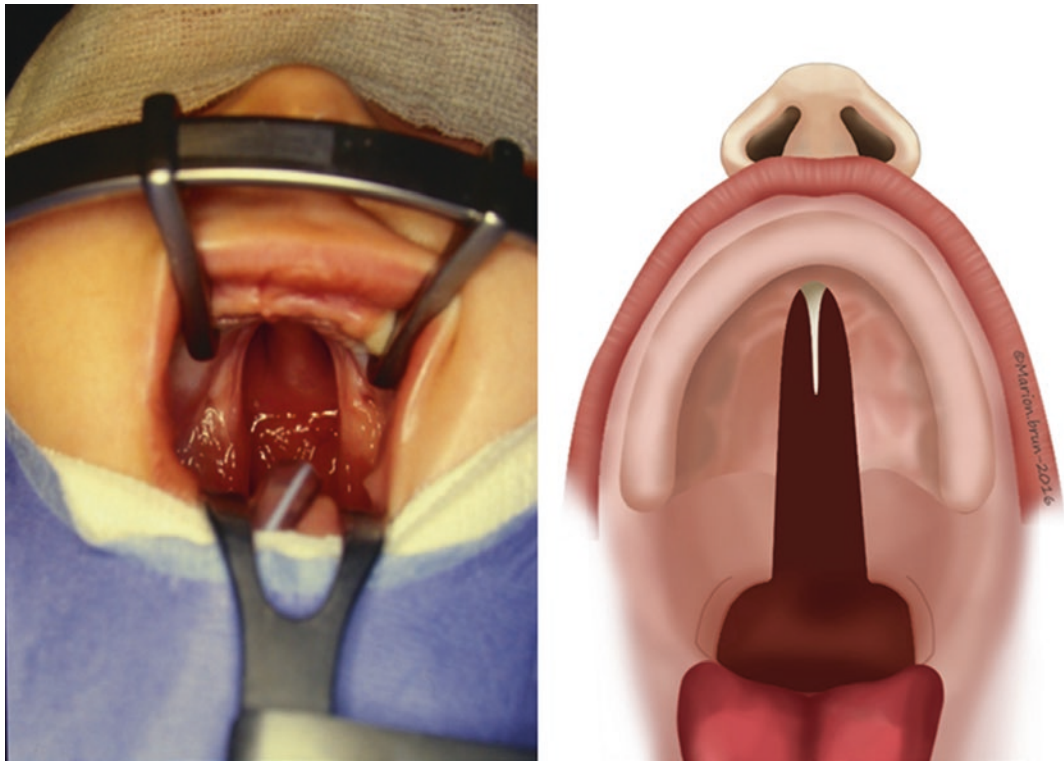

Fig. 6.11 Large palatal cleft in U-shape

6.5.7 Veloplasty

For veloplasty, incisions are made along each margin of the cleft as far as the half uvulae in order to create two flaps (Fig. 6.13). The hamulus is then broken with a Trélat elevator in order to relax the tendon of the tensor velo-palatine. One then proceeds to the undermining, with the tissues being pushed back and carefully divided until the detachment of the soft palate is completed. Homeostasis is drawn normally if necessary. The mucosa that lines the nasal sides of the palatal shelves is easy to detach by displacing the velum toward the inside. This procedure creates two layers, one in the oral cavity and one in the buccal cavity. The surgeon then sutures the first layer of the nasal mucosa with 5-0 or 4-0 absorber filament. Sutures begin at the very front and the knots are tied inside the nose. Each stitch must include a bit of periosteum to guarantee a firm hold. Mattress stitches are continued as far as the anterior extremity of the flaps. When direct suturing is not possible, it becomes necessary to create a nasal layer using vomerine mucosa, a procedure practiced by Veau and later by Petit. A longitudinal incision is made in the lower edge of the vomerine mucosa and nasal mucosa, on either side, from front to back, and is then sutured. The naso-vomerine suture continues until the tension appears to diminish, and then, at this point, direct suturing of the nasal mucosa can be performed [41, 42].

6.5.8 Staphylorraphy

Staphylorraphy is a perfectly reliable conventional technique which allows the closure of the whole palate. This technique must be postponed until maxillary growth is well developed. It does create scars and retraction with retrognathia. In this technique, a longitudinal incision divides the border and continues forward up to the apex of

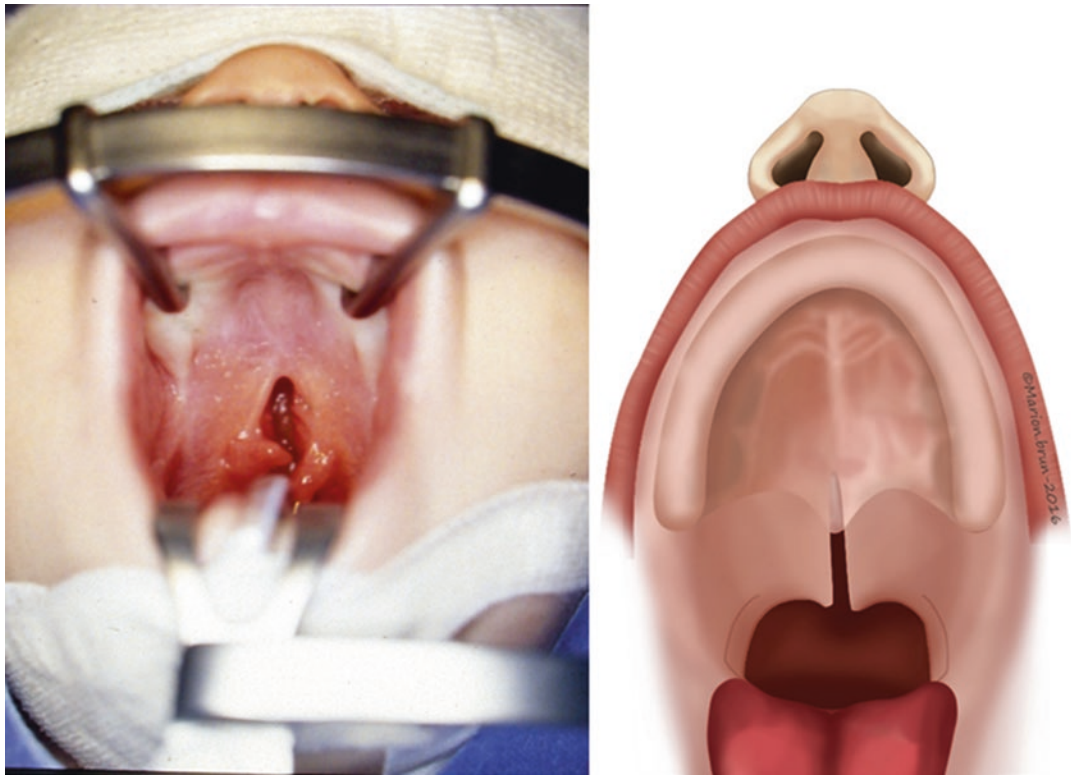

Fig. 6.12 Palatal cleft in V-shape

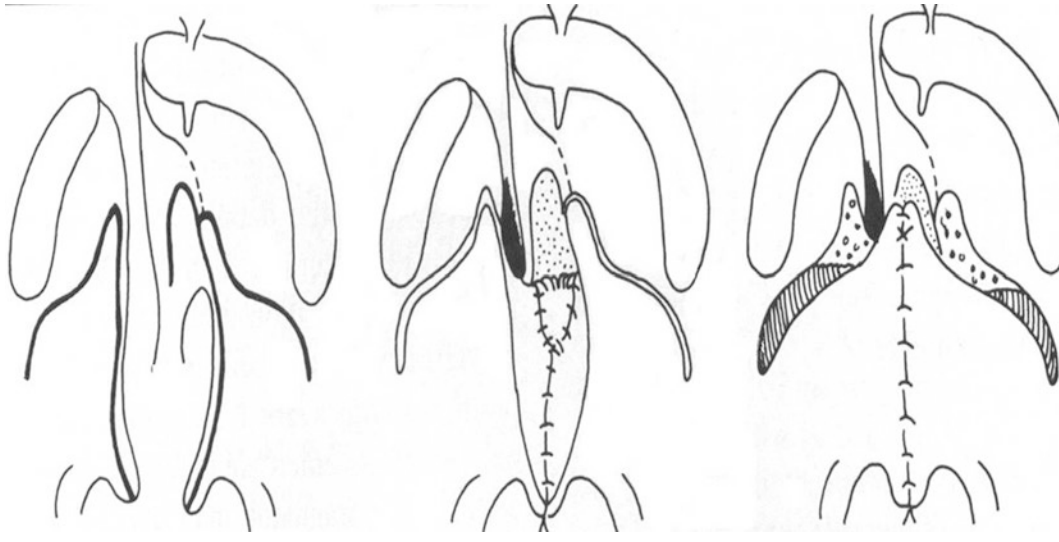

Fig. 6.13 Schematic description of the veloplasty

the cleft, which often extends into the bony vault. A curved incision starts behind the maxillary tuberosity, continues along the inside of the alveolar arch, and stops at the premaxillae (Fig. 6.14). Undermining of the mucoperiosteum is the next step, after fracture of the hamulus with the Trélat hook. Sutures begin with the nasal layers and proceed from front to back. Again, vomerine and lateral nasal mucosa should be sutured together first, taking in a larger bit of muscle than of nasal mucosa (Fig. 6.15). Separate stitches are used for palatal repair after reaching the uvulae [40, 41].

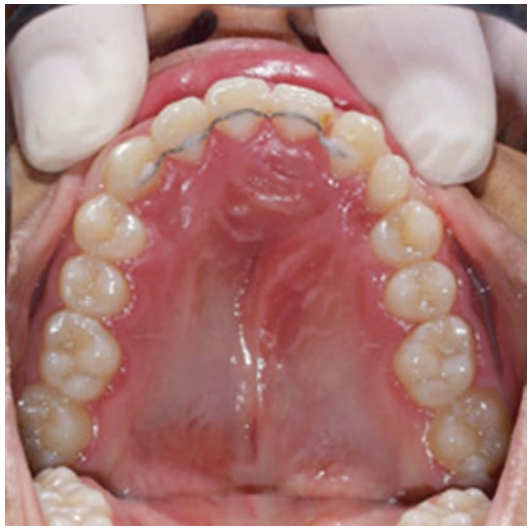

Fig. 6.14 Palate after surgery with small amount of scar tissue in the middle. The cleft was closed with a minimal mucoperiosteum undermining and no lateral palatal scarring tissue

The Furlow technique [43] offers a different version of the Z-plasty and makes it possible to lengthen the soft palate. This surgery is based on the retrodisplacement of the velar muscles, primarily the levator veli palatini. It rests on the intravelar dissection of the muscle fibers, which are then directly sutured end to end so as to reconstruct a muscle sling. It implies an extensive dissection of the muscles which strikes us as a source of fibrosis. It lengthens the soft palate without using the mucoperiosteum, a factor favorable to satisfactory growth, and it allows a better muscular suture which does not impair velar contraction. The technique is based on a large Z-plasty, and the design of the mucosa incisions is traced in the oral and nasal layers. Because of this lengthening, the technique is recommended in the treatment of velar inadequacy over and above the other techniques of pharyngoplasty.

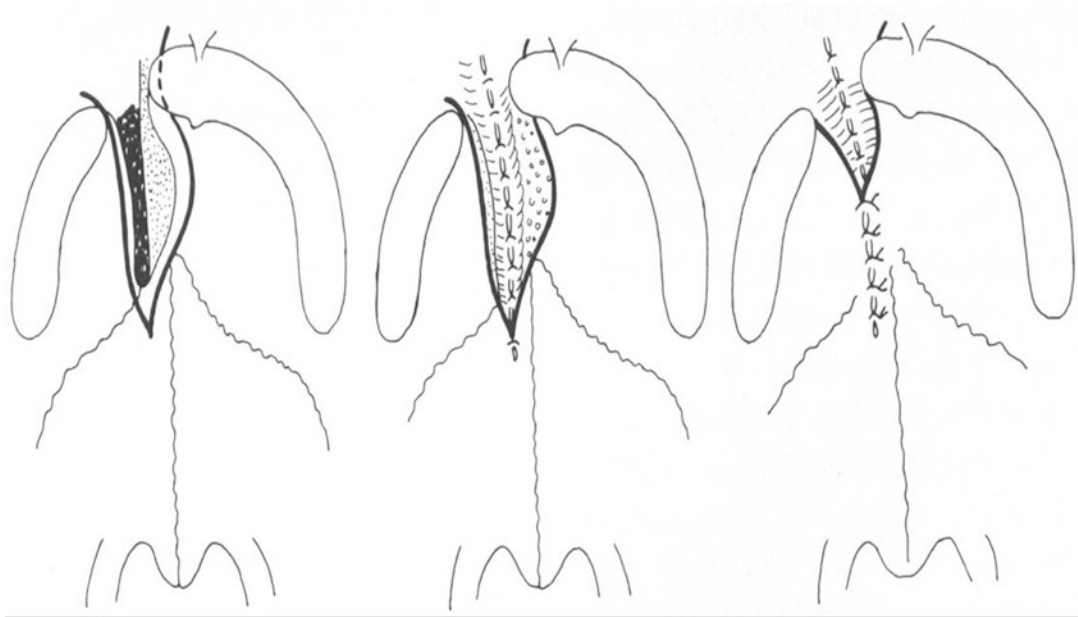

Fig. 6.15 Schematic description of the staphylorraphy

6.6 Ear, Nose, and Throat Problems

Normal hearing during the early phase of infancy is critical in order to develop understanding and use of speech and help cognitive development. Intelligible speech must be acquired as early as possible for good social integration [44].

Due in part to velopharyngeal dysfunction and problems such as secretory otitis media (OMS), children born with a UCLP/BCLP or a CP have significantly more speech and hearing problems than children born without a cleft [7]. The high prevalence of OMS and its associated hearing loss may affect the development of speech and language and lead to lower verbal activity [45, 46]. The hearing loss caused by OMS can be persistent or recurrent and variable in degree and affect one or both ears. The diagnosis of OMS may be difficult, as otitis media with effusion is a condition which presents fluid in the middle ear without signs and symptoms of infection.

Many studies have shown that Eustachian tube function may remain impaired even after surgery in cleft children [47]. OMS is related to the functional obstruction of the Eustachian tube as a result of anatomical and physiological variations of the tensor and levator palatine muscle. The tensor veli palatini and the levator veli palatini are inserted laterally in children with a palatal cleft. This insertion provokes a dysfunction of the opening of the Eustachian tube that compromises the normal ventilation of the middle ear cavity. Without normal ventilation, the cavity is filled with a secretion of mucus and the tympanic membrane is retracted. The presence of secretion in the middle ear or of tympanic membrane retraction/perforation causes difficulties in sound transmission. This impaired anatomical and physiological integrity may therefore hinder the acquisition and development of verbal language. In order to develop speech in the early months and years, the preservation of an aerated mastoid seems to be crucial [48]. Grant et al. showed that 97% of children with a cleft palate had OMS [49]. The incidence of OMS seems to remain very high, up to 90%, even after cleft repair [47].

The surgical insertion of a tympanostomy/ventilation tube (grommet) allows the fluid to drain and thus provides aeration and equalization of pressure in the middle ear cavity. The use of grommets is largely debated because their indication and the right time to insert them are not clearly defined. Tympanometry has been the most common and widely accepted tool for assessing the presence of fluid in the middle ear. It seems to have a high degree of sensitivity and a good specificity for detecting OMS [50, 51]. Taking into account the different ages of the children may therefore be crucial for the detection of OMS and consequently for deciding whether or not to insert a grommet. The meticulous examination of the middle ear is crucial. The insertions should be performed by means of a small incision with a microsurgical knife and under direct vision with a microscope. A beneficial effect of the preventive use of grommets to improve hearing has not yet been verified.

Grommets may be inserted at the time of the palatoplasty, under one single anesthesia. However, complications of their insertion are numerous, for instance, atelectasis, perforation, tympanic membrane scarring (tympanosclerosis), and cholesteatoma. Kay et al. revealed that the incidence of tympanic membrane perforation was higher after repeated tube insertions, after grommet insertion at a young age, and with the use of a long-stay tube [52]. Goudy et al. found a 25% incidence of conductive hearing loss and a 5.9% incidence of cholesteatoma following the insertion of grommets in cleft palate patients [45]. For Shapiro et al., the incidence of tympanic perforation in children with cleft palate related to the insertion of grommet is about 64% [53]. But according to Shaw, children with cleft palate and grommets had a better language acquisition and prognosis than children with cleft palate and no grommets [54, 55].

6.6.1 Tympanometry and Audiometry

A hearing assessment is performed at variable ages and repeated over the following years in response to individual needs. In his evaluation of

the results of tympanometry and audiometry, the ENT has to take into account the cognitive and linguistic capability of the children and also the possibility that they may be tired at the time of the examination. The hearing loss is reported if it is conductive, but sensorineural or mixed hearing loss is excluded. Depending on the age of the child, a speech evaluation can also be performed on the same day.

6.7 Speech

Speech is a cornerstone of social integration and peer acceptance [44]. Intelligible speech must be acquired as early as possible for good social integration. Speech of children born with UCLP and CP is characterized primarily by abnormal nasal resonance. Nasal resonance due to velopharyngeal insufficiency (VPI) diminishes the volume and intelligibility of speech. VPI results from an incomplete closure of the soft palate and the posterior pharyngeal wall. Its etiology can be anatomical (cleft palate), neurologic, or iatrogenic (after adenoidectomy) [56]. The evaluation of a VPI begins with a thorough speech and language assessment and can be complemented by instrumental investigations. Articulation errors, including compensatory misarticulation, worsen the situation.

Perceptual speech evaluation is subjective by nature. If instrumental means of VPI evaluation have the advantage of being more objective than perceptual evaluation, no single instrument has yet proved a reliable alternative to perceptual evaluation in clinical practice [57]. There is no agreement in the literature on the methodology to be used to obtain a reliable rating. In French-speaking countries, the reference for the evaluation of VPI or nasal air emission is usually the Borel-Maisonny [58] score (Table 6.1). Perceptual speech evaluation by qualified speech pathologists experienced in cleft pathology is the mainstay of speech evaluation in our institution. The children should be interviewed in a quiet playroom in the presence of a parent. Standard upper airway assessments should be documented, including the presence or absence of snoring, mouth breathing, apnea, and nasal airway obstruction. Hypernasality, hyponasality, audible nasal emission, voice quality, misarticulations associated with VPI, and intelligibility should be assessed. Nasal emission on separate phonemes may be measured with a nasometer. Fluoroscopic velopharyngeal evaluations can be also done. Video nasopharyngeal endoscopy is a technique which allows direct observation of velopharyngeal movement during speech [59], but it requires the cooperation of the child, which is not easy to achieve, and its interpretation is subjective or operator-dependent. Cinefluoroscopy gives a dynamic visualization of the velopharynx but involves high radiation exposure. The ideal method must be reliable, reproducible, practical, noninvasive, and capable of grading the severity of VPI. No single technique provides reproducible results, and most teams, including ours, evaluate the children using a combination of perceptual evaluation and nasometry. Children with type 1/2 Borel-Maisonny score or worse should be referred to a speech therapist near their home and seen by the university hospital's specialist once a year to evaluate progress.

Articulation errors are divided into categories based on their anatomical origin: labial, alveolar, palatine, velar, nasal, pharyngeal, and glottal. Backing, stops, and fricative sounds are recorded for each anatomical region as compensatory articulations. Other articulation problems, such as simplification, replacement, or deletion of consonants, are also recorded (Table 6.2).

Table 6.1 The Borel-Maisonny classification for the phonation

Type 0	No phonation
Type 1	Excellent phonation, no nasal air emission
Type 1/2	Good phonation, intermittent nasal air emission, good intelligibility
Type 2	Phonation with continuous nasal emission
Type 2b	Phonation with continuous nasal emission but good intelligibility and no social discomfort
Type 2M	Phonation with continuous nasal emission, bad intelligibility
Type 2/3	Phonation with continuous nasal emission with compensatory articulation, bad intelligibility
Type 3	Continuous compensatory articulation, no intelligibility

Table 6.2 Compensatory phenomenon related or not to velopharyngeal insufficiency (VPI)

Simple misarticulation, not related to VPI	Heavy misarticulation	Voice trouble	Compensatory movements	Added sounds
Sigmatisms	Articulations compensation	Hyponasality	Facial (syncinesia)	Snoring
Posteriorizations	Glottic sounds	Hypernasality		Mouth breathing
Deletion of consonants	Raucity	Raucity		Clicks
Confusions Fricative sounds Confusions oral nasal Backing				

Speech therapy aims at strengthening the velopharyngeal muscle complex and can begin at 1 year of age ("guidance") [60]. Using age-appropriate games and increased parental awareness of their active role in speech acquisition, breath control and correct positioning of the tongue and lips can be obtained early. Speech therapy sessions can only do so much, and regular daily exercises at home must complete the treatment. Continued speech therapy is mandatory in order to improve the mobility and strength of the velopharyngeal muscle complex.

After surgical palate repair, a significant number of patients born with a cleft palate have persisting velopharyngeal dysfunction, as lateral pharyngeal wall mobility also plays an important role in VPI, and limited adduction of the lateral pharyngeal muscles may result in a persisting VPI in spite of good velar mobility. If speech therapy is unsuccessful, velopharyngeal dysfunction can be treated prosthetically or surgically [61]. The two major surgical procedures are cranial-based pharyngeal flap and sphincter pharyngoplasty [62]. The criteria for recommending pharyngeal flap surgery are based on perceptual analysis: hypernasality, weak pressure consonants, weak pharyngeal musculature, and nasal emission.

6.8 Orthodontics and Alveolar Bone Graft

The presence of a facial cleft disturbs the harmony of the alveolar process by its negative influence of the formation of the teeth, their eruption, and their final position. Both deciduous teeth and eventually permanent teeth may be affected in terms of shape, size, number, and position. It is mostly the lateral incisors, the teeth in the direct neighborhood of the cleft, that are involved. The teeth may have enamel hypoplasia, meaning malformation of the crown with calcification or demineralization; they may be in a wrong position with various degrees of malrotation or inclination [63]. Supernumerary teeth may also be present, in a wrong position sometimes. The scars resulting from the primary surgery may also affect the growth of the upper jaw and the alveolar process, as well as the position of the teeth [64].

Indications for orthodontic treatment are functional and esthetic. In general, orthodontic treatment is recommended only when the permanent teeth are present. It is useless to correct the position of teeth which are to be replaced. The deciduous dentition lasts up to about 7 years of age. During this period, parents are advised to control the exercise of the necessary dental hygiene. As for all children, dental care for prevention of caries is mandatory, and as soon as the baby teeth appear, they must be brushed with a soft brush in order to accustom the child to regular dental hygiene. Malposition of the teeth is not usually treated, because of the transitory nature of this stage. Mixed dentition lasts between 7 and 12 years of age. The orthodontic treatment is correlated with the planning of the alveolar bone graft when a maxillary cleft exists with, most of the time, missing teeth (canine, incisor, molar) or hypoplastic or improperly placed teeth [65, 66].

To summarize, the first phase of active treatment concerns the normalization of the shape of

the dental arch using an asymmetrical expanding plate before consolidation by means of a bone graft [65, 67]. Normally, and except in rare cases, the incisors, even when malpositioned, are not aligned before the graft. The aim of the bone graft is to close a cleft in the alveolar process. The permanent teeth, especially the canines, emerge when the bone of the maxilla is complete. A bone graft allows the alveolar process to develop almost normally and so provides the necessary environment for the development and stabilization of the adjacent teeth, which need to be set in adequate bone [68]. The planification of the alveolar graft (GOA) must be well thought out, even if its exact timing cannot always be precisely determined and varies largely between children. It is generally accepted that the bone graft should be done before the age of 9 or 10, but some teams perform this graft precociously, at about 5 years of age. The spongious bone for the graft must be taken from inside the normal bone, usually from the iliac crest, or from the mandibular bone. This graft will create a bridge in the gum ridge between the left and right edges of the cleft and allow the permanent teeth to come in. Only autologous bone has the capacity to create a bridge. It is important to do a bone graft before the eruption of the definitive canines, as without bone the permanent canines cannot erupt.

The second phase starts with the complete healing of the bone graft (autograft). The aim is to align the upper incisors and canines, mainly for cosmetic reasons. The aligned teeth are stabilized by a retainer made of fine steel wire bonded to the lingual side of the teeth with composite resin [62, 69]. This treatment allows a good healing of the bone and the integration of the graft. The permanent canines/incisors will be able to erupt naturally and in a nearly normal bony environment. Orthodontic alignment will then be possible, and the chances that the canine and lateral teeth will remain stable are considerably improved.

The third phase starts around the age of 12. It concerns the relationship between the upper and lower jaws and the malposition of the teeth. In this case a purely orthodontic approach is insufficient and maxillofacial surgery is necessary. For combined orthodontic and surgical approaches, three phases can be described: (1) preparation of the upper and lower dental arches with braces for several months, (2) surgical correction, and (3) orthodontic treatment for fine alignment during a few months (Fig. 6.16).

Fixed orthodontic braces are the only quick-release treatment of the complex adjustments necessary to correct the often misplaced teeth. Even with highly effective fixed braces, the quality of the outcome also depends on the collaboration of the patients and the parents. This collaboration begins with dental hygiene. The presence of braces encourages a large number of bacteria (bacterial plaque) responsible for caries and periodontal disease.

In general, it is important to limit interventions to a minimum in order to avoid straining the patient's potential for cooperation. Their timing must be discussed within a multidisciplinary team. There are periods in the growth and development of the bone during which orthodontic treatment is recommended. The duration of the conservative treatment has to be determined not only in view of its final result but also in relation with the child's behavior and his capacity to put up with it. A long-lasting and possibly poorly effective conservative treatment must be avoided, not only for the sake of the child and his family but also because of its cost.

6.9 Maxillofacial Surgery

During the growth process, the intermaxillary relations remain good as long as the articular congruence, esthetically and functionally, responds to conservative treatment. But in 10–20% of cases, a maxillary growth deficiency is obvious, confirmed by an analysis of cephalometric measurements (Fig. 6.17). These measurements must be made regularly, because bone growth of individual parts may happen at different speeds and a good articular congruence with a good esthetic profile may deteriorate quite quickly during puberty. Maxillary and mandibular bones must grow in harmony, esthetically and functionally [63]. If they do not, conservative

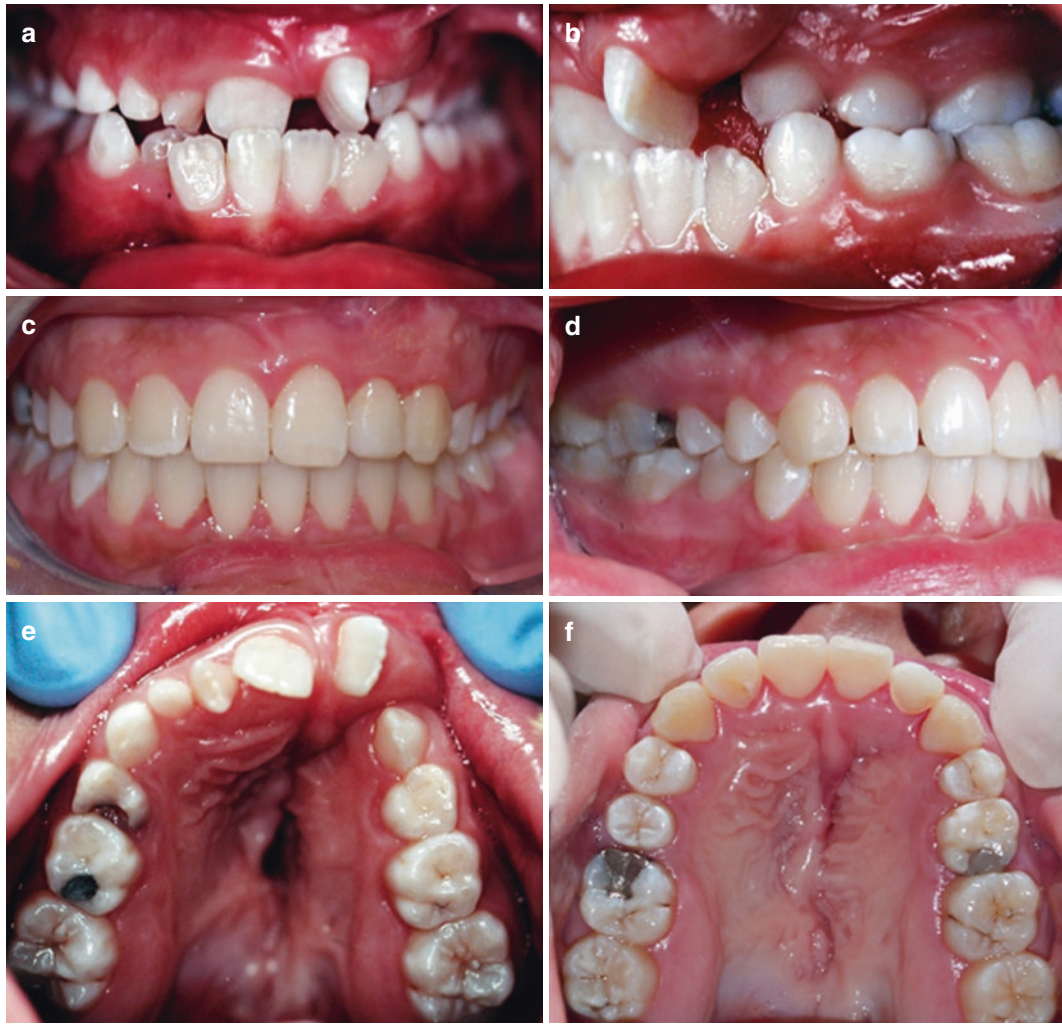

Fig. 6.16 Evolution of the position of the teeth during the follow-up: (**a**, **b**) at the beginning of the treatment, (**c**, **d**) at the end of the treatment, (**e**, **f**) before and after the alveolar graft. Note the presence of an oronasal fistula before the graft

treatment is not sufficient and surgical treatment proves necessary, in the form of maxillary advancement (LeFort I), associated or not with mandibular retraction (sagittal). This surgical treatment must be correlated with the orthodontic treatment and performed at the end of the growth period, between the ages of 16 and 18.

Impairment of maxillary growth resulting in retrusion of the maxilla is a frequent finding in children born with cleft lip and palate. These children often have midfacial growth deficiency, with a reduced upper lip support, leading to a characteristic concave profile. This generally increases during adolescence. According to a few authors, these growth disturbances are intrinsic to the cleft itself, as they were observed in children whose clefts had never been surgically repaired [70, 71]. However, these studies have been questioned, and many authors hold that maxillary growth deficiency is mainly iatrogenic in nature and a consequence of the primary surgical repair of the palate [72]. Liao and Mars [73] compared the follow-up of children born with UCLP and operated only for their lip with children born with UCLP and operated for both lip and palate; they concluded that primary

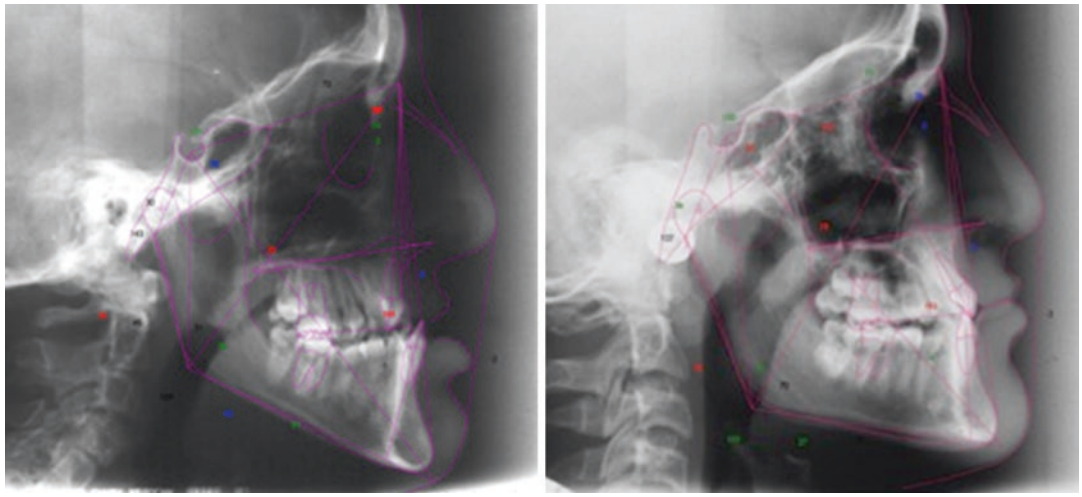

Fig. 6.17 Lateral cephalogram of a patient with a maxillary retrusion and severe impact on profile (left) and lateral cephalogram of a patient with a similar maxillary retrusion, but a diminished impact on profile (right)

surgery on the palate was the main cause of maxillary retrusion.

Consequently, special care must be taken during the primary surgery to avoid the elevation of the mucoperiosteum. As a result, there will be only a small area of denuded palatal bone, lateral to the incisions on the palate, which will heal spontaneously by secondary intention. If the surgery during the first months is too aggressive, with a high elevation of the mucoperiosteum, large areas of palatal bone are left to heal by secondary intention, and the amount of scar tissue on the palate is thus greatly increased, leading to retractions and difficulties in bone growth.

Orthognathic surgery to correct facial disharmony is part of the normal follow-up of children born with UCLP. When planning corrective surgery, many factors, such as facial profile, intermaxillary discrepancies, and dentoalveolar relationship, are taken into account. Unfortunately, as there is no standardized protocol, the choice of procedure often remains subjective, and this can explain why it is difficult to compare the results obtained in different centers [74, 75]. Ross et al. in 1987 [76] compared lateral cephalograms of UCLP children whose palate surgery had followed different techniques, operated for their palate by different techniques, and showed very similar results and measurements for children whose clefts were closed following the Malek procedure and children whose clefts were closed following a conventional technique.

An objective determination of the need for orthognathic surgery may be based on the data available from the analysis of the lateral cephalograms: the anteroposterior relationship of the maxillary basal arch to the anterior cranial base uses the SNA, SNB, and ANB angles (S = sella, N = nasion, A = subspinal, B = supramental); anteroposterior jaw dysplasia may be measured according to the Wits appraisal (perpendiculars from points A and B onto the occlusal plane), and the distance from the upper lip to the e-plane (line drawn from the tip of the nose to the chin) is the most used criteria. Children with poor facial esthetics despite a more favorable lateral cephalogram may also be considered for an orthognathic correction, even if this criterion is mostly subjective and a matter for a family discussion.

Orthognathic surgery to correct these dentofacial deformities may therefore be indicated [77]. A maxillary advancement with a LeFort I osteotomy is the most common orthognathic procedure. Due to a possible transversal collapse of the maxillary arches on each side of the cleft, caused by the scarring tissue, this advancement cannot always be achieved in one piece. In these cases, the maxilla needs to be segmented in two or three

pieces. The frequency of indications in the literature for a LeFort I osteotomy in unilateral cleft lip and palate (UCLP) varies from 22% to 48.3% [75]. These differences may arise from different management protocols and depend also on the patient's access to adequate presurgical orthodontic care. The criteria used to determine the need for orthognathic surgery are also subjective to some extent and therefore may vary between surgical teams.

6.10 Psychological Impact

A birth in itself modifies the family harmony, and the arrival of a child causes psychological and physiological upheavals that specialists define as periods of crisis in maturation. For most people, planning a child implies a large measure of dreaming, high expectations, and the fulfillment of a part of oneself. The fact that the parents "meet" their child before birth during ultrasound examination intensifies these expectations and dreams in the sense that the new baby can suddenly be pictured and is the basis of a real representation. The literature shows that the majority of parents wish to be informed of an expected defect of the baby as early as possible, in order to learn to face the reality of the problem. After the diagnosis, they are overcome with worry and anxiety and need time to accept it. In the course of the follow-up and the exchanges with the medical team, they will absorb the shock of the diagnosis and prepare to welcome their baby. Progress in surgery nowadays allows parents to hope for high esthetic and functional results.

Psychological problems start before birth. Parents either find it impossible to imagine their child's face or have a lot of images and fantasms in their mind. Each parent thinks, be it for one instant only, of interrupting the pregnancy, and this thought brings with it a strong sensation of culpability. The question of whether there could possibly be another malformation in their child, especially concerning the brain, is quite often present. The parents must go beyond the diagnosis and their fear in order to accept the baby. They question the why and how. The presence of competent people is therefore mandatory to give confidence to the parents and to reassure them. The knowledge that a team is dealing with the malformation and is competent is essential [5, 78].

The announcement of the diagnosis is extremely delicate, and people present during the diagnosis must show tact and respect, especially in the matter of the words used. Prenatal discussions will provide advice for the remaining course of the pregnancy and also give the parents information on where the mother should give birth. By example, for a suspicion of Pierre Robin sequence, it is quite important that the birth take place in a specific hospital, with a pediatric anesthetist and pediatric reanimation. Respiratory and feeding problems must be discussed in order to prepare the parents to the fact that in the case of a total cleft or palatal cleft, breast-feeding, for instance, will be impossible. The esthetic follow-up, the difficulties in language development, and the nature and schedule of the surgery to be expected must be discussed [15]. Individual resources and specificities play an important role. It is impossible to predict the future of the child and his relationship to his parents.

In most cases, the traumatism of the diagnosis can be expressed in parental terms through intense images or some kind of protective shield. If these phenomena last for too long a time, they may resemble post-traumatic stress with characteristic symptoms of avoidance, feeling of intrusion, and neurovegetative reactions. As time goes on, we observe a progressive acceptance of their role as parents and often a reaction of overprotective behavior.

The child, or adolescent, will be confronted with difficult episodes at different times of his life, for instance, and to name only a few, the start of school, the relation with peers, puberty, and the relation with girl- or boyfriends. The intervention of a third person at a special moment may be necessary.

The revelation that their unborn child has a defect, for instance, a cleft, is undoubtedly a shock for the parents. It is a painful event which can often give rise to psychological problems. Certain parents develop a feeling of culpability, of loss of control, and of inadequacy as genitors,

which could well have an incidence on the psycho-affective development of the child [5, 15, 16]. This is why a psychological support to the parents from the very moment the prenatal diagnostic is established can be useful. The social skills of the child himself, the adolescent, may also be affected, with resulting manifestations of anxiety, poor self-esteem, or depression.

The psychological consultation offered by specialists in the course of each pluridisciplinary consultation helps to spot risky situations and to set up a program of support adapted to each individual child.

6.11 Secondary Surgery

The first installment of secondary surgery, between 5 and 10 years of age, is considered a complementary surgery to the primary surgery. It includes, first of all, a pharyngeal flap or a true pharyngoplasty and closure of a bucco-nasal fistula. Early rhinoplasty is also possible if the deformation of the columella or of the nasal wing is especially unesthetic.

Subsequent surgery, after 10 years of age, includes dental repair, the purview of orthodontists (Sect. 6.8), and alveolar grafts, the purview of maxillofacial surgeons (Sect. 6.8), with or without maxillary advancement. Correction of the lip with a labioplasty is always possible for esthetic purposes, especially in the case of BCLP, where the muscle of the central part of the lip is missing. Rhinoplasty with lengthening of the columella, especially for bilateral cases, correction of the asymmetry of the nasal wing for unilateral cases, and lip surgery are performed, if possible, after the final growth of the maxillary.

6.11.1 Pharyngoplasty and Pharyngeal Flap

Secondary surgery for the palate is proposed when continued therapy no longer improves the child's speech. Surgery on the palatal cleft must be done before 18 months of age to facilitate language acquisition [79]. Results in terms of phonation are very bad if surgery is performed after this age [79–81]. Nevertheless, surgery induces scars with retrognathia, and the palate may be short, weak, or stiff. VPI results from an incomplete closure of the soft palate and the posterior pharyngeal wall. Nasal resonance due to VPI diminishes the volume and intelligibility of speech.

The possible types of surgery are (a) injection of autologous fat in the retropharyngeal space in order to diminish the retro palatal space [82]; (b) reconstruction of the anatomy by a simple veloplasty, possibly associated with a Z-plasty [83]; (c) lengthening of the palate by means of a pharyngeal flap (Fig. 6.18) based superiorly, inferiorly, or laterally [84–87]; (d) pharyngoplasty with or without push-back of the palate [86, 88]; and, finally, (e) a lengthening of the palate by means of a jugal flap (Buccinateur) [89, 90].

The surgical procedures described for the treatment of VPI all aim at lengthening the soft palate. The aim is to correct velopharyngeal dysfunction and create a central subtotal velopharyngeal obstruction, leaving two narrow lateral passages for nasal airflow. The cranial-based pharyngeal flap surgery was performed first by Schönborn [91] and then Sanvenero-Rosselli [92]. A broad, cranially based pharyngeal flap is incised and elevated from the prevertebral fascia to be sutured to the nasal side of the incised velum (Fig. 6.18). The donor site is closed directly. The soft palate is dissected and two mucosal flaps are prepared. The two mucosal flaps are incised on the dorsal velar side. The pharyngeal flap, including its muscle layer, is sutured to the nasal mucosa of the velum. In the midline, the two buccal flaps are joined and sutured in their entire thickness to the surface of the flaps. This technique was modified by Fischer-Brandies and Nejedlo [93] because in its original version, the pedicle created between the dorsal pharyngeal wall and the soft palate was too narrow, due to healing by granulation, scar contraction, and narrow bed. The modified technique entails the creation of two mucosal flaps on the dorsal velar side to cover the pharyngeal flap and increase its width to produce a voluminous and broad flap. This modification leads to a better

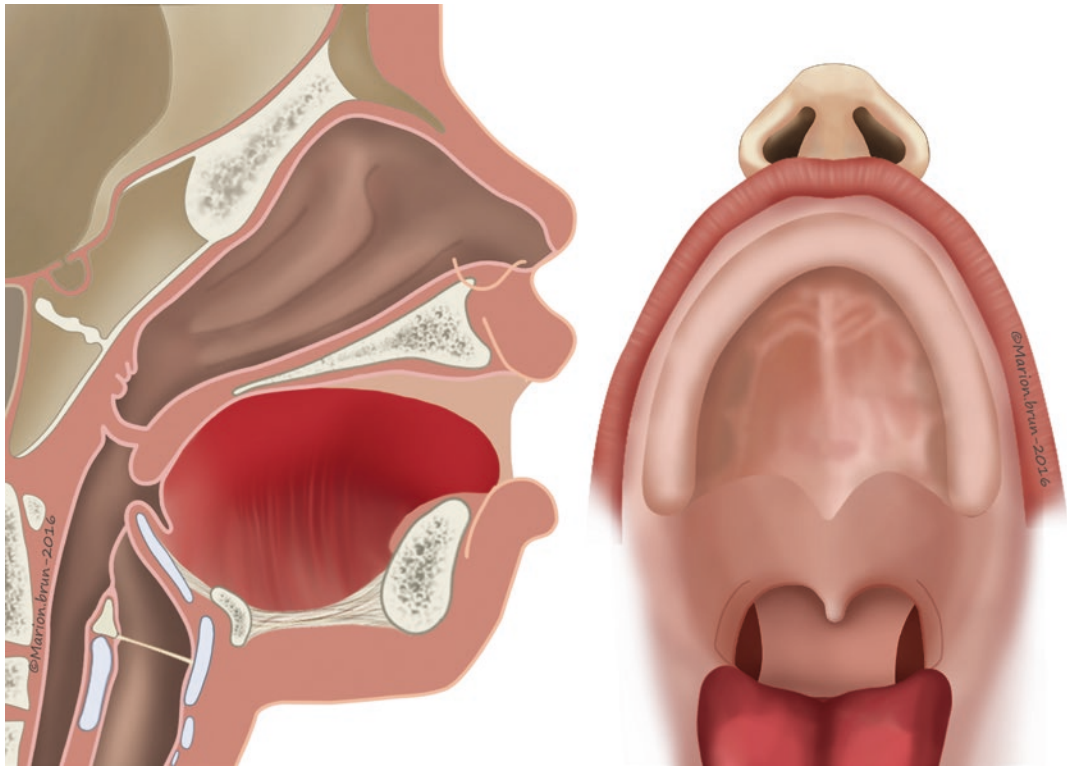

Fig. 6.18 Cranial-based pharyngeal flaps following the technique described by Schönborn in 1865 [91] and Sanvenero-Rosselli [92]. A broad, cranially based pharyngeal flap is incised and elevated from the prevertebral fascia to be sutured to the nasal side of the incised velum

velopharyngeal occlusion of the muscles and results in improved speech. However, there have been reports of airway obstruction and obstruction sleep apnea associated with pharyngeal flap surgery [7]. A polygraphy or a polysomnography must be done before and after the surgery.

Because of the variation in the degree of shrinkage of the flap and scar contraction, the final size of the lateral velopharyngeal apertures cannot always be accurately predicted. The failure of this technique is obvious when hypernasality persists. It can be the result of surgical error and/or inadequate lateral pharyngeal wall motion [85]. Surgical errors include a too narrow flap, a poor short flap, or scar contraction [83]. They can also result in a velopharyngeal flap which is too broad, causing hyponasal speech and sleep apnea. Preoperative assessment of the velopharyngeal mechanism is essential in choosing which type of pharyngeal flap will best assist closure of the velopharyngeal port during speech. Barot et al. [94] reported that 15% of patients who underwent pharyngeal flap surgery for velopharyngeal dysfunction over a 9-year period required revision. Witt et al. [89] described the same results in children who had received a velopharyngeal flap or sphincter pharyngoplasty. Post-surgery examinations are necessary to check for nasal obstruction that persists after 1 month and for sleep apnea.

Surgical success is defined in terms of the elimination of perceptible hypernasality or oral resonance and of instrumental evidence of complete velopharyngeal closure by nasoendoscopy. Velopharyngeal assessment is generally performed 4 months after surgery. Surgical failure is defined in terms of persistent hypernasality and/or nasal turbulence observed during a perceptual

speech evaluation and of incomplete velopharyngeal closure evidenced by nasometry at least 6 months after surgery.

6.11.2 Oronasal Fistula

Fistulas of the palate remain the major complication in the early primary palate technique. These fistulas do not appear to be linked exclusively to a defective surgical technique. A weakness in the sutures may obviously be a contributing factor. Single-layered closures of the nasal mucosa on the bony vault make fistulas more likely. A second layer of closure on the oral side significantly reduces the incidence of fistulas but does not eliminate them all together. One of the major causes is the positive and negative pressure which the child can produce in the oral cavity after it has been completely closed. The best preventive measure is a suture technique based on double-layered closure. However, when the customary technique is followed, there is always a zone in the retroalveolar region that is covered by only one oral layer. A number of therapeutic theories have been elaborated to help prevent these fistulas. One simple solution might lie in the use of prosthetic obturation. The obturator could be left in place for a short period to allow satisfactory healing.

When a fistula does exist, there is never spontaneous closure. The consequences are, first, the leakage of fluids or soft food such as milk or water through the nose. It is known as the "signe du chocolat," when chocolate food falls from the nostril. The passage of food through the nostril can also result from a too short or scarred soft plate. The second consequence is a speech disorder, called rhinolalia, meaning air coming through the nose during speech. The speech therapist must distinguish between VPI and air coming from the mouth through the fistula. Indication for closure of a fistula depends on the severity of its consequences, but the child must be followed by the speech therapist to be sure that compensatory phenomena are not present, due to the leakage of air (Table 6.2). A technique of closure of the fistula is based on the elevation of the mucoperiosteum of the entire palate. Simple closure of the hole is just not possible. Closure of the fistula must be postponed as long as possible in order to minimize adverse consequences on the growth of the maxilla.

6.11.3 Labioplasty

Secondary surgery for the lip in UCLP children is normally done when the Cupid's bow is not perfect or when the height of the repaired lip is too short. In the first case, surgery is simple, with a local correction and alignment of the white skin. In the second case, where the distance from the nose to the lip is not satisfactory, the height of the "normal lip" must again be calculated and compared with the opposite side. The height of the lip is determined by using a caliper to measure the height of the outer border on the vertical line from the outer alar base. In most cases, the repaired lip is short, and a Z-plasty must be done by opening the skin from the lip to the nostril. The precise position of the Cupid's bow must again be determined and the triangular flap plasty adapted so that the top edge of the lip and the lateral superior points of the Cupid's bow will be aligned with the middle reference point set by the nostrils.

In cases of bilateral clefts, normal references do not exist and the vermilion could be too short: Z-plasties must be done on both sides by opening the lip up to the nostrils [37, 38]. Additional length is gained between two points thanks to the dissection of two triangular flaps that share a common side. The apices of the triangles are situated at each end of the joined triangular flaps. After the incision, inversion of the flaps results in inversion of the diagonals on the parallelogram initially traced. The long diagonal replaces the short and vice versa, so that the desired additional length is obtained. In most cases, the muscles are separated on both sides of the central part of the lip. In these cases, the lip must be opened and the muscles sutured together, removing if possible the scar tissue in the middle of the lip.

6.11.4 Rhinoplasty

Early rhinoplasty is performed by different surgeons during the primary surgical repair, the labioplasty. Results in terms of growth and of esthetic success are still being evaluated. A thermoformable splint may be used for several weeks after the surgery. Intermediate rhinoplasty is done between 5 and 10 years of age. It is reserved for severe deformations accompanied by psychological and social manifestations. This type of surgical intervention is therefore discussed during our multidisciplinary meetings. Both objective and subjective indications must be considered. The operation consists in repositioning the alar cartilage through an incision inside the nostril [95]. A thermoformable splint may also be used for several days or weeks. Late rhinoplasty is planned at the end of the growth. It is wise to do the surgery after the orthodontic treatment is completed. The operation involves a small incision below the nose and necessitates a cartilage graft taken from the ear. The deviation of the nasal septum is also corrected during the same surgery. A thermoformable splint may also be used for several days or weeks. This surgery is not easy and takes time. It represents the final step after years and years of follow-up, knowing that primary surgery certainly determines the growth of the face and of the bone and therefore the success of the rhinoplasty.

6.12 Support Group and Multidisciplinary Team

The multidisciplinary cleft team is composed of a pediatric surgeon, a plastic surgeon, a pediatric ENT specialist, a craniofacial surgeon, an orthodontist, a speech therapist, and a psychologist. A geneticist and a gynecologist are also present to offer their collaboration to the discussion. The child and its parents must be seen as required by the child's and the parents' needs.

There is a risk of the parents being destabilized or losing their landmarks when facing what may at times appear to be contradictory informations, notably in the matter of various treatment

Table 6.3 Basic general follow-up of children with a cleft

When?	What?	Who?
Antenatal	Information Psychological help Genetic counseling	Pediatric surgeon Psychologue
Birth	Information Alimentary problems	Pediatric surgeon Nurse Orthodontist (plaque)
3 months	Primary surgery	Pediatric surgeon
5–10 months	Primary surgery	Pediatric surgeon
18 months−3 years	Check-up Parental guidance	Pediatric surgeon ENT, pediatrician Orthophonist
3 years	Bilan	Team
3–9 years	Follow-up Guidance (speech) Secondary surgery: fistula, pharyngoplasty Early secondary surgery (nose)	Team Pediatric surgeon
9 years	Orthodontist	Team
6–10 years	Bone graft	Maxillofacial surgeon Orthodontist
12–18 years	Follow-up Secondary surgery: LeFort, rhinoplasty, labioplasty	Team Pediatric surgeon ENT
18–20 years	Genetic counseling	Team

methods and timing of the operations. The cleft team must be a strong source of help, always ready to answer the parents' requests for information (Table 6.3). Association of parents may be also very helpful.

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Macroglossia

7

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7.1 Introduction

Macroglossia is defined as an abnormally enlarged tongue (from the Greek "*makros* + *glossa*"). Macroglossia was documented as early as 1550 BCE in the ancient Egyptian Papyrus Ebers.

From a clinical perspective, macroglossia is characterized by an extension of the tongue beyond the teeth or the alveolar ridge at rest, although other definitions and criteria exist [1]. In this sense, two main classifications for macroglossia are clinically useful. The Myer classification [1] distinguishes between local and general macroglossia based on the extent of lingual involvement. The Vogel classification [2] in contrast defines true macroglossia as an enlarged tongue with underlying histological alterations. Relative macroglossia designates an abnormally enlarged tongue in proportion to other structures surrounding the oral cavity (Fig. 7.1).

Macroglossia is most often encountered within the frame of an underlying condition, whether congenital or acquired. Isolated congenital macroglossia is rare but possible [3]. Macroglossia may be absolutely asymptomatic or present with mild symptoms like drooling and articulation impairment, while severe macroglossia may lead to swallowing difficulties, upper airway obstruction, and obstructive sleep apnea.

Chief among congenital causes of macroglossia are Down syndrome, Beckwith-Wiedemann syndrome, primary amyloidosis, and congenital hypothyroidism. Acquired causes may include trauma, tumors, and inflammatory or infectious conditions.

Given the fact that macroglossia is most often an associated finding in several conditions, the exact prevalence of macroglossia is difficult to determine.

The treatment of macroglossia depends both on its severity and clinical presentation. Management possibilities include symptomatic relief of drooling, speech therapy, or surgical reduction of the tongue for the most severe cases.

7.2 Diagnostic Approach

The goal of the diagnostic approach in children with macroglossia must address three essential issues:

1. Establishing the diagnosis and more specifically distinguishing true vs. relative macroglossia

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2. Assessing for presence of comorbidities
3. Assessing the anatomical and functional impact of macroglossia

Presenting symptoms and their intensity depends on macroglossia severity and clinical context (Table 7.1). As mentioned above, macroglossia can be strictly asymptomatic or present with drooling or impaired articulation. Macroglossia can also affect the oral and pharyngeal swallowing phases and result in feeding problems and in small children possible bronchoaspiration. Finally, severe forms of macroglossia can also lead to upper airway obstruction, especially in supine position. During sleep this can be responsible for snoring and obstructive

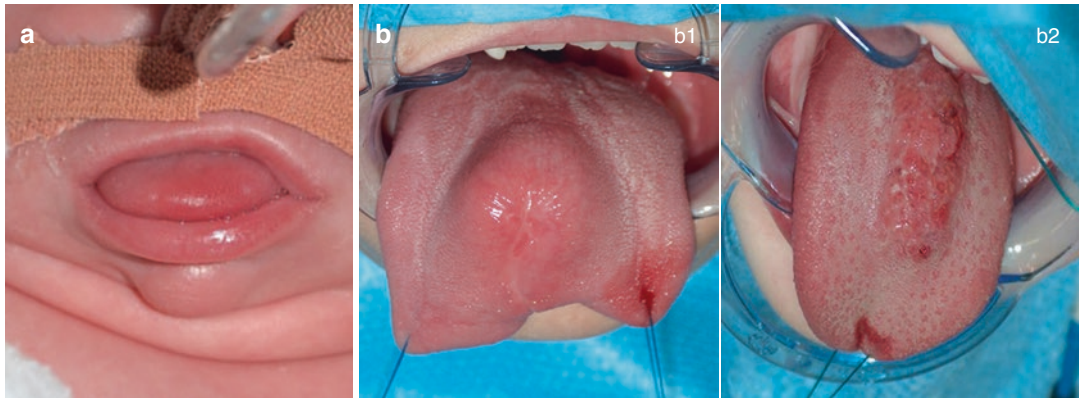

Fig. 7.1 (**a**) Generalized macroglossia in Beckwith-Wiedemann syndrome. (**b**) Localized macroglossia. (**b1**) Foregut duplication cyst of the tongue. (**b2**) Tongue hamartoma. *Pictures with kind permission from Dr. Anthony De Buys Roessingh*

Table 7.1 Clinical features

1. Airway obstruction	
Obstructive sleep apnea	
Bronchoaspiration	
2. Dysphagia Speech articulation disorders	
Glossitis	
Scalloping (fissuring of the tongue)	
Lingual tip necrosis	
Pain	
Drooling	
3. Temporomandibular joint pain	
4. Dental deformities	Class III malocclusion
	Open bite
	Crossbite
	Buccal tipping of posterior teeth
5. Facial deformities	Increased width of maxillary/mandibular arches
	Mandibular prognathism
	Accentuated or reverse curve of Spee (in maxillary or mandibulary arch respectively)
	Facial asymmetry in asymmetric tongue
6. Psychological	

sleep apnea syndrome (OSAS). Constant exposure of the oral mucosae due to the fact that the mouth remains constantly open may lead to angular cheilitis, ulceration, or glossitis. Cases of acute exacerbations of previously existing macroglossia leading to local complications such as necrosis, often following trauma, have been reported [4].

If not properly addressed in due time, macroglossia can result in dentoskeletal deformities such as open bite, prognathism, malocclusion, crossbite, buccal tipping of posterior teeth, and other alterations of the mandibular or maxillary arches. In the long term, temporomandibular joint dysfunction tends to occur.

7.2.1 Diagnostic Methods

The diagnosis of macroglossia in children is first and foremost made on the basis of clinical history and physical examination. A comprehensive history regarding pregnancy, birth, and family diseases should be obtained. Prenatal diagnosis of congenital macroglossia is sometimes evident on ultrasound examination, showing a tongue protrusion beyond the lips [5].

It is essential to keep in mind that newborns tend to have a relatively large tongue. However, congenital macroglossia is often apparent at birth, especially if airway or swallowing symptoms are present. This is, for instance, the case in children with relative macroglossia such as those with Pierre Robin sequence [6]. It is nevertheless important to keep in mind that macroglossia in children can slowly develop, even over a period of months to years. It is therefore essential to follow up children with macroglossia to ensure proper intervention if and when needed.

Since macroglossia can lead to dentoskeletal deformities, evaluation by an oral or craniofacial surgeon should be considered for all cases of macroglossia, whether absolute or relative.

Clinical examination should carefully evaluate tongue size and mobility, as well as transnasal flexible pharyngo-laryngoscopy to assess the base of the tongue and upper airway. This can be combined with functional endoscopic evaluation of swallowing (FEES) in children with suspected swallowing disorders [7].

Complementary studies should be guided by clinical context and may include chromosomal studies, urine mucopolysaccharides, or evaluation of thyroid gland function. Imaging studies are most commonly reserved for vascular or lymphatic malformations, tumors, or other causes of focal macroglossia, in order to obtain preoperative assessment of lesional extent/vascular supply [8].

Regarding genetic causes of macroglossia, it is recommended that newborns and young infants undergo evaluation by means of abdominal ultrasonography and genetic studies for Beckwith-Wiedemann syndrome (see Sect. 7.2.2.2). A study on the genetic causes of macroglossia reported that macroglossia was the main reason for genetic workup in almost two-thirds of the patients (median age of 5 months) [3].

7.2.2 Associated Comorbidities

It is essential to realize that macroglossia most often results from an underlying cause, whether or not in the frame of a wider condition. It is therefore essential to approach children with macroglossia in the context of a multidisciplinary team including otolaryngologists, pediatricians, geneticists, and maxillofacial surgeons, among others. Generalized macroglossia in children is primarily seen in the frame of congenital diseases, primarily Down and Beckwith-Wiedemann syndromes, and mucopolysaccharidoses. Rarer causes include congenital hypothyroidism and systemic amyloidosis (the latter being exceptionally rare in children). An ectopic lingual thyroid can equally cause congenital localized macroglossia. Other causes of macroglossia include lymphovascular malformations, which most often present within the first year of life and slowly progress.

Here are briefly discussed some of the most common causes of macroglossia.

7.2.2.1 Down Syndrome

Down syndrome is a well-known condition and the most common genetic cause of development

impairment, resulting from chromosome 21 trisomy. Its estimated incidence is of approximately 1:650 live births [9]. Macroglossia is considered to be a standard feature in children with Down syndrome. Nevertheless, these patients commonly feature midface as well as mandibular hypoplasia, therefore resulting in a smaller oral cavity. Several studies suggest that children with Down syndrome have smaller tongues than age-matched controls, along with smaller bony confines of the oral cavity. As a result, the relative tongue size is larger in children with Down syndrome than in healthy children [10, 11].

7.2.2.2 Beckwith-Wiedemann Syndrome (BWS)

BWS consists of an organ overgrowth syndrome resulting from methylation of key regulatory genes on chromosome 11p15. Its incidence is of approximately 1:10,000–1:15,000 live births [12–14]. In the head and neck region, BWS features macroglossia in over 95% of the cases and earlobe creases. Macroglossia in children with BWS tends to be marked and impairs chewing and swallowing. In severest cases, it may even compromise breathing [15, 16].

Moreover, it has been shown that parents of children with BWS are commonly concerned about the negative social impact caused by a large protruding tongue, drooling, and impaired intelligibility. Other than the cosmetic appearance, macroglossia tends to be associated with learning difficulties in the general society. BWS children tend to have an age-appropriate intellect [17, 18].

It is important to keep in mind that macroglossia in children with BWS tends to improve with age, and it is therefore important to carefully evaluate the surgical indications on an individual basis [18]. Children with BWS have the risk of severe postoperative hypoglycemia [19].

7.2.2.3 Mucopolysaccharidosis (MPS)

Mucopolysaccharidoses are a group of metabolic diseases due to a functional defect of lysosomal enzymes histologically characterized by accumulation of mucopolysaccharides in the soft tissues. So far, nine main types of clinically heterogeneous MPS have been described. MPS are diagnosed on the basis of clinical examination and by measuring urine mucopolysaccharides [20]. MPS commonly feature orofacial alterations, especially a delay in tooth eruption and macroglossia, as well as hypertrophy of the tonsils and adenoids. Children with MPS often feature severe obstructive apnea.

7.2.2.4 Systemic Amyloidosis

Amyloidosis is a group of systemic disorders characterized by deposition of insoluble amyloid fibers within the extracellular matrix of tissues. The most common form of amyloidosis is light-chain (AL) amyloidosis, resulting from deposition of monoclonal immunoglobulin light chains. Amyloid deposits can be systemic or localized to specific organs. The most commonly involved sites within the head and neck region are the larynx and the tongue, usually within a context of systemic disease [21, 22]. Macroglossia within the context of AL amyloidosis occurs in approximately 40% of cases and can equally occur in other types of amyloidosis [23–25].

7.2.2.5 Congenital Hypothyroidism (CH)

CH is characterized by deficient thyroid hormone production at birth, most commonly secondary to problems with the gland development (dysgenesis or agenesia) or by impaired hormone biosynthesis. CH can be transient or permanent. In the latter, normal thyroid function occurs usually within the first months of life. CH can be diagnosed within a syndromic context, especially in children with Down syndrome [26]. CH has multiple underlying causes. For instance, in a small fraction of cases, mutations in the *TTF-2* lead to thyroid dysgenesis. CH incidence ranges between 1:3000 and 1:4000 cases/living births and is most often diagnosed within the frame of newborn screening [27]. Clinically, CH has a wide spectrum of presentations and may affect multiple organs. However, the most common clinical manifestations are macroglossia, umbilical hernia, and skin alterations [28, 29].

Macroglossia in the context of CH can be present already at birth or more often develop as the child

grows up. Moreover, children with CH often present an impaired primary dentition, vertical facial growth, decrease of length, and skull base angle.

7.2.2.6 Lymphatic Malformation

Lymphatic malformations affect the head and neck region in approximately 75% of the cases. Lymphatic malformations may be present at birth or manifest later in life, usually within the first 2 years of life, due to infection or trauma [30]. Lymphatic malformations are classified as macrocystic (cysts of >2 cm) or microcystic (<2 cm). Lymphatic malformations are a relatively common cause of focal macroglossia [31].

7.2.3 Diagnostic Workflow

Children who present general macroglossia, without an obvious diagnosis, should undergo a full physical examination in order to determine the underlying cause. Having ruled out obvious causes such as Down syndrome or if the diagnosis of BWS is probably specific, molecular testing should be performed (if it is clinically driven). In case of seemingly isolated macroglossia, an abdominal ultrasound could provide arguments for the diagnosis of BWS. In case of pathological findings, molecular testing should be used to confirm the diagnosis.

From a functional perspective, the role of the otolaryngologist as well as of the oral surgeon is essential. As mentioned above, FEES and diagnostic workup to rule out OSAS can be performed. The functional impact will then be classified as mild (no real functional impact), moderate, or severe. This should provide important information when it comes to the decision-making process (Fig. 7.2).

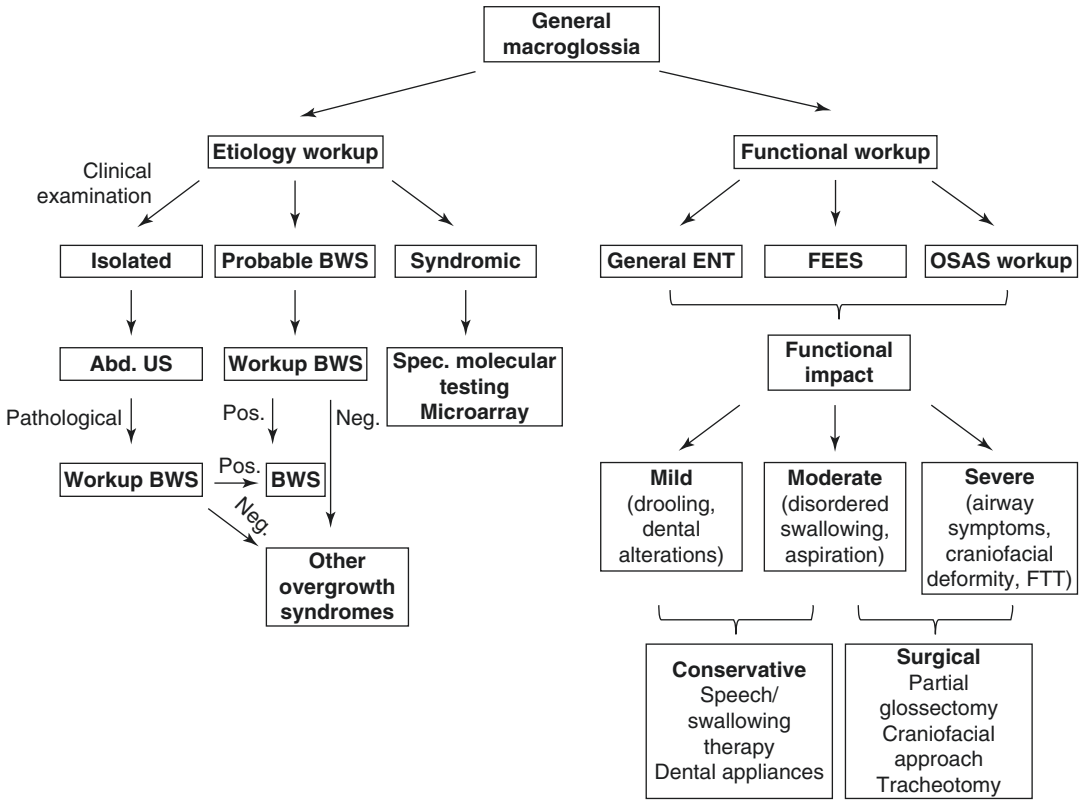

Fig. 7.2 Workflow for diagnostic and therapeutic approach to macroglossia

Cases of focal macroglossia are most often assessed by histological examination and/or imaging.

It must be stressed that interdisciplinary collaboration for the diagnosis and management of children with macroglossia is essential.

7.3 Management

7.3.1 Nonsurgical Management

The indications for medical therapy are restricted to treatable underlying causes of macroglossia such as hypothyroidism or amyloidosis [32].

Several conservative approaches to lymphatic malformations have been proposed, including radiotherapy, sclerotherapy, cryotherapy, and sirolimus or steroid injection [33]. Minimally invasive approaches such as electrocautery, embolization, and ligation are equally possible [33, 34].

Acute tongue swelling (for instance, after trauma on an underlying lymphatic malformation), despite the lack of strong evidence, can be treated conservatively with a raised head, eventually adding steroids and/or antibiotics [35].

Speech and swallowing therapy can be the first approach to children with macroglossia and impaired speech/swallowing. However, in cases of muscular hypertrophy or hyperplasia, there is no proven effective conservative management.

7.3.2 Surgical Management

Indications for the surgical management in children with macroglossia are a matter of ongoing controversy. It is generally accepted that in patients with disordered feeding, breathing and speech are the main candidates for surgery. Moreover, improving teeth malalignment, malocclusion, and cosmetic considerations should also be taken into consideration [3, 36, 37]. Indeed, a nationwide survey of surgery for tongue reduction in children in the USA showed that while children with airway or feeding difficulties tend to undergo surgical approaches within the first year of life, indications are increasingly dominated by occlusal and craniofacial issues within the second year of life [36].

As mentioned above, prior to undertaking any surgical procedure, it should be kept in mind that in mild cases of macroglossia, normal mandibular and midfacial growth may improve the clinical situation, thus avoiding surgery. In cases of airway compromise, tracheotomy may sometimes be needed (Fig. 7.2).

Any surgical approach to the tongue aims at achieving a tongue size as close to normal as possible, namely, a tongue which remains behind the lower dental arch at rest but which can wet the lips on protrusion [38–40]. Particular attention should be paid to tongue mobility, mastication, and swallowing (i.e., oral and pharyngeal phase of swallowing). Other important features are obviously enunciation, taste, and cosmetic considerations.

In this sense knowledge of the surgical anatomy of the tongue is essential. The tongue consists of eight muscles, four intrinsic and four extrinsic. When removing muscle mass, it is essential preserving both the intrinsic and extrinsic functions of the tongue. The neurovascular tongue supplies, namely, the lingual artery and nerve as well as the hypoglossal nerve (CN XII), access the tongue posteriorly and laterally and advance anteriorly without crossing the midline [41].

Forms of focal or localized macroglossia, such as in lymphatic malformations, can be managed by partial resections depending on lesion's location. Resection techniques (Figs. 7.3 and 7.4) include anterior wedge, central ellipse, lateral glossectomy, or submucosal resections

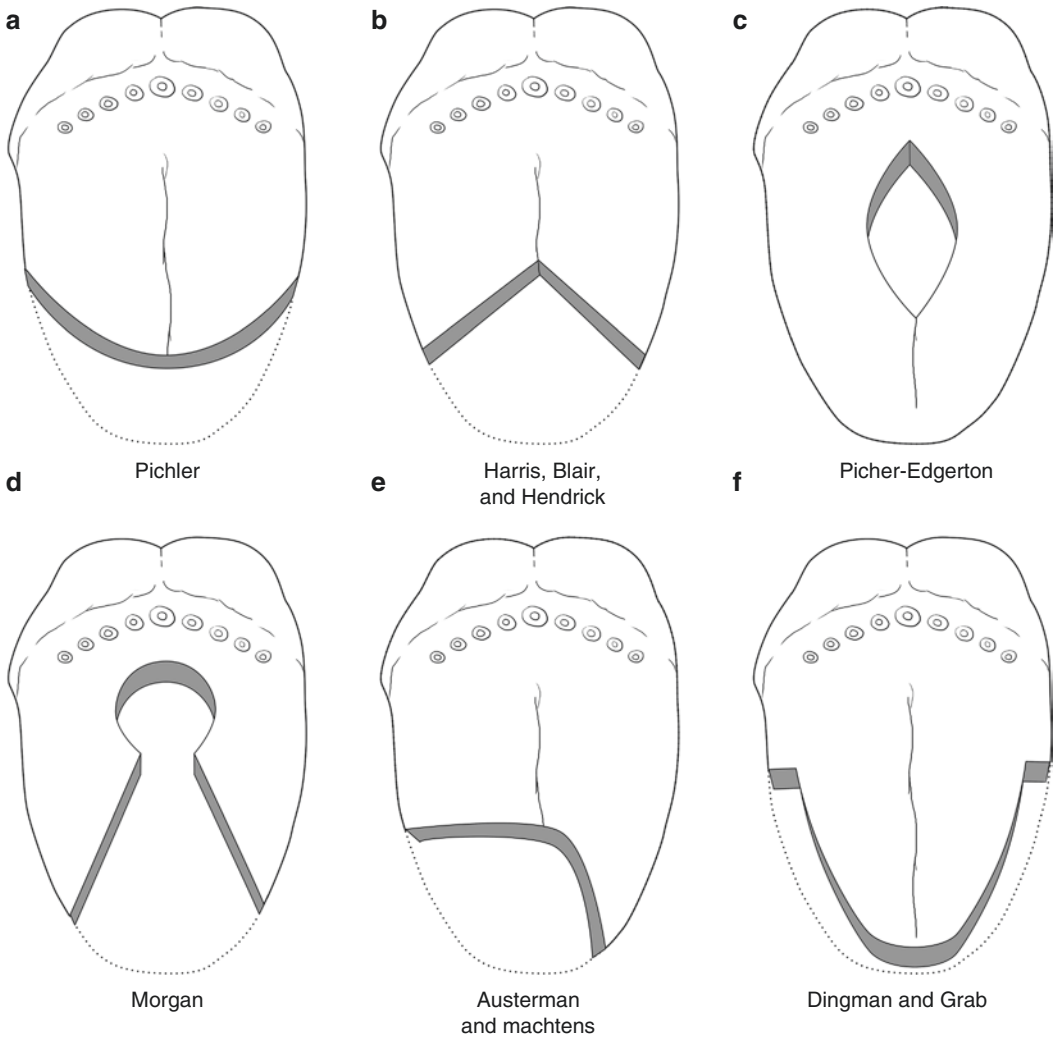

Fig. 7.3 Types of tongue reduction techniques. (**a**) Pichler; (**b**) Harris, Blair, and Hendrick; (**c**) Pichler-Edgerton; (**d**) Morgan; (**e**) Austerman and Machtens; and (**f**) Dingman and Grab

(i.e., mucosa sparing). Some authors advocate for the use of the CO_2 laser for such lesions [42].

As discussed above, the relative macroglossia seen in children with Down syndrome results from the shorter skull base and underdeveloped palate. As such, management approaches should be focused on orthodontic increase of oral volume and forward growth of the jaws early in life. Consequently, every child with Down syndrome and symptomatic "macroglossia" should be evaluated by oral surgeons. Oral appliances may be interesting adjuvants for OSAS in older and compliant patients but have obviously a very limited role in young infants [43].

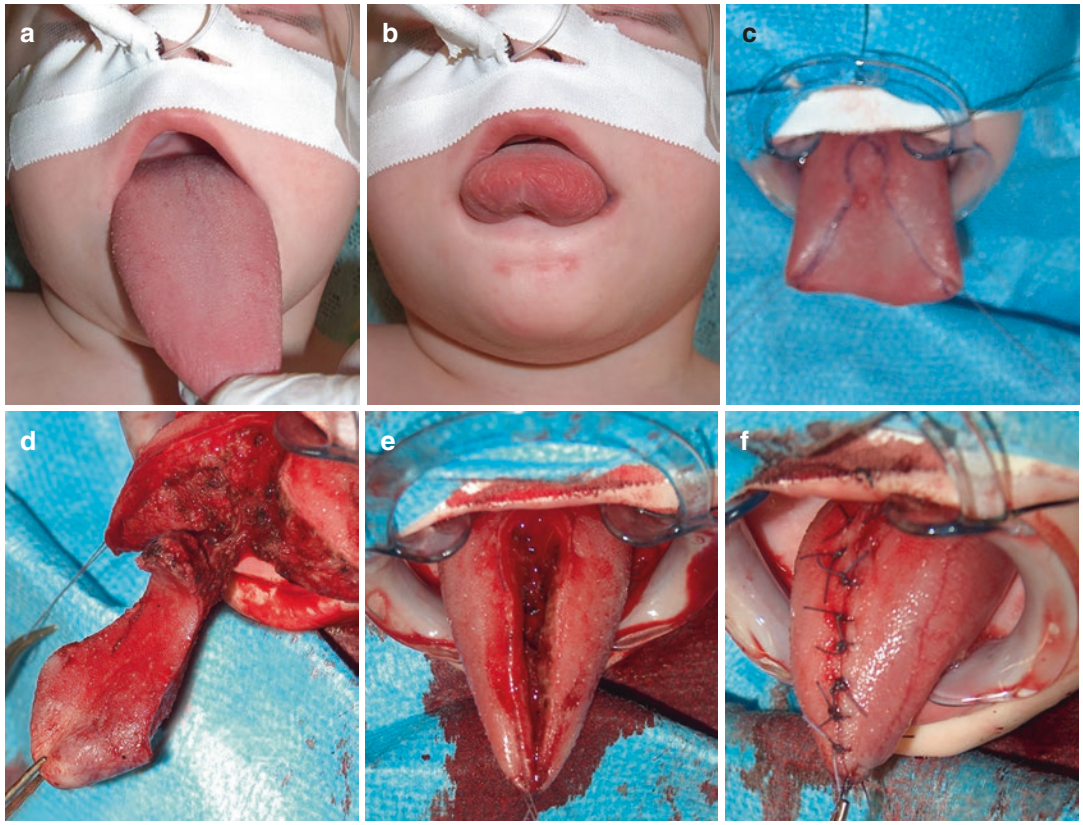

Fig. 7.4 Surgical treatment of macroglossia in an infant with Beckwith-Wiedemann syndrome using the keyhole technique. (**a**, **b**) Macroglossia; (**c**) Tongue incision marked; (**d**, **e**) Reduction of tongue substance; (**f**) Closure of tongue incison. *Pictures with kind permission from Dr. Anthony De Buys Roessingh*

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8 Midline and Lateral Cysts and Sinuses of the Neck

Francesco Fascetti-Leon and Piergiorgio Gamba

8.1 Midline Cervical Swellings

Thyroglossal cyst (TC) is the remnant of the thyroglossal duct. The duct goes from the *foramen cecum* in the dorsal aspect of the tongue to the pyramidal lobe to the thyroid gland. The first description dates back to 1723 when Vater named it *lingual duct* [1–4].

Embryology of the thyroid gland sees the development of a diverticulum moving caudally after the tongue formation between the fourth and seventh week of gestation. The primitive thyroid comes from the fourth and fifth branchial pouch. The descent along the neck occurs at the same time with the formation of hyoid bone from the second branchial arch. The duct loops inferiorly and posteriorly around the bone before continuing its descent anterior to the thyrohyoid membrane. A remnant of the tract may persist as a pyramidal lobe in 50% of people.

The thyroglossal tract does not regress completely in 7% of the adult population.

A cystic lesion may form at any point along this residual tract.

The thyroglossal cyst is the most common cause of midline cervical swelling in childhood accounting for about 70–75% in most reported series. Its clinical presentation is rare in neonatal age. Half of the thyroglossal cysts are diagnosed and treated within 20 years of age.

The cyst normally presents as an incidentally noticed asymptomatic soft mass. A small number will present as an abscess or intermittently draining sinus because of spontaneous rupture due to infection. Surgical incision and drainage can be the temporizing maneuver in these situations.

The physical examination demonstrates a midline swelling, elastic at the palpation and following the hyoid bone during swallow movements.

Ultrasound of the neck can help the diagnosis and is mandatory to confirm a normally formed thyroid gland. The most common differential diagnoses are dermoid cyst, lymph node, isthmic thyroid adenomas, thyroid carcinoma, ectopic thyroid gland, and lipomas (Table 8.1).

Table 8.1 Main diagnosis of cervical swellings

Lateral	Midline
Lymph node	Lymph node
Neurogenic tumors	Dermoid cyst
Vascular tumors	Ectopic salivary glands
Parotid and salivary gland enlargement	Thyroglossal cyst
Branchial cyst	Ectopic thyroid
Soft tissue sarcomas	Ectopic thymus
Teratomas	
Lymphangiomas	

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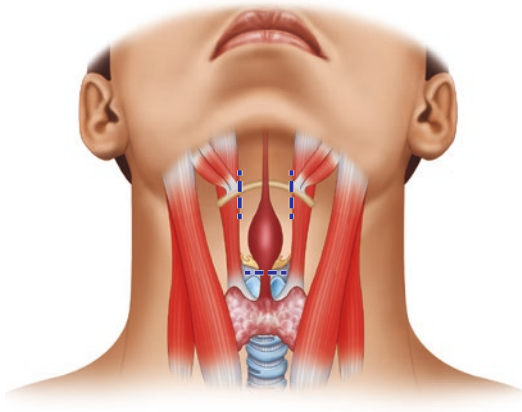

Fig. 8.1 Thyroglossal cyst in common location and margin of resection (interrupted lines) in Sistrunk modified operation

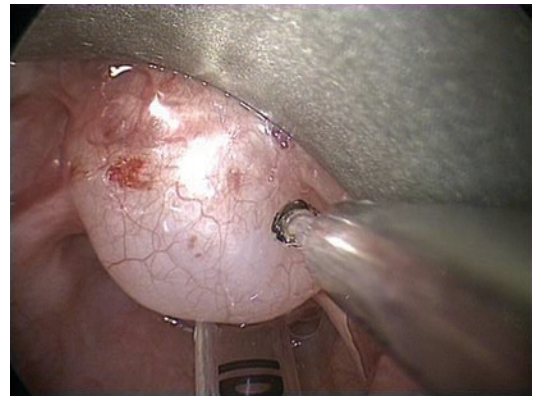

Fig. 8.2 Thyroglossal cyst in neonatal presentation as a cyst at the level of *foramen cecum*. Endoscopic view of the cyst and laser probe applied for marsupialization. Picture kindly given by Dr. Manuelli, ENT Department, Azienda Ospedaliera Università, Padova, Italy

Rarely CT scan or MRI is needed to confirm the diagnosis. Fine needle ago-biopsy can be used to differentiate TC from dermoid or lymph nodes [3, 4].

Risk of infections and tumor degeneration are main indications for surgical excision [5, 6]. The modified Sistrunk technique is the most used approach (Fig. 8.1). It involves the removal of the cyst, the central segment of the hyoid bone, and the tract of muscle tissue ending at the *foramen cecum.* Palpating the base of the tongue from the mouth can help the surgeon to determine the end of dissection [7].

The presentation in the neonatal period is extremely rare. Most of the reported TCs diagnosed at this age are localized in the upper end of the tract. One to eight of the TCs are "lingual" (Fig. 8.2).

In these cases the clinical presentation in newborns differs from that observed in children or adults, as lingual TCs usually cause respiratory distress due to upper airway obstruction. These infants present with stridor. Direct laryngoscopy in the operating room demonstrates a bulging mass at the base of the tongue. CT of the neck is useful for the etiological work-up. Endoscopic treatment by aspirating the cyst content can acutely resolve the symptoms. Endoscopic marsupialization in this case can be the definitive treatment [8–10].

Differential diagnosis with other cervical swellings is reported in Table 8.1.

8.2 Lateral Cysts and Sinus of the Neck

Branchial remnants (cysts and sinuses) represent 24% of congenital neck lesions.

From fourth to eighth gestational week, the mesoderm of the cranial part of the embryos forms branchial arches. The arches are ectoderm-lined externally and endoderm-lined internally. The external layer forms cleft, while the internal pouches. Arches and clefts are four (the fourth is double). First and second arches grow considerably, while third and fourth deep into the embryo wall (Fig. 8.3).

If cleft and pouches fail obliterating, fistulas or cyst communicating with skin and mucosa can occur (Table 8.2). The majority of the lateral fistulas and cysts of the neck are originating from the second branchial arch (90%).

This distribution differs in Asian population, where incidence of third and fourth arch fistulas has been reported in more than 50% of cases.

Lesions are left-sided in more than 90% of patients; bilateral lesions account for 1%.

The opening of the fistula at the level of the skin can indicate its origin and internal ending (Fig. 8.4).

Fistulas of the third and fourth branchial arch are often difficult to distinguish on the base of surgical findings in regard to relationship with laryngeal nerve. They should be treated as a sin-

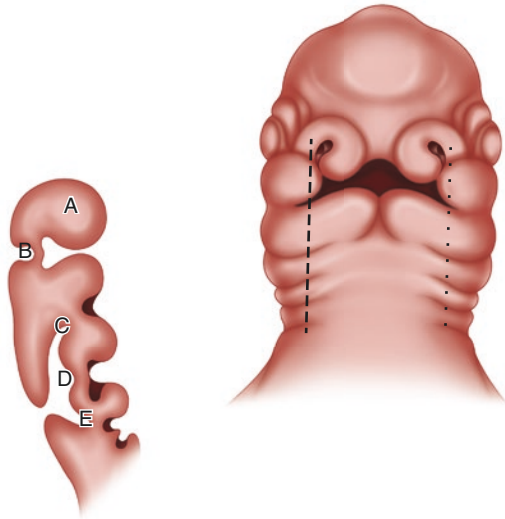

Fig. 8.3 Embryo and branchial structures. (**A**) Mandibular process; (**B**) first branchial clefts; (**C**) second branchial clefts; (**D**) third branchial cleft; (**E**) fourth branchial cleft

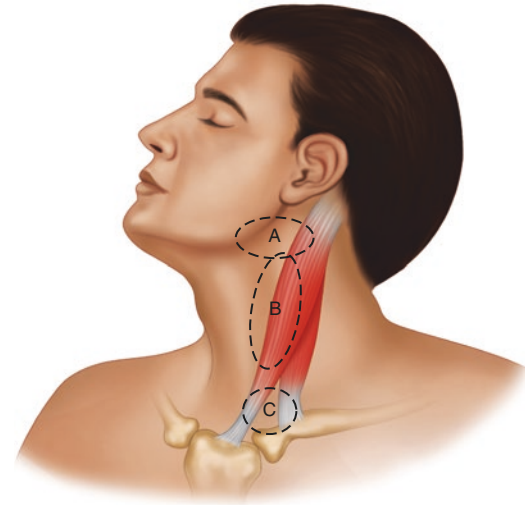

Fig. 8.4 Skin opening helps predicting the origin of the tract. Common sites of branchial fistulas opening. (**A**) first branchial fistula; (**B**) second branchial fistula; (**C**) third to fourth branchial fistula

Table 8.2 Structure originating from the arches and possible fistula openings

First arch	Jaws, cheek, lateral portion of upper lip, helix, tragus, middle ear, eustachian tube, mastoid cells, ear canal, tympanic membrane	Fistula opening into the ear canal and middle ear
Second arch	Antitragus, anthelix, small wing of the hyoid bone, pharynx	Fistula opening into the tonsillar fossa
Third and fourth arche	Wings of the hyoid bone, thymus and the inferior parathyroid (third), superior parathyroid (fourth)	Fistula opening into the pyriform sinus (third at the cranial end, fourth at the apex-caudal end)

gle entity as a "pyriform sinus fistulas." Pyriform sinus fistulas can have a neonatal or childhood presentation. In the first group, the patient may manifest respiratory distress due to large cervical mass compressing or deviating the larynx and trachea, while the second group tends to present with cervical infections.

CT scan or MRI are used to clarify the diagnosis in the majority of cases. Contrasting the fistula prior to scan is rarely helpful due to the edema that closes the lumen.

Fistulectomy is the most used treatment in particular for the first branchial arch remnant. For the second to the fourth arch fistulas, the endoscopic treatment has gained popularity in particular for third and fourth. Endoscopic assistance may be helpful by injecting methylene blue via rigid scope into the pharyngeal fistula opening.

Large masses often require cervical open access for excision. For fistulas of the pyriform sinus, endoscopic CO_2 laser cauterization has been proposed with acceptable relapse rate. The endoscopic treatment can be repeated in those cases. Endoscopic assessment is advisable in all cases of relapse after excision of fistula tract from the lateral cervical skin.

Transitory facial paralysis occurs after excision of first arch fistulas in 6% of cases. Transient recurrent laryngeal nerve injury has been reported with the same rate in cases of third and fourth arch remnant [11–14].

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Part III

Chest

Congenital Thoracic Deformities

9

Giovanna Riccipetitoni, Sara Costanzo, and Francesca Destro

9.1 Introduction and Classification

Congenital deformities of the chest wall or chest wall malformations (CWMs) comprise a complex spectrum of anomalies which range from those that do not impact on the health and quality of life of the patient to those which are life-threatening [1–3].

CWM occurs when there is anomalous skeletal development and/or formation of the thoracic cavity. The formation of the thoracic cavity occurs after the intraembryonic cavity has formed (around the 4th week of gestation). At the beginning of the 5th week of gestation, the lung buds rapidly grow caudally and laterally at the pericardioperitoneal canals inducing development of the thoracic wall and pleuropericardial membranes. The sternum also develops during the 6th week of gestation. The complex development of the sternum can be simplified into three stages: formation, chondrification, and ossification [4]. Formation begins with the condensed mesenchyme where paired parallel mesenchymal bands migrate from the lateral plates and fuse in the midline by the 10th week of gestation. Chondrification begins immediately once the sternal plates fuse. Ossification begins approximately during the 6th month of gestation. It occurs in isolated centers starting in the manubrium, subsequently in the middle body during the 7th month, and finally in the lower body during the first postnatal year. The xiphoid process will undergo ossification between the 5th and 18th years of life, and the multiple ossification centers do not coalesce until after puberty.

Thoracic deformities may also be acquired, established postnatally as secondary to other conditions that disrupt the thoracic wall. Acquired chest wall deformities typically follow prior chest surgery (e.g., costal fusions caused by thoracotomies carried out in any period of childhood, sternal diastasis secondary to an infection of a sternotomy wound) or a posterolateral diaphragmatic hernia repair (Bochdalek) or spine deformities (i.e., kyphoscoliosis, hemivertebrae, wedge vertebrae, defects of vertebral segmentation). Secondary CWM may also follow fetal procedures carried out for congenital pulmonary malformations, such as thoracentesis or thoracoamniotic shunt [5].

Chest wall can be markedly deformed, by various degrees of anteroposterior flattening, in patients affected by bronchopulmonary dysplasia (BPD), a common complication of preterm birth (Fig. 9.1). The reason of this phenomenon is not completely explained, although the combination of many factors, such as the long-standing lung function abnormalities, the presence of

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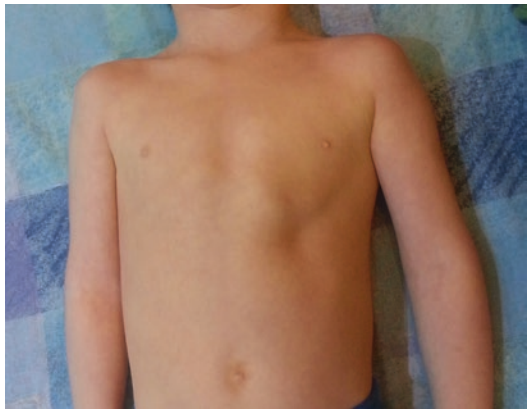

Fig. 9.1 Unilateral costal deformity in an ex-preterm child with bronchopulmonary dysplasia

demineralized and sometimes fractured ribs, and chronic sternal retraction, which is common in respiratory distress of any cause in infants, may contribute to chest flattening [6, 7].

A straightforward and complete classification of CWM was proposed by Eduardo Acastello in 2006, distinguishing CWM into five types, according to the origin of the anomaly [8, 9] (Table 9.1):

1. Cartilaginous
2. Costal
3. Chondrocostal
4. Sternal
5. Clavicle-scapular

It is difficult to accurately determine the overall incidence of CWM. This is due to multiple factors, among which their broad spectrum and the poor record of some mild deformities which do not even come to the medical attention. However, the specific incidence of the majority of them is clearly established in the published literature and will be detailed in the subsequent analysis of each malformation. Type I deformities are the most frequent, comprising more than 90% of the entire spectrum.

CWMs are rarely diagnosed prenatally. Three-dimensional ultrasound offers a way to visualize fetal skeletal dysplasias such as Jeune syndrome. Other CWM can be indirectly suspected on the basis of other anomalies detected, for example, the presence of hypoplasia or aplasia of one forearm or one hand in Poland's syndrome or the visualization of an ectopic heart in sternal anomalies [10–12].

Table 9.1 Acastello classification of chest wall malformations

Type I	Cartilaginous anomalies	Pectus excavatum
		Pectus carinatum
Type II	Costal anomalies	Simple
		Complex
		Syndromic (always complex)
Type III	Chondrocostal anomalies	Poland syndrome
		Thoracopagus conjoined twins
Type IV	Sternal anomalies	Sternal cleft
Type V	Clavicle-scapular anomalies	Clavicular
		Scapular
		Combined

A detailed evaluation is required for each CWM patient that comes to the medical attention [13]. It should start with an interrogation about personal and family history, since familial cases can be detected in up to 30% of patients. Great relevance has to be paid to the presence of associated malformations, which can affect vital organs (e.g., heart and lungs) and might allow to diagnose a syndromic form (Marfan, prune belly, etc.). The moment of detection, its evolution, and possible related symptoms must be always documented.

The physical examination of the patient has to be accurate. Inspection in the different positions (standing, in front and lateral view, in dorsal decubitus) will provide the most relevant data, in order to classify the type of deformity, its symmetry or asymmetry, the degree of alteration (mild, moderate, or severe), functional compromise, secondary deformities (kyphosis, scoliosis), and postural defects (scoliotic attitude).

The determination of thoracic measurements has a fundamental value in standardizing medical observations. The thoracic measurements to be evaluated are:

1. Thoracic circumference: measured during expiration on a line that crosses the nipples on the anterior aspect of the thorax and just below the scapular angles in the posterior region.

2. Intermamillary distance: it measures the distance between the two nipples and the distance from the half-sternal line to each nipple separately and serves to assess the symmetry or asymmetry of the chest.
3. Thoracic index: it is the ratio between the anteroposterior and the lateral diameters of the thorax (measured at the level of the nipples) multiplied by 100.

Imaging studies are necessary to complete the diagnostic work-up [14]. Chest radiograph in double view (front and profile) can provide basic information about the type and the degree of alteration and changes produced; it can identify, for example, the form of dysmorphic ribs or alterations in the shape of the thoracic cage; it is also useful for long-term postoperative follow-up. Second-level imaging techniques, such as computed tomography with or without three-dimensional reconstruction or magnetic resonance imaging, are usually indicated to better define the anatomy of the malformation.

The level of cardiopulmonary impact of each malformation is variable and depends on the particular characteristics of each pathology. Every patient with a CWM should undergo cardiac evaluation, comprising at least electrocardiographic exam and cardiac ultrasound; the specialist will determine the following steps, after evaluating the presence of congenital heart diseases and their possible functional repercussion.

A pulmonology evaluation has to be always requested, although a proper respiratory functional assessment is usually not feasible before 3 years of age.

The orthopedic evaluation completes the assessment of CWM children, given the high incidence of other skeletal anomalies, such as congenital scoliosis and vertebral deformities, in this group of patients.

With regard to treatment, not all CW malformations require surgical correction. Each pathology presents its particular indications to treatment, and it is fundamental to identify the right timing for it, to achieve the best esthetic and functional results [15].

9.2 Pectus Excavatum

Pectus excavatum (PE), also termed funnel chest, is characterized by the presence of a variably deep sternal depression associated with a malformation of the lowest chondrosternal joints. PE is the most frequent thoracic malformation, with an incidence of 1/100–1/1000 live births, and accounts for around the 90% of all CWMs. It occurs more frequently in males than females by a 5:1 to a 3:1 ratio. About 95% of cases occur in Caucasian patients, whereas Asian, African American, and Hispanic patients represent only the minority of PE cases. PE is most often congenital and noted in the first year of life (86%) (Figs. 9.2 and 9.3), while in the remaining cases, it appears later during development; in this last group of patients, there is a frequent association with malformations of the muscular connective tissue, such as Marfan and Ehlers-Danlos syndrome. Cases of spontaneous resolution during growth are very uncommon, and the more typical course is worsening of the depression, either gradual or more dramatic during phases of rapid vertical growth and puberty.

9.2.1 Etiopathogenesis

The etiology of PE is not clear, and many hypotheses have been proposed. The overgrowth of costal cartilages could be the pathogenetic mechanism leading to the development of PE. Another mechanism proposed is an abnormal tethering of the sternum to the diaphragm posteriorly. This theory is supported by a 33% incidence of acquired PE in patients after repair of posterolateral congenital diaphragmatic hernias (Bochdalek). Collagen type II disorders have been demonstrated in the costal cartilages in PE, as well as overexpression or downregulations of some genes playing a role in the metabolism of cartilage and connective tissues, as collagen genes, matrix metalloproteinases, tumor necrosis factor-alpha, and filamin [16, 17]. Although there is no confirmed chromosomal abnormality, there is a genetic predisposition supported by a familial recurrence in up to 40% of the cases [18]; more

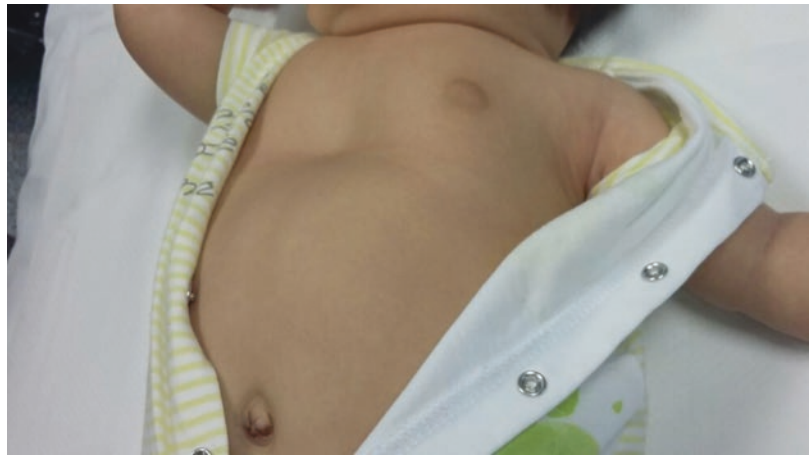

Fig. 9.2 Neonate with pectus excavatum [*Courtesy by Dr. Michele Torre, G. Gaslini Children's Hospital, Genoa, Italy*]

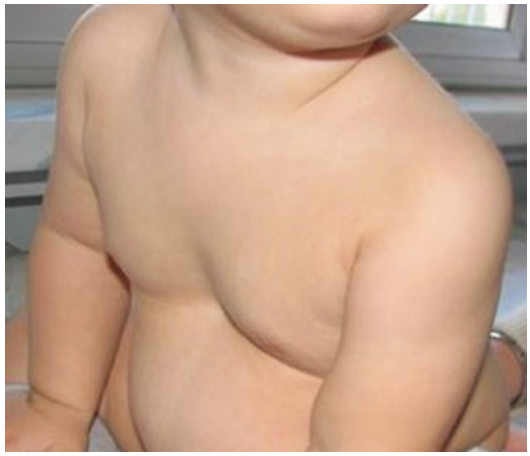

Fig. 9.3 Infant with pectus excavatum [*Courtesy by Dr. Michele Torre, G. Gaslini Children's Hospital, Genoa, Italy*]

rarely we can observe the presence of other CWM (such as PC) in a PE family. Four different possible patterns of inheritance have been suggested: autosomal dominant, autosomal recessive, X-linked recessive, and complex.

9.2.2 Pathophysiology

In cases of severe malformations, there can be physiological repercussions. Many studies have tried to elucidate the implications of PE on the respiratory and cardiac function [19]. Thoracic CT and MRI scans often demonstrate a leftward displacement of the heart and a compression of the right ventricle or atrium, deformed by the rotation and posterior displacement of the sternum, with different degrees of dysfunction on the echocardiogram. Mitral valve prolapse and mitral valve regurgitation are frequent, due to the deformation of the mitral valve annulus [20].

Pulmonary function tests (PFT) can be altered, more on stress conditions than on rest [21]. The most common pattern of PE is a restrictive one, but also obstructive or mixed patterns are not uncommon. A possible explanation for ease of fatigability in PE patients can be a less efficient mechanism of breathing [22, 23]. Using motion analysis technology, PE patients were determined to have significantly impaired chest wall motion at the area of the pectus defect and increased abdominal contributions to respiratory activity [24]. Other studies support the theory that exercise capacity is limited as a result of reduced filling of the right heart by the compressive effects of PE.

PE can be observed in some neonates with congenital diaphragmatic hernia or children with respiratory obstruction (bronchomalacia, hypertrophic tonsils). These particular cases of PE are the only ones that can improve during infancy. PE is otherwise usually mild at birth and progresses over the years, especially during preadolescent and adolescent age.

9.2.3 Clinical Evaluation

A complete history has to be collected, including questions regarding onset and progression of chest wall deformity and investigating the possible presence of symptoms, associated conditions, and familial cases. Most young children with PE are asymptomatic, but, as they become more active, particularly in their pre- and early teenage years, exercise intolerance and lack of endurance can appear.

The morphology of the PE should be described in detail [25, 26]. The deformity may be described as symmetric or asymmetric; asymmetry is often associated with sternal rotation that has to be underlined too.

PE can be morphologically classified as follows:

- Grand Canyon: It is a severe form of PE, with a deep long canal in the sternum, which is usually extremely rotated. This type is often asymmetric.
- Punch or cup shape: Localized deformity, usually on the inferior part of the sternum. It is more often symmetric. It has been observed that the punch type is the most common variant of PE (67%), more commonly symmetrical (80%), to the right of the midline (80%), and involving the lower sternum (99%).
- Saucer shape: It is a diffuse depression involving the complete anterior chest, where the thorax is usually quite flat. It can be symmetric or asymmetric.
- Transversal PE: The depression is transversal and below the sternum.
- Eccentric PE: The sternal depression is eccentric to the midline. It is the highest degree of asymmetric PE.
- PE with flaring chest: The lower ribs are flaring at each side of the depressed sternum.
- PE-PC: It is a combined malformation with a sunken chest and unilateral or bilateral protrusion of the cartilages beside the sternum edge.
- Superior PE: Very rare PE, localized in the upper part of the sternum; lower sternum is normal.
- Photographic documentation with different angles (frontal, left and right lateral, left and right oblique) is very helpful for the follow-up of these patients.

A thorough chest and cardiac physical exam completes the first part of the evaluation of these children [27].

9.2.4 Tests and Imaging

CT or MRI of the chest, PFT, and cardiac evaluation including electrocardiogram and echocardiogram are a routine part of the evaluation for a patient with PE [28].

There are several numeric indexes, usually calculated on CT and MRI, that have been developed over time to help quantify the severity of PE [29–31]. The most relevant are:

- Haller index (HI): described in 1987 by J. Haller et al., [32] it is calculated dividing the transverse maximum diameter of the rib cage by the anteroposterior diameter at the deepest point of the deformity. The cutoff point for PE patients is >3.25.
- Sternal depression index (SDI): it is the ratio between the maximal internal sagittal diameter of the left side of the chest and the minimal distance between the anterior surface of the vertebral column and the posterior border of the deepest portion of the sternum. An SDI of <2.4 is associated with mild sternal deformity, moderate sterna deformity is associated with an SDI of 2.4–2.9, and an SDI of >2.9 is conclusive of severe sternal deformity.
- Asymmetry index (AI): it is the ratio between the anteroposterior diameter of the right and the left part of the rib cage, multiplied by 100. Chest wall is considered asymmetric if AI is <−0.05 or >0.05.
- Others: correction index (CI), eccentricity index (EI), and others.

PE causes displacement of the heart into the left hemithorax. In order to measure the extent of cardiac compression, specific indexes, calculated

on CT or MRI, have been calculated, such as the cardiac compression index (CCI) and the cardiac asymmetry index (CAI).

9.2.5 Management

The optimal age for repair is 10–14 years old because at this time the rib cage is more malleable, thus allowing for rapid recovery, better results, and a lower recurrence rate as the bar remains in place during musculoskeletal maturation [33, 34]. Fixing PE in the first years of life is probably unnecessary, and it could carry the risk of relapse or postoperative severe complications as acquired Jeune syndrome [35].

9.3 Pectus Carinatum

Pectus carinatum (PC) is a protrusion of the sternum and chondrocostal joints (Fig. 9.4). It is the second most common CWM, and its incidence is estimated to be five times less frequent than PE in North America, although in other countries, it is much more common, for example, in Argentina, where it has been reported to comprise 55% of chest wall deformities. There is a strong male predominance (4:1). Most cases of PC are sporadic; however, familial incidence has been reported in about 26% of cases; in some families, it is possible to observe both PC and PE cases.

9.3.1 Etiopathogenesis

The etiology is unknown, although the origin of PC is considered to be similar to that of PE, related to abnormalities of connective tissue development, giving its frequent association with other skeletal abnormalities such as scoliosis (12%), and some genetic predisposition.

PC can be either an isolated condition or part of a syndrome (i.e., Poland syndrome) or connective tissue disorder.

9.3.2 Classification

PC can be classified into the following types:

– Type 1, inferior or chondrogladiolar: It is the most frequent type; the protrusion is located in the inferior sternum, with maximum prominence at the sterno-xiphoidal junction, which can be very noticeable (“pyramidal” or “keel chest”); it

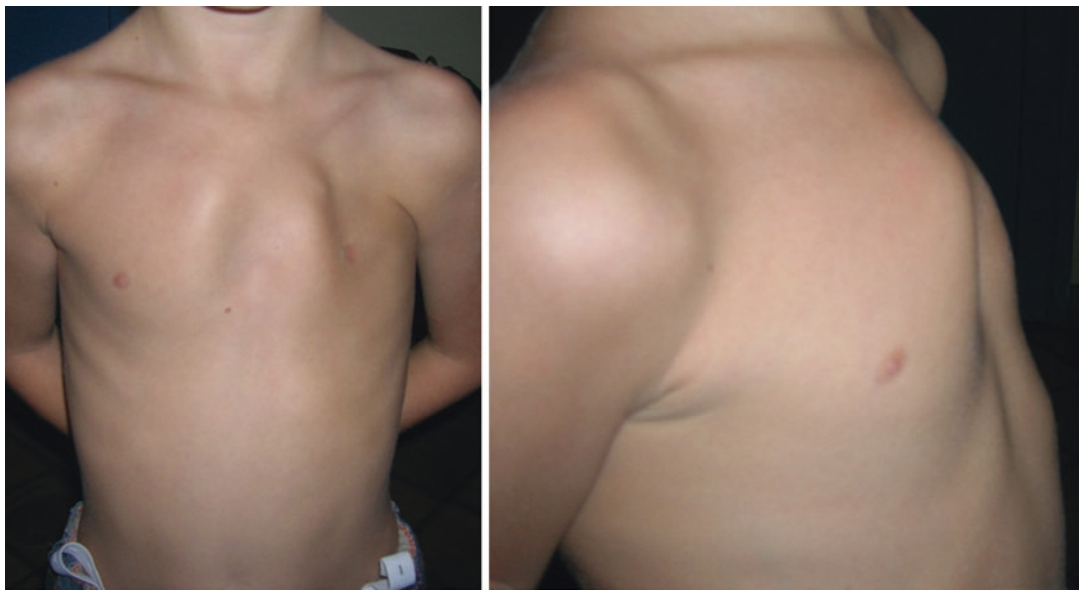

Fig. 9.4 Asymmetric pectus carinatum in frontal and lateral view

is usually symmetric. This type of PC can be associated with lateral depressions of the ribs.
– Type 2, superior or chondromanubrial: The protrusion is localized above the intermammary line. A variant of this form is called *Currarino-Silverman syndrome* or pouter pigeon breast, characterized by a high symmetric carinatum chest deformity with a short thick sternum with a depression in the lower third [36]. Its aspect is of a superior PC with an inferior PE, and the sternum is typically S-shaped on a lateral view.

A rarer form called lateral PC has also been described: always asymmetric by definition, it consists in the protrusion of some costal cartilages, besides the chondrosternal joints, on one side, with often concomitant rotation of the sternum (30–60–90°) toward the opposite side.

9.3.3 Clinical Presentation and Imaging

In contrast to PE, PC usually appears later in life. Only about one-sixth of the patients show a carinate deformity within the first year of life, while in almost half of them, PC is diagnosed noted during prepuberty or puberty. The deformity, which may be mild at birth, often worsens rapidly during the growth spurt.

Most PC patients are asymptomatic, although those affected by a severe anomaly may complain of some degree of thoracic pain. Cardiac and pulmonary functions are usually less affected than in PE. Only the variant "pouter pigeon breast" can be associated with congenital heart disease in 18% of cases.

Imaging studies include posteroanterior and lateral chest radiographs, although CT scan remains the gold standard radiologic evaluation for PC. Some radiological indexes, measurable on CT scan, have been proposed, but in clinical practice, they are less used than those calculated for PE.

9.3.4 Management

PC is usually not treated during the first years of life. Its management, either conservative through an orthotic brace system [37, 38] or surgical with different techniques [39], is deferred until at least preschool age or early teenage years, respectively.

9.4 Costal Anomalies

Costal anomalies represent the 3.2% of thoracic wall malformations. They are divided into simple and complex.

Simple malformations involve one or two ribs, up to three nonconsecutive ones, with isolated malformations. The effects on the thoracic cage are limited.

Complex malformations compromise large sections of thorax affecting the respiratory dynamic.

Ulterior division is shown in Table 9.2.

Table 9.2 Classification and frequency of costal anomalies

Costal anomalies	Simple	Unique (45.3%)	Agenesis Hypoplasia Supernumerary Bifid Fusion Dysmorphic
		Double (2.6%)	
		Combined (10.7%)	
	Complex	Strange (5.5%)	
		Fusions (29.4%)	
		Syndromic (6.5%)	Jeune Jarcho-Levin Cerebrocostomandibular Others

9.4.1 Simple Costal Anomalies

- *Agenesis and costal hypoplasia*: They are rare isolated malformations or, more frequently, part of a syndrome (Poland, trisomy 13, cerebrocostomandibular). Patients are asymptomatic, and the management is conservative with radiological and clinical evaluation during growth.
- *Supernumerary cost*: It identifies the presence of more than 24 ribs. The extra rib usually corresponds to the cervical vertebra, and it is rudimentary, unilateral, or bilateral. It is uncommon and can be part of a syndrome. Most patients (70%) are asymptomatic. In symptomatic cases, signs and symptoms do not depend on cost size and can be related to vascular or nervous involvement (pain for arterial spasms and paresthesias). The physical examination shows a tumor in the supraclavicular gap. The thorax X-ray confirms the diagnosis. Asymptomatic patients do not require treatments. Surgery is performed in case of symptoms and consists of resection of the extra rib.
- *Bifid cost*: Bifurcation of the distal end of a rib. It is uncommon and usually isolated. In most cases it is a radiological finding. Sometimes there is a tumor of the costal wall ad pain in the deformed area caused by cartilaginous deformity. Thorax X-ray permits the diagnosis. Surgery is reserved for symptomatic patients (pain) or for esthetic reasons, and it consists of excision of the bifid cost together with the altered cartilage.
- *Costal fusion*: It is characterized by the union of two ribs and it is usually an incidental finding. Thorax X-ray shows the ribs involved and the level of the fusion. When necessary the evaluation is completed with CT (Fig. 9.5). In the evaluation of patients, it is important to detect the presence of malformations, the vertebral fractures, and the degree of scoliosis. The need for surgery is established on the base of the curvature progression.
- *Dysmorphic cost*: Alteration of the costal morphology with widening of the anterior end of the costal arch, a spur, or an irregularity of the entire costal length. Patients present with a small tumor on the anterior or lateral thoracic wall with localized pain (Fig. 9.5).

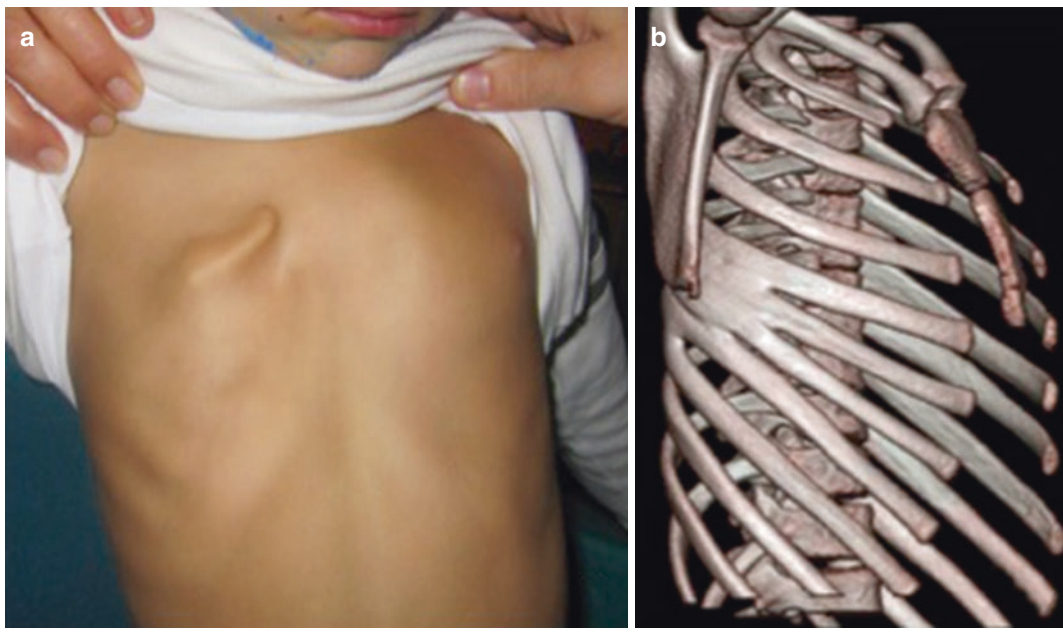

Fig. 9.5 Example of costal anomalies: patient with a dysmorphic cost (**a**) and 3D CT reconstruction of costal fusions (**b**) [*Courtesy by Dr. Michele Torre, G. Gaslini Children's Hospital, Genoa, Italy*]

9.4.2 Double Costal Anomalies

Double malformations include two unique malformations homolateral or contralateral. In case of agenesis of two ribs, there is a paradoxical mechanism during breathing with symptoms onset. Clinical evaluation together with thorax X-ray during growth spur is important during follow-up. Surgery consists of rib spit and placement of autologous costal graft/prosthetic mesh and muscular flap.

9.4.3 Complex Costal Anomalies

– *Strange malformations*: Malformations that do not follow a specific pattern are defined strange. They are extremely rare and each patient corresponds to a unique case. We can have costal hypoplasia, fusion, or intercostal space widening with lung hernia. The right side is affected more than the left one. Hydrocephalus and myelomeningocele are identified in 55% of cases. Clinical manifestations depend on the extent of the deformity. Children with severe deformity change their anatomical thoracic configuration with risk of constrictive thoracic disease. The involvement of cardiopulmonary function is always possible. Neonates may have respiratory distress requiring mechanical ventilation. After this period, symptoms arise during breast-feeding, and they are related to the presence of pulmonary sequelae (dysplasia). A small number of patients are asymptomatic, but the thorax is always abnormal. Thorax X-ray identifies the degree of parietal alteration. The spine should be investigated, as well. When required, surgery consists of costal block removal.
– *Costal fusion*: Costal fusion is a congenital malformation characterized by the union of three or more ribs in any spinal segment. It may cause varying degrees of deformity on the chest wall or spine. It is rare and associated to vertebral anomalies in 90% of cases. The thoracic deformity may be evident soon after birth. Restrictive respiratory symptoms are typical of older patients. Thorax X-ray permits to identify location and features of the malformation. It is important to evaluate the spine praecox. Surgery is indicated in case of severe scoliosis or other deformities.

9.4.4 Syndromic Costal Anomalies

In this group the costal anomaly is part of a specific syndrome.

9.4.4.1 Jeune Syndrome

It is also known as asphyxiating thoracic dystrophy, a congenital malformation (autosomal recessive inheritance) with small thorax, short limbs, and pelvic dysplasia. Fortunately many children do not develop respiratory asphyxia and survive the neonatal period.

The incidence is 1/100.000–130.000 without sexual preponderance.

Patients present with narrow bell-shaped thorax and prominent abdomen (Fig. 9.6); ribs are short, and costochondral junctions do not pass the anterior axillary lines. Costal cartilages have a rosary shape and clavicles are fix and horizontals. This reduces the respiratory movements and leads to an abdominal/diaphragmatic respiration. Hypoventilation causes hypoxia and respiratory distress. The severity is variable and sometimes it causes neonatal demise.

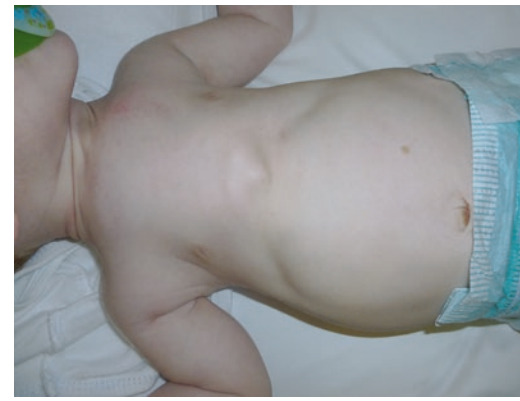

Fig. 9.6 Neonate with Jeune syndrome [*Courtesy by Dr. Michele Torre, G. Gaslini Children's Hospital, Genoa, Italy*]

Renal and hepatic alterations are common: progressive nephropathy from the second year of age due to glomerular sclerosis or tubular cystic dysplasia and hepatic fibrosis or cirrhosis for ductal anomalies. Pancreatic cysts are rare. The pelvis is small and radiological abnormalities tend to decrease during growth. In neonates there is a praecox ossification of femoral head and other bones resulting in growth retardation. Congenital heart disease, retinal degeneration, and dolichocephaly are less frequent associations.

Two forms are identified based on the clinical picture.

Type I, Major Form (70%)

The major form includes patients with small, rigid, and narrow thorax and abdominal respiration. In these cases, respiratory symptoms have early onset (severe neonatal distress), and patients require mechanical ventilation soon after birth. Mortality is high in the first year of age. Together with ventilator support, patients need surgery to enlarge the thorax increasing the lung capacity. The correction should be praecox to avoid long mechanical support and improve survival. Primary and stage repairs have been described starting from the first months of life. Among the surgical options, there is the median sternotomy with bone graft or prosthetic patch interposition. The aim is to enlarge the thoracic cavity with median sternotomy and to keep the two sternal segments open with different rigid material. The sternotomy is performed in the neonatal period and the defect is closed with a prosthetic patch. Once patients are stable (infancy), the patch is replaced by homologous grafts. Grafts include methyl methacrylate and bone grafts. Titanium patches have been used for staged procedures. Vertical expandable titanium rib (VEPTR) improves chest wall movements: they are attached to the ribs and to transverse spinal processes and progressively lengthened. The procedure may lead to scoliosis and patients require long-term follow-up (Fig. 9.7).

Despite the immediate relief from symptoms, surgery doesn't seem to affect long-term results and mortality. The only improvement is prenatal ultrasound diagnosis that allows for consultation and leads to an increment of pregnancy termination.

Type II, Minor Form (30%)

In these patients costal malformations are intermediate and symptoms are limited or absent. Radiological abnormalities tend to reduce over time. Physical examination is sufficient to suspect the syndrome. Thorax X-ray shows the small and narrow thoracic cage with bell-shaped configuration. Ribs and clavicles are horizontals. The

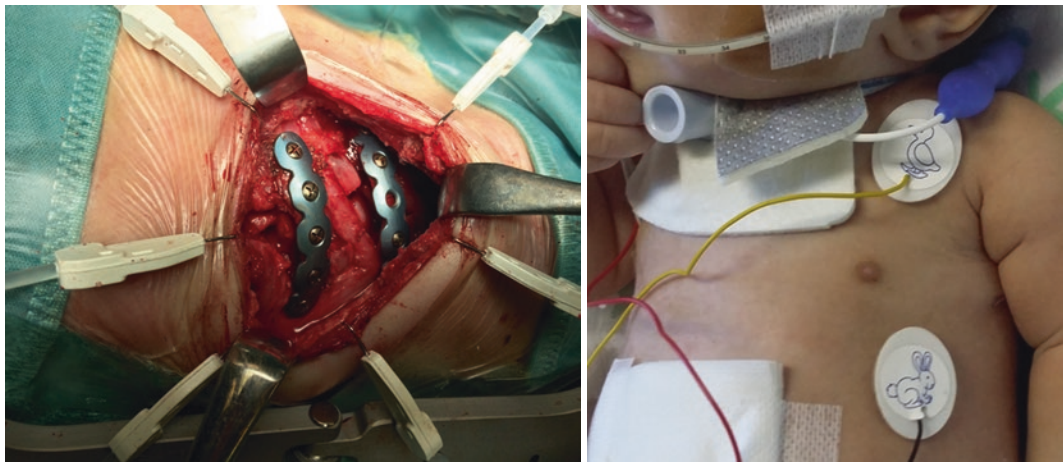

Fig. 9.7 Jeune syndrome: intra- and postoperative pictures [*Courtesy by Dr. Michele Torre, G. Gaslini Children's Hospital, Genoa, Italy*]

latter are shaped as bicycle handlebars and are high. These alterations are well detected on CT scans with 3D reconstruction. Pelvis X-rays show small pelvis and irregular acetabular roof (trident). Iliac wings are small and squared.

Some authors associate the measure of the thoracic perimeter with prognosis: a perimeter <28 cm correlates with bad prognosis. The measure of the thoracic cage might be responsible for pulmonary hypoplasia detected in some patients. The clinical spectrum runs from mild to severe forms where the rigidity of the chest does not allow proper expansion.

Type 2 form does not always require treatments being patients asymptomatic or mildly affected.

9.4.4.2 Jarcho-Levin Syndrome

It is called costovertebral dysplasia or hemivertebral syndrome, and it is characterized by a short thorax with vertebral and costal abnormalities. The inheritance is autosomal recessive with mild male preponderance.

The hemivertebra typically involves all or almost all the spine with fusion or absent vertebral bodies. Vertebral anomalies deform the thoracic cage and lead the posterior costal arches to be fused at the costovertebral junction. Shape and number of ribs are abnormal. The effect is a short and crab-shaped thorax.

Neonates have respiratory distress that progress into respiratory failure, and most of them die within the first year of age. The association with congenital heart disease and urological abnormalities (hydronephrosis, ureteral and urethral stenosis) is frequent. Rarely there are gastrointestinal malformations. Thorax X-ray shows the crab shape due to the short dorsolumbar column. There hasn't been any attempt of surgical correction to date.

9.4.4.3 Cerebrocostomandibular Syndrome

This syndrome is also called the one with segmented rib. It is rare and characterized by microcephaly, micrognathia, and costal anomalies. The type of inheritance has not been defined yet, but it is responsible for the altered cartilage development. There are only costal vestiges. The typical costal anomaly is the aplastic segment at the posterior costal arch with fibrosis, muscular elements, and calcifications. The extension of the costal defect is variable as it is variable to the number of affected ribs. The thorax is short and flat, and the deformity worsens the glossoptosis and the tracheal cartilage hypoplasia. The effect is a severe respiratory distress. Forty percent of patients die within the first months of life. Between the survivors, 50% have moderate mental retardation. Described associations are vertebral malformations, scoliosis, feet deformities, and hip dislocation.

9.4.4.4 Others

Rare type II congenital thoracic deformities include deformities that have been described but do not fit in any standard classification. They have different features and require personalized treatment and management.

9.5 Poland Syndrome

Named after Sir Alfred Poland who described it in 1841 [40], Poland syndrome (PS) is a rare congenital anomaly, occurring in 1:20,000–30,000 live births. Its main diagnostic criterion is the hypoplasia or agenesis of the pectoralis major muscle, although its phenotype can be extremely variable and frequently combined with other ipsilateral abnormalities of the chest wall, breast, and upper limb. PS is almost always unilateral, right-sided in two-thirds of cases; very rare bilateral cases have been described [41]. There is a male preponderance with a 2:1 male to female ratio. It is mainly sporadic, with around 4% of familial cases described [42].

9.5.1 Etiopathogenesis

The etiology of PS is unknown. The most accredited hypothesis regards a possible interruption of the vascular supply in subclavian and vertebral arteries during embryonic life, determined by both genetic and environmental factors, leading

to different malformations of the corresponding districts [43]. The occurrence of familial cases has raised the hypothesis of a possible genetic etiology with different inheritance patterns, although a specific gene has not been identified yet [44].

9.5.2 Clinical Presentation and Assessment

PS phenotype is extremely variable. Partial or total deficit of the pectoralis major muscle is present in 100% of patients, and the thoracic defect is usually evident at birth (Fig. 9.8a) [10].

Other clinical features are [45]:

- Anomalies of other chest wall muscles: Pectoralis minor results to be affected in more than 90% of cases in some series; less frequently an involvement of serratus anterior, latissimus dorsi, trapezius muscle, rhomboid muscle, and rectus abdominis can also be detected.
- Chest wall anomalies: Rib dysmorphisms, hypoplasia, and agenesis and anomalies like a PE or PC or both can occur; in case of rib agenesis, particularly if multiple (most frequently the third and the fourth ribs), lung herniation and paradoxical respiratory movements can be present.
- Breast hypoplasia or aplasia: Breast involvement regards the majority of PS patients, particularly significant in females, and ranges

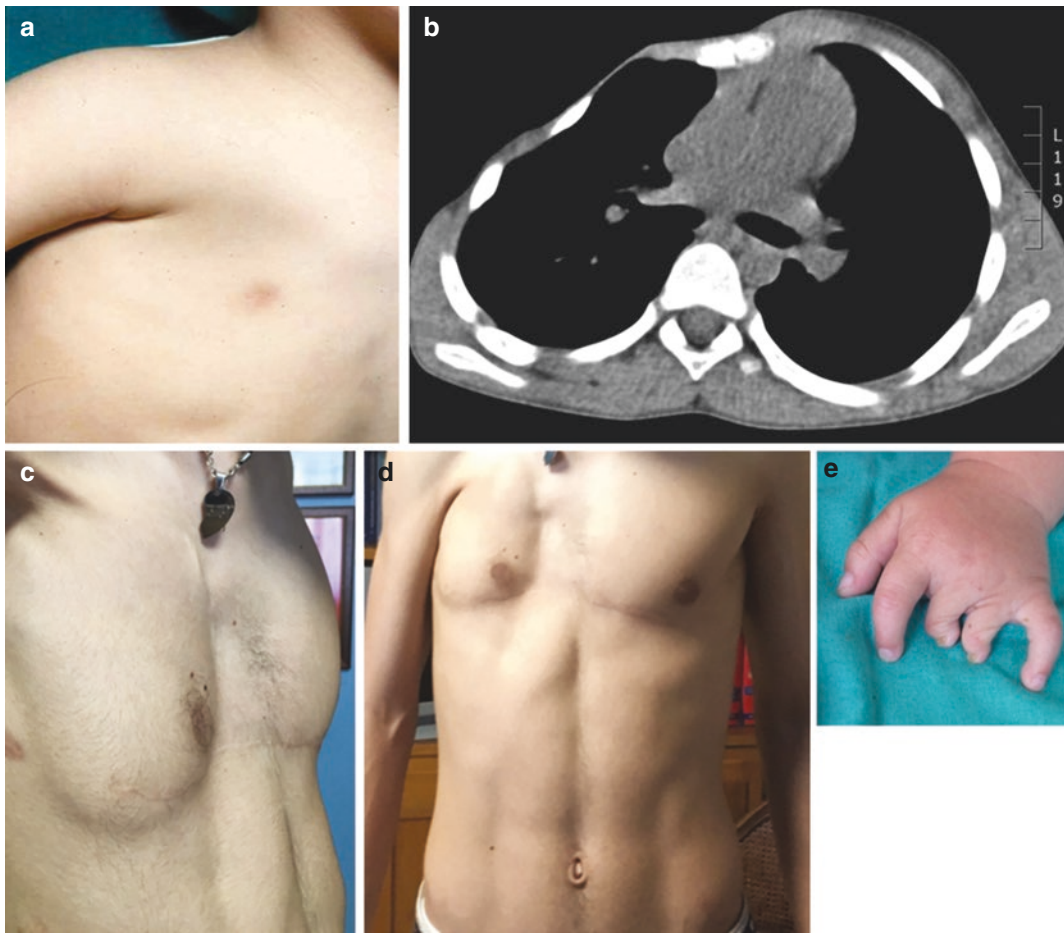

Fig. 9.8 Poland syndrome: chest wall asymmetry in a patient with right form (**a**); CT picture of a right PS (**b**); postoperative pictures of the same patient at long-term follow-up (**c**, **d**); brachydactyly in PS (**e**)

from varying degrees of breast hypoplasia to complete absence of the breast (amastia) and nipple (athelia), usually with hypoplasia of the subcutaneous tissue of the region (Fig. 9.8b).
- Upper limb anomalies [46, 47]: Shortness of the fingers (brachydactyly) (Fig. 9.8e), joined fingers (syndactyly), and a combination of both (brachysyndactyly) are frequently seen hand anomalies, although others can be present, affecting more than half of PS patients.
- Other skeletal deformities: Scoliosis and other spine deformities, Sprengel deformity (congenital elevated small scapula), etc.
- Cardiac/renal anomalies: They are uncommon and usually mild. Dextroposition, always reported in cases of left PS with rib anomalies, seems to be caused by mechanical factors during embryonic life in patients with multiple left rib agenesis [48].
- Other syndromic conditions, such as Moebius and Klippel-Feil syndromes, have been reported in association with PS [49].

The extreme variability of the phenotype imposes a multidisciplinary approach to all children with PS. Diagnostic work-up includes the evaluation of all the organs and systems that can be affected and should be completed as early as possible. Conversely, surgical correction is almost never necessary in the first years of life; nevertheless, since it may require multiple procedures and stages over the years [50] (Fig. 9.8c, d) (hand surgery, restoration of the structural integrity of the rib cage, improvement in the appearance of the chest, breast implants, etc.), a correct information and presentation of all the surgical possibilities should be early offered to the families.

9.6 Sternal Anomalies

Sternal defects are rare and include relatively benign anomalies, such as the partial sternal cleft, and major defects resulting in ectopia cordis. Four main defects can be identified: cervical ectopia cordis, thoracic ectopia cordis, thoracoabdominal ectopia cordis, and cleft or bifid sternum. The heart is displaced in ectopia cordis [51].

9.6.1 Thoracic Ectopia Cordis

Thoracic ectopia cordis presents with naked heart (entirely bare heart outside the thorax) and no overlying somatic structures (pericardium, skin, etc.). The heart has an anterior superior apex. Intrinsic cardiac anomalies are frequent. Upper abdominal wall defects (omphalocele, diastasis recti, eventration of the abdominal viscera) might be associated, as well. The sternum may be partially or completely split with the heart protruding through the defect. This condition differs from ectopia cordis in which the heart is in an orthotopic intrathoracic position, has a normal anatomy, and is covered by normal skin.

The lack of midline somatic tissues and the presence of a small intrathoracic cavity make the repair difficult with risk of heart failure. The correction (primary or stage repair) should be performed early in the first days of life. Different surgical approaches have been reported including the use of skin flaps, prosthetic meshes, rib grafts, and pectoral muscle flaps. Diaphragmatic mobilization and pericardial division from the anterior attachments of the chest wall might help in the closure. In all successful cases, the creation of a partial anterior cavity surrounding the heart avoids heart failure. The presence of intrinsic cardiac lesions and associated abdominal defects severely affects the prognosis, more than the surgical technique chosen for the correction. Postoperative complications include infection and extrusion of the graft.

9.6.2 Cervical Ectopia Cordis

Cervical ectopia cordis is distinguished from the thoracic ectopia cordis on the base of the superior heart displacement. The heart protrudes at the base of the neck, and it is often fused with the mouth, and there are many craniofacial

anomalies or other fetal deformities. The prognosis is bad and surgical repair is very difficult.

9.6.3 Thoracoabdominal Ectopia Cordis

Thoracoabdominal ectopia cordis presents with heart covered by thin and pigmented skin. It is associated with sternal cleft. There is no severe anterior heart rotation seen in thoracic ectopia cordis, but the heart is displaced within the thorax with diaphragmatic and pericardial defect below it or within the abdomen. Described associations are somatic defects, diaphragmatic anomalies, intrinsic cardiac malformations, and abdominal wall defects (omphalocele, diastasis recti). This ectopia cordis is often part of the Cantrell pentalogy (a cleft lower sternum, a half-moon anterior diaphragmatic defect due to failure of development of the septum transversum, absence of the parietal pericardium, adjacent or completely separate omphalocele, ventral hernia or diastasis recti, and in most patients a major form of congenital heart disease, most commonly tetralogy of Fallot or diverticulum from the left ventricle). Surgical correction is possible, and long-term survival rate is more frequent than that of other ectopia cordis. The first step is skin closure to avoid infections and mediastinitis and omphalocele excision. The correction is required early with primary closure or prosthetic mesh closure. The rectus muscles are distant with difficulties in obtaining a good primary closure.

9.6.4 Sternal Cleft or Bifid Sternum

The sternal cleft (SC) is caused by a defect in the fusion process of mesenchymal cells that starts at around the 6th week of gestation. The effect is an anomaly in which the heart is in the orthotopic position in the thoracic cavity but the sternum is clef or partially fused over the heart (Fig. 9.9). The skin coverage is normal and the pericardium is intact. The condition is idiopathic and accounts for 0.15% of all chest deformities with a female preponderance (Table 9.3).

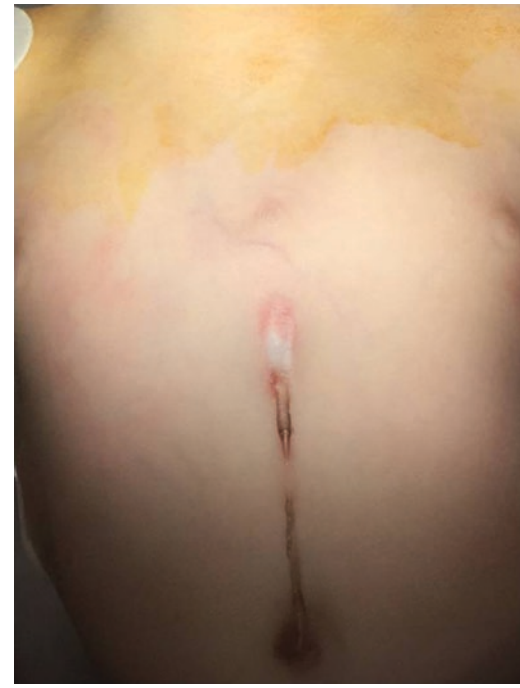

Fig. 9.9 Newborn with sternal cleft

Table 9.3 Sternal cleft types and frequency

Sternal cleft types	
Partial superior form	67%
Complete form	19.5%
Partial inferior form	11%
Sternal foramen	2.5%

Sternal clefts are classified into complete or partial [52]. The partial form can be superior or inferior: the partial superior SC is usually isolated and relatively easy to repair; the partial inferior SC is often associated with complete sternal fissure resulting in ectopia cordis. Other associated defects are vascular dysplasia, PHACES syndrome, midline fusion defects, and pentalogy of Cantrell (heart, pericardium, diaphragm, anterior abdominal wall defects) (Fig. 9.10).

PHACE(S) syndrome is a neurocutaneous disorder of unknown etiology. The acronym refers to the commonest features of PHACE: posterior fossa malformations, large facial hemangiomas, cerebral arterial anomalies, cardiovascular anomalies, and eye anomalies. When ventral developmental defects such as sternal clefting or

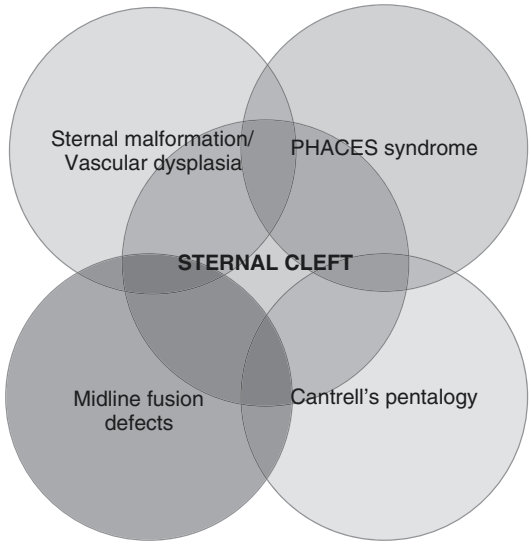

Fig. 9.10 The relationship between sternal cleft and other rare syndromes/associations (*From Torre et al. Phenotypic spectrum and management of sternal cleft: literature review and presentation of a new series. Eur J Cardiothorac Surg. 2012;41(1):4–9*)

supraumbilical raphe occur, the PHACES acronym may be used. The hallmark feature of PHACE is the presence of one or more large facial infantile hemangiomas that occupy at least one facial segment. Cerebral vascular anomalies are probably the most common extracutaneous feature. Given that several organ systems are involved, a multidisciplinary approach to disease surveillance and treatment is advised. In particular the assessment of affected babies should include the endoscopic evaluation of upper airways and cerebral MRI.

Intrinsic cardiac defects are rare. The presence of a fusion defect in the middle part of the sternum is called sternal foramen. SC determines paradox movements during respiration with risk of mediastinal viscera damage. Therefore the correction in neonatal age should be recommended. The difficulty in repairing the defect is related to the fact that the chest is small and cannot accommodate the heart with the risk of cardiovascular failure.

Some neonates are asymptomatic but present a paradoxical midline thoracic bulging due to the protrusion of viscera during expiration.

Older patients present respiratory symptoms such as dyspnea, cough, respiratory distress, and recurrent respiratory tract infections. Asymptomatic patients usually have partial defects and require repair to provide protective coverage for the heart (high risk of trauma-related injuries).

Several associations are seen, the most common being the bandlike scars from the umbilicus to the inferior part of the defect (supraumbilical raphe) that represent only a cosmetic anomaly, cardiac defects (22%) and vascular anomalies (9%).

Early repair in infancy is important because the chest is more flexible and primary closure is the preferred treatment. The primary closure can be challenging or impossible due to a stiff thorax. Alternatives include the use of prostheses (prosthetic materials such as Gore-Tex or Gore, DualMesh, calcium phosphate cement (Fig. 9.11), polyester, or various autologous grafts such as bone graft interposition, muscle flap interposition), partial or total thymectomy [53], cartilage resection, sliding chondrotomies, and clavicle dislocation.

In most series the primary repair is performed within the 3rd month of life. The first year of age is considered a favorable age for repair.

The preoperative evaluation should exclude associated anomalies that can lead to major complications and should define the thoracic anatomy. Some anomalies are evident (maxillofacial hemangiomas, cleft lip or palate, pectus excavatum, precordial skin tags, supraumbilical raphe, gastroschisis, connectival nevus of the anterior thoracic wall). Other defects (cardiac anomalies, aortic coarctation, eye abnormalities, posterior fossa anomalies, hidden hemangiomas) require investigations. Preoperative examinations include the study of the chest with X-ray and CT (Fig. 9.12) and cardiologic evaluation (electrocardiogram and echocardiography). Neuroradiologic imaging and ophthalmologic exams are performed in selected cases. Genetic evaluation completes the screening. Prior to surgery, laryngo-tracheo-bronchoscopy might identify subglottic hemangiomas.

For surgery, the midline vertical incision extends from the jugular notch to the end of the defect (Fig. 9.11). The dissection proceeds down-

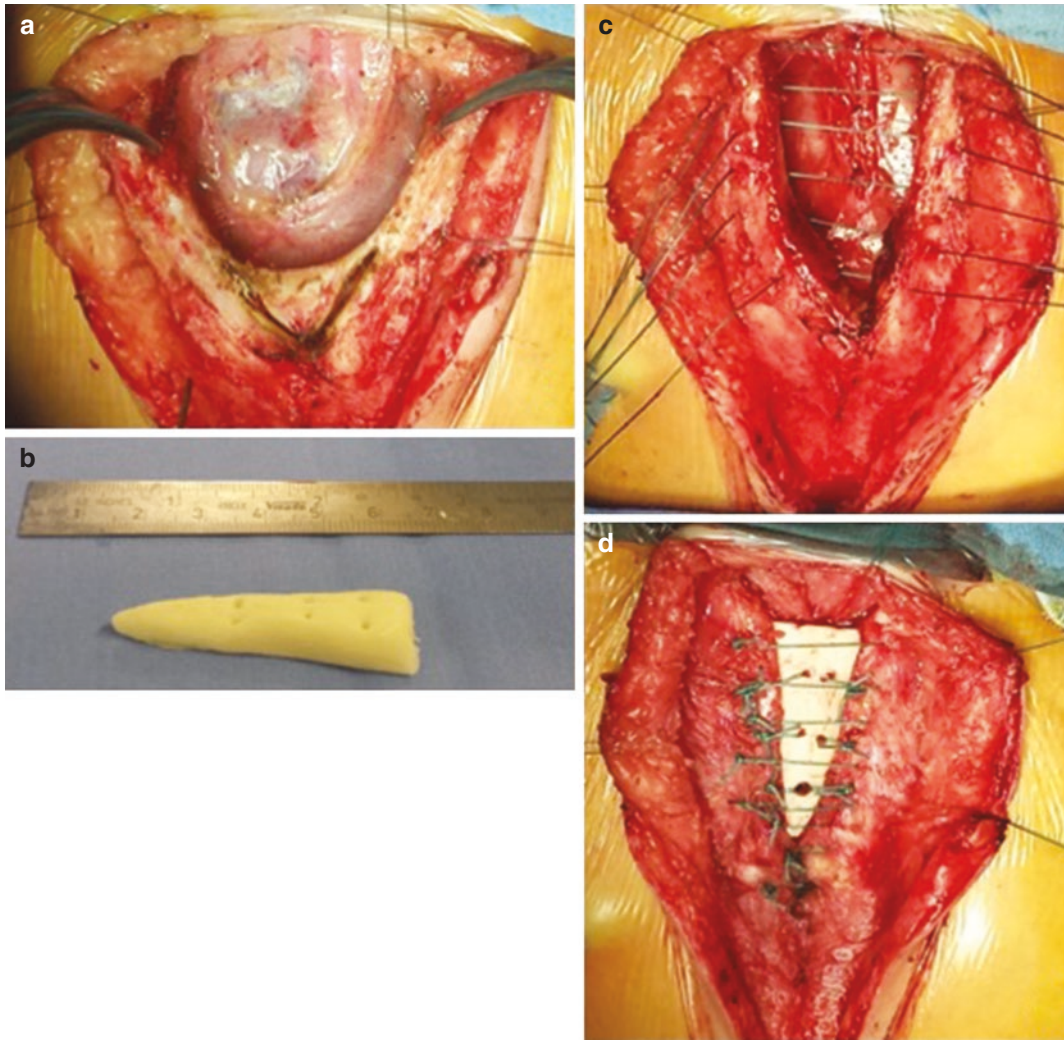

Fig. 9.11 Sternal cleft (**a**) repair (**c**, **d**) with a prosthesis in calcium phosphate cement (**b**)

ward to expose the sternal bars. Vertical strap neck muscles are divided at their insertion on the sternal upper margins and the two sternal halves are freed from the underlying pleura and pericardium. A U-shaped incision is performed in the inferior part of partial SC to facilitate the closure. The sternal bars are approximated on the midline and closed with nonabsorbable sutures when possible (Fig. 9.13).

Reported complications are pericardial or pleural tears during sternal dissection, retrosternal seromas, and pneumothorax. In females, care should be taken not to injure the mammary gland. Patients with severe associated anomalies have unfavorable events related to the underlying disease. No recurrences have been described.

The required follow-up is a close one since patients can develop other congenital wall malformations (e.g., pectus excavatum).

9.7 Clavicle-Scapular Anomalies

Clavicle-scapular malformations represent 0.5% of all the CWM. They are divided into malformations of the clavicle, malformations of the scapula, and combined malformations.

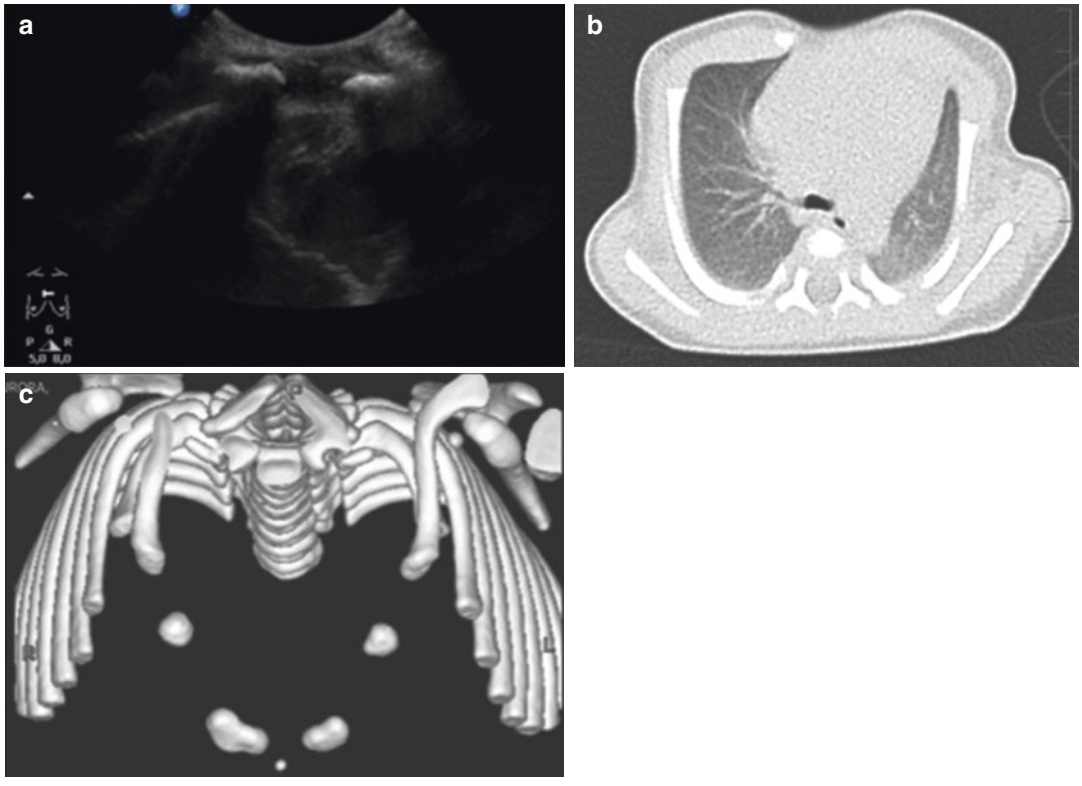

Fig. 9.12 (**a**) US showing "V-shaped" sternum with proximal diastasis; (**b**, **c**) CT evaluation of the sternal deformity: diastasis of the middle and proximal portion of the sternum, costal hypoplasia

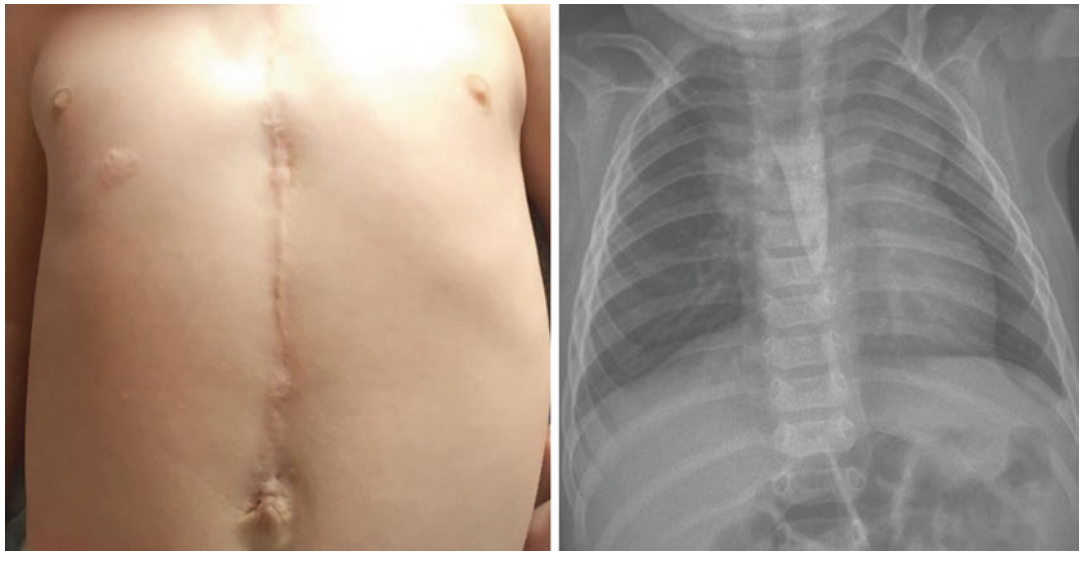

Fig. 9.13 Postoperative pictures after sternal cleft repair with a prosthesis in calcium phosphate cement

9.7.1 Clavicular Malformations

They originate from alterations in the growth or structure of the clavicle that can be aplastic, hypoplastic, or dysmorphic, on one or both sides. Clavicular malformations can be isolated (simple) or part of a syndromic association. They usually cause very little functional alteration, except when associated with other malformations of the scapula and/or upper ribs. Several syndromes, such as pseudohypoparathyroidism (Albright), Holt-Oram, and Pierre-Marie syndrome, among others, can present clavicular abnormalities as part of their clinical picture, usually associated with other skeletal deformities. The chest of these children is narrow in its upper part, with decreased lateral diameter. Functionally, this facilitates the realization of atypical movements, such as the approximation of the shoulders in front of the thorax. The muscles of the area can also be involved, presenting developmental and insertional anomalies. In the neonatal period, respiratory disorders can appear due to the narrowness of the chest. Chest X-ray shows the absence or hypoplasia of one or both clavicles. Clavicular malformations can be associated with pectus carinatum or excavatum.

9.7.2 Scapular Malformations

These anomalies are characterized by alterations in development and position of the scapula with variable joint mobility. The deformities occur at birth and their severity is variable; they are usually unilateral. They are classified as simple, with hypoplastic or winged scapula, or syndromic. Syndromes that favors scapular winging are, for example, muscular dystrophies or other conditions with muscular hypoplasia such as Poland syndrome. It can be associated with PE, PC, scoliosis, vertebral, and rib deformities.

Sprengel deformity is characterized by an elevated anomalous position of one or both scapulae, with variable disorders of joint mobility. The deformity is the result of a failure in the descent of the scapula from its fetal position in the neck to its normal position on the posteroexternal face of the thoracic wall. It is more common in women (4:1 ratio). It occurs sporadically, but an apparent pattern of autosomal dominant inheritance has been sometimes noted. The affected scapula is hypoplastic, with decreased vertical diameter and apparent increase of its horizontal width. The muscles connected to the scapula can be altered, most commonly the trapezoid, the deltoid, the rhomboid, the elevator of the scapula, and the serratus anterior, so that the amplitude of shoulder movements may be limited.

Scapular malformations can also be part of the Klippel-Feil syndrome, in association with anomalies of the cervical spine, a characteristic short neck with movement limitations, dorsal and lumbosacral vertebral malformations, anomalies of the ribs, malformations of the upper and lower limbs, and rarely cardiovascular malformations.

Chest X-ray in front and profile projections and CT with 3D reconstruction of the chest wall are the imaging techniques of choice. MRI is carried out when intramedullary alterations are suspected. Differential diagnosis includes other causes of shoulder asymmetry, such as scoliosis, asymmetry of lower limbs, and obstetric paralysis of the brachial plexus.

The goals of surgical treatment are to improve the function and the esthetic appearance of the shoulder. When indicated, surgery is recommended between 9 and 18 months of life.

9.7.3 Combined Malformations

They are the most frequent variant and are characterized by the association of different types both clavicular and scapular defects. They can be unilateral or bilateral, and they comprise the simple subtypes of each group of malformations.

9.8 Associated Spinal Deformities

The normal development of the vertebral column includes the longitudinal and axial growth of the vertebrae [54] that requires:

1. The skeletal growth (the growth of the axis for muscular development).
2. The symmetrical growth of the spine in the longitudinal and axial plane, preventing the development of deformities (scoliosis). The scoliosis is the spinal lateral deviation of more than 10° with vertebral body rotation. According to their origin, the scoliosis can be classified into idiopathic, congenital, neuromuscular, osteopathic, and neoplastic.
3. Protection of neural elements, ensuring that the child reaches adulthood without neurological complications.
4. The development of physiological spinal curvatures, which allow proper balance in the standing position.

The spine is intimately associated with the thoracic cage and any alteration of these two elements is reflected in the other. Under normal conditions, the development of the thorax is a dynamic process that involves the sternum, the ribs, the spine, and the diaphragm. Its growth shows a higher velocity in the first years of life. Everything that interferes with the thoracic normal development will reduce the respiratory capacity, especially in younger ages.

Also the thoracic morphology changes with growth: the thorax is cylindrical with horizontal ribs at birth; it has an oval shape, with an oblique orientation of the ribs at 2 years, and it is rectangular at 10 years. It has been established that the growth of 50% of the thoracic volume happens in the first 10 years and the other 50% is completed at the age of 16. An alteration in the longitudinal or anteroposterior growth of the thorax, thoracic volume, and alveoli will produce respiratory failure syndrome.

Spinal and thoracic deformities can be divided as:

1. Primary
   (a) Anterior deformities (pectus excavatum, carinatum, etc.)
   (b) Connective tissue deformities (Marfan)
   (c) Costal fusion and strange malformations
2. Secondary
   (a) Of the wall: costal resections, costal fusions
   (b) Of the content: retraction after empyema, pulmonary resections, diaphragmatic palsy

Hemivertebra is a type of vertebral anomaly and results from a lack of formation of one half of a vertebral body. It can be a common cause of a congenital scoliosis. The curve progression and the ultimate severity of the curve depend on the type of hemivertebrae, the location, the number of hemivertebrae, and their relationship with each other. It falls under the spectrum of segmentational anomalies and can involve one or multiple levels. Recognized associations are many and include Aicardi syndrome, cleidocranial dysostosis, gastroschisis, Gorlin syndrome, fetal pyelectasis, Jarcho-Levin syndrome, OEIS complex, VACTERL association, and mucopolysaccharidosis.

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Mediastinal Masses

10

Mario Lima and Michela Maffi

10.1 Introduction

The mediastinum is defined as the thoracic region limited by the pleural spaces laterally, the sternum anteriorly, the vertebral column posteriorly, the thoracic inlet superiorly, and the diaphragm inferiorly. The mediastinum contains different types of tissue including the thymus gland, part of trachea and esophagus, the great vessels, the heart, lymph nodes, fat, and nerves. Mediastinal masses can derive from each of those tissue and can be malformative, neoplastic, or infective [1–5]. Table 10.1 illustrates the different origins of mediastinal masses.

10.2 Incidence

Congenital mediastinal malformations are rare entities, with estimated incidences of 1 in 20,000–30,000 live births [6, 7], while the most common are the masses of neoplastic origin. The 34% of the mediastinal masses are neurogenic tumors, followed by lymphomas (24%), foregut malformations (14%), germ cell tumors (11%), mesenchymal tumors (7%), thymic masses (6%), and vascular anomalies (4%). Mediastinal tumors include a wide spectrum of pathologies. Most (65–72%) of the illnesses are malignant, and about 40% of children are under the age of 2. The mediastinum can be divided into three compartments: anterior, middle, and posterior. Anterior mediastinal tumors account for approximately 46% of mediastinal lesions, neoplastic lesions of the middle mediastinum account for 20%, and posterior mediastinal tumors account for 34% [1, 8–10].

10.3 Embryology

The embryology of the mediastinum is closely linked to the development of the organs contained within it. In the embryo, the mediastinum is still not formed, and the chest and the abdomen are not separated. During the fourth gestational week, the coelomic cavity becomes a closed cavity partially separated into two parts by the transverse septum. The primitive pericardial cavity superiorly and the peritoneal cavity inferiorly communicate with each other through two wide dorsolateral channels, called pericardio-peritoneal canals. At the end of the fourth week, the pulmonary buds grow in the cavity. As the lungs grow, it also increases the cavity that contains them that takes the name of pleural cavity. Initially, the pleural cavity communicates with both the pericardial cavity and the peritoneal cavity.

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Table 10.1 Anatomical classification of mediastinal masses

Anterior mediastinal masses
Solid lesions
1. Normal thymus
(a) Prominent thymus (pseumass)
(b) Ectopic thymus
2. Thymic hyperplasia
3. Thymoma
(a) Noninvasive thymoma
(b) Invasive thymoma
4. Thymic carcinoma
5. Lymphoma
(a) Hodgkin lymphoma
(b) Non-Hodgkin lymphoma
6. Teratoma
Cystic lesions
1. Thymic cyst
2. Lymphatic malformation
Fatty lesions
1. Lipoma
2. Thymolipoma
Middle mediastinal masses
Vascular lesions
1. Double aortic arch
2. Right aortic arch with aberrant left subclavian artery
3. Left aortic arch with aberrant right subclavian artery
4. Pulmonary artery sling
5. Duplicated superior vena cava
Nonvascular lesions
1. Congenital foregut duplication cysts
(a) Bronchogenic cyst
(b) Esophageal duplication cyst
(c) Neurenteric cyst
Lymphadenopathy
(a) Neoplasm
• Primary (i.e., lymphoma)
• Metastatic disease
(b) Infection
Posterior mediastinal masses
Sympathetic ganglion tumors
1. Neuroblastoma
2. Ganglioneuroblastoma
3. Ganglioneuroma
Nerve sheath tumors
1. Schwannoma
2. Neurofibroma
3. Malignant peripheral nerve sheath tumor

During the fifth week, the lateral walls of the body form the pleuropericardial folds that face each other, interposing between the heart and the primitive lungs. The fusion of these folds occurs at the end of the fifth week and permanently separates pericardial cavity from pleural and peritoneal cavity. The communication between these two cavities remains until the seventh week when the diaphragm separates the chest from the abdomen. Different malformative frameworks may occur during these complex phases, while tumors may also result from migration alteration of cellular precursors as in the case of germ cell tumors. These are derived from precursors of germ cells that undergo early differentiation near the region of the primitive cephalic pole and migrate to the lumbar region. During this migration, these elements may prematurely interrupt maturation and become teratomas.

10.4 Clinical Implication

Mediastinal masses can cause a wide spectrum of signs and symptoms ranging from being asymptomatic to causing compressive symptoms such as coughing, dyspnea, dysphagia, superior vena cava syndrome, and Claude Bernard-Horner syndrome [11].

The severity of symptoms depends on localization, structures involved or infiltrated, and size of the mass.

In asymptomatic cases, diagnosis is mostly occasional during a radiograph performed for other reasons.

10.5 Prenatal and Perinatal Management

By prenatal screening, many lesions are already suspected during fetal life. An accurate prenatal diagnosis can highlight the risk or the presence of airway obstruction and allow for taking measures during pregnancy or at delivery. A comprehensive evaluation includes prenatal morphology ultrasound to further detect additional associated abnormalities, karyotype, echocardiogram, and fetal magnetic resonance imaging (Fig. 10.1). Fetal MRI provides detailed information about the mass and the

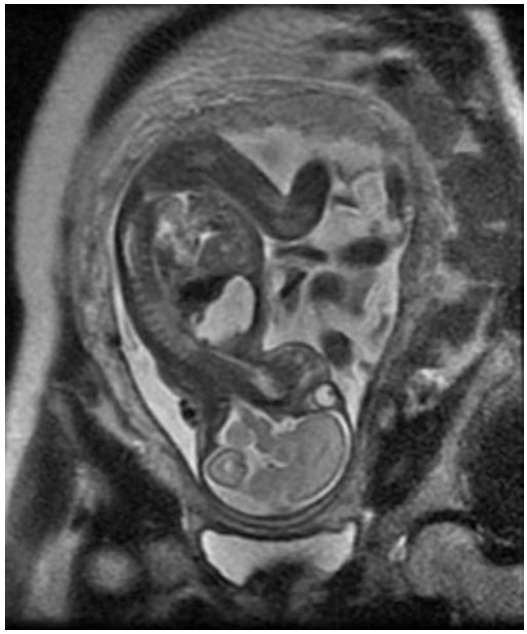

Fig. 10.1 Fetal MRI can be useful in evaluation of thoracic lesions

entity of the associated obstruction compared to ultrasound [12].

Also during pregnancy, mass effect depends on location and size. Compression on the esophagus may lead to polyhydramnios; compression on the mediastinal lymphatics, great vessels, and heart may lead to hydrops, heart failure, and fetal demise if not treated; compression on lung tissue may lead to pulmonary hypoplasia and respiratory failure after birth.

Treatment options depend on the nature of the complication and the age of the fetus at the time the complication occurs. Early in gestation when a cystic mass is present and causes hydrops and heart failure, treatment options include percutaneous decompression or thoracoamniotic shunt [13].

Most mediastinal lesions diagnosed prenatally can be managed after birth; however, if the fetus develops hydrops before viability, prenatal surgery may be the only option to avoid fetal demise. Recently, successes have been reported in the management of upper airway obstruction in cervical teratoma [14]. It is advisable to be cautious, but fetal surgery will probably play a role in treating these patients.

10.5.1 EXIT Procedure

The ex utero intrapartum therapy procedure aims to ensure placental uterine flow for a prolonged period, so that a procedure on the fetus can be safely performed.

It is a complex procedure involving a multidisciplinary team that takes care of the mother and the fetus at the same time. The procedure consists of a hysterotomy to allow the delivery of the upper part of the fetus. During the procedure, it is essential to maintain the uterine relaxation that is achieved with tocolytics and inhalation anesthetics and an adequate uterine volume that is maintained by continuous replacement of the amniotic fluid with warmed physiological solution. Once the patient is partially delivered, an intravenous access is obtained, and the fetus is strictly monitored with a pulse oximeter and echocardiography. The first step is to secure the fetal airway through endotracheal intubation or tracheostomy if clinically indicated. The range of procedure that can be performed during an EXIT procedure includes different maneuvers both diagnostic and therapeutic. When the respiratory and cardiac stability of the fetus have been reached, the delivery is completed.

Exit procedure was firstly described for airway stabilization in fetuses that had undergone tracheal occlusion for CDH, but currently, any fetus with a potential airway impairment or cardiorespiratory instability at birth can be a candidate for EXIT procedure [13, 15–18].

10.6 Diagnostic Tools

10.6.1 Laboratory

The laboratory data can help the diagnosis in cases of malignancy. In patients with a mass located in the paravertebral site, it is important to evaluate catecholamine catabolites (homovanillic acid and vanillylmandelic acid) in urine produced by neurologically active tumors. In case of germ cell tumors, common markers are beta-HCG and alpha-fetoprotein, which must be interpreted by knowing age-related values as they are normally elevated in the neonatal age.

10.6.2 Imaging

10.6.2.1 Chest X-Ray

Chest radiographs (frontal and lateral views) are usually the first diagnostic imaging for evaluating mediastinal masses in infants and children (Fig. 10.2). CXR are sensitive (97–100%) for detecting mediastinal masses depending on the size and location of the mass but has a low diagnostic specificity (36%). For this reason, additional imaging studies (i.e., US, CT, or MRI) are mandatory in order to further characterize a mass and narrow the differential diagnosis [1, 19].

10.6.2.2 Ultrasounds

US can be useful in infants younger than 12 months. The unossified sternal and costal cartilages allow evaluation of anterior mediastinal structures and detection of masses. US has the advantage to avoid ionizing radiation exposure but is operator dependent [20].

10.6.2.3 Echocardiography

It is useful to differentiate mediastinal masses from other intracardiac or pericardic lesions.

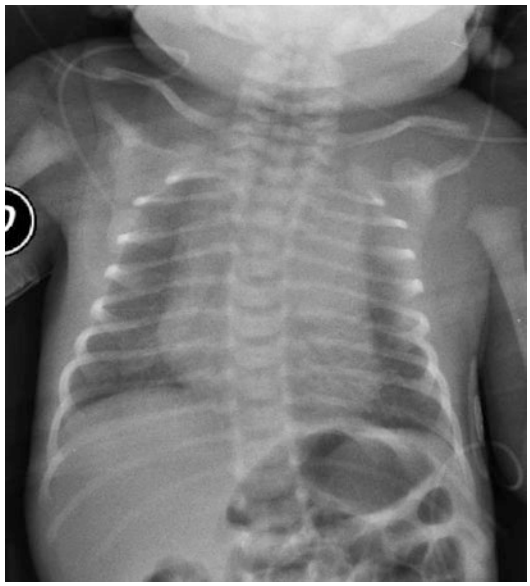

Fig. 10.2 Chest X-ray is the first-line imaging technique in suspected mediastinal masses. It typically shows an enlargement of mediastinal profile or in some cases a well-defined opacity

10.6.2.4 Upper Gastrointestinal Tract X-Ray

If an esophageal duplication is suspected, upper GI tract X-ray highlights the deviations and possible communication between the mass and the esophagus (Fig. 10.3).

10.6.2.5 Computed Tomography

CT is the method of choice to permanently characterize a mediastinal lesion (Fig. 10.4).

It can provide high diagnostic accuracy (88%) in diagnosing the nature, size, location, and involvement of other organs by mediastinal masses, and it yields additional diagnostic information (82%) and affects clinical management (65%). However, a cautious use of CT is appropriate especially in neonatal and pediatric patients who may necessitate repeat imaging during life,

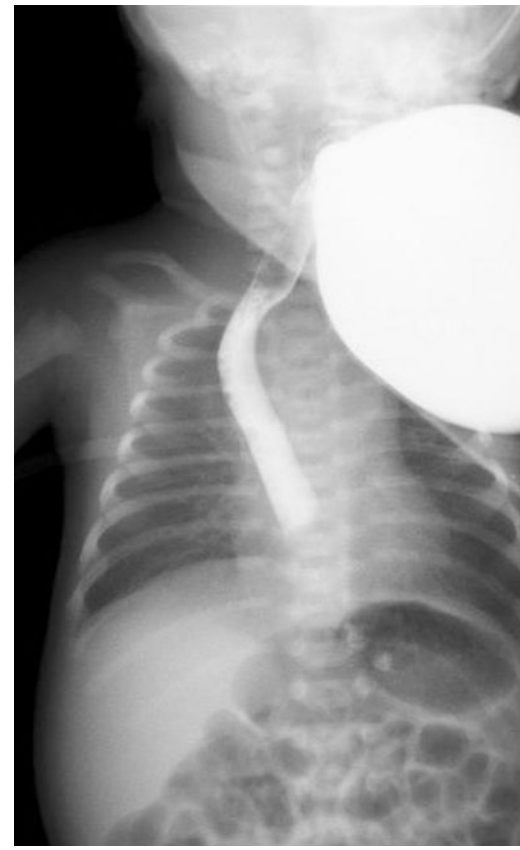

Fig. 10.3 Upper GI tract X-ray highlights deviations of esophagus or communications between the mass and the digestive system

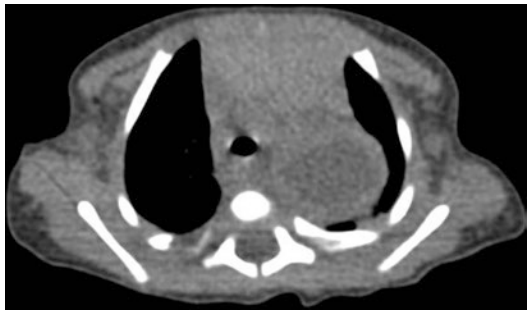

Fig. 10.4 CT scan plays a central role in defining diagnosis of mediastinal masses

keeping in mind the harmful potential of high radiation exposure [21, 22].

10.6.2.6 Magnetic Resonance Imaging

Magnetic resonance has a sensitivity slightly lower than TC. It finds particular utility on the study of vascular anomalies, evaluates posterior mediastinal neurogenic tumors with possible intraspinal extension, and assesses foregut duplication cysts with high attenuation on non-contrast CT.

MRI provides a superior soft tissue characterization in comparison with other currently available imaging modalities. However it has the disadvantages of image artifacts caused by cardiac and respiratory motion and the need for sedation in newborns and infants [2, 4].

10.6.2.7 Positron Emission Tomography (PET)

Positron emission tomography (PET) is a noninvasive imaging modality using 2 fluoro-2-deoxy (18 fluorine)-D-glucose (18 FDG). PET is currently not used as an initial imaging modality for evaluating mediastinal masses in infants and children, but it can be useful for staging and follow-up of patient with lymphoma including detection of tumor involvement in normal-sized lymph nodes, discrimination of fibrous scar and necrotic tissue from active tumor in residual masses after treatment, and evaluation of disease involvement in extra-nodal sites (e.g., liver or bone marrow).

In addition, PET/CT provides both functional and anatomic information necessary for a complete evaluation of lymphoma in the pediatric population [23–27] .

10.7 Esophageal Duplications

Intestinal duplications are esophageal in approximately 20% of cases. They can occur anywhere along the esophagus, although the cervical esophagus is most affected and most of these occur on the right side of the thoracic esophagus; they usually are a round, well-defined cystic lesion and may cause extrinsic compression of the trachea with respiratory symptoms or pneumonia.

As an esophageal duplication may contain gastric mucosa in about half of cases, they can cause hematemesis or anemia.

Esophageal duplication cysts should be considered in the differential diagnosis of any mediastinal mass; in 20% of cases, spinal cord communication has been described.

Among the congenital anomalies associated with esophageal duplication, the most common are esophageal atresia and vertebral anomalies.

Once suspected a duplication on the basis of chest X-ray, it is usually necessary to perform a TC or MR. It is also useful to perform abdominal ultrasound, as a high percentage of patients (about 25%) with esophageal duplication also have intestinal duplication.

The scintigraphy with 99mTC pertechnetate allows to diagnose the presence of gastric mucosa within the mediastinal cyst.

Differential diagnosis includes thyroglossal duct cysts, bronchial cysts, cystic hygroma, cervical lymphadenopathies, and a variety of cervical solid tumors.

Although most of the esophageal duplication is adjacent to the esophagus wall, in the literature are also described esophageal duplications in the right pleural space, detached from the esophagus.

Esophageal duplications require removal by thoracotomy or thoracoscopy (Fig. 10.5). If bone communication is present, it is advisable to perform a bone section and, possibly, a laminectomy in collaboration with the neurosurgeon [28–30].

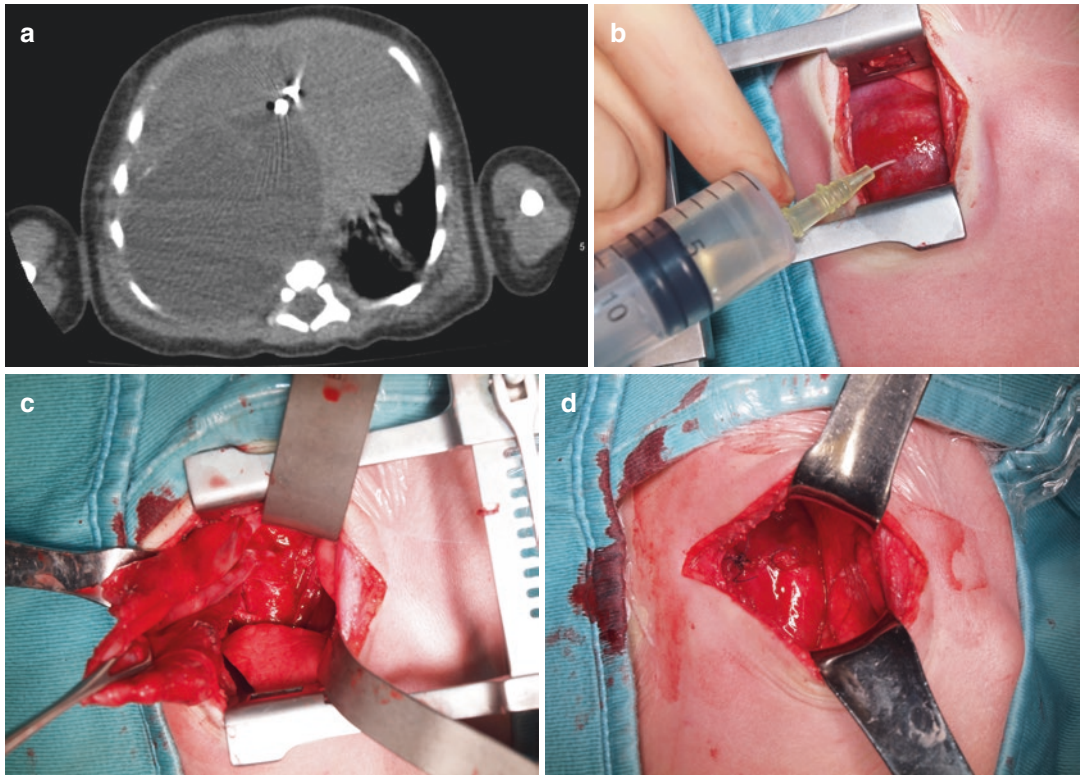

Fig. 10.5 Large esophageal duplication removal. Preoperative CT scan shows a large fluid-filled cystic lesion (**a**) that can be reduced by puncture (**b**) and totally removed (**c**). In case of communication with the esophagus, the residual defect should be sutured (**d**)

10.8 Bronchogenic Cyst

Bronchogenic cysts are uniloculated cavities containing mucoid material, sometimes in communication with the bronchial lumen, located in the mediastinum, tongue, neck, chest wall, pericardium, pancreas, and adrenal gland. They can cause bronchial obstruction resulting in secondary lobular emphysema. The clinical course can be asymptomatic or associated with the development of respiratory infections or tracheobronchial compression symptoms. The first level imaging is chest X-ray that can reveal rounded homogeneous opacity with well-defined margins associated with compression on the esophagus, trachea, or bronchi.

Ultrasound is a noninvasive, economical, and non-irradiating method. Nonetheless, preoperative diagnosis and evaluation requires TC and RM.

Also in this case surgical removal is required which can be performed with toracotomic or thoracoscopic access. Radicality is mandatory to avoid recurrences [31, 32].

10.9 Lymphangiomas

Lymphangioma is a congenital anomaly of the lymphatic system. It is usually present at birth (60%), and 80–90% of cases are symptomatic under 2 years of age. Typical symptoms include dyspnea, cough, chest pain, acute respiratory distress, and respiratory failure. This lesion is usually located in the head and neck, while the axilla and mediastinum are the second frequent location site. Although it is a benign lesion, it can lead to complication because of its infiltrating nature, indefinite demarcation, and the

involvement of vital structures. Lymphangiomas are classified morphologically as macrocystic, microcystic, and mixed. Ultrasounds, CT scan, and MRI are all used to evaluate a patient preoperatively. Typical CT appearance is a well-circumscribed cystic mass with compression of surrounding structures. MRI visualizes cystic component with multilocular aspect, low signal intensity on T1W1 and high signal intensity on T2W1.

Surgical therapy consists of complete resection, but radicality can be difficult because of high risk of damage to the surrounding structures. For this reason, sclerotherapy is mostly used. Several sclerosing agents are available, but the most commonly used are bleomycin and the Ok-432 [33–36].

10.10 Neurogenic Tumors

Tumors derived from neural crests are the most common lesions of the posterior mediastinum. These neoplasms arise from the sympathetic chain and vary from benign ganglioneuroma to malignant neuroblastoma.

Twenty percent of neurogenic tumors are located in the posterior medium. Neuroblastoma, a malignant neoplasm of the autonomic nervous system, originates from the neuroectodermal cells of the primitive neural crest that migrate in the course of embryonic life, giving rise to the sympathetic ganglia and adrenal medulla. Neuroblastoma is the most common solid tumor in subjects <5 years old.

Ganglioneuroma, on the other hand, is a tumor composed mainly of schwannian stroma with completely differentiated ganglionic cells (mature ganglioneuroma) or incompletely differentiated (immature ganglioneuroma). It affects older children and adolescents and manifests as asymptomatic lesions, which are sometimes accidentally identified with chest radiography. They can appear anywhere along the paravertebral spaces and are usually encapsulated and quite easily resectable.

Symptoms of compression can be associated to a large mass or to masses infiltrating spinal

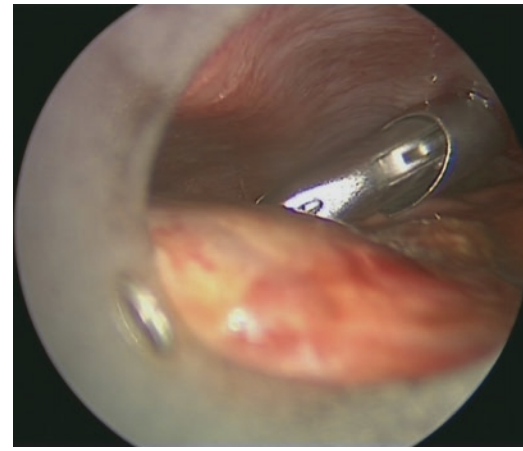

Fig. 10.6 Thoracoscopic biopsy allows to obtain neoplastic tissue to perform molecular studies

spaces. CT and MRI are the imaging techniques of choice in assessing these lesions.

Surgery plays a key role in the treatment at diagnosis and after chemotherapy. The goals of surgery at onset are to define the diagnosis, acquire tissue for biological studies, and remove the tumor with minimal morbidity (Fig. 10.6). Since complete excision is the main goal of the intervention, this should not be "tempted" before chemotherapy if any of the risk factors, such as a tumor that encloses large vessels (aorta and vein veins) or nerve plexus, are present. The treatment includes chemotherapy and radiotherapy depending on the type of lesion. Surgical resection is the treatment of choice and is curative for benign lesions [37–41].

10.11 Teratomas and Germ Cells Tumors

Germ cell tumors are the second most common neoplasm in newborn accounting for 35–40% of all tumors in the first month of life. In the newborn period, the majority of GCTs are extragonadal (mainly sacrocoggygeal) but are located in mediastinum only in 3% of cases.

Most teratomas are located in the anterior mediastinum, intrapericardial and intracardiac locations are described.

Only 5% of germ cell tumors in neonatal age are malignant. They are more common in females with ratio F:M = 3:1 which is again a reversal of the ratio seen in the rest of childhood. Children with anterior mediastinal teratoma usually have respiratory symptoms (distress, coughing), but in older patients, teratoma may also be an accidental finding at chest X-ray. Other symptoms include erosion of thoracic wall, hemoptysis, due to erosion of a bronchus or cardiac failure.

TC is the imaging technique of choice in evaluating these injuries, as it can define the extent of the lesion and possible tracheal compression.

Important markers for germ cell tumors are α-FP and β-HCG.

Surgical resection by thoracotomy, median sternotomy, or thoracoscopy (Fig. 10.7) is usually curative, although the detection of malignant elements within the lesion may require further therapies. Thoracoscopic removal is generally not indicated for tumors with signs of malignancy.

Patients with signs of malignancy should receive neoadjuvant chemotherapy. Benign tumors or persistent masses after chemotherapy should be resected aggressively [42–45].

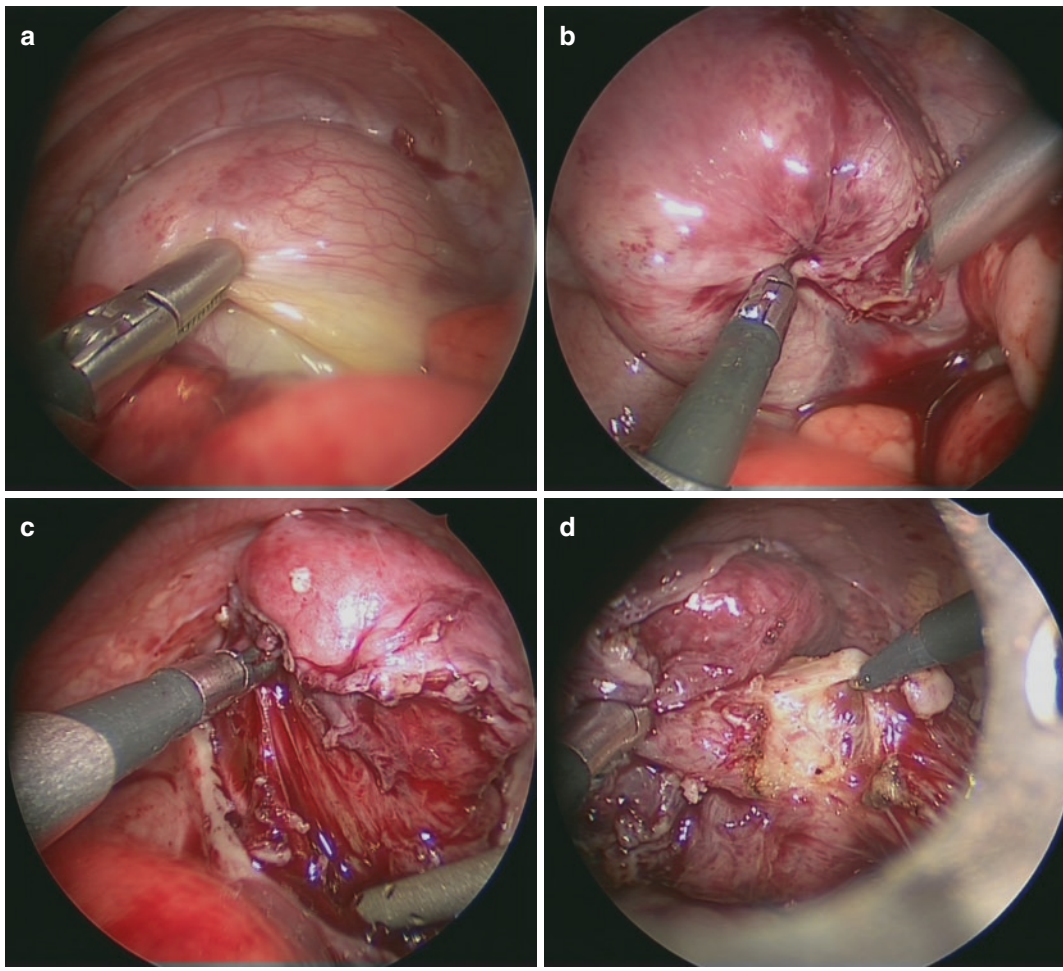

Fig. 10.7 Left mediastinal teratoma removal. After the mass identification (**a**), parietal pleura is opened and the mass removed (**b**, **c**, **d**)

10.12 Thymic Tumors

Masses derived by thymus include thymic cyst, thymic hyperplasia, and thymoma.

These masses represent less than 5% of mediastinal tumors in children. Thymic hyperplasia can take the form of a lymphoid follicular hyperplasia, which is often present in myasthenia gravis and associated with a good response to thymectomy; this lesion can also be found in thyroid pathologies (hypothyroidism, hyperthyroidism). Thymomas are rare in children when compared with adults, with only 2% that appears in the first two decades of life. These lesions are usually benign and appear in the anterior mediastinum or at the base of the neck.

Although thymic cancers can be large in size, they generally compress the surrounding structures rather than invade them. The main symptoms are respiratory distress (respiratory distress, cough) and/or superior vena cava syndrome. Occasionally they are associated with myasthenia gravis. TC is the imaging technique of choice in evaluating these lesions, as it can define the extension.

Surgical resection is curative and recurrence is rare (2%). Malignant thymomas are usually aggressive, and surgical resection is complex, and the response to chemotherapy and radiotherapy is limited. The pleura, lung, diaphragm, superior vena cava, and pericardium resections may be required to achieve complete surgical removal [46–48].

10.13 Lymphoid Tumors

Various lymphoid tumors may affect the mediastinum; lymphoma is the most common tumor of the middle mediastinum and represents about 60% of all mediastinal lesions in pediatric age. Two-thirds of mediastinal lymphomas are non-Hodgkin lymphomas; one third are Hodgkin lymphomas. Lymphomas are quite rare in neonatal age.

Lymphomas can involve all the mediastinal compartments. Lymphoblastic lymphomas are the most common lesions even if in pediatric age they occur primarily in the anterior and middle regions. Along with Burkitt's lymphoma, large B-cell lymphoma, and large-cell anaplastic lymphoma, lymphoblastic lymphoma is one of the most common non-Hodgkin lymphomas (LnH) of the pediatric age. They account for about 10–15% of all malignant neoplasms of the pediatric age, thus forming the third most common group in the Western countries. LnHs show a steady increase in age.

Hodgkin lymphoma (LH), on the other hand, accounts for about 6% of the pediatric neoplasms. It shows a predilection for the male, especially in the younger age and a bimodal distribution of incidence, with a peak between 15 and 30 years of age and a second after 50 years. LH is rare in individuals <10 years of age. The incidence varies significantly in different geographic areas and populations.

Children with LH may have systemic symptoms such as fever, malaise, weight loss, night illness, and rarely pleural effusions. In most cases, the diagnosis is transmitted through lymph node biopsy, as often babies have involvement of cervical or supraclavicular lymph nodes that are easily accessible to biopsies. Diagnostic evaluation also includes chest X-ray, which is the first routinely used imaging technique, and the thoracic TC that establishes localization, consistency and mass architecture, and the relationship with adjacent structures.

Mediastinal locations are often extended over the original site, and other organs such as the pleura, the pericardium, and the bone marrow are affected.

Children with LnH often have symptoms due to local compression of the upper respiratory tract or compression of the superior vena cava. Systemic symptoms such as fever, malaise, weight loss, nighttime awakenings, and pleural effusions are often present. In most cases, the diagnosis is performed through lymph node biopsy. Diagnostic evaluation includes chest X-ray and thoracic CT.

Treatment of such neoplastic lesions (LH) involves chemotherapy and radiotherapy. The

prognosis is good, with overall survival rates of over 80% at 5 years after diagnosis. In LH surgery is not the primary treatment. Only in case of chest compressions surgery is indicated.

LnH therapy is basically based on the use of chemotherapy. The role of surgery is mostly limited to diagnostic testing (biopsy) or evaluation of residual tumor. The "open" procedure allows the best therapeutic and diagnostic approach. Radiotherapy, much used for LH, is not used in LnH first-line therapy, except for selected cases [49–52].

10.14 Other Lesions

Other masses that may cause enlargement of the mediastinum are vascular malformations (Table 10.1). For more details on these and previous topics, refer to the dedicated chapters.

There are also some less frequent tumors that affect the mediastinum such as lipomas, lipoblastomas, and lymphoblastomas. Other sarcomas such as rhabdomyosarcoma, Ewing's sarcoma can affect the mediastinum. In addition, rare cases of fibromatosis are described. When diagnosing these rare lesions is not possible through imaging techniques, thoracoscopy, with biopsy, can be useful.

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Pneumothorax and Chylothorax

11

Sebastiano Cacciaguerra, Pieralba Catalano, Enrica Antonelli, and Salvatore Arena

11.1 Introduction

Pneumothorax (PTX) is the most common air leak occurring when air accumulates in the pleural space [1]. Especially during the neonatal period, PTX is considered life-threatening and is associated with high mortality and morbidity [2, 3]. Neonatal PTX (nPTX) was defined as radiologically verified PTX occurring up to the 28th day of life. Despite the high incidence, just 0.5% of cases of nPTX are symptomatic [2, 4]. nPTX is more frequently observed in neonates (1–2%), and in particular in very low birth weight (3–9%) [5, 6], than in older children (1.2–28 per 100,000) [2, 3, 7] and the rate can increase to up to 30% in patients who have concurrent underlying lung disease or requiring mechanical ventilation [2, 7]. Rates may change due to obstetrical, perinatal, clinical course, and management strategies [8]. Furthermore, PTX can develop due to high transpulmonary pressure generated at the onset of respiration.

PTX can be classified as uni- or bilateral and with or without the presence of tension. It has been reported that two-thirds of unilateral nPTX involves the right lung and between 15% and 25% of nPTX cases are bilateral [4].

In general, the most common classification system divides PTX into:

- Spontaneous (non-traumatic)
  - Primary spontaneous—no predisposing lung disease or history of thoracic trauma
  - Secondary spontaneous—underlying lung abnormality is present
- Traumatic
  - Iatrogenic—caused by invasive medical procedures, e.g., central vein cannulation, fine needle aspiration and baro-trauma due to mechanical ventilation
  - Accidental—following direct injury to the thorax, e.g., penetrating chest injury and laceration of visceral pleura by a fractured rib [9, 10]

Pneumothorax may also be classified as:

- Simple pneumothorax—no shift of the heart or mediastinal structures
- Tension pneumothorax
- *or*
- Open—"sucking" chest wound
- Closed—intact thoracic cage [10]

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11.2 Risk Factors

It has been reported that incidence of nPTX is more frequent in males and is improved in various pulmonary disorders, such as respiratory distress syndrome (RDS) and meconium or blood aspiration syndrome [3, 11–13]. In particular, incidence of nPTX of 5–20% was found in infants with RDS, with and without the use of assisted ventilation, and of 20–50% in term infants affected by meconium aspiration syndrome [14]. Single-lung ventilation, high peak inspiratory pressure, high positive end-expiratory pressure application, and ventilator nonconformity are among the factors that can induce nPTX during mechanical ventilation [2, 15, 16]. Although there are some conflicting results, nPTX was also found to be associated with the use of continuous positive airway pressure (CPAP) and positive pressure ventilation [11, 17, 18]. The risk is also shown to increase in certain conditions including low birth weight, prematurity, low Apgar score, vacuum extraction, and elective cesarean delivery before 39 weeks [11, 19, 20].

In a Malaysian study, although 42% of the affected infants were of birth weight >2500 g, the incidence of nPTX was highest (7.3%) in the extremely low birth weight (<1001 g) infants. Among infants of birth weight between 1001 g and 1500 g, the incidence was only 3.4%. In a similar manner, the incidence of nPTX was a more common complication in the extremely preterm infants, being 6.8% in infants of gestation 26 weeks, 5.8% in the 27–29 weeks group, 3.4% in those of gestational age 30–32 weeks, and 3.4% in infants of gestation 33–36 weeks [21].

The Apgar score at 5th minute is also considered an important parameter in evaluation of the nPTX. A low Apgar score in 50% of nonsurvivors and in only 12% of survivors has been found in patients complicated by nPTX [14].

Furthermore, there is a strong association between modes of delivery and the incidence of nPTX, in particular in preterm neonates. It has been suggested that vaginal delivery might have a positive influence on the pulmonary system in neonates. Specifically, nPTX was significantly more frequent after cesarean section than after vaginal delivery. After an elective CS, the baby is not stressed and often has "wet lungs" followed by forced respiration that may lead to PTX. Moreover, cesarean section increases the need for mechanical ventilation, and, among neonates delivered by cesarean section at term or moderately preterm, the incidence of nPTX and respiratory distress has been reported to be significantly increased [22].

As far as potential maternal risk factors for nPTX are concerned, there was not found a significant difference in the proportion of infants with maternal diabetes mellitus, with different maternal ethnic groups, different gender groups, and different places of birth or born with multiple pregnancies [21].

11.3 Sign and Symptoms

Many infants in PTX are asymptomatic [22]. When symptoms do occur, they can include:

- Difficult breathing, use of accessory muscles to breathe, tightening of the neck muscles, and use of the chest and abdomen to aid breathing (retraction).
- Faster breathing. In particular, an increase of at least 10 per minute above the baseline in the respiratory rate is a reliable parameter with 77% sensitivity and 90% specificity to help determining the development of nPTX.
- Cyanosis/bluish discoloration of the skin as well as of the nails and tongue. This is considered an important symptom of nPTX and one of the vital signs to be noted.
- Flaring of the nostrils.
- Grunting with breathing.
- Irritability.
- Restlessness [22].

The time between onset of nPTX and a definitive clinical diagnosis was found to range from 1 to 10 h [5, 11, 23].

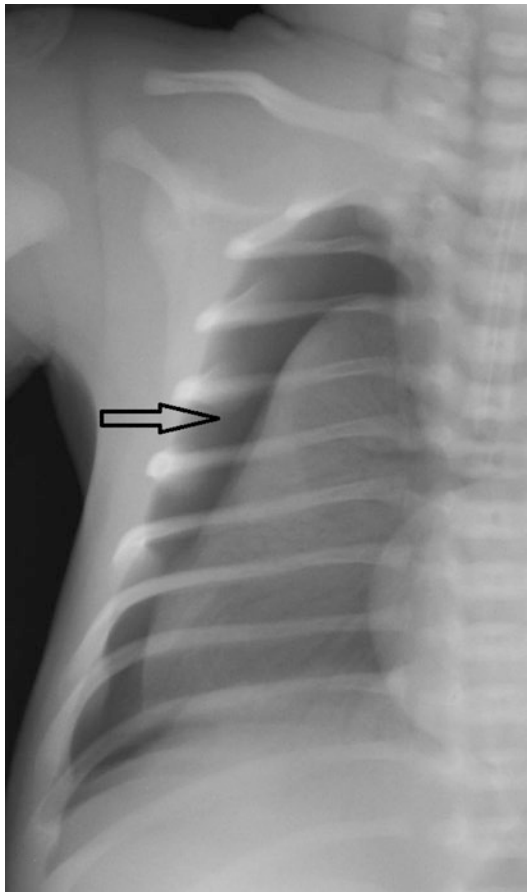

Fig. 11.1 Supine projection showing a large right-sided pneumothorax with an evident visceral pleural line (arrow)

11.4 Diagnostic Tools

11.4.1 Chest X-Ray

Radiographic diagnosis of PTX is usually straightforward [24]. However, a nPTX can be missed easily on supine position chest radiographs and, as a consequence, the diagnosis may be made even later [11, 25].

A visceral pleural line is seen without distal lung markings (Fig. 11.1). Lateral or decubitus views are recommended for equivocal cases. On standard lateral views, a visceral pleural line may be seen in the retrosternal position or overlying the vertebrae, parallel to the chest wall [24].

In the supine patient, air in the pleural space will usually be most readily visible at the lung bases in the cardiophrenic recess and may enlarge the costophrenic angle (the deep sulcus sign). Artifacts can mimic the presence of a PTX and should be born in mind during the evaluation of a chest X-ray. The medial border of the scapula can imitate a lung edge but once considered can be traced in continuity with the rest of the bone. Skinfolds overlying the chest wall can simulate a visceral pleural line. However, skinfolds are usually seen to pass outside the chest cavity, are straight or only minimally curved, and do not run parallel to the chest wall as with a true visceral pleural line [24].

11.4.2 Sonography

The use of ultrasound for detection of nPTX had been shown to be particularly sensitive and in fact some studies reported that it is comparable to chest X-ray [26].

The main ultrasonic features of nPTX are as follows:

- Lung sliding disappearance. In a PTX, there is air present that separates the visceral and parietal pleura and prevents visualization of the visceral pleura. In this situation, lung sliding is absent. The accuracy and reliability of the lung sonographic signs of lung sliding disappearance in diagnosing PTX were to be found up to 100% in sensitivity, 100% in specificity, and 100% in positive predictive value. However, lung sliding could be abolished in a variety of conditions other than PTX, including acute respiratory distress syndrome (ARDS), pulmonary fibrosis, large consolidations, pleural adhesions, atelectasis, right mainstem intubation, and phrenic nerve paralysis [27–30].
  The negative predictive value for lung sliding is reported as 99.2–100%, indicating that the presence of sliding effectively rules out a nPTX [31–33].

"Comet-tail artifacts" or "B-lines": Ultrasound demonstrates the loss of "comet-tail artifacts" in patients with a PTX. These reverberation artifacts are lost due to air accumulating within the pleural space, which hinders the propagation of sound waves and eliminates the acoustic impedance gradient [34]. In addition, "comet-tail" artifacts are generated by the visceral pleura, which is not visualized in a PTX [33]. The negative predictive value for this artifact is high, reported at 98–100% [28, 33, 35].

- "A-lines" are other important thoracic artifacts that can help in the diagnosis of pneumothorax. These are also reverberation artifacts appearing as equally spaced repetitive horizontal hyperechoic lines reflecting off of the pleura. The space in between each A-line corresponds to the same distance between the skin surface and the parietal pleura. In the normal patient, when "B-lines" are present, they extend from the pleural line and erase "A-lines," as they emanate out to the edge of the screen. "A-lines" will be present in a patient with a PTX, but "B-lines" will not. If lung sliding is absent with the presence of "A-lines," the sensitivity and specificity for an occult PTX is as high as 95 and 94%, respectively [33].
- Lung-point sign. The "lung-point sign" occurs at the border of a PTX. It is due to sliding lung intermittently coming into contact with the chest wall during inspiration and is helpful in determining the actual size of the PTX. The "lung-point sign" is 100% specific for PTX and defines its border [28, 36]. The location of the lung point is beneficial in determining the size of the PTX. Although the specificity is high, the sensitivity of the "lung-point sign" is relatively low (reported at 66%) and is not seen in cases of total lung collapse [36].

11.4.3 Other Signs

The "power slide" refers to the use of power (angiography) Doppler to help identify lung sliding. Power Doppler is very sensitive and picks up subtle flow and movement. If there is lung sliding present, power Doppler will light up the sliding pleural line with color flow.

The "lung pulse" refers to the rhythmic movement transmitted to the lung pleura in synchrony with the cardiac rhythm. The "lung pulse" is a result of cardiac vibrations being in poorly aerated lung. Cardiac activity is essentially detected at the pleural line when there is absent lung sliding [28].

11.4.4 Transillumination

Transillumination consists in the placement of a cord fiber-optic light source next to the infant's skin that should transilluminate the whole hemithorax in the presence of a large PTX. It should be compared to the other side of the chest for reference [37]. Transillumination is most useful in small babies.

In particular, the physician should lower the lights in the room to enable hyperlucent areas to be seen (if present) and place the transilluminator along the posterior axillary line on the side on which the air collection is suspected. Large infants require a bright source and a very dark room for transillumination to be visible, therefore this thechnique is only useful if it is positive. The transilluminator may be moved up and down along the posterior axillary line and above the nipple to detect any areas of increased transmission of light. Moreover, transilluminator should be placed in the third or fourth intercostal space on the left midclavicular line and angle the light toward the xiphoid process to detect any areas of increased transmission of light. In a negative result, a halo of light appears around the light source only. A false-negative result may occur in infants with a thick layer of subcutaneous fat, small air leaks, a weak light source, or a bright room. A false-positive result may occur with severe subcutaneous chest wall edema, pulmonary interstitial emphysema, or pneumomediastinum. Reported sensitivity is 87–100% and specificity 95–100% [37].

11.5 Management

nPTX may be managed with a variety of approaches, including observation ("watchful waiting"), simple needle aspiration (thoracentesis), or insertion of a chest tube (chest tube placement).

For asymptomatic patients who had PTX occupying less than 15% of hemithorax, no surgical intervention is usually required. Mild PTX may be treated conservatively; the rate of spontaneous reabsorption is about 1.2% of the volume of the hemithorax per 24 h and patients should be followed up with radiographs once daily. In this way, for example, if a patient has a 20% PTX, it will take approximately 16 days to resolve [2]. Differently, for symptomatic patients who had PTX occupying less than 15% of hemithorax or patients with PTX more than 15%, irrespectively of the symptoms, a drainage is suggested.

Thoracentesis may be the only intervention needed in an infant who is not mechanically ventilated and may be a temporary measure in an infant who requires ventilation [3, 38]. Thoracentesis consists in the insertion of a needle into the second or third intercostal space in the midclavicular line, passing just above the top of the rib in order to reduce the risk of lacerating the intercostal artery. Flow of air into a syringe confirms that the PTX has been reached by the needle, which should not be inserted further to avoid lung damage. Air could be aspirated with a 10–20 ml syringe (usually 23 or 25 gauge) or an angiocatheter (18–24 gauge). If using an angiocatheter, the plastic catheter can be left in situ [1, 39].

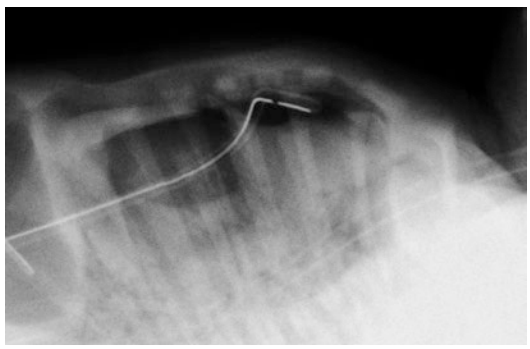

Fig. 11.2 Latero-lateral projection displaying a chest tube draining the anterior pleural space in a right-sided pneumothorax

Chest tube (10 or 12 French size) insertion is usually obtained in the anterior pleural space (Fig. 11.2). After the preparation of the skin with antiseptic solution and a local anesthesia of the subcutaneous tissues, a small incision is made through the skin in the midaxillary line in the sixth intercostal space, the subcutaneous tissue is dissected, and a subcutaneous track to the intercostal space is made. A trocar might be used to facilitate the penetration of the tube, even if this technique may be associated with an increased risk of lung perforation. The chest tube is passed into the pleural opening, turned anteriorly and directed to the location of the PTX, and then connected to a Heimlich valve or an underwater seal with continuous suction at a pressure of 10–20 cmH_2O. A less traumatic approach consists of the use of pigtail catheters, which are usually smaller (8–10 French) and possibly more suitable for preterms. Pigtail catheters can be placed with a Seldinger technique [39].

Both the procedures can be performed under radiological or ultrasonographic guidance.

A post-drainage chest radiograph is essential to document resolution of the PTX, detect complications, and ensure a satisfactory drain position. After satisfactory resolution of the PTX, the drainage catheter can be removed and a further follow-up radiograph obtained to detect recurrence. A straight radiopaque line is occasionally seen here along the line of the removed tube, known as a "drain track." This may be misinterpreted as a recurrent air leak, but its straight course and precise relation to the drain position on the radiograph before removal are usually conclusive [24]. Fibrin glue is an effective treatment for intractable PTX, but this procedure has significant risk [40].

The literature does not clearly define which is the best option for the treatment of PTX, especially if hemodynamically stable. There is insufficient evidence to determine the efficacy and safety of the two techniques. Mortality rate did not differ between the two groups [24].

11.6 Outcome

Although nPTX is one of the few treatable causes of respiratory difficulty in the early days of life, the mortality rate remains high, ranging between 13% and 65% in the literature [14, 40–42]. The variance in mortality is probably large due to differences in gestational age, underlying diseases, and advances in neonatology.

nPTX is also associated with significant morbidity. In this regard, it has been reported that 59% of the neonates affected by PTX required drainage, and about half needed mechanical ventilation. The majority of the nPTX in the non-drainage treatment group could be managed with nasal CPAP and oxygen [43].

Because neonates with RDS and hypoxemia are managed by increasing the inflating pressure and application of positive end-expiratory pressure, the potential for tension nPTX is increased. Additionally, nPTX during respiratory distress is associated with increased risk of intraventricular hemorrhage, chronic lung disease, and subsequent death [14, 44, 45].

11.7 Chylothorax

11.7.1 Introduction

Chylothorax is a rare condition, characterized by chyle collection in the pleural space, secondary to leakage from lymphatic system. Although it rarely represents the cause of pleural effusion in children [46], it is the most frequent cause in newborn age [47–49]. Chylothorax can be congenital, as isolated malformation or associated with other abnormalities, or acquired, as iatrogenic or traumatic. Clinical manifestation depends on the amount of accumulated chyle, ranging from asymptomatic patients or with only mild respiratory distress to life-threatening conditions that require urgent drainage and other resuscitative management. Moreover, because chyle is composed of fats, immune cells, and proteins, persistent losses may be associated with malnutrition, immunodeficiency, and metabolic acidosis. In congenital chylothorax, severe fetal pleural effusion can compromise normal lung maturation and progress to fetal hydrops, resulting in pulmonary hypoplasia and premature birth, with high rate of perinatal mortality [50, 51]. Generally, chylothorax resolves with nonoperative measures (respiratory and life support, diet restriction, and medical therapy), but, if spontaneous healing does not occur, surgical treatment becomes necessary [52, 53]. Recently prenatal therapies have been proposed for congenital chylothorax in order to improve the perinatal outcome [54–56].

11.7.2 Embryology and Anatomy

The lymphatic system, essential for fluid homeostasis, immune responses, and fat absorption, is an endothelium-lined network of blind-ended capillaries found in nearly all tissue, draining via collecting vessels into large trunks that eventually empty into the blood circulatory system [57]. This system begins its development in the sixth gestational week through a centrifugal budding process starting from six different outpouchings of the venous endothelium: two jugular sacs, two femoral sacs, a retroperitoneal sac, and the cisterna chyli. These sacs grow longitudinally and link together by the ninth gestational week, forming a bilateral system of lymphatic trunks connected by numerous horizontal and diagonal anastomoses. The final thoracic duct is the result of resorption of the superior portion of the right trunk and the inferior portion of the left trunk [58]. This explains the potential for anatomical variations in lymphatic pathways presenting in 35–50% of the population [46, 59, 60].

From the lacteals, lymphatic fluid is collected in the cisterna chyli, located at the level of the second lumbar vertebra, from which it passes into the thoracic duct and then reaches the venous system. The duct passes through the aortic hiatus of the diaphragm and ascends in the posterior mediastinum to the right of the midline between the azygous vein and the descending aorta. At the fourth to sixth thoracic vertebrae, the duct crosses to the left and continues its ascent into the left neck, where it forms an arch that rises 3–4 cm

above the clavicle. It then drains into the left subclavian vein near the junction of the subclavian and left internal jugular veins [61].

11.7.3 Physiopathology

Chyle is a milky fluid produced by mucosal cells of the small bowel during digestion and consists of emulsified fats (especially triglycerides and cholesterol), electrolytes, proteins, glucose, and cellular elements, most of which are small lymphocytes (≥80%). At birth or after fasting, chyle is clear because it is lacking in fats. The thoracic duct transports about 1.4 mL/kg/h of chyle, but the flow varies depending on different factors, particularly fatty meals may increase up to ten times the basal flow [62, 63]. Chyle loss can result in a serious state of depletion characterized by hyponatremia, hypoproteinemia, metabolic acidosis, and lymphocytopenia [64, 65].

11.7.4 Etiology

There are several causes of pediatric chylothorax, grouped into two main categories: congenital and acquired.

Congenital chylothorax is the most common form of pleural effusion in the first few days of life [47]. The studies have reported an incidence range from 1:5775 to 1:24000 in live-born neonates, a predominance of male patients with a male-to-female ratio of 2:1 [48, 51, 66], and a prevalence of bilateral forms. However, right-sided chylothorax has been described as more frequent in unilateral presentations, because of the anatomy of the thoracic duct [47, 50]. Congenital chylothorax may occur alone, secondary to malformation of the lymphatic system or in combination with genetic syndromes (Down syndrome, Turner syndrome, and Noonan syndrome) and chromosomal anomalies [67, 68]. Pulmonary lymphangiomatosis (focal proliferation of well-differentiated lymphatic tissues) [69–71] and lymphangiectasia (diffuse dilatation of the interlobular and subpleural lymphatics) [72–74] are the two major lymphatic abnormalities associated with chylothorax, but the atresia of the thoracic duct may be another cause [75, 76]. Congenital chylothorax may be discovered in the antenatal period and can be associated with hydrops fetalis, whose presence is the most important predictor of outcome, decreasing the overall survival from 75% to 24% [77–79]. Other associations with uncommon disorders, such as mediastinal neuroblastoma and thyrotoxicosis, have been reported in newborn [80, 81].

Acquired chylothorax results from iatrogenic or traumatic injury of the thoracic duct. It occurs as a postoperative complication after surgery involving structures in the neck and thorax, especially after repair of cardiovascular anomalies, congenital diaphragmatic hernia, and esophageal atresia [82–85]. Other causes are catheterization of the subclavian vein, thrombosis of the superior vena cava or subclavian vein secondary to central venous catheters [86, 87], chest tube insertion [88], and traumatic delivery with trunk hyperextension [89]. Furthermore, cases of abuse leading to rupture of the thoracic duct have been reported in infants [90, 91].

11.7.5 Clinical Manifestations

The onset symptoms of chylothorax are usually related to accumulation of lymphatic fluid within the pleural cavity. Then, symptoms of respiratory distress such as tachypnea, dyspnea, cyanosis, and chest retraction develop in association with signs of pleural effusion (dullness on percussion and reduction of breath sounds on the affected side, mediastinal shift to the opposite side) [48].

Timing of the clinical manifestations varies according to the type of chylothorax. Congenital chylothorax, antenatally discovered, can alter normal lung development, resulting in a respiratory distress at birth; however, in absence of pulmonary hypoplasia, symptoms become evident within 2 weeks of life. In acquired chylothorax an interval of 1–2 weeks generally occurs between the injury and the appearance of pleural effusion. Lymphatic fluid extravasation, in fact, collects first extrapleurally in the posterior mediastinum and only after mediastinal pleural rup-

ture accesses to the pleural space producing pulmonary compression. The time is shortest when there is a direct injury to the thoracic duct (5–7 days) and longest when there is high pressure or thrombosis of the vena cava (10–14 days).

The effects of prolonged loss of chyle may include malnutrition, fluid and electrolyte imbalance, metabolic acidosis, and finally immunological compromise because of lymphocyte depletion and hypogammaglobulinemia with high risk of nosocomial infections and sepsis [92].

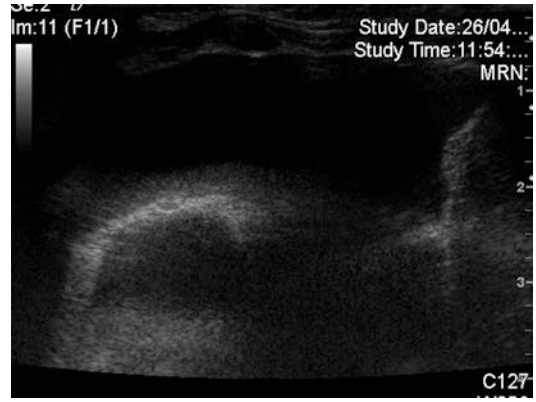

Fig. 11.4 Sagittal view of pulmonary ultrasound demonstrating the presence of pleural effusion

11.7.6 Diagnosis

Chest radiograph can reveal signs of pleural effusion: opacification of one or both hemithoraces with compression of lung and displacement of mediastinal structures in unilateral chylothorax (Fig. 11.3). However, in premature babies the diagnosis is not simple, because of concurrent pulmonary disease. In these cases ultrasound is a useful diagnostic method of detecting chylothorax (Figs. 11.4 and 11.5). Nevertheless, diagnosis must be confirmed with the analysis of drained pleural fluid. Initially the pleural fluid is serous and becomes chylous when milk feeding is started. Typical chyle is composed of elevated

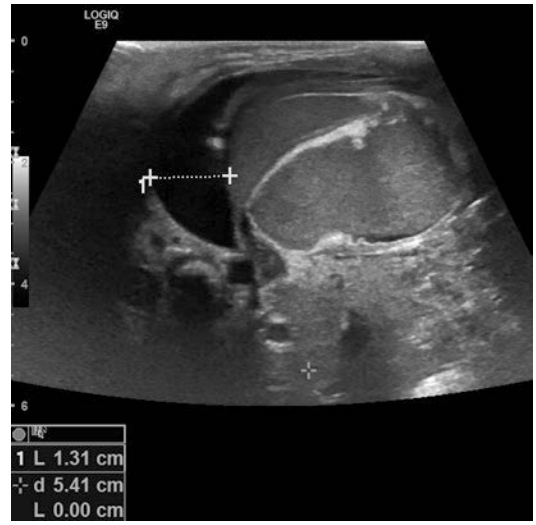

Fig. 11.5 Transverse view of pulmonary ultrasound demonstrating the presence of pleural effusion

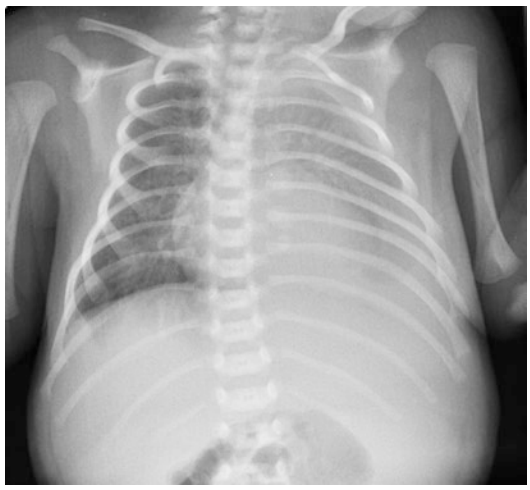

Fig. 11.3 Chest X-ray showing opacification of the left hemithorax

total protein, albumin, and electrolyte levels, presence of white blood cells with a predominance of lymphocytes, and elevated triglycerides, cholesterol, and total fat levels. Total fat more than 400 mg/dL with triglycerides greater than 110 mg/dL and lymphocyte count 80–100% of white blood cells are useful diagnostic tool in differentiating chylothorax from other types of pleural effusions. However, in unfed newborn fat content of the fluid is low and the amount of proteins and electrolytes is similar or inferior to the serum. Therefore, in a fasting neonate, the most

useful test for diagnosis of chylothorax is to perform a complete blood cell count and differential on the fluid and, when lymphocytes exceed 80–90% of the white blood cells, a lymphatic effusion can be confirmed [93]. If making a positive diagnosis of chylothorax is easy by examination of pleural fluid, its mechanism and the integrity of thoracic duct and its branches are difficult to determine.

Lymphoscintigraphy is a useful test for etiopathogenetic diagnosis in refractory chylothorax. This diagnostic tool can be combined with single-photon emission computed tomography-computed tomography (SPECT-CT), providing more specific anatomical information [94].

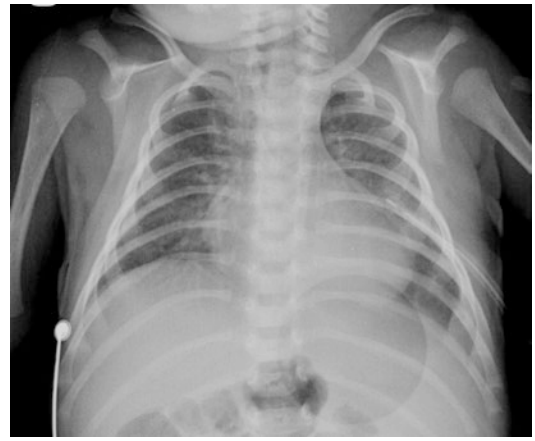

Fig. 11.6 Pleural effusion resolution after chest tube placement

11.7.7 Therapy

Supportive and conservative methods (effusion drainage, mechanical ventilator support, and dietary restriction) are considered as first-line treatment in patients with chylothorax, accounting more than 80% of successful cases [46]. Surgical therapy should be kept into account if medical treatment fails to decrease chyle flow and allow thoracic duct healing [95]. Most authors recommend at least 2–4 weeks of non-operative therapies, before surgery is considered [96, 97]. However, these series are not specifically congenital cases, in which medical management has been associated with mortality rates up to 20% [51]. Then, if the infant's nutritional or metabolic status declines measurably during that time, surgical intervention should be undertaken.

Management of chylothorax primarily involves aspiration of the pleural fluid (thoracentesis) for diagnostic purpose and immediate relief of respiratory failure. In severely ill patients, assisted ventilation may be necessary. Chest tube insertion for continuous drainage of the pleural space is indicated if the effusion causes respiratory symptoms or if the effusion recurs [46]. It keeps the lungs fully expanded, which is necessary for sealing chyle leakage (Fig. 11.6). Time to cessation of drainage generally ranges from 1 to 4 weeks, although more recent authors have recommended more aggressive treatment in the case of high output or persistent leak [51, 66]. In fact chest tube insertion for a long period of time results in hypoproteinemia, electrolytes loss, lymphopenia, and prolonged ventilator use with high risk of morbidities and mortality [65]. Therefore, if the site of leaking is identified and the amount of daily drainage is high, early surgery is suggested, because it shortens the duration of chest tube insertion, reducing the risks of its complications [98].

Nutritional support aims to provide adequate caloric intake preventing malnutrition and to minimize chyle production waiting for leakage to heal; it ranges from aggressive fasting with total parenteral nutrition (TPN) to medium-chain triglyceride (MCT)-enriched formula. MCT are absorbed directly into the portal venous system, bypassing lymphatic drainage and so not contributing to chyle flow; however even water intake by mouth and a formula containing MCT can cause reaccumulation of pleural effusion [46, 63, 99]. Most reports indicate little difference in outcome between parenteral nutrition and high MCT enteral nutrition, as initial therapy, with about three-fourths of patients responding to these measures and chest drainage alone [100]. Nevertheless, the generally suggested approach consists in the use of TPN until the drainage is minimal, followed by enteral nutrition with a formula high in MCT and eventually by normal

feeding. Close monitoring of reaccumulation of pleural fluid must be performed either by chest tube drainage or ultrasound [99]. Supplementation of lost electrolytes and proteins, such as albumin, gamma globulin, fibrinogen, and fat-soluble vitamins, is frequently needed.

A recent additional treatment to the medical options is represented by the pharmacological therapy with somatostatin or octreotide [101–105]. Somatostatin is an endogenous hormone with actions that include inhibitory effects on the release of growth hormone, insulin, and glucagon. Octreotide is a synthetic somatostatin analogue more widely used because of its longer half-life period, greater potency, and the option of subcutaneous administration without necessity of continuous infusion. They act on gastrointestinal receptors to reduce intestinal blood flow by vasoconstriction of the splanchnic vessels, decrease motility, and inhibit gastric, pancreatic, and biliary secretions, thus reducing fat absorption and the amount of chyle production [102, 106]. These drugs have been used in the treatment of both the acquired and the congenital chylothorax, appearing to be a safe and effective adjuvant therapy in cases resistant to dietary measures. However, a 2010 Cochrane review [105] was unable to draw any conclusions regarding its use, and in a following study [103], the authors felt that the decrease of pleural effusion, observed in their patients, might reflect the natural history of congenital chylothorax, not identifying a consistent effect of octreotide. In a recent relatively large group of neonates with congenital chylothorax, somatostatin/octreotide treatment significantly reduced the volume of pleural drainage and the need for respiratory support without side effects and without need for surgical procedure in any patient [107]. Nevertheless, there is no consensus on the optimal timing of introduction, route, dosage, and duration of treatment, due to the small numbers of reported cases and the need for randomized controlled trials. Moreover, a current retrospective review, conducted in order to develop an evidence-based management algorithm for infants with chylothorax, concluded that octreotide has no advantage over complete enteric rest/total parenteral nutrition alone [108]. Another agent used in the treatment of chylothorax is nitric oxide. Some case reports described its use for the successful management of refractory postoperative and congenital chylothorax in neonates with pulmonary and central venous hypertension. Nitric oxide decreases the pulmonary artery pressure that causes functional systemic venous obstruction and then persistence of chylous leak [109, 110]. Recently, oral sildenafil, a specific inhibitor of phosphodiesterase-5, was reported to be effective in resolving a case of congenital chylothorax secondary to congenital pulmonary lymphangiectasia in a late preterm infant, in whom octreotide was unsuccessful. Its action mechanism involves generation of new lymphatic vessels, allowing resolution of lymphatic obstruction and then chylothorax [111].

If conservative treatment fails, surgical therapy is performed. No treatments have been subjected to a randomized controlled trial, and then there are no standardized guidelines. Some centers use daily drainage as a guide for clinical improvement or failure, with >10 ml/kg/day draining failure after 4 weeks of nonsurgical management [96]. Actually, there is no defined amount of output that suggests nonresolution, but drainage that does not gradually decrease or that fluctuates is less likely to respond to nonoperative management [98]. Surgical options, often used in combination, include thoracic duct ligation, pleuroperitoneal shunt placement, pleurodesis, and pleurectomy. If the site of leakage can be identified, ligation of the thoracic duct represents a definitive treatment of chylothorax. Fibrin glue and argon beam coagulation have also been used as an adjunct for ill-defined areas of leakage, especially in small premature infants [112, 113]. The traditional surgical technique involves a posterolateral thoracotomy and attempt ligation of the thoracic duct, where it passes into the chest. This area is hard to visualize, especially in an infant. Thoracoscopy has several advantages, including a magnified view that may aid in identification of the duct and the site of chyle leak. Moreover, this minimally invasive approach significantly reduces the postoperative pain and avoids future chest wall deformity. The possibil-

ity of combining direct sealing, local pleurodesis, and fibrin glue application results in high rate of successful sealing of the leak [114]. Pleuroperitoneal shunt is a method to treat chylothorax that connects the pleural space to the peritoneal cavity, providing chyle drainage without losing the fluid. Shunts have been used with success in children refractory to conservative treatment and also in preterm infants and in fetuses [77, 115]. However, this procedure is less performed today in neonates because of severe complications, such as shunt occlusion and displacement, reported in 30–50% of cases [116]. Pleurodesis can be performed either chemically, instilling sclerosing agents (povidone-iodine, OK-432, tetracycline, talc) into the pleural cavity through the chest tube, or surgically mechanical irritating the parietal pleura, possibly in association with pleurectomy. This procedure has been used in cases where medical therapies failed and duct ligation was not performed. During the last years, chemical pleurodesis has been proposed as an alternative to surgery in young infants, in order to limit aggressive procedures in these patients. Oxytetracycline has been described as effective in the treatment of chylothorax in a premature baby [117]. OK-432 has been used as an effective sclerosing agent in neonates and in fetuses affected by severe chylothorax associated with nonimmunologic hydrops [118, 119]. Povidone-iodine is reported as a safe and effective option to treat refractory chylothorax in newborns, and, considering reported results (success up to 80% of cases, no mortality and side effects manageable without long-term sequelae), it seems to be the agent of choice for chemical pleurodesis, although multicenter randomized studies are needed [120]. Infants with congenital chylothorax are exposed to significant fluid shift and potential serious metabolic, immunologic, and nutritional complications [121]. The high risk of nosocomial infections in these patients suggests the need for early surgical intervention. However, in congenital cases, the thoracic duct can be more difficult to locate and ligate because of the variations in the course, shunts malfunction because of fibrinous clotting or unfavorable pressure gradients, and pleurodesis has variable success rates [96]. A recently proposed safe and successful option is thoracoscopic parietal pleural clipping [98], a relatively easy technique, resulting in rapid control of the chylothorax with drop in chest tube output. An alternative described method is the mass ligation of the thoracic duct and surrounding tissue between the aorta, azygos vein, and esophagus, adjacent to the vertebral body [122]. Another method to manage chylothorax is fluoroscopically guided percutaneous embolization of the thoracic duct, a successful interventional strategy even in children as well as in adults [123, 124]. However, literature regarding pediatric lymphangiography with thoracic duct embolization is limited to some case reports, because results a challenging procedure, especially in infants. In fact in a series of six children aged 9 months or younger, central lymphatics were visualized in only two cases, both successfully treated. The authors concluded that in these smaller children, technical success is decreased, given recommended low dosages of contrast and the small size of lymphatics [125].

11.7.8 Prenatal Management

Congenital chylothorax occurs in 1 in every 12,000–15,000 pregnancies and is the most common cause of pleural effusion in the neonatal period [126]. Because the normal mean percentage of lymphocytes in the fetal blood is >80%, this parameter cannot be used prenatally to characterize an effusion as chyle; therefore the term hydrothorax is used indifferently [54]. With the advent of prenatal ultrasound, chylothorax has been diagnosed with increasing frequency, presenting variable natural history, ranging from cases with spontaneous resolution to cases showing progression to hydrops that can be life-threatening [127]. Overall mortality has been reported to be between 22% and 53% based on associated findings (abnormal karyotype, congenital anomalies, and hydrops fetalis), gestational age, and chylothorax duration and severity [99]. Secondary causes of hydrothorax, including chromosomal anomalies, infections, cardiac malformations, and other structural abnormalities,

have a higher rate of fetal demise and neonatal mortality [126]. Chylothorax has a much better prognosis when diagnosed after birth than when discovered in utero, since during fetal life pleural fluid can act as a space-occupying mass resulting in lung growth impairment and then pulmonary hypoplasia [128].

With advances in fetal therapy, fetuses with severe pleural effusions seem to have an improved outcome [129]. Prenatal interventions, such as repeated transabdominal thoracocentesis, thoracoamniotic shunt placement, and, less frequently, in utero pleurodesis, may alter natural course, improving survival rate [54, 55, 130]. The comparative efficacy of these therapies remains controversial. In fact, the indications for each intervention may vary, depending on effusion progression, state of pregnancy, and overall condition of the fetus [131]. Benefits of antenatal therapy consist in prevention of pulmonary hypoplasia, resolution of fetal hydrops, and facilitation of neonatal resuscitation and respiratory management in the delivery room. Especially among the cases with prenatal diagnosis at ≤34 weeks of gestation, infants who received prenatal therapy had a significantly higher survival rate, compared to infants who did not receive prenatal therapy [56]. However, complications have been described after these procedures, especially after shunt placement. Early complications include preterm labor and premature rupture of membranes with prematurity, direct chest wall trauma, shunt migration or obstruction, and fetal demise [128, 132, 133]; chest wall deformity has been reported as a late complication, more common if the shunt is placed before 20 weeks of gestation [134]. Factors associated with poor prognosis after antenatal detection of fetal pleural effusion are abnormal karyotype and accompanying genetic syndrome, fetal hydrops, prematurity, low birth weight, and early-onset pneumothorax [127, 131]. A recent study established the prenatal factors associated with neonatal survival, namely, thoracoamniotic shunting and reversal in utero of fetal hydrops, significantly improving survival; also the longer the interval between thoracoamniotic shunting and birth, the more likely is neonatal survival [135]. A management algorithm for fetal pleural effusion has been proposed [54], but no consensus has been reached regarding the management of congenital chylothorax in the prenatal period. Although the antenatal management is still a matter of debate, early diagnosis, prenatal thoracocentesis, and aggressive nonoperative postnatal treatment seem to decrease the mortality rate.

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12 Congenital Pulmonary Airway Malformations: From the Prenatal Diagnosis to the Postoperative Follow-Up

Arnaud Bonnard

12.1 Introduction

Since a couple of years now, several things evolved and changed for congenital pulmonary airway malformations (CPAM). From the understanding of the malformation to the prenatal diagnosis and the rising place of the minimally invasive surgery, CPAM became a subject of interest for all pediatric surgeons all over the world. Most of the recent publications are related to the surgery itself and the growing place of minimal invasive surgery helped by new instruments pushing further the indications. This does not have to hide the recent progresses made in the comprehension of the pathology of these malformations and especially the closed relations between CPAM and pleuropulmonary blastoma (PPB). In the first part, we will talk about the classification and the pathology of these malformations. Then, we will move to the prenatal diagnosis and specifically the prenatal procedures sometimes required in the severe form of CPAM. At last, we will talk about surgery and the follow-up.

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12.2 Histopathology and Lung Development

Congenital pulmonary malformations encompass all the cystic lung diseases which found an origin during the morphogenesis. This includes congenital cystic adenomatoid malformation (CCAM), pulmonary sequestration, bronchogenic cyst, and pulmonary pneumoblastoma (PPB). The formation of cysts may be responsible of prenatal complications principally related to the volume of the cyst (hydrops, fetal distress) and the compression of the surrounding organs. Although many genes have been identified to explain and better understand the lung morphogenesis, the main reason of CPAM occurrence remains unknown.

12.2.1 Lung Development

The classical lung organogenesis has been described in five overlapping steps [1]. During the embryonic phase (26–52 days of gestation), an endodermal outgrowth derived from the primitive foregut divides and forms the early tracheobronchial tree. In the pseudoglandular phase (52 days to 16 weeks of gestation), the primitive airway epithelium begins its differentiation in neuroendocrine, ciliated, and goblet cells, while cartilage and smooth muscle cells emerge from the mesenchyme. The airway

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branching pattern is completed in the canalicular or acinar phase (16 to 24–26 weeks of gestation), and the prospective gas-exchange region is developing: the respiratory bronchiole increases, vascularization of peripheral mesenchyme increases, and distal cuboidal epithelium differentiates into alveolar types I and II cells with the start of the surfactant production. Development of the distal pulmonary circulation by vasculogenesis with capillaries is present at 20 weeks. The saccular phase (24–26 to 36 weeks of gestation) is characterized by maturation of the surfactant system, growth of the pulmonary parenchyma, and thinning of the connective tissue or interstitium, going with an important capillary network development. The alveolar phase extends from 36 weeks of gestation to at least 18 postnatal months in which true alveoli, with increased acinar complexity and increased gas-exchange surface area, are formed. This important point is considered when the pediatric surgeon is dealing with a CPAM and especially when the time to undergo for surgery has to be decided.

12.2.2 Genes' Involvement

The discovery of numerous genes involved in lung malformation revolutionized the idea that congenital lung malformation was coming from a simple incident occurring during one of the five steps previously described. Moreover, these genes share a common molecular pathway between different malformations either the cystic adenomatoid disease or the PPB making the decision to be active for the surgeon instead of conservative crucial.

The current idea gives a preponderant role on bud elongation, bud induction, and bud arrest under the influence of different signaling pathway [2]. Fibroblast growth factor (FGF) signaling pathway appears to play an important role with its tyrosine kinase receptor allowing to stimulate migration, proliferation, differentiation, and survival. In this family, the role of FGF10 and its receptor FGFR2 in lung branching is of particular interest (Fig. 12.1). It appears as a driving force for branching capable to induce epithelial proliferation and budding in lung organ cultures. Thus, the hypothesis that

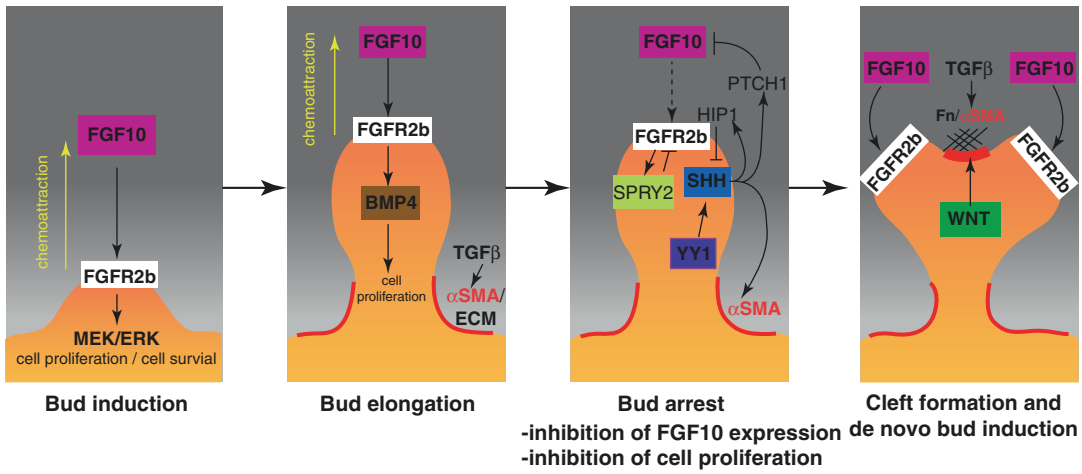

Fig. 12.1 Lung branching morphogenesis. *From: O. Boucherat. Paediatr Resp Rev 19 (2016) 62–68. Reproduced with the permission of the authors. Mesenchyme is depicted in gray and the epithelium in orange. FGF10 is expressed dynamically in the mesenchyme. Epithelial cells, expressing the receptor FGFR2b, respond to the FGF10 gradient by bud formation and bud extension toward the local source of FGF10. As the bud elongates, the expression of SPRY2 and SHH increases. Both act in a negative feedback loop that modulates FGF10 expression and activity leading to inhibition of bud outgrowth. Subsequently, new foci of high FGF10 concentration emerge and induce bud tip bifurcation and cleft formation. In this area, the synthesis of ECM components induced by TGFb and WNT signaling pathways prevents further budding*

FGF10 controls the directional outgrowth of lung buds during branching morphogenesis has been established [3, 4]. Different signaling pathways (sonic hedgehog (SHH), etc.), with feedback control and inhibition control, are playing also an important role in this phenomenon. Mouse knockout has been used to demonstrate this hypothesis. This underlined the similar molecular pathway shared by lung morphogenesis and pleuropulmonary blastoma (PPB). Based on findings gained in animal models and microscopic similarities between CCAM and type I PPB, it is tempting to speculate that CCAM and PBB constitute distinct but related diseases whose etiology derives predominantly from the deregulation of SHH-FGF10 signaling. The majority of the research studies have been done on surgical specimens; thus, data on human fetus are lacking, and it is still difficult to strictly relate these two entities. Nevertheless, this must stay in the surgeon's mind when he/she is dealing with pulmonary malformation.

12.3 Prenatal Diagnosis

Progress has been made in both diagnosis and prenatal intervention on fetus diagnosed with congenital pulmonary malformation. In 2009, the incidence has been reported to be between 1/11000 and 1/35000 [5]. There is an increasing awareness of clinicians and the universal use of latest ultrasound technology making the diagnosis more frequent. Recently, the incidence has been reported to be 1/7200 [6].

Two principal US findings are described prenatally when a pulmonary malformation is suspected usually on the second ultrasonography screening: hyperechogenic lung or cystic lung. Bronchogenic cyst is usually diagnosed easily showing an isolated cystic mass in the chest. Several questions are coming then for an adequate prenatal management.

12.3.1 What Term Is It?

It's well known that these malformations used to decrease in size along the gestation. This has been reported in literature [7]. In a personal non-published series, 37 patients were diagnosed prenatally with 12 pulmonary sequestration, 20 cystic adenomatoid malformation, and 5 hybrid lesion. Twenty-four (65%) decrease in size, and 11% increase, while 24% remained stable and neither progressed nor regressed. This allows predicting the prenatal evolution and the clinical presentation at birth. A serial US monitoring is necessary to detect any sign of fetal distress or predict a neonatal respiratory distress immediately after birth, meaning the mother should be transferred to a level 3 pediatric center before delivery.

12.3.2 Are There US Findings Predictive of Neonatal Respiratory Distress?

Different US findings have been reported in the literature to predict this postnatal evolution [8]. Measurements of mass-to-thorax ratio (MTR), congenital pulmonary airway malformation volume ratio (CVR), and observed-to-expected lung-to-head ratio (o/e LHR) were conducted and correlated to fetal or neonatal morbidity and mortality and/or the need for prenatal intervention. Fetuses with a CVR of <0.91 were significantly less likely to experience adverse outcome or need for prenatal intervention with good sensitivity, specificity, and positive/negative predictive value. A MTR (mass-to-thorax ratio) of <0.51 had a negative predictive value of 0.96 of adverse events with a sensitivity of 0.95. The o/e LHR was reported to be less sensitive with sensitivity of 0.84 and specificity and positive predictive value of 0.73, 0.68, and 0.52, respectively. MRI is not always necessary, but for bilateral lesion, it can help to decide for future management.

Basically, the size, the mediastinum shift persistent during the third trimester, and the association with hydrothorax are good indicators for in utero transfer before delivery in a level 3 center with NICU and pediatric surgery available. In this case, the risk for a neonatal respiratory distress is high and very predictive of an early neonatal surgery.

12.3.3 Are There Any Signs of Fetal Distress?

Prenatal surgery may be required in case of severe neonatal distress. If a hydrops fetalis developed during pregnancy, indications to do something is principally based on the type of CPAM. Macrocystic form with hydrops is a good indication of drainage [9]. It may improve the neonatal survival rate ($P < 0.005$). Drain can migrate and be dislodged. For this reason, a serial monitoring is needed after drain placement to make sure that the hydrops is resolving and the drain is still in place. Sometimes, an iterative drainage is required.

In case of microcystic form (hyperechogenic lung), drainage is not indicated. Steroids have been reported to be efficient in this indication [10]. In this retrospective study, all patients referred to the center with CPAM were reviewed. Betamethasone was given to 13 patients with microcystic form of which 9 presented with a nonimmune hydrops. Hydrops resolved in seven (77.8%) of nine patients. Not all fetuses respond to a single course of steroids, and, sometimes, multiple courses might be indicated [11]. In this retrospective study, single-course recipients demonstrated a reduction in lesion size and resolution of hydrops in 82% and 88% of patients, respectively, compared to 47% and 56% in recipients of multiple steroid courses. Survival of multiple-course patients (86%) was comparable to that of single-course patients (93%) and improved compared to non-treated historical controls. Multiple-course recipients demonstrated an increased need for open fetal surgery and may be predictive of postnatal surgery at a younger age.

At last, fetal surgery has been purposed for some cases [12]. A retrospective review of fetuses undergoing either open fetal surgery or steroids for predominantly microcystic CPAM with hydrops fetalis was conducted. Thirteen patients were treated with steroids, and 11 patients got open fetal surgery. In the steroid group, 12 (92%) survived to delivery versus 9 (82%) in the open fetal surgery group. Only five (56%) in the open fetal surgery group survived to neonatal discharge compared to ten (83%) in the steroid group. The authors concluded that steroids should be considered for first-line therapy in these cases.

12.3.4 What Prenatal Workout Should Be Done?

The main question is about the possibility to have associated lesions and malformations in fetus diagnosed prenatally with CPAM. Although rare cases of CPAM associated with tracheo-esophageal fistula or corpus callosum anomalies have been reported [13], included in the new 5 types of Stocker's classification [14] where Type I and Type III were described to be associated sometimes with renal hypoplasia and cardiac abnormalities, prenatal amniocentesis for karyotype is not usual. Ultrasound large screening looking for other malformations should be done anyway routinely as a "non-CPAM" fetus. In contrary, look for prenatal factors predictive of postnatal respiratory distress, and patients needing early surgery are required. MRI has been proposed and reported in this indication. In our current practice, the MRI is not done systematically but only for fetus presented with bilateral lesion, and/or important mediastinal shift persistent during the 3rd trimester with an important volume. Zamora and Coll studied and reported in 2014 the need for the lung mass volume ratio (LMVR), observed/expected normal fetal lung volume (O/E-NFLV), and the lesion-to-lung volume ratio (LLV) [15]. LMVR was the strongest predictor of fetal hydrops (OR, 6.97, 1.58–30.84; $P = 0.01$) of NNRD (OR, 12.38, 3.52–43.61; $P \leq 0.001$), and its value >2.0 predicted worse perinatal outcome with 83% sensitivity and 99% specificity (AUC = 0.94; $P < 0.001$).

12.3.5 Do Parents Need a Prenatal Counseling?

Every parent should be seen for a CPAM diagnosed prenatally. Explanation on the CPAM, type, predictable evolution along the pregnancy, management at birth, surgery, and long-term outcome has to be discussed with them. To date, no paper have been published reporting the effect or the influence of the prenatal CPAM diagnosis on the outcome. Recognition of prenatal factors predictive of neonatal respiratory distress as described before is a crucial point and certainly

may play a role on the good outcome of such malformation with the level 3 in utero transfer, allowing a quick postnatal management for these babies.

12.4 Postnatal Management

12.4.1 At Birth

Because more than 90% of babies diagnosed prenatally with CPAM are doing great, these are only managed by the pediatrician without even being seen by the surgeon. A chest X-ray should be done to rule out any mediastinal shift related to an emphysema or a large cyst which can be complicated by a pneumothorax (Fig. 12.2). Usually, this X-ray is not showing something in particular, and the baby is sent back home before being followed up in an outpatient clinic. In our center we used to perform a CT scan between 1 and 3 months old.

About 10% of patients present a neonatal respiratory distress requiring for the worse cases of mechanical ventilation and an admission in an intensive care unit [16]. A discussion between a pediatrician, a surgeon, and an anesthesiologist is important to decide whether or not to undergo for surgery and about the timing. A CT scan is often done before the surgery to plan the type of resection and give an accurate explanation to the parents (Fig. 12.3). Usually, postoperative courses are simple allowing to discharge back home the baby after few days, depending essentially on the term of birth, his/her weight, and the possibility to wean the mechanical ventilation off. We have to keep in mind that babies with severe CPAM with macrocyst diagnosed prenatally would require for most of them prenatal procedures such as repeat puncture and thoracoamniotic shunt placement. Both are at risk of preterm

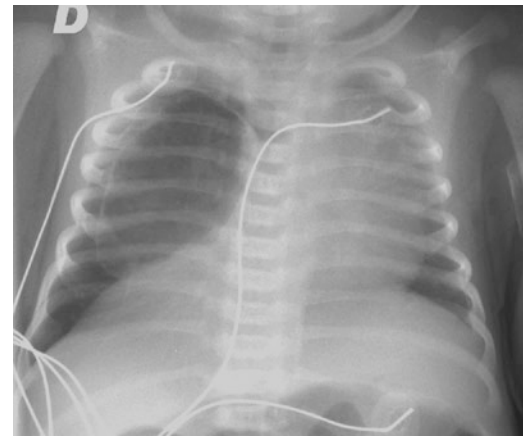

Fig. 12.2 Chest X-ray at 1 day of life – cyst in the right chest

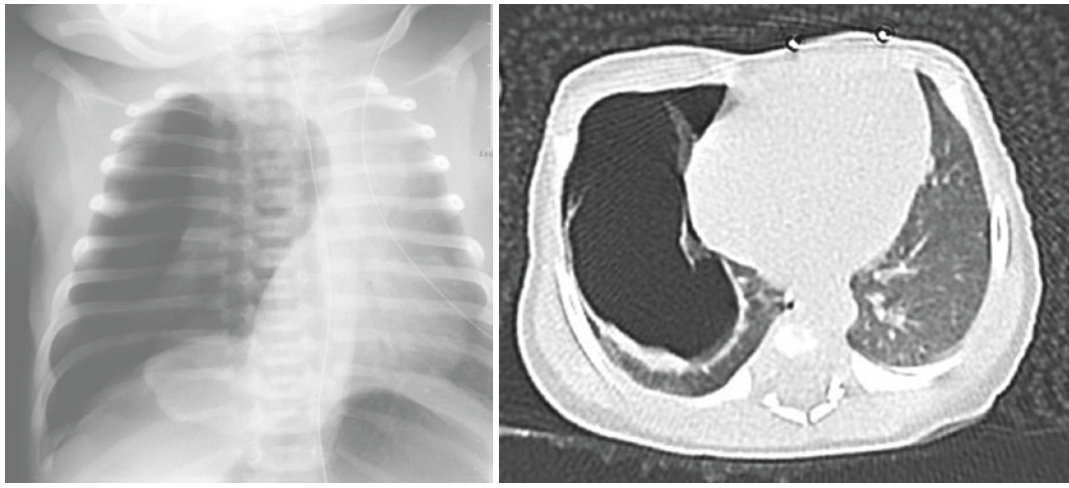

Fig. 12.3 Chest X-ray and CT scan showing a large cyst. This baby required a surgery within 10 days of life for respiratory distress

delivery. Hydramnios if present can increase this risk. This make sometimes the fetus at risk for preterm delivery making the postnatal management difficult with a preterm baby requiring an admission in NICU, eventually needing mechanical ventilation, and with complications related to the preterm delivery (membrane hyaline disease, brocho pulmonary dysplasia) [17].

Rarely, thoracoamniotic shunt is completely internalized and required a neonatal surgery to remove it because it is at risk for complication [18]. This can be done thoracoscopically.

12.4.2 Treatment

For the majority of the patient, as previously mentioned, the postnatal course from the respiratory wise is uneventful. A CT scan is done between 1 and 3 months to confirm the diagnosis of CPAM, type, localization, and the presence of a systemic artery, allowing planning the surgery or the conservative treatment.

Do all CPAM prenatally diagnosed should be treated surgically or conservatively?Infectious complications and malignancy with a risk of misdiagnosing a PPB in balance with the low postoperative complication rate after pulmonary resection often make the surgical decision in these patients. This question has also been raised by 18 experts questioned on what could be the most relevant question about CPAM treatment [18]. A response has been reported in this article by a review and a meta-analysis conducted on ten articles selected on the criteria that can be analyzed based on the primary outcome of interest which was postoperative morbidity including respiratory distress, respiratory infection, pneumonia, pneumothorax, and death and the secondary outcome of interest which was the length of stay in hospital following surgery. One hundred sixty-eight patients were asymptomatic at birth. Seventy (41.7%) underwent elective surgery with seven (10.0%) cases of postoperative complications. The 98 remainder patients were managed expectantly (58.3%), with 64.3% developing symptoms between 1 month and 7 years of age and consequently requiring surgery. Twenty of these experienced postoperative complications (31.8%). The results of this meta-analysis showed that total morbidity (number of patients who experienced postoperative complications) was significantly higher when surgery was performed after symptom development compared to resection when patients were asymptomatic (OR 4.59, 95% CI 1.40–15.11, $P = 0.01$). No death was reported.

Once you decide to operate, the question is should I perform a radical lobectomy or a segmentectomy?

Multiple arguments are available in the literature in favor of both sparing surgery and radical lobectomy. The surgeon should do what he/she used to. In the area of mini invasive surgery, segmentectomy is obviously more difficult to perform, and for the majority of this kind of surgery, a pure anatomical segmentectomy is rarely done, and a wedge resection using stapler or coagulation devices is performed. The CT performance to detect adenomatoid lesion extension within the lobe was reported [19]. All patients who had undergone a thoracoscopic lobectomy for CCAM located to one pulmonary lobe were reviewed retrospectively. A thoracic radiologist performed a single-blind review of all preoperative computed tomographic (CT) scans, mentioning the presence or absence of distant lesions from the main cysts of CCAM within the pulmonary lobe. The pathologist who analyzed the pulmonary lobectomy specimen was aware of the diagnosis but not the CT report. The median age at surgery was 12 months (range, 2–24 months). On 12 patients diagnosed with CPAM, the preoperative CT showed only two cases with distant lesions within the affected pulmonary lobe, whereas the histologic study of the surgical specimen identified six cases. The sensitivity to detect distant lesions of the CT scan was low, 33%, whereas its specificity was high, 100%. Furthermore, the preoperative CT negative predictive value was 60%. Because of poor sensitivity and very poor negative predictive value (60%) of the preoperative CT to determine distal adjacent lesions, lobectomy has our preference.

More important is the risk of residual disease left in place after the surgery. Furukawa T published his data and evaluated the risk to be 11% [20]. In a paper presented to the EUPSA annual congress in Limassol in 2017, this rate has been reported to be 17% [21]. Once you decide to undergo for surgery,

explanations given to parents should be clear and talk about this risk. Thus, in case of sparing parenchyma surgery, monitoring has to be done, and all children would require a postoperative CT scan to evaluate the presence or absence of this residual disease. If it's present, a redo surgery should be proposed to complete the resection.

Should I prefer mini invasive surgery (MIS) or classical open thoracotomy surgery?

Obviously, development of 2, 3, or 5 mm instruments is making the mini invasive surgery required for the congenital pulmonary malformation. A 3 mm coagulation device and a 5 mm stapler are now available to help the surgery (JustRight Surgical, Boulder, Colorado, USA) [22]. If for some reason, mini invasive surgery is not the preferable surgical approach and the team want to start a MIS program in pulmonary resection, the results at least have to be reported as good as the open approach. In a study from 2015, on univariate analysis, thoracoscopic resection was associated with decreased postoperative complications (9.8% vs. 25.3%, $P = 0.001$) and length of stay (3 vs. 4 days, $P < 0.001$). However, after adjusting for similar patient and operative characteristics, no significant differences were encountered between techniques. In this paper, both techniques provide comparable 30-day outcomes and safety in the management of congenital lung malformations [23] (Fig. 12.4).

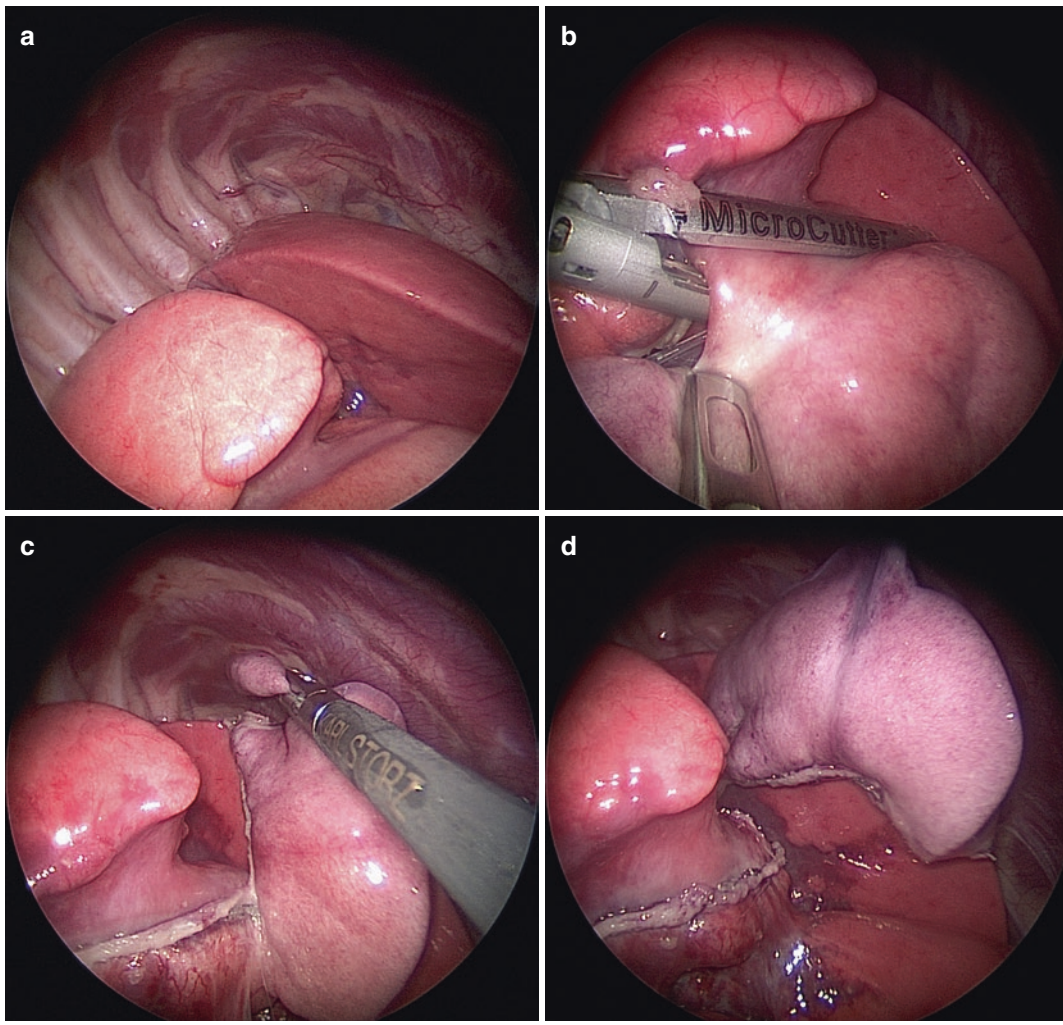

Fig. 12.4 Thoracoscopic removal of CCAM. Thoracoscopic view of the malformation (on the left) (**a**); resection with 5 mm stapler (**b**, **c**); final view after removal (**d**)

Most importantly, MIS associated with multimodal analgesia allowed to treat patients with a fast-track way. The length of stay is reduced to 1 day for lobectomy, and even some patients with extra-lobar sequestration are operated on as day case surgery [24] (Fig. 12.5).

Does all the congenital lung malformation have to be operated?

If macrocystic CPAM, bronchogenic cyst, and intralobar sequestration are lesions which required a surgery without any doubt, surgical resection of small cystic lesion less than 3 cm, emphysema, or extra-lobar sequestration is still a matter of debate. The reflection is based on the profit and risk balance of the surgery. As we have seen, the risk of MIS in experienced hands is very low. In contrast, in case of conservative management, a serial monitoring has to be done, mostly using a CT scan every year for congenital cystic malformation which is raising the risk of cumulated doses of irradiation in the child. Extra-lobar sequestration is theoretically not at risk for infectious complication, but leaving in place this lesion for a long time period is certainly something risky as it can grow and develop and cause complications in adulthood [25]. Emphysema has also been treated conservatively. Langer [26] reported 14 children managed without surgery doing well but with a median follow-up of 2.5 years (range, 0–8 years). Significant mediastinal shift was observed at diagnosis in seven of them, and two demonstrated collapse of adjacent lobes or segments. Follow-up imaging showed no significant radiological change in 12, making difficult to know what will occur on the adjacent lobe with a longer period time of follow-up.

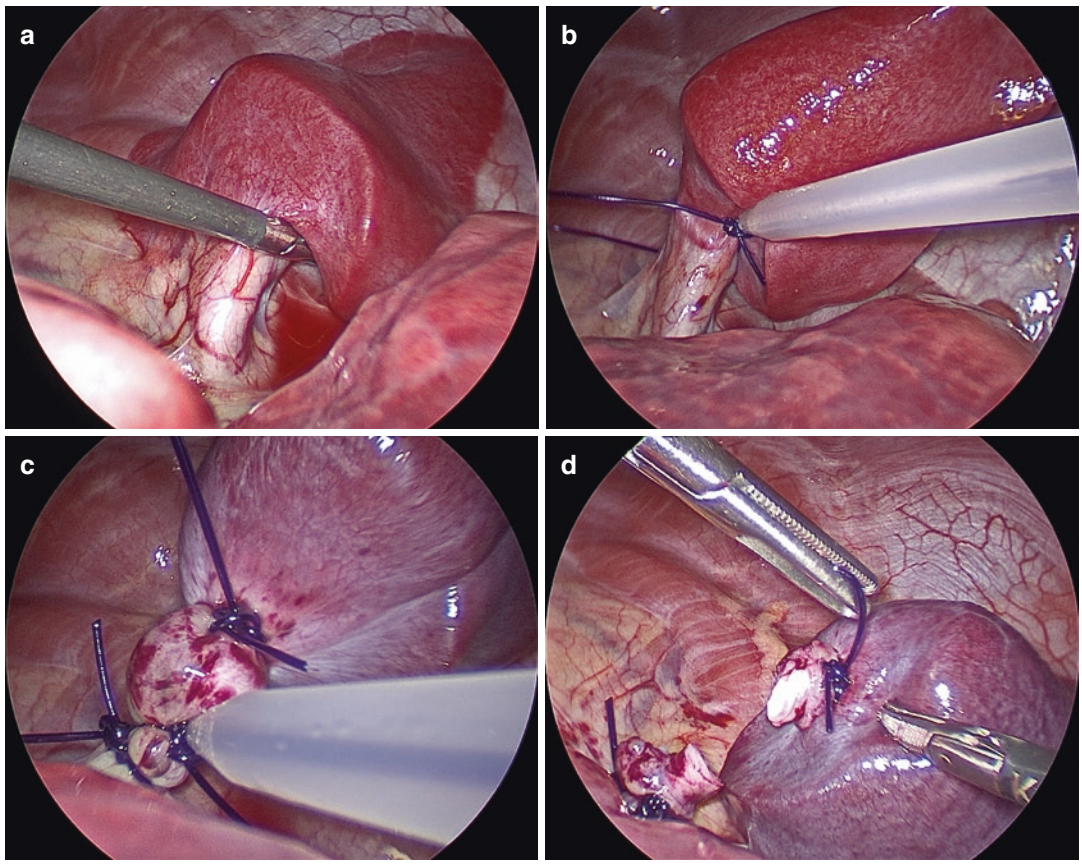

Fig. 12.5 Thoracoscopic removal of extra-lobar pulmonary sequestration (**a**). Thoracoscopic view of the sequestration: ligature of feeding vessel with two endoloops (**b**, **c**); section of the vessels (**d**)

12.5 Conclusion

At the light of what has been said and published, for all lesions diagnosed prenatally, we proposed a CT scan between 1 and 3 months of life and a surgery if the lesion is confirmed between 2 and 4 months. Mini invasive surgery is the surgical approach of our choice allowing to operate as a day case surgery for bronchogenic cyst and intra- or extra-lobar sequestration or with a 1-day length of stay for noncomplicated CPAM. Follow-up is done by a combined team with a pneumonologist and a surgeon, principally based on the clinical evolution and the clinical exam, every 3 months at the beginning and every 6 months or year if the patient is doing well. For other lesions (symptomatic at birth, complicated, etc.), attitude can be changed from the time to undergo for surgery to the surgical approach, the length of stay, etc. making this pathology interesting by all the varieties that it can offer to the pediatric surgeon.

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Congenital Diaphragmatic Hernia

13

Mario Lima, Michela Maffi, Giovanni Parente, and Chiara Cordola

13.1 Introduction

Diaphragmatic hernia of the newborn is a congenital malformation due to an anomaly in the diaphragm's development causing the herniation of the abdominal viscera into the thorax.

Birth prevalence of this condition is estimated to be 1 per 3300 live births with no differences between geographical regions or race.

The development of intensive neonatal care changed the natural history of this condition decreasing the mortality rate from 50% to 60% in the 1970s to 20% at present, even though the disability burden in survivals is still high.

The etiology of this congenital defect is still unknown. It is considered a sporadic malformation, although about 40% of the cases have associated anomalies, most frequently of the cardiovascular system followed by the genitourinary (23%), gastrointestinal (14–17%), central nervous (14%), and musculoskeletal systems (10%). Far from identifying a gene responsible for this malformation, some series talk about a multifactorial etiology involving both genetics and the environment. It can occur as part of a syndrome (Fryns, Donnai–Barrow, Beckwith–Wiedemann, Denys–Drash) in addition to chromosomal anomalies (13, 18, 21 trisomy and chromosomal deletions) [1–6].

The current classification of congenital diaphragmatic hernia (CDH) is based on the anatomy of the defect:

- Posterolateral hernia (Bochdalek's hernia): accounts for more than 90% of all CDHs; in 80% of the cases the left side of the diaphragm and in 15–20% the right side is affected. A bilateral posterolateral defect is extremely rare (Fig. 13.1a).
- Anterior hernia (Morgagni–Larrey): 2% of all CDHs; it involves the parasternal or retrosternal part of the diaphragm (Fig. 13.1b).
- Central hernia: central tendon defect of the diaphragm, 1% of all cases (Fig. 13.1c).
- Diaphragmatic eventration: abnormal elevation of the diaphragm, which appears intact but thinner, allowing the protrusion of the abdominal viscera upward (Fig. 13.1d).

13.2 Embryology

The diaphragm formation determines the separation of the abdominal cavity from the thoracic cavity, and is completed at gestational week 8. Four different structures are required for this process:

- Septum transversum
- Pleuroperitoneal membranes
- Esophageal mesentery

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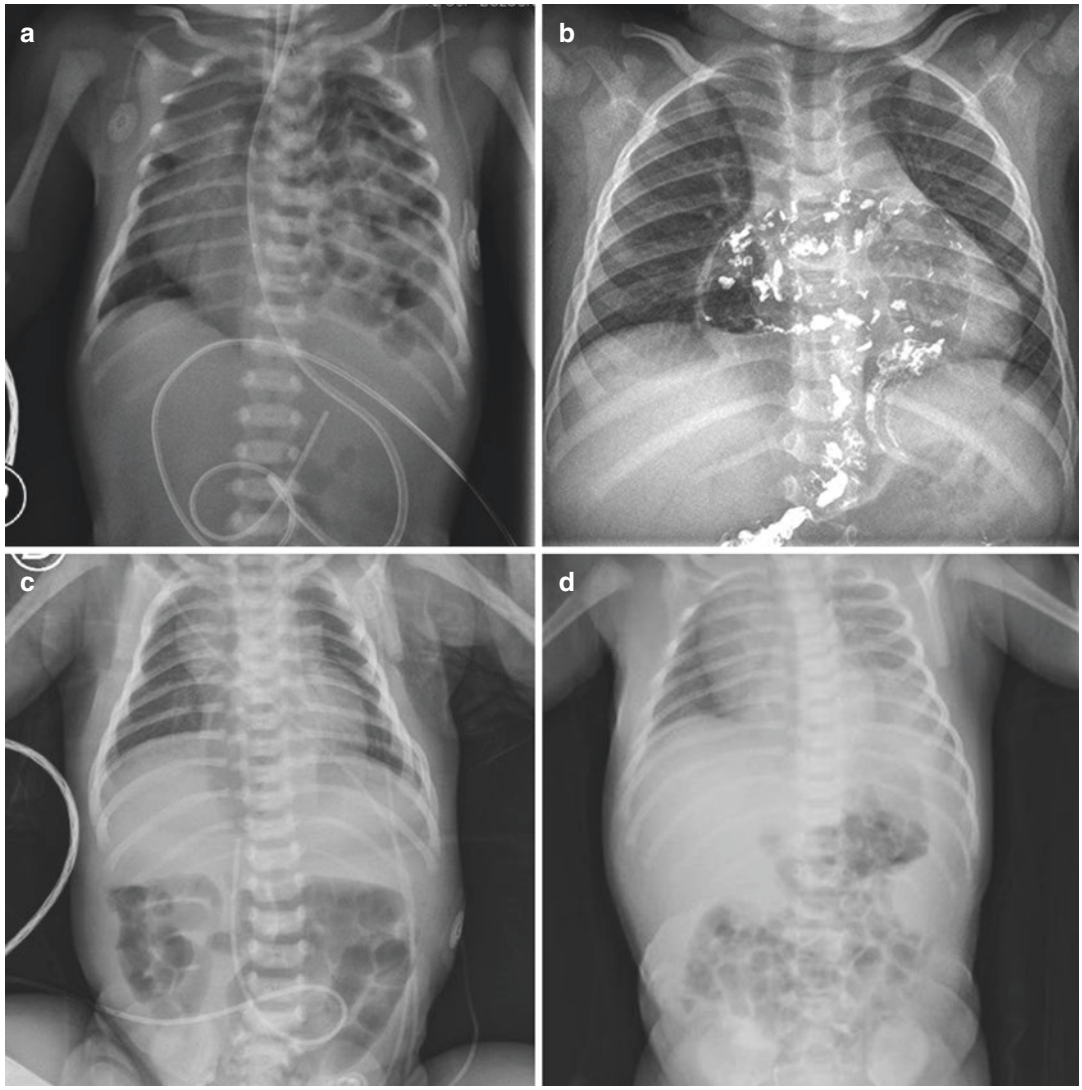

Fig. 13.1 (**a**) Posterolateral hernia. (**b**) Anterior hernia. (**c**) Central hernia. (**d**) Eventration

- Muscle fibers from the thoracic intercostal muscle groups

The septum transversum, destined to become the central tendon of the diaphragm, forms at gestational week 4 from the inferior portion of the pericardial cavity and represents the first but incomplete separation of the abdomen from the thorax and defines the pleuroperitoneal canals.

At about the sixth week of gestation, the pleuroperitoneal membranes start to grow from the posterolateral body wall running medially and ventrally to fuse with the septum transversum and the esophageal mesentery obliterating the pleuroperitoneal canals. The right side closes before the left side, and the entire process is complete at gestational week 8. At this moment, myoblasts migrate from the thoracic intercostal muscle groups, and the muscularization of the diaphragm takes place.

An anomaly at various levels of the described process results in CDH formation [1–6].

13.3 Diagnosis and Clinical Features

13.3.1 Antenatal

Currently, more than 56% of CDHs are diagnosed prenatally during routine ultrasound, which can reveal the presence of the defect from gestational week 14.

Sonographic signs that should lead the clinician to the diagnosis of CDH are:

- The presence of cystic images or heterogeneous echoes on the fetus thorax
- An interrupted hypoechoic line separating the thorax from the abdomen
- A gastric bubble above the diaphragm
- An abdominal circumference below the expected values for gestational age
- A mediastinal shift that may lead, if remarkable, to fetal hydrops

In severe right CDH with herniation of the liver, its identification in the chest cavity could be difficult owing to the very similar echodensity between the lung and liver itself.

A reduced amount of lung tissue seen on ultrasound from the 18th week onward may be another sign of CDH.

Polyhydramnios, even if nonspecific, could be a sign of CDH as its presence depends on the herniation of the stomach kinking the esophagogastric junction, making the fetus unable to swallow the amniotic fluid.

Differential diagnosis includes all intrathoracic isolated lesions such as congenital cystic adenomatoid malformation, sequestration, and foregut duplications.

If available, fetal magnetic resonance imaging (MRI) helps clinicians to give a better assessment of lung volume and organ herniation and guides them to differential diagnosis [7–11].

A recently introduced parameter, called the lung-to-head ratio (LHR), could be evaluated as a prognostic value. The LHR could be obtained by dividing the area of the contralateral fetal lung at the level of a four-chamber view of the heart for the fetal head circumference at the level of the lateral ventricles. The LHR can be measured using either ultrasound or fetal MRI, and for values lower than 0.8, mortality is almost 100%, whereas a value higher than 1.5 gives a good prognosis.

As the LHR is strictly dependent on gestational age, it has nowadays been replaced by the more reliable observed/expected LHR (O/E LHR) obtained by dividing the LHR calculated for the mean LHR of the respective week of gestation.

All fetuses with a prenatal diagnosis of CDH should undergo a chromosomal evaluation with fetal karyotyping [12–17].

13.3.2 Neonatal Period

Owing to pulmonary hypoplasia, these patients experiment varying degrees of respiratory distress.

A peculiarity of the disease is an initial moment in which these babies present with almost adequate ventilation and oxygenation (“honeymoon”) followed by a quick worsening of respiratory function due to the occurrence of permanent pulmonary hypertension with regression to the antenatal pattern of blood circulation that leads to hypoxia, hypercarbia, and acidosis, exacerbating in a vicious cycle the pulmonary hypertension itself.

The situation becomes even more critical as the neonate starts to swallow air, which distends the intrathoracic viscera, worsening lung compression and thus function.

At the clinical examination, the neonate shows signs of respiratory distress (tachypnea, tachycardia, chest wall recession, nasal flaring) with decreased or absent respiratory sounds ipsilateral to the hernia together with a clearly visible barrel chest and a scaphoid abdomen.

The diagnosis is confirmed with a chest X-ray, which typically shows:

- Intrathoracic intestinal loops
- Nasogastric tube up in the thorax
- Absence of a diaphragmatic profile
- Contralateral mediastinal shift
- If herniated, an intrathoracic liver segment

13.3.3 Misdiagnosed CDH

There are sporadic cases of CDH diagnosed in infancy or childhood that had been previously asymptomatic.

Occasionally, it is diagnosed by a chest X-ray done for reasons other than suspected CDH (respiratory infections, reactive airways disease, dyspnea on exertion), but frequently it becomes symptomatic as a result of intestinal loop incarceration or even a volvulus.

13.4 Management

13.4.1 Antenatal

If a CDH is suspected, it is strongly recommended to refer the parents of the future baby to a center that can guarantee a multidisciplinary team of physicians (neonatologists, geneticists, pediatric surgeons).

Fetal karyotyping should be routinely performed to exclude chromosomal anomalies.

Prenatal treatment of CDH is focused on contrasting pulmonary hypoplasia and based on fetal tracheal occlusion. The best tolerated method with fewer adverse events (tracheomalacia, tracheomegaly, tracheal ring injury) consists in the endoscopic placement of a balloon in the fetus' trachea (fetoscopic tracheal occlusion, FETO) creating an obstruction that contributes to lung development. The timing of the procedure is extremely important: FETO is performed between 28 and 30 weeks' gestation, and the balloon is removed 4–6 weeks later. Nevertheless, FETO is associated with a significant risk for prematurity, and current reported survival rates are on average around 50%. As only a few trials are evaluating the benefits of FETO, it should not be used until more significant results are available [11].

13.4.2 Postnatal

The priority for this type of patient is to guarantee adequate ventilation; therefore, most need endotracheal intubation.

A nasogastric tube should be placed to decompress the stomach and the intestinal loops herniated.

Monitoring is essential and requires:

- An umbilical artery catheter to evaluate systemic arterial pressure
- A vesical catheter to obtain a reliable urine output
- Preductal pulse oximetry (right arm)
- Postductal pulse oximetry to evaluate the entity of right-to-left shunting

Echocardiography should be performed to study cardiac function and diagnose cardiac anomalies.

In the literature there is evidence for pulmonary immaturity and surfactant deficiency; exogenous surfactant is thus immediately administered.

As pulmonary hypertension is one of the most significant causes of mortality, its treatment plays a remarkable role in postnatal management. Inhaled nitric oxide (iNO) has been introduced with great results as it effectively reduces the ventilation/perfusion mismatch with a selective action on alveolar capillaries and it is quickly degraded once it reaches the systemic circulation. Moreover, iNO does not appear to have any major side effects. Unfortunately, tachyphylaxis often occurs.

If conventional ventilation with gentle pressure (it is important to avoid barotrauma) is not sufficient, the passage to high-frequency oscillatory or jet ventilation should be considered.

If adequate control of hypoxia, hypercapnia, and pulmonary hypertension is not reached, extracorporeal membrane oxygenation (ECMO) is indicated [9, 18–28].

13.5 Surgical Repair

13.5.1 Surgical Timing

In the past, CDH was considered a surgical emergency; nowadays, even though the debate around the perfect timing is still open, delayed surgical repair is widely practiced.

The latest guidelines of the Canadian Congenital Diaphragmatic Hernia Collaborative

emphasize the importance of medical stabilization and suggest that the following physiological criteria should be met before surgery:

- Urine output >1 ml/kg/h
- FiO_2 <0.5 mmHg
- Preductal oxygen saturation between 85% and 95%
- Normal mean arterial pressure for gestational age
- Lactate <3 mmol/L
- Estimated pulmonary artery pressure less than systemic pressure

However, the failure to meet these criteria within 2 weeks should not prevent an attempt at a surgical approach, which still remains the only treatment that gives a chance of long-term survival.

The perfect timing is a subtle equilibrium among the potential improvements in pulmonary hypertension that can occur when delaying surgery, the risk of pulmonary injury associated with prolonged ventilation, and the possible suffering of herniated viscera [29–33].

13.5.2 Open Transabdominal Repair

Laparotomy is usually performed with a subcostal incision on the side of the hernia approximately one fingerbreadth below the costal margin (Fig. 13.2a).

The diaphragmatic defect is exposed by retracting the upper portion of the wound in a cephalic direction (Fig. 13.2b). Then, the abdominal viscera are gently reduced in the abdomen to avoid trauma (Fig. 13.2c, d).

In the case of small defects, extraction of the viscera should be performed in the following order:

1. Left CDH: stomach, small intestine, cecum, ascending colon, transverse colon, and spleen.
2. Right CDH: the liver has to be replaced last after the small intestine and colon.

The reduction of the abdominal viscera requires a careful check of the orientation of the mesentery.

At this point, the diaphragmatic defect can be examined: in about 20% of patients a hernia sac can be found, formed of the parietal pleura and the peritoneum, and this sac has to be excised to allow complete healing and to reduce the risk of recurrence.

If there is enough tissue after mobilizing the anterior and posterior edges of the defect, it can be primarily closed with simple or mattress sutures. The posterior edge may be deficient; in this case, the surgeon should try to expose it better by sharply incising the overlying peritoneum or suturing the anterior rim directly to the chest wall, placing sutures around the ribs.

During this process, the surgeon should take care not to cause a chest deformity because of the closure attempt was too aggressive.

If the native diaphragm is not enough to close the defect, several techniques for overcoming the lack of tissue have been described in the literature: using a muscular flap, prerenal fascia, or a rib structure (Fig. 13.2e, f). However, the use of prosthetic material to close the gap has gained consensus, and the latest recommendations on CHD suggest the use of tension-free polytetrafluoroethylene/GORE-TEX patches; bio-prosthetic materials can be used too, but because of a higher risk of recurrence, they are not recommended.

The chosen patch has to be carefully cut to resemble the shape and size of the defect and then fixed with interrupted sutures to the edges of the diaphragmatic defect.

After closing the diaphragm, accurate control of the bowel and other herniated viscera has to be managed to identify any sign of suffering or other anomalies that must be corrected before complete closure.

The abdomen is closed in layers when possible. If primary closure generates significant abdominal pressure, it should be avoided so as not to cause an abdominal compartmental syndrome.

These situations require either a simple closure of the skin delaying that of the abdominal wall or the use of a temporary prosthetic material such as a GORE-TEX patch.

A chest tube can be placed in the side of the repair depending on the surgeon's preference and on the presence of bleeding or possible air leakage [34–37].

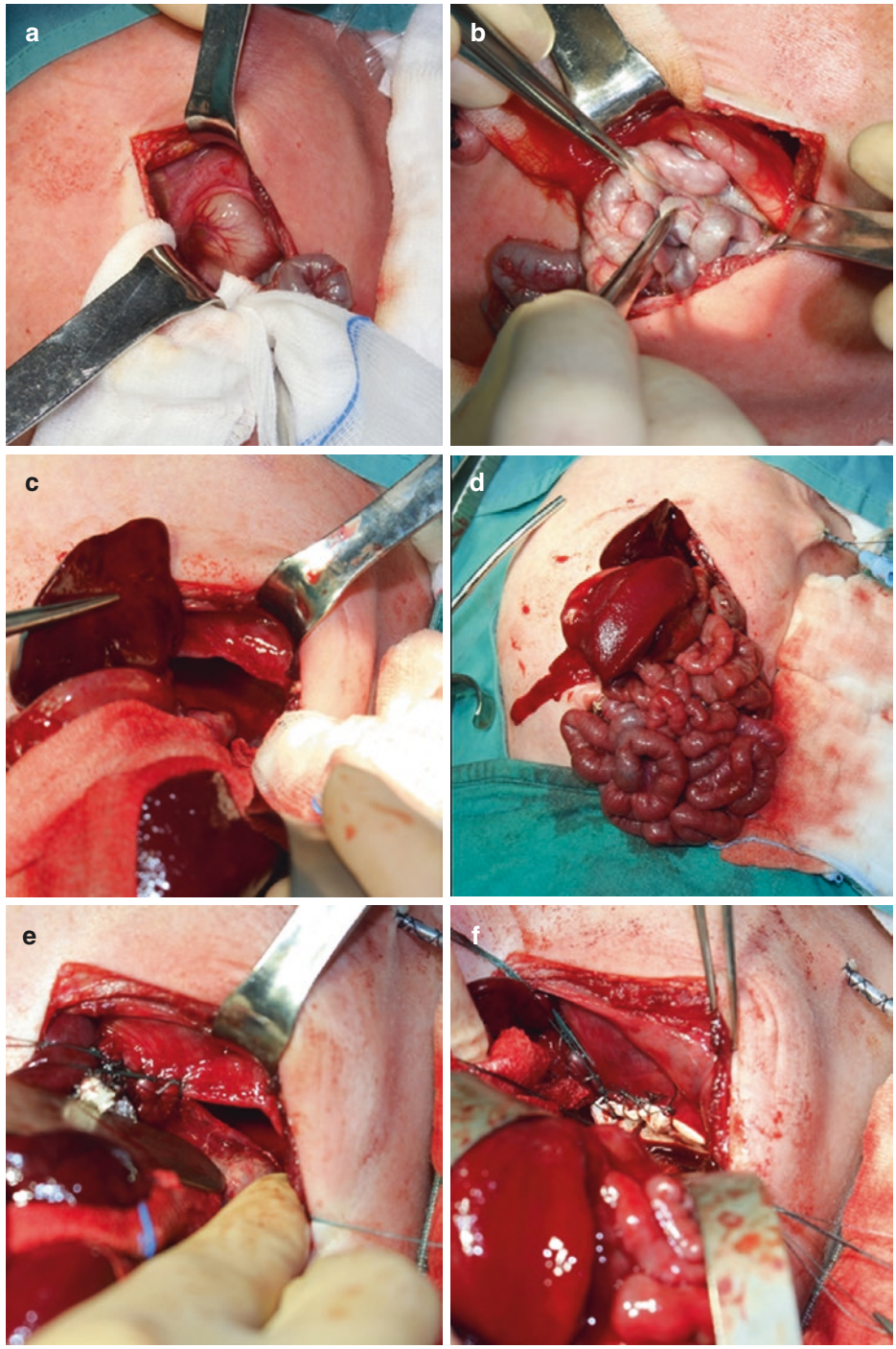

Fig. 13.2 Open transabdominal CDH repair: (**a**) subcostal incision; (**b**–**d**) reduction of viscera into the abdomen; (**e**, **f**) closure of the defect (GORE-TEX patch)

13.5.3 Video-Assisted Thoracoscopic Repair

Video-assisted thoracoscopic surgery (VATS) combines great visual clarity with less postoperative pain and better cosmesis. Despite these significant advantages, thoracoscopic CDH repair is afflicted by a higher risk of recurrence; thus, the author recommends that VATS should be performed only by expert teams well trained in minimally invasive surgery and in a restricted selected population of patients.

The patient is placed in a lateral, slightly semiprone position (Fig. 13.3); the surgeon is at the patient's head with the monitor in front of him/her. The assistant stands in front of the patient and the scrub nurse at the end with the baby.

Thoracoscopic repair requires the placement of three trocars:

- An optic port (5-mm trocar), below the tip of the scapula
- An anterior working port (3-mm trocar), fifth intercostal space on the anterior axillary line
- A posterior working port (3-mm trocar), fourth intercostal space between the optic port and the spinal column

Once the optic port is correctly allocated, insufflation of CO_2 is started taking care not to expose the baby to prolonged insufflation and high pressure (4–8 mmHg and intermittent insufflation are generally safe). At this point, the lung collapses, and the surgery can begin (Fig. 13.4a).

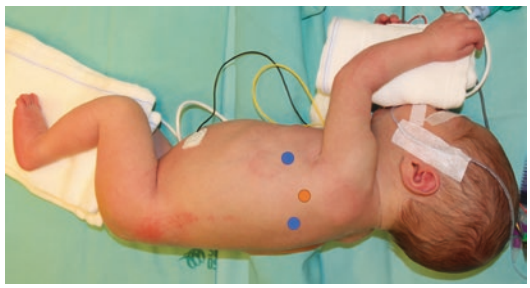

Fig. 13.3 Patient position and trocar placement for performing a thoracoscopic CDH repair. The orange dot indicates the site of the optic port and the blue dots indicate the two working ports

If there is a hernial sac, the insufflation itself reduces the organs in the abdomen; the stomach and intestinal loops are reduced first, followed by the spleen, which should always be the last organ to be repositioned (Fig. 13.4b–d).

Next step is the correction of the defect, which should be closed using nonabsorbable interrupted sutures (the author prefers Ethibond 2/0 or 3/0).

If the posterior edge is difficult to obtain, a patch of GORE-TEX should be placed instead of performing direct closure. The author suggests the introduction into the chest cavity of a piece of sterile glove that can be cut to the size and shape of the defect (Fig. 13.4e). Once extracted, the glove is used as a template for the GORE-TEX, which can be placed to close the diaphragmatic gap (Fig. 13.4f).

We suggest a chest drain (aspiration, 5–10 mmHg), which may help lung expansion [38–40].

13.5.4 Complications

- Recurrence represents the main complication of CDH repair. It accounts for 10% of operated patients, especially those who needed a prosthetic patch. It mostly occurs within the first year of life.
- Adhesion-related bowel obstruction.
- Chylothorax due to lesions to the thoracic duct.

13.5.5 Outcome

Nowadays, the overall survival rate is 67% and 61% of those receiving ECMO survive.

The main causes of CHD mortality are pulmonary hypoplasia and hypertension.

Children who have undergone CDH repair are likely to suffer from gastroesophageal reflux, exercise intolerance and wheezing, scoliosis, and chest wall asymmetry.

Nonisolated CDH carries all the morbidity and mortality of the associated syndromes and accompanying anomalies [41–50].

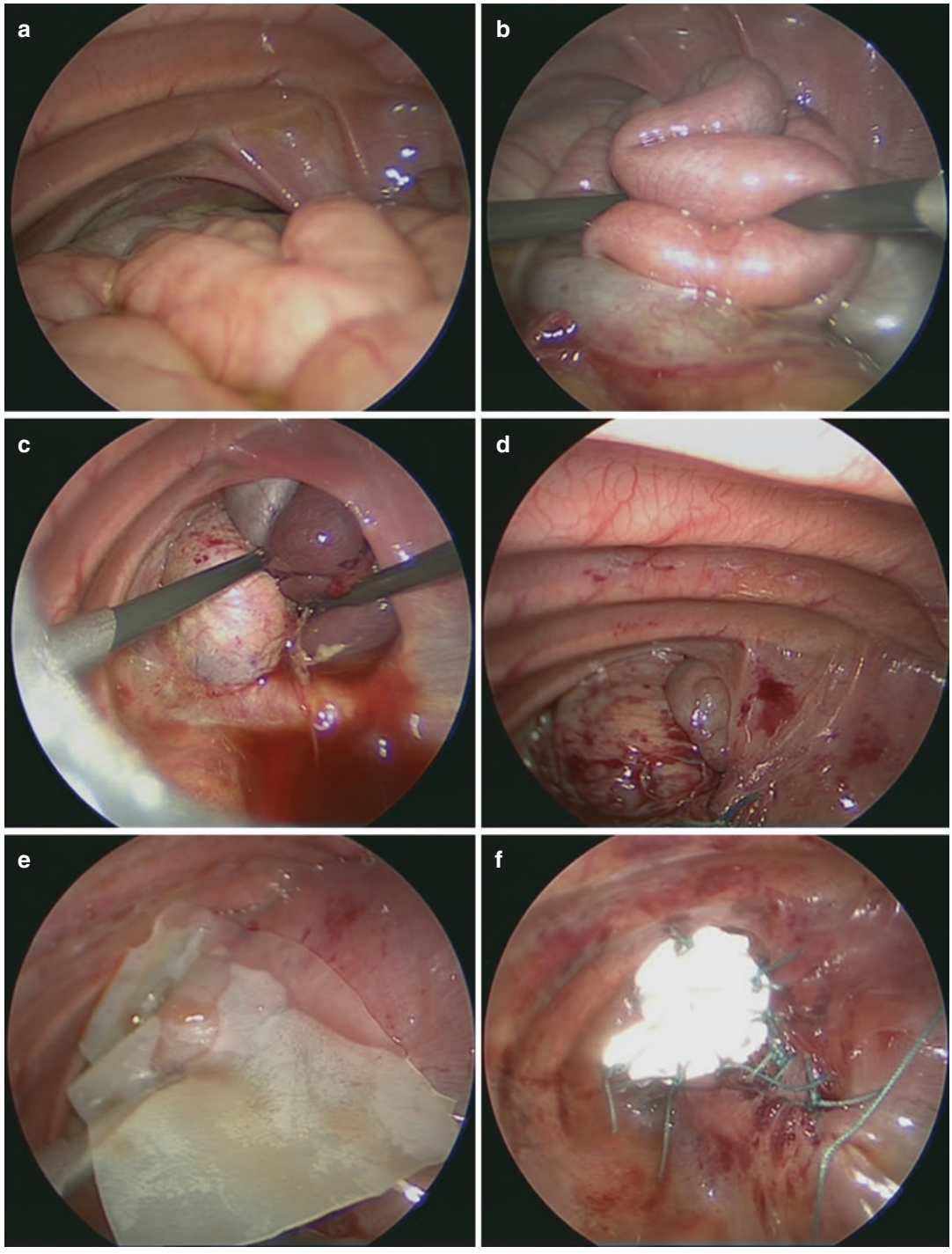

Fig. 13.4 Thoracoscopic CDH repair. (**a**) CDH presentation; (**b**, **c**) viscera reduction; (**d**) diaphragmatic defect; (**e**) modeling of a sterile finger glove as a template for the patch; (**f**) GORE-TEX patch

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14 Esophageal Atresia and Tracheoesophageal Fistula

David C. van der Zee, Maud Y. van Herwaarden, Stefaan H. Tytgat, Michela Maffi, and Mario Lima

14.1 Definition

Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) represents a congenital developmental anomaly. It is the most common congenital malformation of the esophagus characterized by an esophageal discontinuity (the upper esophagus terminates in a blind-ending pouch) and a possible tracheoesophageal connection [1–3].

14.2 Epidemiology

The reported incidence is between 1 in 2500 and 1 in 4500 live births with males having a slight increased incidence. Mothers of white ethnicity have a higher prevalence of EA with or without TEF. The great majority of cases occur as a sporadic phenomenon although an increased incidence in twins is described. The advancement of surgical techniques and neonatal intensive care has increased the survival rate up to 90% [1–3].

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14.3 Pathogenesis

EA-TEF occurs early (22–23 days) in foetal life when the endodermal epithelium, shaped as a tube that runs from the oral ectoderm to the cloacae, undergoes morphologic changes that precede the development of the respiratory and digestive tracts. In normal development, the proximal part of the endodermal tube, that is, the foregut, branches starting from two ventral evaginations generating either the tracheobronchial tree and the lungs (proximal) or the ventral pancreas, biliary system and the liver (distal). The respiratory system develops by the separation of the anterior part of the foregut from the posterior component (future esophagus). In this model, the single foregut tube divides longitudinally in two by the progressive development of two lateral epithelial ridges.

The division of the respiratory and esophageal tracts is complete by the time that the embryo is 6–7 weeks old. The exact pathogenesis of congenital EA-TEF remains unknown and no single unifying theory has been proposed. The first abnormal embryogenetic event seems to be a late separation of the respiratory component of the foregut related to defective epithelial-mesenchymal interactions. The upper pouch seems to be the result of degeneration or atrophy of the digestive half of the foregut. The notochord is abnormal at the level of the atresia playing an

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important role in the separation process. The aetiology of EA-TEF is likely multifactorial including environmental, genetic and epigenetic factors. Most of the cases are related to de novo mutations, while familial recurrence rate is 1%. Studies of mouse and rat models have led to the assumption that several molecular pathways are involved in the separation of the primitive foregut tube into dorsal and ventral components: vitamin A seems essential for proper foregut development; hedgehog pathway (including the family components shh, dhh, ihh and the zinc-finger transcription factors Gli1, Gli2, Gli3) plays an integral role in foregut morphogenesis allowing proper tracheoesophageal separation and foregut development [1–4].

14.4 Clinical and Syndromic Associations

EA-TEF is associated with a very high incidence of congenital anomalies, affecting other parts of the alimentary canal or other systems of the body and impacting both treatment and outcome. Anatomic malformations are described in more than 50% of cases. Half of all EA-TEF-associated anomalies can be included in recognizable syndromes: the most common are those within the VACTERL spectrum (vertebral anomalies, anorectal atresia, congenital heart lesions, tracheoesophageal defects, renal and limb abnormalities); other genetic syndromes are CHARGE (coloboma, heart defects, choanal atresia, growth and mental retardation, genito-urinary defects, ear abnormalities), Feingold syndrome, AEG (anophthalmia, esophageal, genital), x-linked Opitz syndrome, Goldenhar syndrome and Fanconi anaemia. Specific chromosomal disorders are found in up to 10% of cases. All these rates are higher in patients with pure EA than in patients with EA-TEF.

The other 50% of patients have non-syndromic associations: heart and great vessels are involved in 24%, the digestive tract in 21%, the skeletal system including the vertebral column in 14% and the central nervous system in 7%.

14.5 Classification

In 1929 Vogt recognized and classified EA based on radiological findings. After the first successful surgical approaches, various new anatomical classifications were proposed. In 1944 Ladd introduced a classification system that was later used by Gross in 1953 replacing the Roman numerals with alphabets. Later, Swenson returned to a numeric classification with Arabic numbers (1962) and Kluth added a list of EA variations that lead to ten separate classes and additional subclasses (1976). The anatomic classification is still the most used (Fig. 14.1).

In particular the malformation may present in five forms:

– Type I EA = esophageal atresia without fistula (pure atresia) is the second most frequent anomaly (8.4%) and consists of two blind esophageal ends with a “long-gap” between the two pouches. It should be differentiated by

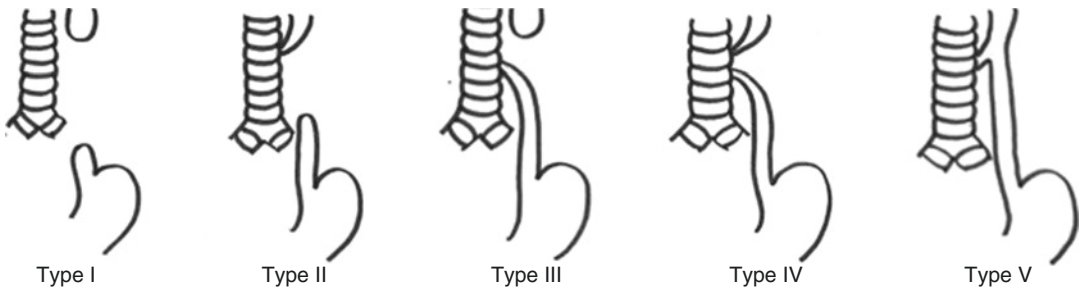

Fig. 14.1 EA-TEF anatomic classification

type II EA as there is often a "missed fistula" between the upper pouch and the trachea.
- Type II EA = esophageal atresia with a proximal tracheoesophageal fistula is an uncommon anomaly (2.1%). The abdomen is airless, and their anomaly is frequently misdiagnosed as type I EA unless accurate endoscopic evaluation or contrast studies are performed.
- Type III EA = esophageal atresia with distal tracheoesophageal fistula is the most common abnormalities (82.2%). It occurs when the upper esophagus ends blindly, the distal esophagus opens in the trachea (about 1 cm above the carina or rarely in the left/right main bronchus) as an end-to-side fistula and there is a 1–2 cm long-gap between the two esophageal stumps. Variations of this type include a wider or shorter gap that can be more than 2 cm long or absent (a membrane interrupts the lumen, and the muscular layers of the esophagus are in continuity).
- Type IV EA = atresia with double (proximal and distal) tracheoesophageal fistula is found in 3.4% of cases.
- Type V EA = tracheoesophageal fistula without atresia (H-type, 3.3% of cases) may present in older children with cough, recurrent pulmonary infections and abdominal distension.

Patients with EA-TEF have also other anatomical features that influence the clinical picture and the prognosis:

- Hypertrophy of the proximal pouch related to foetal amniotic fluid swallowing and tracheoesophageal adhesion at the level of the posterolateral wall of the trachea.
- Hypoplastic distal esophagus and fistula due to the absence of a functional challenge.
- Tracheomalacia that is a condition related to the reduction of the cartilage amount with a relative increase of the muscular component in the tracheal wall. The effect is the tracheal collapse and obstructive respiratory difficulty. The prevalence of tracheomalacia is estimated to be 5–15% (half patients require surgical correction). Symptoms include feeding difficulties, barking cough, expiratory stridor and cyanotic spells. Tracheomalacia may sustain respiratory symptoms unresponsive to medical treatment and may impair clearance of secretions. The diagnosis is established by bronchoscopy. Most infants do not require surgical corrections as the situation improve with time. In case of life-threatening events, the operation of choice is aortopexy that consists of suturing up the aortic arch and the ascending aorta to the posterior surface of the sternum after partial thymectomy. The operation is performed through a left anterior mediastinotomy, anterolateral thoracotomy, cervical incision or thoracoscopy. In case of failure, airway stent can be considered as alternatives, and tracheostomy is the final treatment.

In 1962, in addition to the reported classifications, Waterston proposed a risk-based stratification of patients with EA-TEF considering birth weight, the presence of pneumonia and associated congenital anomalies (Table 14.1). This scheme permits the identification of factors that predict the prognosis and guide the management. Infants with "low" risk (A) undergo immediate surgical repair, "moderate"-risk (B) patients were operated on after a period of adequate stabilization, and "high"-risk (C) patients were treated with staged repair. Some authors questioned the validity of this classification scheme and searched for others factors related to survival. Randolph (1989) included the evaluation of the overall

Table 14.1 Waterston classification

Waterston risk-based classification		
Group	Survival (%)	Waterston classification
A	100	Birth weight > 2500 g and otherwise healthy
B	85	Birth weight 2000–2500 g and well Birth weight > 2000–2500 g with moderate associated anomalies (noncardiac anomalies plus patent ductus arteriosus, ventricular septal defect and atrial septal defect)
C	65	Birth weight < 2000 g or higher with severe associated anomalies

Table 14.2 Okamoto modification of the Spitz classification

Okamoto-Spitz classification			
Class	Description	Risk	Survival (%)
I	No major cardiac anomaly, birth weight ≥ 2000 g	Low	100
II	No major cardiac anomaly, birth weight < 2000 g	Moderate	81
III	Major cardiac anomaly, birth weight ≥ 2000 g	Relatively high	72
IV	Major cardiac anomaly, birth weight < 2000 g	High	27

physiologic status to establish the management. Poenaru proposed to use severe pulmonary dysfunction, preoperative need of mechanical ventilation and severe associated anomalies as risk factors, and Brown and Tam tried to establish long-term outcomes on the base of the esophageal gap length. In 1992 Spitz suggested the assessment of birth weight and major cardiac disease to predict survival (Table 14.2). According to Okamoto, major cardiac disease plays a key role in assessing prognosis.

14.6 Diagnosis and Clinical Findings

The diagnosis of EA-TEF is usually made within the first 24 h of life. Prenatal diagnosis has increased since the introduction of the antenatal US screening. Delayed diagnosis is described in case of type V esophageal atresia.

14.6.1 Prenatal Diagnosis

Antenatal diagnosis was first described by Farrant (1980) who reported polyhydramnios and absent stomach in a 26 weeks foetus. The obstruction of the esophagus means that the foetus cannot swallow the amniotic fluid in a proper way with consequent polyhydramnios. Polyhydramnios is a non-specific feature (it is also associated with myopathies, neurological defects, congenital diaphragmatic hernia, congenital cystic adenomatoid malformation and duodenal atresia), and it may be absent in patients with EA-TEF and renal affections. The absence of the stomach is non-specific as well, and it is not described in some cases of EA-TEF because the fistula permits enough fluid passage to fill the stomach. It is estimated that only 1/3 of cases have both a small-absent fluid-filled stomach and polyhydramnios, but when both present, the positive predictive value is 39–56%. Another EA-TEF predictive parameter is the US detection of the blind-ending upper pouch that may be identified late in gestation and seems to correlate with a higher risk of trisomy 18. The accuracy of antenatal US is between 75 and 91% in case of pure EA, but it is lower with other types of EA-TEF, and in all cases it remains a challenge. Foetal MRI still has limited use although it has a significant positive predictive value. Once the diagnosis is suspected, chromosomal anomalies (karyotype) and associated defects (foetal ECHO) should be excluded in order to provide an accurate counselling. After birth, in case of prenatal polyhydramnios with or without prematurity (that is common in infants with EA-TEF), the suspicious should always rise in order to avoid feeding and aspiration pneumonitis [1–3].

14.6.2 Diagnosis at Birth

The newborn infant usually has symptoms before or during the first feed because it is unable to swallow saliva and requires repeated suctioning. He may choke and cough and may have emesis, cyanosis and respiratory distress. Those with distal fistula may have distended abdomen, while the abdomen is usually scaphoid in patients with pure EA. The respiratory symptoms worsen and become more evident when there is a delay in diagnosis. Pulmonary compromise is related to gastric fluid reflux through the fistula, spillage into the trachea and lungs with chemical pneumonitis and diaphragmatic elevation after gastric distension. Aspiration manoeuvres exacerbates the respiratory distress. The diagnosis is confirmed by passing a 10Fr gastric tube beyond 10–13 cm from the lips (if the esophageal lumen is patent the tube easily reaches the stomach) (Fig. 14.2). The use of smaller or bigger tubes

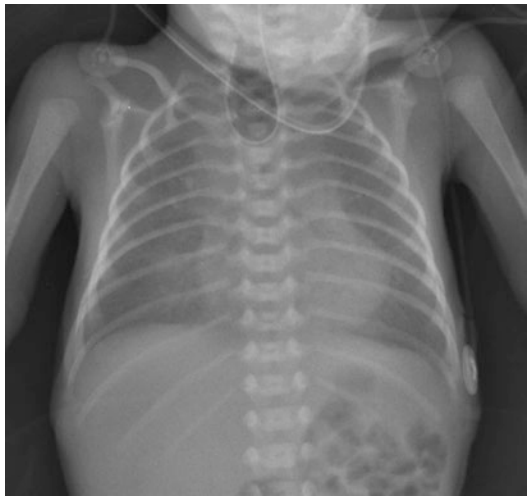

Fig. 14.2 X-Ray evaluation shows the stop of the nasogastric tube in the upper esophagus

should be discouraged since they may curl in the upper pouch or pharynx and they may cause esophageal perforation. The tube should be taped once a resistance is felt and plain x-rays of neck, chest and abdomen taken. A few millilitres of air can be injected through the tube and used as a contrast agent. The tip of the tube lies at the fundus of the upper pouch. The lateral film gives information regarding the level of the pouch related to the thoracic inlet. The pouch usually reaches the second–third thoracic vertebra; if higher, a type II EA should be suspected. The absence of air below the diaphragm suggests that there is no distal fistula although it is not conclusive (narrow or occluded distal fistula).

The presence of a double bubble may indicate duodenal obstruction, a known associated anomaly. The heart size should be checked, as well as the pulmonary spaces to exclude the presence of congenital heart disease and pneumonitis. Skeletal abnormalities may indicate a syndrome (VACTERL, CHARGE). Esophagograms are useful to establish size and location of the proximal pouch and to visualize the proximal fistula, but they may cause serious complications and should be performed only in centres with high radiological expertise.

Investigations are used not only to confirm the diagnosis but also to provide additional information guiding the surgical management and to determine the presence of associated anomalies. In this light an ECHO and renal US are used as a routine investigation in children appearing clinically normal. The assessment should be more carefully conducted when there is the suspicion of associated anomalies (cardiologic evaluation, genetic counselling, etc.).

Preoperative bronchoscopy is increasingly used to detect the fistula in the upper pouch and to find additional defects (fistula from a main pulmonary bronchus, laryngeal cleft, vallecular cyst) [1–3].

14.6.3 Delayed Diagnosis

A delay in the diagnosis is more common in case of "H- or N-type fistula". Patients have coughing episodes during feed, recurrent pneumonia, choking spells with feeding and intermittent abdominal distension with excessive flatulence. Symptoms are usually present from birth, but severity may vary. The diagnosis is made by upper gastrointestinal study and airways endoscopy.

14.7 Management

Following diagnosis, the baby should be stabilized and resuscitated. A double-lumen Replogle tube is used to suction secretions from the upper pouch reducing the risk of aspiration. Placing the head slightly elevated helps the drainage of secretions. These interventions avoid chemical pneumonitis and respiratory distress that is the most critical preoperative problem. Intravenous fluid therapy is started to maintain fluid, electrolyte and glucose balance. Intubation and ventilation may increase gastric distension leading to respiratory embarrassment and perforation with consequent pneumoperitoneum. The endotracheal tube should be placed beyond any distal fistula, and the ventilation should be based upon low pressures. Biochemical and haematological studies are performed to assess the homeostasis of the baby. Blood is grouped and crossmatched. Vitamin K is given. Physiotherapy is instituted and prophylactic antibiotics are given. The timing of surgery is established when the baby is stable [1–3].

14.8 Surgery

The surgical correction of EA-TEF aims at interrupting any trachea-esophageal connections and establishing end-to-end esophageal continuity. The approach varies depending on the type of anomaly and the general clinical conditions of the baby (including the presence of associated anomalies): immediate operation is carried out when the baby is stable (a few hours after the admission, usually in the first few days of life), delayed repair is the optimal strategy when the baby's conditions can be improved after a period of intensive care, and the staged approach is advocated in case of long-gap malformations in unstable patients with respiratory distress and other associated congenital abnormalities. The staging approach includes the establishment of a gastrostomy and the placement of a central line in order to feed the baby and start a proper support therapy towards an improved respiratory status. The fistula can be ligated and divided during the same operation. Associated anomalies may be treated or palliated (e.g. colostomy in case of anorectal malformation). In some cases (long-gap) the proximal pouch is mobilized and opened as an end cutaneous cervical esophagostomy. Prior to surgery a tracheobronchoscopy (TBS) is performed to evaluate the presence of a proximal TEF, and it offers the possibility to evaluate vocal cord motility and to assess the presence of foregut-associated anomalies, and it may help to define the esophageal gap. The definition of the gap is important to choose the proper surgical approach (Fig. 14.3).

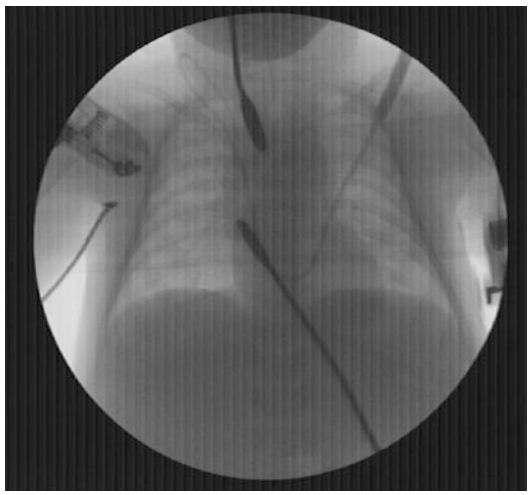

Fig. 14.3 Prior to surgery the gap is measured in order to establish the best surgical approach

14.8.1 Esophageal Atresia with Distal Tracheoesophageal Fistula (Type III EA, Short Gap)

Primary repair is now achieved in the majority of patients. Surgery is preceded by TBS that gives the possibility of probing the fistula facilitating its identification during the operation (Fig. 14.4).

The standard approach remains the right posterolateral thoracotomy (the baby is placed on its left side, with the right arm draped over the head) in the fourth interspace, adopting an extrapleural approach (Fig. 14.5). This approach avoids an empyema in case of anastomotic leaks. The curved excision extends from the anterior axillary line to the paravertebral region, passing about one finger below the inferior angle of the scapula.

Subcutaneous tissue and muscles are divided with electrocautery (the operative field is created between the latissimus dorsi and the serratus anterior muscles in case of muscle-sparing thoracotomy); the scapula is elevated, and the fourth intercostal space is identified. The extrapleural dissection (that consists of stripping the parietal pleura off the ribs and intercostal spaces) is performed with a "peanut" swab or the finger until there is enough space to put a rib retractor. During this phase, small pleural tear can be repaired whereas large defects involve a transpleural approach. Figure 14.6 shows the steps of the procedure. The dissection proceeds permitting the exposure of the azygos vein (it can be ligated and divided) and of the posterior mediastinum after medial lung retraction. The upper pouch, distal TEF, trachea and vagus nerve are then identified. The descending aorta may hide the lower esophageal pouch, and care should be taken to avoid the mobilization of the artery mistaken for the esophagus. The mobilization of the distal segment, using a silk suture, tape or a vessel loop passed around it, helps identifying the fistula. The fistula is then ligated and divided.

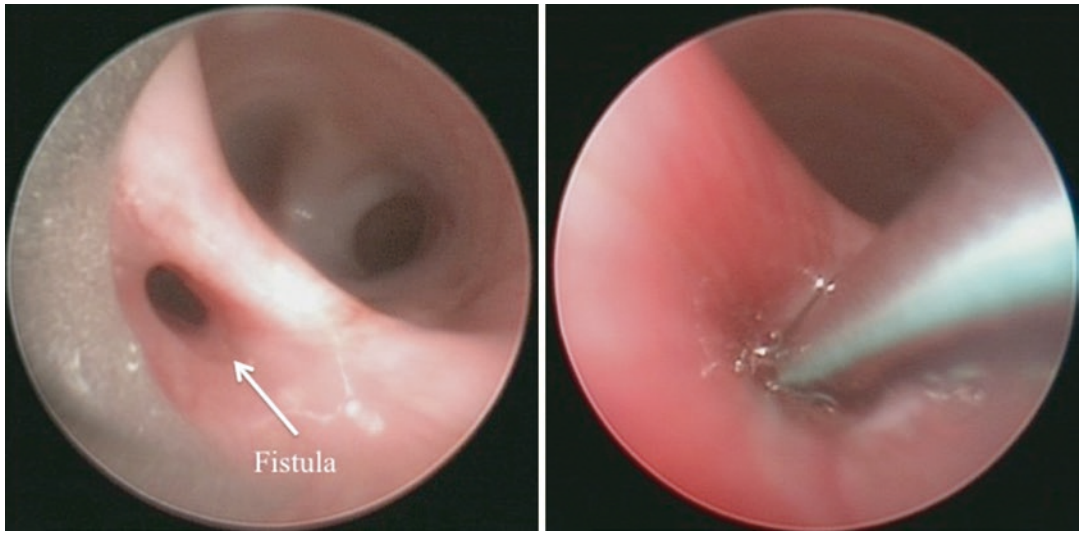

Fig. 14.4 Preoperative bronchoscopy permits the identification of the fistula and the placement of a probe that will facilitate the surgical repair

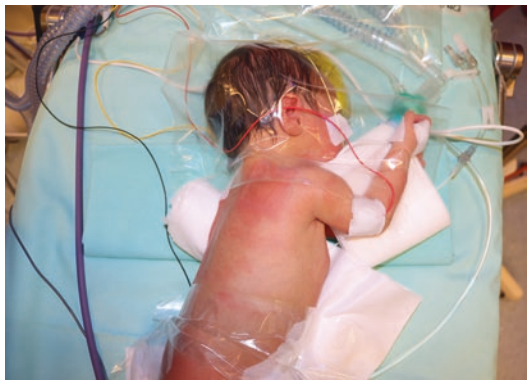

Fig. 14.5 The baby lies on its left side with the right arm elevated. A roll is placed under the chest in order to obtain a better exposure of the operative field

The residual stump is ligated with 4-0 non-absorbable sutures. Leaving excessive amount of esophagus on the tracheal end may lead to tracheal diverticulum but not leaving enough tissue may cause tracheal stricture. Filling the thorax with warm saline and looking for bubbles during positive pressure ventilation test the airtightness. The distal esophagus mobilization proceeds using two stay sutures in order to ensure a primary tension-free anastomosis although it should be minimized to avoid nervous or vascular damages. The next step is to visualize and mobilize the proximal pouch: the anaesthesiologist can help by pushing and moving the tube placed in the upper pouch. Once identified, a traction suture is placed on the tip of the pouch to help its mobilization. The dissection should be extensive (ischemic injuries are rare as the vascular supply is excellent), and the esophagus should be separated from the trachea minding their intimate relation in the esophageal antero-medial part (do not open the membranous trachea). Once the abovementioned steps are completed, the end-to end esophago-esophageal anastomosis is performed using 5-0 or 6-0 absorbable sutures. The suture should include all layers (especially the mucosa) starting from the posterior wall and inserting the entire back row of suture before tying them. It is of help to the passage of a feeding tube under vision across the anastomosis into the stomach to ensure patency and start early enteral feeding. Once the suture is completed, a chest tube can be placed in the retropleural space.

The use of minimally invasive surgery (MIS) has increased in children with AE-TEF, and it has been supported by many centres reporting the same results as for open surgery.

Thoracoscopic repair uses three 5 mm trocars and a 5 mm camera. The TEF is identified and clipped or ligated, the proximal esophageal pouch is mobilized, and an end-to-end esophago-esophagostomy is performed (Fig. 14.7).

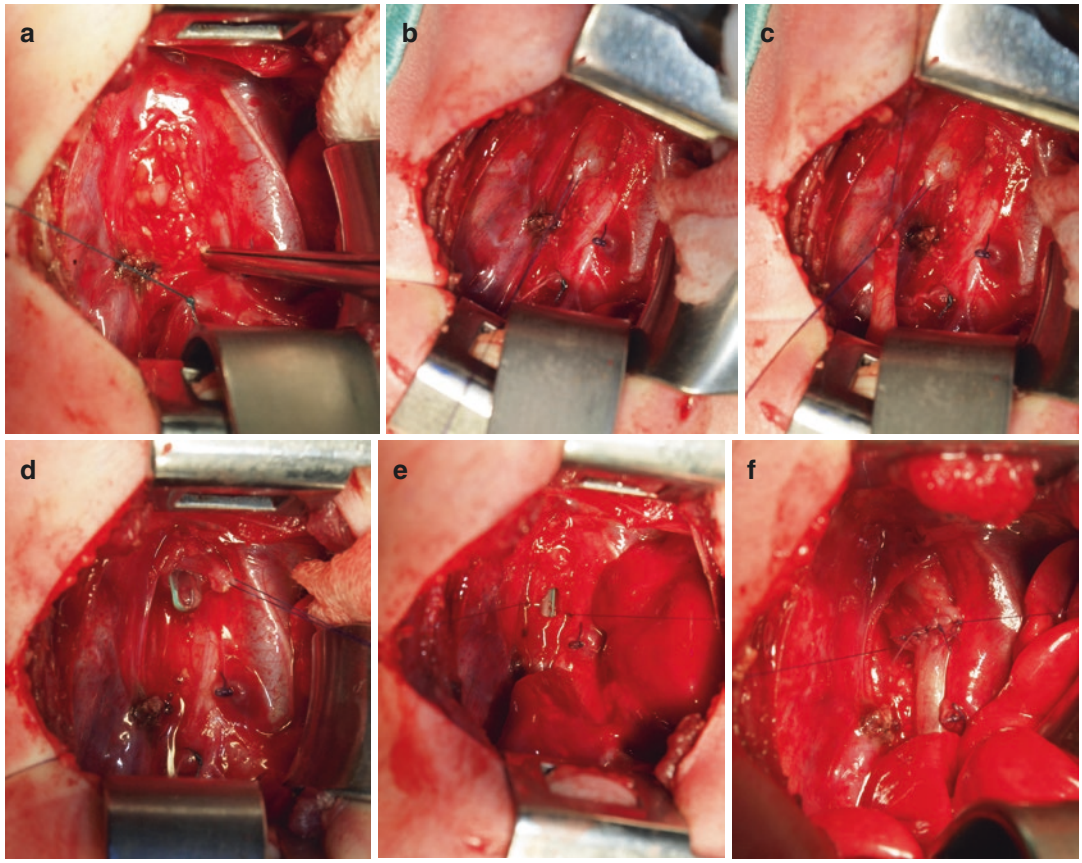

Fig. 14.6 Identification of the tracheoesophageal fistula after ligation of azygos vein (**a**). Mobilization of the upper pouch (**b**) and the lower stump (**c**). Opening of the upper pouch and exteriorization of the probe (**d**). The primary esophago-esophageal anastomosis is then performed (**e**, **f**)

After surgery the baby is admitted to the intensive care unit for mechanical ventilation (when required: premature infants and anastomosis performed under tension). The feeding starts after 48 h through the nasogastric tube unless there is concern about the anastomosis. Ten days after surgery, the anastomotic site is visualized during contrast X-ray that is followed by the removal of the drain and nasogastric tube. Oral feeding is then carefully started as there is a mandatory anastomotic relative stenosis of the anastomosis due to the different diameters above and below the EA. In most cases it will improve with feeding and do not require dilatation [5–7].

14.8.2 Difficult Cases

Difficult cases are related to general patient's characteristics, such as prematurity or associated anomalies (life-threatening cardiac and bowel anomalies that may represent a priority over esophageal surgery, delayed between 3 days and 3 months) and surgery-related issues (airways and esophageal anatomy and redo surgery).

Prematurity is the factor that has the major influence in timing surgical correction. Very low birth weight neonates usually develop respiratory distress requiring mechanical ventilation. The inflated air easily passes through the fistula towards the esophagus (low-resistance) instead of reaching the lungs that have lost their compliance determining a high-resistance system. The effect is the gastric distension with consequent worsened respiratory distress, gastroesophageal reflux, inhalation and risk of gastric perforation. Several approaches have been described to manage this problem including gastric division, banding of the gastro-esophageal junction, distal positioning of the endotracheal tube, fistula occlusion with a Fogarty balloon, water seal gastrostomy and

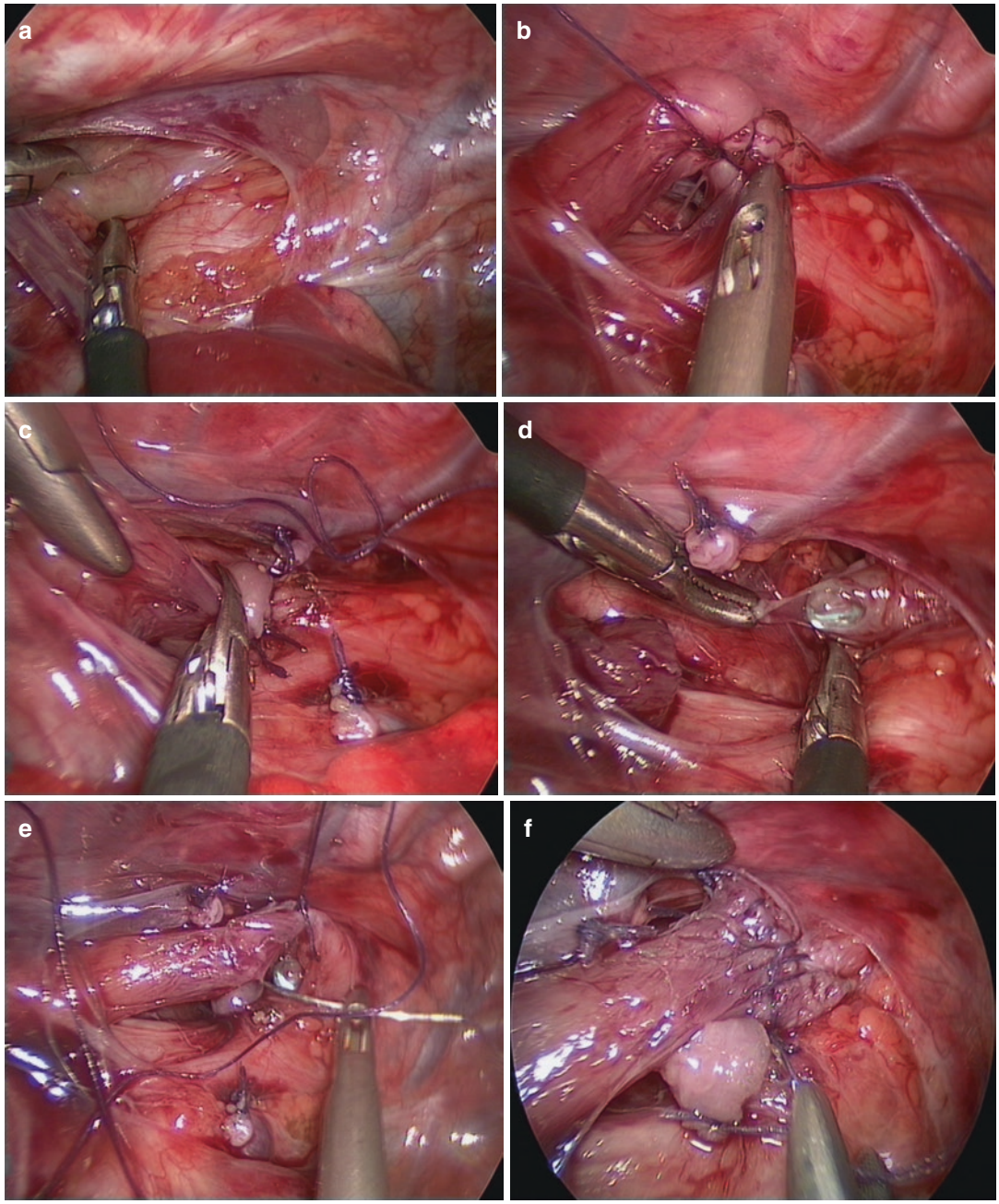

Fig. 14.7 View towards the thoracic inlet during thoracoscopy: the mediastinal pleura is opened, and the fistula is identified (**a**), sutured and divided (**b**, **c**). The upper pouch is mobilized and opened exteriorizing the probe (**d**). The anastomosis is performed with interrupted stitches (**e**, **f**)

high-frequency ventilation. Urgent thoracotomy and fistula division seems to be the best approach, followed by delayed primary anastomosis (the esophageal tissue is often too fragile to try a direct suture).

In case of right aortic arch (5% of cases), the suggestion is to perform a left thoracotomy or at least paying attention not to mistake the aorta for the esophagus. Right thoracoscopy is an alternative that gives a good view on the esophagus and the

aorta. It is also important to notice that this condition is usually associated with cardiac anomalies.

Other associations that make EA-TEF management difficult include congenital diaphragmatic hernia (that carries a very poor prognosis) and chromosomal anomalies, found in up to 10% of patients (trisomy 21, 18 and 13).

14.8.3 Long-Gap Esophageal Atresia

It includes patients with a high upper pouch and a long distance between the esophageal segments that limits the possibility to perform an anastomosis with acceptable tension. The condition is occasionally seen in case of EA with TEF, but it is frequent in case of pure EA. Unfortunately there is no consensus regarding the definition and the measurement of the "long gap" that remains a subjective condition. However, preoperative evaluation of the esophageal gap remains a critical part of assessment. The gap can be measured by inserting a tube in the proximal pouch and an endoscope in the lower pouch through the gastrostomy and performing a X-ray evaluation; some surgeons prefer measuring directly the gap during the operation or using a TBS evaluation (X-rays are taken after a radiopaque tube is inserted in the upper pouch and the tracheoscope's tip is placed at the level of the tracheal opening of the fistula). The literature would suggest that a distance of four or more vertebral bodies defines the long gap. Once the long gap has been confirmed, efforts should be made in order to maintain the native esophagus.

Placing a feeding gastrostomy is part of the management in case of pure EA, followed by a period of observation (anatomical investigations and management planning). This gastrostomy can be difficult to perform as the non-used stomach can be very small. The gap shortens during the first several months of life (3–6 weeks or until the baby is 3.5–4 kg), and waiting may be sufficient to achieve enough length for the anastomosis. This process is facilitated by the administration of bolus gastrostomy feedings that promotes spontaneous growth by meal and gastric reflux into the lower esophagus. The gap is measured every 15 days, and the anastomosis is attempted once it is less than two vertebral bodies.

Various techniques have been proposed to deal with long-gap EA when spontaneous growth fails. They consist of gradual traction of esophageal segments in order to favour growth and reduce the gap. There are also techniques used to reduce the anastomotic tension (flaps and myotomy).

- Upper pouch bougienage (traction an growth): a weighted bougie is inserted through the mouth into the upper pouch, and daily pressure is applied for 6–12 weeks; traction can be applied also to the lower pouch; the use of an electromagnetic field, hydrostatic pressure and nylon thread bridge has been described for the same purpose. All these procedures have never gained widespread popularity.
- External traction: traction sutures can be placed in both the proximal and distal pouches in order to exit them form the chest and apply an opposite traction (Foker technique). Time to achieve esophageal repair is almost 10–14 days. Early complications include anastomotic leak (50% of patients, mostly minor), major disruption and need for reoperation (15%) or for esophageal replacement (14%).
- Extrathoracic elongation: the upper esophagus is mobilized and brought out as an end cervical esophagostomy that is progressively moved down along the anterior wall (Kimura technique). The procedure permits to maintain the native esophagus, early oral feeding and short hospital stay. The esophagostomy is preferably created on the right side of the neck. Long-term outcomes are limited.
- Upper esophageal flap: anterior full-thickness flap of the upper pouch to bridge the long gap (Gough, Bianchi). It is an elongation technique of the proximal pouch. Complications include leaks (27%), strictures (87%), gastroesophageal reflux (20%), recurrent TEF (13%) and esophageal motility incoordination (60%).
- Myotomy: circular myotomy of the upper part of the esophagus is advocated by Livaditis to gain length for primary anastomosis. It is an elongation technique of the proximal pouch. Complications include esophageal leak,

impaction of food and ballooning (pseudodiverticulum) of the myotomized segment.
– Elongation of the distal pouch: during surgery there is the possibility to elongate the distal pouch in order to reduce the distance between the esophageal segments. This can be obtained with the cardiac and gastric fundus mobilization – "gastric pull-up" suggested by Spitz. The procedure is performed along with the fundoplication.

Once the methods of esophageal elongation used to preserve the native esophagus have failed, the esophagus may need to be replaced. The esophageal substitution is performed around 1 year of age. During this time a cervical esophagostomy is used to drain secretions, and a gastrostomy helps feeding the baby. The indications for esophageal replacement include long-gap esophageal atresia, peptic and caustic stenosis. The ideal esophageal substitute should permit a valid orogastric passage of food to satisfy the need of the baby, avoid the acid gastric reflux and be acid-resistant, do not interfere with cardiac and respiratory function and grow with the baby ensuring its function also in adult life. Unfortunately there is not an optimal esophageal substitute, and the proposed substitutes partially adapt to the abovementioned requirements. The colon (retrosternal or intrathoracic passage) is still the most used segment as it guarantees adequate calibre and length. Complications of surgery are stenosis (22–26%) and leak (19–30%) related to the precarious circulation. There are also problems associated to the reduced peristalsis (interposed colon redundancy). The stomach (total pull-up or partial tubulisation) is appreciated for the rich vascularization and acid resistance. On the other hand, it gives constant acid reflux damaging the upper esophagus and airway. It has a delayed emptying, as for the colon. The jejunum is rarely used because of the precarious vascularization, despite some favourable features (adequate calibre and peristalsis) [3, 8, 9].

14.8.4 Type V Esophageal Atresia (H-Type Isolated Tracheoesophageal Fistula)

It is a congenital TEF without EA. It gives symptoms in the first days of life or in older children: repeated chokes during feeding, cyanotic spells, intermittent abdominal distension and recurrent pneumonia. Chest X-ray shows the signs of infection and gastric distension. The fistula is missed in more than 50% of cases on contrast X-ray. Bronchoscopy (Fig. 14.8) and esophagoscopy

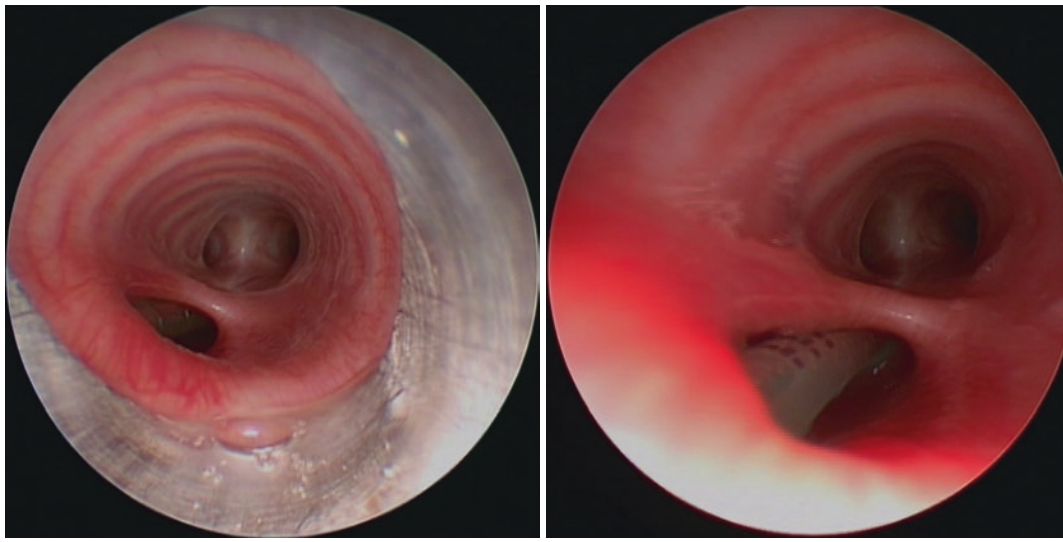

Fig. 14.8 This child has recurrent respiratory infections and coughing during feeding. Endoscopic evaluation shows a large communication between the trachea and the esophagus (left). The latter is regularly patent, as shown by the insertion of a nasogastric tube, visible through the trachea (right)

confirm the diagnosis and allow the positioning of a guidewire through the fistula that helps its identification during surgery. The operation is performed through a right-sided low cervical incision. The sternocleidomastoid muscle is retracted, and the dissection proceeds to the carotid sheath. The inferior thyroid artery and middle thyroid vein are divided. Care should be taken to spare the recurrent laryngeal nerve. Once the fistula has been identified, traction sutures are placed on the esophagus thus avoiding its rotation. The fistula is divided after suturing [3, 10].

14.9 Complications

The standard of paediatric care in patients with EA-TEF is good, and the overall quality of life is favourable. However, many patients suffer from chronic long-term problems or develop early postoperative complications. The rate of complications is higher in premature babies and after complex operations. Predictors of complications are twin birth, low birth weight (<2500 g), preoperative intubation, long-gap atresia, anastomotic leak, long postoperative intubation (>4 days) and inability to feed after the first month.

Short-term complications include anastomotic leak, sepsis, esophageal stricture and chylothorax, and they are usually managed conservatively. Recurrent tracheoesophageal fistula may instead require surgical correction.

14.9.1 Anastomotic Leak

It occurs in 13–16% of patients and most of them are successfully managed conservatively (drainage and nutritional support). A stenosis may form after leak healing. Major leaks account for 3–5% of cases and are diagnosed early after surgery requiring a surgical revision (drainage and toilette, repair of the anastomosis or esophagostomy and delayed esophageal replacement). Risk factors are poor surgical technique, ischemia, myotomy and excessive tension of the anastomosis.

14.9.2 Esophageal Stricture

It is a common complication reported in more than 80% of patients (40% being clinically significant). Risk factors include poor surgical technique (excessive tension of the anastomosis, etc.), long-gap, ischemia, GERD and anastomotic leak. Symptomatic strictures (dysphagia, recurrent respiratory problems from aspiration or foreign body obstruction) are treated by endoscopic dilatations. The Savary-Gilliard dilators permit an anterograde dilatation over a guidewire. Balloon dilators offer the advantage of a radial and uniform force applied over the stricture instead of a shearing axial force. Stenting has been proposed as an alternative method. Recalcitrant strictures require resection and reanastomosis or esophageal replacement. Mitomycin C application has recently been used to reduce stricture formation. In the treatment of strictures is also important to reduce GERD that prevent dilatation to be effective and worsen the stricture.

14.9.3 Chylothorax

It is related to thoracic duct damage during surgery. It requires prolonged hospitalization, suspension of oral feeding, total parenteral nutrition and thoracic drainage. Surgical correction (thoracic duct closure, pleuroperitoneal shunt, pleurodesis) is advocated in case of persistent chylothorax after 2–5 weeks of conservative treatment.

14.9.4 Recurrent Tracheoesophageal Fistula

It occurs in 3–14% of cases and it is related to anastomotic leak, inflammation and erosion. A preventive manoeuvre is the use of flaps (pleural, pericardial, azygos) interposed between the esophagus and the trachea. Recurrent fistula usually occurs as an early complication, but it can be misdiagnosed and identified later. The baby presents with cough and cyanosis during feeding and

Table 14.3 Long-term complications in patients affected by EA-TEF

Active long-term conditions	
Condition	Prevalence (%)
Dysphagia	50.3
GERD (±esophagitis)	40.2
BE	6.4
Cancer (squamous cell carcinoma)	1.4
RTI	24.1
DDA	22.3
Persistent cough	14.6
Persistent wheeze	34.7

GERD gastroesophageal reflux disease, *BE* Barrett's esophagus, *RTI* respiratory tract infections, *DDA* doctor-diagnosed asthma

recurrent pulmonary infections. This complication requires surgical or endoscopic correction.

Long-term complications (Table 14.3) represent chronic long-term problems with implications on the adulthood management.

14.9.5 Dysphagia and Esophageal Dysmotility

Half of patients experience dysphagia with a reported prevalence of 18.2–84.2% (mean 50.3%). Dysphagia is associated with a poorer quality of life. The anomaly is related to the abnormal esophageal development (impaired and interrupted innervations and anatomy) and to the surgical iatrogenic damage. It has been recently noticed the absence of peristalsis at the site of the anastomosis and a lower esophageal sphincter hypotony in patients with EA-TEF. Dysphagia and dysmotility are risks factors for GER and subsequent metaplasia and a common cause of respiratory symptoms (inability to protect the airways during swallowing and pooling of secretions). Some infants require a gastrostomy to facilitate feeding and adequate growth in the first years of life. Although improved, symptoms of dysphagia remain very common in children and adults after AE-TEF repair. Strategies used to improve swallowing are chewing slowly, avoiding meat and drinking fluids to promote the bolus propulsion. A common consequence of dysmotility is food impaction.

14.9.6 Gastroesophageal Reflux (GER)

The reported prevalence of GER symptoms is 18.2–62.9% (mean 40.2%). The aetiology of GER is based on congenital factors and surgical effects (in particular surgical techniques applied to preserve the native esophagus favour the onset of GER). At the base of GER, these are the following factors: abnormal esophago-gastric junction, reduced intra-esophageal length, His angle widening, esophageal dysmotility, increased lower esophageal sphincter relaxation and impaired nervous control.

GER is related to the onset of esophagitis (that is present in over half the patients) and Barrett's esophagus. The latter is a long-term morbidity that is more frequent in patients older than 35 years of age and with severe GERD symptoms (>3 times per week). The Barrett's esophagus is the replacement of normal squamous esophageal epithelium with columnar epithelium containing goblet cells (intestinal metaplasia). It is a premalignant condition. The treatment consists of aggressive medical management (thickening of feedings, positioning the baby in the upright posture, administering acid reduction agents) and often surgery (fundoplication).

14.9.7 Persistent Respiratory Symptoms

Respiratory symptoms are common and may be significant into adulthood. The aetiology is multifactorial: (1) developmental and anatomical anomalies of the upper airways (e.g. tracheomalacia, abnormal innervation, vocal cord problems, etc.), (2) gastrointestinal problems (chronic GERD, esophageal dysmotility, esophageal strictures, etc.), (3) recurrent aspiration and (4) lower airway abnormalities (bronchomalacia, airway hyperresponsiveness, associated chest wall deformities, etc.). Respiratory symptoms include cough, wheeze, recurrent infections and asthma. A quarter of patients have a diagnosis of asthma even if it would be better to speak about "asthma-

like symptoms" because bronchial inflammation in EA-TEF patients does not lead to extensive remodelling present in asthma patients [11–16].

14.10 Focus on Thoracoscopic Management of Esophageal Atresia and Congenital Stenosis

14.10.1 Introduction

Esophageal atresia has always been the hallmark of paediatric surgery. With better perinatal intensive care, survival has significantly improved to approximately 90–95% [17, 18]. Therefore, focus nowadays has shifted from survival to morbidity and long-term follow-up [19–24].

With the introduction of minimal invasive surgery (MIS), also an increasing number of neonatal procedures can now be performed using MIS, including esophageal atresia [25–27].

A recent study described a deterioration of the physiologic status of the neonate during thoracoscopic repair of esophageal atresia and congenital diaphragmatic hernia [28, 29]. The drawback of this study, however, was the fact that very high pressures of CO_2 insufflation, up to 10 mm Hg had been used. In an animal study using 4 kg piglets, intrathoracic insufflation pressures of 5 and 10 mm Hg were compared. This study confirmed the adverse effects due to high insufflation pressures when using 10 mm Hg, while insufflation with only 5 mm Hg caused no adverse effects [30]. Consecutively, a prospective study in patients with esophageal atresia demonstrated no adverse effects from CO_2 insufflation with 5 mm Hg [31]. It is, however, of paramount importance to have a continuous monitoring of brain perfusion in neonates before, during and after surgery, whether open or by MIS [32]. Neonates are particularly sensitive to hemodynamic changes causing fluctuation in brain perfusion. This is due to the fact that, contrary to adults and older children, neonates have no or only immature cerebral autoregulation. Variation may be induced by changes in arterial saturation, end-tidal CO_2, mean arterial blood pressure, haemoglobin levels, mean airway pressure and glucose levels. When the arterial blood pressure decreases, the cerebral blood perfusion decreases in a linear way. On the other hand, an increase in CO_2 tension gives rise to vasodilatation, which may give some compensatory effect [31, 32].

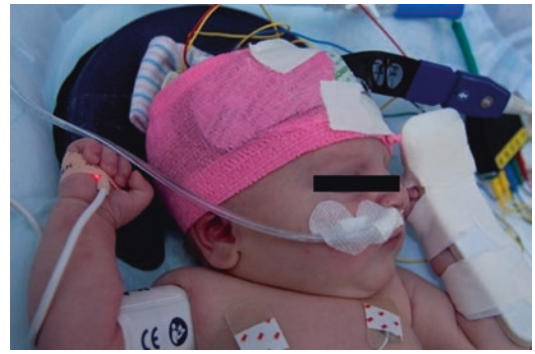

Fig. 14.9 Monitoring cerebral perfusion with NIRS (near-infrared spectrometry)

Since 2012, brain monitoring using near-infrared spectrometry (NIRS) has become a standard procedure in all neonates undergoing surgery in our institution [31] (Fig. 14.9).

Esophageal atresia is not just a congenital anomaly with an obstruction of the esophagus but is a lifelong anomaly with sequelae such as dysmotility, gastroesophageal reflux disease (GERD) and airway pathology [17, 19–23, 33–36]. The approach to esophageal atresia should therefore be multidisciplinary in close collaboration with the following departments: paediatric gastroenterology, paediatric pulmonology, paediatric ENT, genetics, nutrition, physiotherapy, psychology and paediatric cardiology, paediatric urology and orthopaedics. The Department of Pediatric Surgery in Utrecht is a centre of expertise for esophageal atresia and forms part of a centre for upper gastrointestinal (GI) and airway pathology, recognized by the Dutch government. The department is also a centre of expertise for minimal invasive surgery.

14.10.2 Centre for Upper GI and Airway Pathology

14.10.2.1 Esophageal Atresia

When there is suspicion of esophageal atresia on antenatal ultrasound, the patient is presented at the multidisciplinary meeting with the departments of gynaecology, paediatric surgery and neonatology

[37, 38]. In case of VACTERL association, the paediatric cardiology, paediatric urology, geneticist and/or neurology are consulted.

After birth, patients are admitted to the neonatal intensive care unit (NICU) with a Replogle tube placed in the proximal esophagus and arterial and venous access (Table 14.4). In case of respiratory insufficiency, the neonate is intubated. NIRS sensor and a-EEG electrodes are placed for continuous monitoring. A preoperative ultrasound of the brain is performed. Postoperative follow-up cerebral ultrasound will be performed in all patients, as well as a MRI of the brain [31, 32, 39].

Preoperatively ultrasound of kidneys and heart is performed to determine major anomalies and the position of the descending aortic. The rest of the VACTERL diagnostics can be performed postoperatively.

Surgery is performed semi-electively and is preceded by a multidisciplinary meeting between paediatric surgeon, neonatologist, anaesthesiologist, ENT and other specialists depending on associated anomalies. Details on the surgical procedure and estimated adverse events are discussed extensively. Principally, all neonates can tolerate thoracoscopy [40].

Table 14.4 Workup on admission in NICU

• Preoperative workup
– IV drip, arterial line, lab
– Replogle tube drainage
– Near-infrared spectrometry (NIRS), a-EEG
– X-thorax/abdomen, ultrasound kidneys
– Consultation paediatric cardiologist + echocardiogram
– Consultation genetics
– Consultation ophthalmologist
– Other investigations depending on concomitant anomalies
• Preoperative multidisciplinary consultation on intended procedure
• After induction preoperative rigid trachea-bronchoscopy
• Operative thoracoscopic correction esophageal atresia, i.e. under NIRS and a-EEG control
• Postoperative ventilation for 24–48 h on indication
• Start Ranitidine
• Start feeding through nasogastric tube after 24 h
• Start oral feeding when no saliva and/or infectious symptoms
• Transfer to ward when stable and spontaneous breathing
• MRI brain after 1 week
• Life support course parents
• Discharge from hospital when on full enteral feeds and no other sequelae

After induction of anaesthesia, the procedure is started with a tracheoscopy, while the patient breathes spontaneously. This is to locate the fistula, either distal and/or proximal, and to determine the presence and extent of tracheomalacia, anteriorly due to weakness of the tracheal rings and/or posteriorly because of a floppy pars membranacea [41, 42].

The patient is then positioned into a left 3/4 prone position at the left side of the table. During thoracoscopy, good collaboration between the paediatric surgeon and anaesthesiologist is essential to successfully perform the procedure. After open introduction of a 5 mm trocar approximately 1 cm below and anterior to the tip of the scapula, CO_2 is insufflated with a pressure of 2–3 mm Hg and a flow of 1 lt/min. to collapse the lung. The anaesthesiologist usually increases the breathing frequency up to 40–60/min while maintaining the same minute volume. Only after the neonate has adjusted to the new situation the procedure is continued. NIRS monitoring is performed continuously and when indicated by the NIRS, ventilation settings are adjusted, extra fluids are given and cardiotonic drugs can be administered. The haemoglobin level is important as an O_2 carrier. The surgical procedure has been extensively described previously and will only be summarized here [26, 27, 31, 41]. In many patients the distal esophagus lies beneath the azygos vein and taking down this vein facilitates the mobilization of the distal fistula. We emphasize to place a transfixing suture through the wall of the fistula flush on the tracheal side to prevent slipping of the suture during manipulation of the trachea postoperatively, for example, when re-intubation is needed. Sometimes the endotracheal tube preferentially goes into the fistula opening. After cutting the distal fistula, the proximal esophagus can be mobilized. A first suture is placed posteriorly with the proximal esophagus still closed to facilitate the approximation of the proximal and distal esophagus. After tying this suture, it

can be led outside to stabilize the position of the two ends to facilitate the actual anastomosis. After opening the proximal esophagus, a second suture is placed on the anterior side and tied. Now either interrupted sutures can be used for the posterior wall or the needle can be brought inside for a running suture up to the first suture on the posterior side. This usually creates a waterproof anastomosis. After bringing out the needle again, the two threads can be tied off. A transanastomotic tube can be advanced into the stomach, and the anterior wall can be anastomosed, again, either by interrupted or continuous sutures. Principally, a chest tube is not necessary.

Postoperative feeding can be started through the nasogastric tube as of day 1, and an H2 antagonist is started routinely immediately after surgery. Ventilation can be reduced depending on clinical signs and morphine medication. When there is no oral retention of mucus, the patient can be extubated. Oral feeding is usually started 1 day after extubation, which is usually around the fifth postoperative day. Contrast studies are only performed on indication. VACTERL diagnostics, postoperative ultrasound and MRI of the brain are completed, and parents receive a life support training before discharge after 7–10 days. Follow-up is according to standard protocol at the multidisciplinary outdoor clinic (Table 14.5).

Table 14.5 Follow-up protocol patients with esophageal atresia

Follow-up
Follow-up after 2, 4, 8 weeks or earlier when indicated
• Consultation with dietician (by telephone)
• Consultation with paediatric pulmonologist (yearly, antibiotic prophylaxis during winter if necessary, lung function test at 6 years)
• Consultation neonatologist (3, 6, 9, 12, 18, 24 months when Bailey test)
• Consultation paediatric gastroenterologist (esophagoscopy in case of stenosis or reflux; standard Barrett's investigation at 12 and 17 years)
• Consultation paediatrician
• Consultation other specialists on indication
• Regular follow-up at 3, 6, 9, 12 months, then every 2 years thereafter

14.10.2.2 Esophageal Stenosis

A differentiation should be made between congenital and acquired esophageal stenosis. Congenital stenosis usually is part of the spectrum of esophageal atresia, in which cartilage remnants in the esophageal wall cause obstruction and food impaction [43]. However, these cartilage remnants are not always present; in these cases muscular fibrosis may be found on pathology [44]. Endoluminal ultrasound may provide an indication to the cause of obstruction. MRI often is not conclusive. Sometimes the congenital esophageal stenosis can occur together with esophageal atresia. If the transanastomotic tube hitches while introducing, alertness is warranted to exclude a distal stenosis.

The approach for congenital stenosis is thoracoscopic and similar to the repair of esophageal atresia [44]. Depending on the level of the stenosis, the esophagus can be approached from the right or left side. After mobilization of the esophagus while sparing the vagal nerves, the stenosis can either be resected circumferentially (in case of cartilage remnants) or incised longitudinally and closed transversely (muscular fibrosis) [41].

Acquired esophageal stenosis is usually due to gastroesophageal reflux disease (GERD), caustic ingestion or eosinophilic esophagitis (EE). Management for EE is primarily by medication [45]. Initially GERD may be managed with antireflux medication. However, if GERD is refractory, laparoscopic antireflux surgery in indicated [46].

14.10.3 Long-Gap Esophageal Atresia

In case of long-gap esophageal atresia, nowadays, most often a gastrostomy is performed with a Replogle tube in the proximal esophagus, and delayed primary anastomosis is carried out after 2–3 months [47, 48]. In a recent position paper, a uniform definition for long-gap esophageal atresia was finally determined, taking away the confusion what should be called long-gap esophageal atresia: "Any esophageal atresia (EA) that has no intra-abdominal air should be considered a long gap", i.e. type A and B according to Gross [47]. When anastomosis is not possible, alternative replace-

ment techniques are available, such as jejunal interposition, gastric pull-up or colon interposition with a preference to jejunal interposition [47]. In our institution, we use the thoracoscopic traction technique directly after birth without a gastrostomy. Principally, within 5–6 days a delayed primary anastomosis can be performed in all children. Term neonates without concomitant anomalies can usually be discharged after 3–4 weeks [49].

14.10.4 Airway Anomalies

Both the esophagus and upper airways develop from the primitive foregut. It seems logical that if a malformation of the esophagus occurs, hampering of the development of the upper airways is most likely. The majority of children with esophageal atresia also have airway problems [50, 51]. As mentioned before tracheomalacia is an anomaly frequently encountered in children with esophageal atresia and may give rise to a wide range of symptoms, varying from minimal complaints to life-threatening events due to a collapse of the trachea and/or bronchi. If the malacia extends into the bronchi, these children need to be ventilated with positive airway pressure to keep the airways open. Often, they need a tracheostomy until they outgrow the danger of collapsing of the airways. More recently, there have been some developments regarding external stenting with bioresorbable scaffolds, based on 3D prints from CT scans, but it will take some more years before they will become commercially available [52]. If the malacia is more restricted to the trachea, there are treatment options, depending on the location and extent of the collapse [41, 53, 54]. Both the anterior and posterior approach can be performed thoracoscopically [41, 53].

14.10.5 Follow-Up

Now that survival is improving, there is a shift towards dealing with the sequelae these patients are experiencing. Early complications like postoperative leakage, stenosis, recurrent fistula and gastroesophageal reflux occur in 10–20% of the patients [19, 55, 56]. Postoperative leakage can usually be managed with a simple chest tube. Esophageal stenosis is believed to be related to gastroesophageal reflux [57]. If, despite repeated dilatations, the stenosis is refractory, then laparoscopic antireflux surgery is warranted. [46] In our department, indwelling balloon catheters are used to treat recurrent esophageal stenosis. In many patients, we have been able to successfully treat the recurrent stenosis without resection [58]. Recurrent fistula is described in approximately 5–10% of the patients [55]. In some cases, endoluminal sclerosing or injecting fibrin glue may be successful [55], but usually surgical management is necessary to close the fistula [41, 55].

Long-term sequelae mainly consist of esophageal dysmotility, GERD and pulmonary restriction [19, 21–23, 33–36, 41, 45, 50, 51, 57, 59]. Esophageal atresia is a lifelong condition. Patients with esophageal atresia will always have to drink with their meals. They have to pay attention to what they are eating and may need medication to support motility of the distal esophagus [21, 57]. Silent or asymptomatic gastroesophageal reflux occurs frequently and may ultimately lead to Barrett's esophagus [60]. Transition into adult follow-up is, therefore, mandatory. Many of the patients with esophageal atresia experience pulmonary restrictions and may be susceptible to pulmonary infections [33, 61]. Dedicated support and management is important to improve quality of life in these patients [35, 36, 57].

In conclusion, esophageal atresia is a lifelong condition requiring support by a dedicated team of multidisciplinary specialists, preferably in a centre of expertise [41].

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Part IV

Gastrointestinal

Gastroesophageal Reflux in the First Year of Life

15

Juan A. Tovar

15.1 Introduction

Gastroesophageal reflux (GER) is a frequent phenomenon consisting of the retrograde passage of the gastric juice into the esophagus and, occasionally, its expulsion through the mouth. The main harmful consequences of GER are the loss of nutritional intake and the damage to the esophageal mucosa. The larynx, the tracheobronchial tree, and the lung can also be affected, and other complications may arise. However, although GER is extremely frequent, particularly in young babies, most of them do not suffer from any of these complications. Therefore, to a certain extent, GER is "normal" in them, and only when such harmful effects arise the phenomenon is designated gastroesophageal reflux disease (GERD).

In the present chapter, the causes and mechanisms of GERD during the period of life between birth and the end of the first year are addressed together with the sequence of diagnostic procedures and the rationale of the currently recommended therapeutic measures. A particular analysis of the comorbidities that accompany GERD at this age will be made.

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15.2 Why GER Is So Frequent in Newborns and Young Babies

The stomach is located in the abdomen where positive pressures are permanent and reinforced by gastric peristalsis. In contrast, the esophagus is mostly into the thorax where negative pressures are present during each inspiratory movement. As a consequence of this, a GER-driving pressure gradient from the stomach to the esophagus exists in normal individuals, and only the presence of an efficient anti-reflux barrier fights this phenomenon. The barrier has two main components: The first is the "lower esophageal sphincter" (LES) resulting from the permanent contraction of the distal smooth muscle fibers of the esophagus at the gastroesophageal junction. The second is a sort of "external sphincter" created by the phasic contractions of the striated muscle of the crural sling of the diaphragm formed by the pillars of the hiatus. These contract during inspiration and lengthen the intra-abdominal segment of the esophagus while accentuating the angle of His. The synergic play of these two components closes the distal esophagus, particularly when the GER-driving forces are stronger. Swallowing is possible because the barrier opens at this moment during which inspiration ceases and the LES relaxes allowing the passage of the bolus into the stomach. Esophageal peristalsis is regulated by intrinsic and extrinsic innervations that coordinate propulsive

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contractions with simultaneous relaxations of the sphincter. Peristalsis itself constitutes the second anti-reflux barrier because it is able to clear refluxed material form the esophagus.

However, the barrier function is not 100% effective, and GER occurs rather frequently, specially after meals, even in normal individuals. Some GER is therefore "normally" possible at different times of the day particularly in newborns and young babies who often spit or vomit. They spend long time lying flat and receive large-volume feeds. A certain immaturity of the LES mechanism was proposed as the main mechanism for the failure of the barrier and the frequent occurrence of GER in young babies [1]. However, modern manometric methods demonstrated that the barrier is efficient [2] even in the premature [3]. When sophisticated miniaturized manometric probes became available, it was understood that rather than decreased or abolished LES pressure, which only happens rarely, the main mechanism of these episodes of GER at all ages [4], including young children [5, 6], was the occurrence of non-deglutitory transient lower esophageal sphincter relaxations (TLESR). In some cases the anatomy of the gastroesophageal junction and its relationship with the hiatus are abnormal, mainly by ascent of the junction and part of the stomach into the thorax and then it is appropriate to diagnose hiatal hernia.

If GER is frequent in infants and less frequent in grown-up children, a spontaneous tendency to improvement at this age should be acknowledged. Since "maturation" of the anti-reflux barrier has not been demonstrated, other explanations should be sought. The main one is the acquisition of the standing position, and it is generally admitted that babies who spit or vomit improve progressively during infancy and get rid of these symptoms when they are able to stand up most of the day.

15.3 GERD in Newborns and Toddlers Without Concurrent Diseases (Comorbidities)

If GER is "normal" to a certain extent in newborns and young babies, when should we suspect GERD and start diagnostic tests and treatment? It is obvious that a spitting, well-nourished, and happy baby is normal and does not need investigations or treatments. However, when some digestive or respiratory symptoms occur, the suspicion of GERD is reasonable, and some action should be undertaken. GERD induces several symptoms that can manifest themselves simultaneously or not in the same individual:

1. Vomiting: Babies with GERD, in contrast with adults, usually vomit and/or spit. This vomiting is more often post-prandial, but it may occur at any time. Its content is gastric juice with remains of feedings and very rarely with coffee ground staining or bile. In contrast with that of pyloric stenosis, vomiting tends not to be projective and total.
2. Failure to thrive: The loss of nutritional intake due to repeated vomiting may impair weight gain and development. Vomiting and stunting may be the first signs of GERD requiring attention by the pediatrician who should rule out other multiple causes.
3. Irritation, discomfort, and "abdominal pain": Repeated exposure of the esophageal mucosa to refluxed gastric juice leads to esophagitis. A baby with heartburn, dysphagia, or pain can only demonstrate his symptoms indirectly by crying and/or being irritated, unhappy, and unfriendly [7]. Of course, these symptoms can be related to many other conditions, but they should arise the suspicion of reflux esophagitis.
4. Anemia and iron deficiency: Macroscopic bleeding due to esophagitis is rare at this age, but microscopic blood loss may lead to microcytic anemia and low iron levels. Again, other diseases may cause this, but GERD should be actively sought after in these cases.
5. Repeated respiratory tract infection, bronchial reactivity, and pneumonia may be related to micro-aspiration or massive aspiration in children with GER. GERD should be investigated in them in the absence of other reasonable explanations like cystic fibrosis or immune deficiencies.

Most of these symptoms are caused by a variety of pediatric conditions, and pediatricians should rule these out before investigating

GERD [8]. However, given the prevalence of GER in infancy, a high index of suspicion is justified. Fortunately, peptic ulcers, stenosis, or major hemorrhages are not seen anymore, or very seldom, in refluxing infants. Many years ago, Carre pointed out the naturally benign clinical course of what was known at that time as "minor" hiatal hernia during infancy [9]. According to him, two thirds of patients would be asymptomatic (even without specific treatment) after the first 18 months of life, but the remaining third will remain symptomatic or may eventually have serious complications. These are the patients that require active treatment.

15.4 GERD in Newborns and Toddlers with Concurrent Conditions (Comorbidities)

Pediatricians and pediatric gastroenterologists are mainly concerned with children belonging to the above-discussed category of refluxers. Pediatric surgeons, however, have to deal more often with patients in which congenital or acquired concurrent diseases cause or facilitate GERD. Herewith we discuss these conditions and how they impact on the pathogenesis of GERD and its natural course:

1. **Brain damage**: Congenital or acquired diseases of the central nervous system and particularly cerebral palsy are frequently accompanied by GERD. There are many reasons for this: neurologic impairment may trigger the vomiting center and damages the coordination of digestive motility, both at the sphincter and peristalsis levels causing failure of the barrier [10, 11] and defective clearance. TLESRs seems to have less importance in the pathogenesis of GER in these children than in regular refluxers [11, 12] who, on top of this, are often recumbent, scoliotic, spastic, constipated, and affected by frequent respiratory tract infections. GER is facilitated by all these circumstances, and it may be occasionally aggravated by alkaline duodeno-gastric reflux [13] and salivary loss by drooling. These babies are often difficult to feed because of deglutition disorders, choking, or bottle refusal. The irreversibility of these circumstances in brain-damaged children makes spontaneous improvement of GERD over time unrealistic and the benefits of medications limited.
2. **Patients with respiratory tract disease**. There are several circumstances that facilitate GER in patients with respiratory tract disease that is particularly frequent during the first months of life: This may either enhance positive intra-abdominal pressures or accentuate negative thoracic pressures (or both) thus reinforcing GER driving forces. Premature and newborn babies with bronchopulmonary conditions are particularly prone to undergo GERD. Upper airway obstruction, positive airway pressure ventilation [14, 15], medication with xanthines [16], nasogastric tubes [17], and other reasons account for this as well as micro-aspiration or esophago-bronchial reflexes [18]. Weaning off ventilator may be impossible until GER ceases [19]. At this age it is particularly difficult to determine whether respiratory tract disease causes GER or conversely, if GER (aspiration, bronchoconstrictive reflexes, reflux laryngitis or sensitization to allergens after aspiration) accounts for the respiratory disease.

   A particular case is that of babies with apparent life-threatening events (ALTE), (pauses of apnea or cardiorespiratory arrests) that might be related to GER. Whether these episodes are caused by GER or not is an open issue. pH tracings, polysomnographic recordings [20, 21], and pH-MII recordings [22, 23] clarified only in part this issue. ALTE could be related to both acidic and non-acidic reflux episodes [24], but a clear link between both phenomena is not convincingly demonstrated [25, 26].
3. **Patients previously treated for esophageal atresia (EA) with or without tracheoesophageal fistula (TEF)**: This is a rare malformation (1:3500 newborns) consisting in the majority of cases of the interruption of the upper esophagus behind the trachea and the presence of a fistula connecting the

trachea with the lower end of the esophagus. This is the more common type, but about 10% of the patients have no fistula, and the two ends of the interrupted organ are quite far apart (long-gap cases). Smaller proportions have other uncommon varieties of the malformation. Current overall survival of about 90% [27, 28] makes lifelong follow-up and quality of life important issues for these patients and GERD a problem since 25–60% of survivors suffer it [29, 30] with increasing prevalence with time [31]. Swallowing difficulties may be related to the structural anomaly of the esophagus itself, but reflux esophagitis is found upon endoscopic and biopsy assessments in high proportions ranging between 20% [32] and 53% [33], and postoperative anastomotic stenoses refractory to dilation are in part related to the repeated exposure to gastric juices [34]. Barrett esophagus is diagnosed in a growing number of these patients during adolescence and adulthood [35], and the risk of esophageal cancer in the long run is considered manyfolds higher than in the regular population [36]. Vomiting, heartburn, apneic spells, and respiratory tract disease may be related to GER in these children and deserve attention and treatment during the first year.

There are several explanations for the high incidence of GER in survivors of EA/TEF repair: the muscle and mucosal layers of the reconstructed esophagus are definitely abnormal. The esophagus is shortened because anastomosis always involves some tension [37] and the extrinsic and intrinsic innervations that regulate motility are defective [38–40]. The LES is often ascended and functionally poor [41, 42], and, in addition, gastric motility may be abnormal as well, and duodenal emptying may be slow in cases with associated malformations or malrotation. All these dysfunctions are more relevant in long-gap cases and particularly in those without fistula in which the anastomosis is always under important tension and GER is practically constant [35, 43–45].

4. **Patients previously treated for congenital diaphragmatic hernia (CDH)**: This is another rare condition (1:3500 newborns) consisting of a posterolateral defect of either side of the diaphragm allowing the passage of intra-abdominal viscera into the thorax. The lungs are more or less hypoplastic, and persistent pulmonary hypertension threatens survival even with the best prenatal and neonatal care. In addition, these babies may bear other malformations or malrotation due to the distorted anatomy of the fetal abdominal organs. Ultrasonography allows prenatal diagnosis and in some cases treatment. The more sophisticated support measures (vasoactive drugs, nitric oxide, oscillatory ventilation, ECMO, etc.) are necessary after birth in order to keep these babies alive. Survivals close to 70–80% can be expected in high volume centers if hidden mortality (prenatal deaths, terminations, etc.) is excluded. Long-term follow-up and quality of life became also a priority in this condition [46]. That GERD was associated with CDH was pointed out long ago [47] after a dilated esophagus was found in babies with CDH [48]. GERD is more frequent in those with large hernias [49] and in those who require ECMO [50, 51]. It causes problems in up to 54% of cases [31, 52] and produces esophagitis in about 50% and Barrett's esophagus in some of them [53].

In these babies, the play of pressures between the abdomen and the thorax is abnormal due to lung hypoplasia and tight abdominal closure [54, 55]. The hiatus is under tension due to surgical repair or to replacement of one of its rims by a synthetic patch. The esophagus has poor motility as a result of abnormal innervation [56], and gastric emptying may be slowed due to seemingly abnormal innervation and to malrotation or adhesions [49].

GER is frequent during the first year after CDH repair [57, 58], and it tends to taper off in the ensuing years [31]. Apparently, only a small proportion of patients maintain sphincteric and peristaltic dysfunctions over the

years [59]. Feeding difficulties, prolonged respiratory difficulties, and vomiting may require active treatment of GERD.

5. **Patients previously treated for anterior abdominal wall defects (AAWD)**. These are congenital malformations consisting of anterior body wall defects that may be of two varieties: Omphalocele or exomphalos (1:4000 newborns) is an embryonic condition in which a part of the periumbilical wall is replaced by a gelatinous sac containing the bowel and the liver. Gastroschisis or laparoschisis (1:8000 newborns) is a fetal, acquired defect in which there is right-sided paraumbilical abdominal wall orifice that allows for the bowel and other organs to eviscerate into de amniotic fluid. In both cases, surgical repair involves reintegration of viscera into a reduced abdominal space and closure of the wall that to a variable extent causes increased abdominal pressure [60]. In addition, there is always non-rotation or malrotation due to the extra-abdominal position of the bowel during fetal life, and these, together with deficient innervation and interstitial Cajal's cell density [61, 62], delay intestinal transit postoperatively facilitating GER and hiatal hernia. GER often accompanied by esophagitis has been demonstrated in 43% of patients with omphalocele and in 16% of those with gastroschisis [63].

15.5 How and When to Use Diagnostic Tests for GERD in Newborns and Toddlers

Since GER is to some extent a "normal" phenomenon, diagnosis of too frequent or excessively prolonged episodes becomes a quantitative issue, and this explains the variety of the diagnostic procedures applied. Most of them are relatively invasive and costly, and therefore, their use is withheld until well-grounded suspicion of GERD is established. This is particularly true for young babies who do not collaborate, require miniaturized equipment, and, above all, might benefit from the spontaneous tendency to improvement.

ASPGHAN and ESPGHAN recommendations extensively review the diagnostic methods used in children [8]. In short, contrast meal is widely available, but it is irradiating, scarcely sensitive, and definitely unspecific. However, it may show stenosis, hiatal hernia, or malrotation and give some information about gastric emptying. Ultrasonography is too operator-dependent and is of no common use for this purpose. Extended pH monitoring is probably the accepted "gold standard," but it only informs about acid reflux and has "normal" values that vary too much with age. Extended multiple intraluminal impedance measurements coupled with pH monitoring (MII-pH) is currently the more informative tool since it is able to detect non-acidic or alkaline refluxes as well as acidic ones. However, the equipment is expensive, the tracings are difficult to analyze, and computerized measurements may be misleading. Isotopic studies are more specific and less irradiating than contrast meal, but they do not provide the same morphologic information. Manometry in all its varieties, pull-through sphincteric measurements, micro-catheter-perfused and sleeve sensor-prolonged sphincteric and esophageal body measurements, and high-resolution manometry, is too complicated and expensive (in terms of equipment and time consumption) to be routinely used for diagnosis at this age. Endoscopy and biopsy require sedation or anesthesia at this age, and although they inform about some morphologic features of the esophagus and the stomach, their main focus is the mucosal consequences of GER that may be absent in refluxers with apneic spells or respiratory symptoms. Finally, laryngoscopy and studies of lipid-laden macrophages or pepsin in bronchial aspirate are only used in cases of respiratory tract disease of highly suspected GER origin.

A recent review shows clearly the limitations of diagnostic tests for GER in children [64].

15.5.1 How to Test Children Below 1 Year Without Comorbidities

Most infants with suspected GER or GERD do not need any diagnostic procedure and can be managed expectantly under the more usual dietary, postural, and eventually antacid measures (see below). Only those who do not respond to these simple measures, who keep vomiting, fail to gain weight, emit blood in their vomit, or have alarming respiratory symptoms, require diagnostic tests. Contrast meal is widely available, but it is doubtful that it should be used at all in these cases because its "normality" does not exclude GERD and the presence of GER upon it is not diagnostic of GERD. pH monitoring is probably the first line of diagnosis. It is scarcely invasive, does not require collaboration, and informs reliably about excessive acid exposure. However, it has some limitations since babies fed five or six times per day have the gastric juice buffered to pH >4 for 2 h after each meal and this "blinds" the esophageal electrode for almost half the duration of 24 h. Normal values of acid exposure (reflux indexes) are set at higher values than at other ages, but this does not totally compensate for the insufficiencies of the method. It is true that the number of episodes and the timing of acid refluxes are well displayed and can confirm that GERD is present. Most probably impedance studies will replace standard pH metering in the future because the nature of the information provided by this procedure is much richer. However, there are still limitations that have been mentioned already. Endoscopy and biopsy are probably indicated in babies without comorbidities that are extremely irritated and in those with either blood in the gastric content or with microcytic anemia. Manometric studies are not routinely used in the clinical setting at this age. Of course, they may show insufficient LES pressures, excessive number of TLESR, or disturbed motility, but all these will not impact on the therapeutic attitudes, and therefore it can be concluded that it should be reserved for the investigation of the phenomenon rather than for its diagnosis. Isotopic GER and gastric emptying studies are probably not necessary in most of these patients.

15.5.2 How to Test Children Below 1 Year with Comorbidities

Newborns and small babies with concurrent conditions require a different approach. In many of them, GER may seriously threaten their health and even their life. The expectancy of a spontaneously favorable outcome is unrealistic in them due to the persistence of the mechanisms of GER (posture, spasticity, scoliosis, structural anomalies of the esophagus and/or the hiatus, innervation defects, malrotation, delayed gastric emptying or jejunoileal transit difficulties, etc.). It is therefore reasonable to perform GER diagnostic procedures once the suspicion is reasonable.

Contrast meal is probably the first and more accessible one in this group. In spite of its scarce sensitivity and specificity, it depicts the anatomic distortions caused by the concurrent condition (hiatal hernia, flattening of the angle of His, malrotation, gastric emptying, etc.) that should be known in case of surgery. pH monitoring should probably be performed next, and the use of two electrodes (one esophageal and other one gastric) helps to detect alkaline reflux and delayed gastric emptying [13]. It is generally available and scarcely invasive. The interpretation should take into account not only the reflux index but also the number of episodes of GER and the tracings of both the esophageal probe and the gastric one (if available). MII-pH will probably replace pH metering in the near future, but it is not yet available everywhere.

Endoscopy-biopsy is the best procedure to detect esophagitis. It is probably indicated in cases with blood in the vomit or iron deficiency.

In summary, our approach to diagnosis in children with comorbidities should be proactive but limited to contrast meal, pH monitoring (or MII-pH), and endoscopy-biopsy in selected cases.

15.6 Tools for the Treatment of GERD in the First Year of Life

If GER is a consequence of the failure or transient relaxation of the anti-reflux barrier allowing acid and/or alkaline exposure of the esophageal

mucosa, the treatment of GERD should be directed to one or several of these factors:

Non-operative treatment: This cannot reestablish a failing anti-reflux barrier, and it rather aims at decreasing the pressure gradients, at limiting the harmful effect of the refluxed juice on the esophagus, and at facilitating esophageal clearance. However, all these aims are hard to reach in young infants.

Lifestyle changes are limited at this age. Postural treatment pursues reducing GER by gravity and thus minimizing direct contact of the esophagus with gastric juices. Maintaining the baby in an upright position with a chair or crib is of little help. The prone position that was recommended years ago was abandoned because of the increased risk of sudden death, and therefore, the preferred position is supine with the head elevated [8].

Thickening of the feeds with vegetal products like rice cereal, corn or potato starch, or various bean gums decreases regurgitation but does not impact either on the episodes of GER or acid exposure [8, 65]. AR formulas are based on these additions, and they are designed to avoid excessive caloric intake. These formulas should be routinely used as first treatment, together with some postural help, in babies who regurgitate or vomit but maintain weight gain.

Helping the esophagus to get rid of the gastric juice whenever this is refluxed seems a good idea, and prokinetic drugs were introduced to enhance clearance and hasten gastric emptying. However, there is no convincing evidence of the efficacy of these drugs, and, on top of this, the more popular of them, Cisapride, had to be withdrawn from the market because of cardiac risks. Other drugs like metoclopramide, domperidone, erythromycin, or bethanechol cannot be recommended at this age because there is no evidence of their benefits and also because they may have serious secondary effects [8].

Decreasing the number and duration of TLESRs was the reason for the introduction of a new drug, baclofen, that has some success in adults, but it is not approved for young patients [8].

Finally, neutralizing or decreasing the acid contained in gastric juice would reduce its harmful action on the esophageal mucosa. Buffering antacids like magnesium or aluminum hydroxide may be absorbed and increase aluminum serum levels. Surface protective medications like alginate or sucralfate are effective for on-demand decreasing acid exposure, but their prolonged use may also increase serum aluminum, and there are no studies on their long-term effects in babies. Inhibitors of histamine-2 receptors (H2RAS) like cimetidine, ranitidine, or famotidine are effective in reducing acid exposure and help to heal esophagitis, but after some time, their effect decreases (tachyphylaxis). They also have some side effects, and they are being progressively replaced for proton pump inhibitors (PPI) like omeprazole, lansoprazole, and esomeprazole. These are definitely more effective for acid suppression, decrease of acid exposure, and healing of esophagitis. However, they have some side effects at this age like gastroenteritis, respiratory tract infections, parietal cell hyperplasia with gastric polyps, enterochromaffin cell hyperplasia, and others [66]. In addition, they are not approved for use at this age in which the evidence of their benefits is not fully convincing [8, 67, 68].

Surgical treatment: In turn, surgery that has no effect on motility, acid secretion, alkaline exposure, or gastric emptying (except in a few selected cases) can rebuild the failing anti-reflux barrier in a quite efficient and permanent way. The aims of anti-reflux surgery are to relocate the gastroesophageal junction below the diaphragm if it is elevated, to lengthen the intra-abdominal segment of the esophagus to allow the positive abdominal pressures to play on it, to accentuate the angle of His, and to create a full or a partial (anterior or posterior) wrap with the gastric fundus able to compress the distal esophagus and act as a valve when the stomach is full. In some cases in which feeding problems are predominant, the procedure may be accompanied by a gastrostomy. In rare instances when there are demonstrated gastric emptying problems, a pyloromyotomy or pyloroplasty may be a useful adjunct. All these operations are currently performed by laparoscopy except when local factors make this approach more difficult.

The gold standard of anti-reflux operations is the complete fundal wrap-around first described by Nissen [69]. It decreases acid (and alkaline)

exposure, reestablishes a pressure barrier, and reduces the frequency and duration of TLESRs [70–73]. However, this operation reduces gastric compliance leading to early fullness and sometimes to "dumping" syndrome; it may cause transient dysphagia and can have other surgical complications. Anterior hemi-fundoplications, as described by Ashcraft [74] or Boix Ochoa [75], may work well [2, 76, 77] but are less effective in patients with comorbidities [2, 78]. Posterior fundoplication, according to Toupet [79], is quite similar to an incomplete Nissen wrap-around, and its results should be more or less similar [80, 81]. It is interesting to notice that the institutions where Ashcraft's or Boix-Ochoa's operations were developed finally embraced Nissen's operation since laparoscopic approach was introduced. This demonstrated that finally complete wrap-around was not as bad as pretended by the introducers of these alternative techniques.

In a few desperate cases (particularly in neurologically impaired children), esophagogastric disconnection may be an alternative to repeated failures of fundoplication [82–84]. However, this operation is rarely indicated in the first year of life.

15.7 Treatment of GERD in the First Year of Life

In children without comorbidities, the recommendations of the NASPGHAN-ESPGHAN [8] are more than well founded and should be followed. Happy spitters do not need any treatment (except perhaps AR formula if they are bottle fed). Infants with persisting vomiting and other symptoms, like insufficient weight gain, bleeding, or recurrent respiratory tract disease, in which investigation demonstrated GER require thickening agents and acid suppression with either H2RAS or PPIs. However, it should be pointed out that the limitations and scarce solid evidence of the beneficial effects of both changes in lifestyles and medications at this age throw the suspicion that the unquestionable success of these recommendations might be based in most cases on the spontaneous favorable course of events during this period of life.

In cases with comorbidities, proactive treatment should be undertaken once GERD has been demonstrated. Long-term administration of PPIs, although with scarce evidence, remains the first tool. It is recommended in neurologically impaired patients [85] and in those previously operated for EA/TEF [86] although their effects on the latter were not fully conclusive. With the same lack of evidence, they are used in children operated upon for CDH [87]. It is certainly more questionable to rely on acid suppression in cases with respiratory tract disease although the contribution to this of esophago-bronchial reflexes could be minimized. There is no room for prokinetic treatment in these cases with comorbidities given the structural origin of dysmotility.

The role of surgery is certainly limited in the first year of life. In fact, the proportion of patients operated upon for GER below 2 years is small at least in Europe. American series show that a more aggressive surgical approach is often accepted on the other side of the ocean [88–92].

In babies without comorbidities, anti-reflux surgery is indicated when non-operative treatment fails in symptomatic patients (growth failure, persistent esophagitis, or stenosis) and in some cases with respiratory manifestations of GER and particularly in those with recurrent pneumonia due to aspiration [8]. In exchange, surgery is frequently used for the treatment of children with GERD and concurrent conditions.

The most questionable indication for surgery is the presence of repeated episodes of ALTE that can be put in relationship with episodes of GER after profound study with polysomnographic and pH monitoring or MII-pH monitoring [20–23]. Non-acidic reflux episodes are frequent in young infants [93], and ALTE could be related to both acidic and non-acidic ones [24]. However, there is no agreement on this interpretation [25, 26, 94]. Nevertheless, since the association of GER and ALTE may be deadly, anti-reflux surgery might be indicated in a few cases.

Neurologically impaired patients that are undernourished due to obvious feeding difficulties may certainly benefit from anti-reflux operations often accompanied by a gastrostomy. In fact, close to 50% of indications in the USA correspond to this group of patients [95]. The issue

of whether a Nissen should be added if gastrostomy is indicated has not been resolved, but it is reasonable to accept that gastrostomy alone may improve the status of the patient if GERD has not been demonstrated [96–100]. On the contrary, if a Nissen is necessary to treat GERD in a neurologic patient, addition of a gastrostomy may be a useful adjunct.

Babies previously treated for EA/TEF benefit from anti-reflux surgery when their GERD remains symptomatic for several months. Anastomotic stenosis refractory to repeated dilations, recurrent pneumonias, or insufficient weight gain may improve after surgical creation of an anti-reflux valve. However, the particular anatomy of the esophagogastric junction in these cases (high junction, small stomach, no angle of His) makes surgery more difficult and less effective [30, 101].

Up to 15% or 20% of babies operated upon for CDH may require anti-reflux surgery during the first year [57, 58, 102, 103] and definitely less in the ensuing years [31, 59]. Sometimes they can only be extubated after a fundoplication, and more often surgery is offered on the basis of unmanageable respiratory situations accompanied by difficulties for oral feeding. Also in this case, the local anatomy (distorted hiatus, patch, etc.) may make surgery difficult. Preventive fundoplication during CDH repair has been proposed [104, 105], but its benefits are not fully proven [106].

The contribution of GERD to the problems of babies operated at birth for AAWD corresponds rather to later months of the first year. Difficulties in transit due to malrotation, adhesions, or malposition of the hiatus cause GERD that becomes bothersome later. Fundoplication in both omphalocele and gastroschisis may be indivated in up to 50% of cases, and its performance during abdominal wall closure has been proposed [107].

15.8 Results of the Treatment of GERD

The main problem with the assessment of the results of non-operative treatment of GERD in children is the lack of consistent evidence on the effects of these measures at an age in which ethical concerns, lack of collaboration, and age and size diversity preclude (or make very difficult) the performance of randomized controlled trials (RCTs). Not many have been published on the efficacy of PPIs to treat esophagitis [108] or on the benefits of prokinetics [109–111]. In fact, the lack of really "normal" controls at this age is a barrier difficult to overcome. And thus, as stated by the ASPGAHN/ESPGAHN recommendations, no much solid evidence is available about the benefits of most of the non-operative treatments proposed for individuals this young [8]. Moreover, the evidence is even less solid when considering the long-term effects of medications like PPIs or others in infants. The risks of changes in the microbiota, neoplasia, and others are sometimes discussed but have not been studied. Nevertheless, the issue is not whether or not these treatments should be administered or not (probably they should) but whether or not they add substantially to the spontaneous improvement of GERD at that particular age.

For the same reasons, surgical treatment of GERD should be applied cautiously during the first year of life. The objective evidence of its benefits is weak, and the few published RCTs about this matter are restricted to compare two modalities of operation [92, 112, 113] or details of the same operation [90] but not to clarify the key issue of whether operation itself is better than no operation at this age. Of course, it is beyond doubt that some patients benefit from anti-reflux surgery, but they cannot be compared with similar, non-operated patients, and this casts doubts about the appropriateness of such operations.

And surgery has an additional problem that is easily linked to the operation itself: complications [91]. If a child treated chronically with PPIs acquires an infection or a tumor, many explanations can be found for these. However, if a child having a fundoplication has dumping syndrome, ascent of the wrap into the thorax, failure of the new valve or even dysphagia, wound infection, or adhesive obstruction, the operation itself will be blamed at once, and this is why pediatricians and pediatric gastroenterologists are so reluctant to propose indications for surgery [114, 115].

Even if the surgeon is convinced after many years of practice and critical observation of

his/her own results of the benefits of surgery for treating GERD in children below 1 year with comorbidities (and a few without them), it is fair to inform objectively their families about the potential complications and the expectations of success than can be summarized as follows.

In children without comorbidities, a good Nissen holds well in the vast majority of cases, and a normal life without dysphagia or early satiety after the first weeks following the operation can be foreseen.

Neurologically impaired children reunite the conditions for long-term failure of the wrap (not to talk about the outcome of the primary disease). A proportion of 25% after the first 12 months [116] is a reasonable figure. In many cases, the benefits of the wrap are obvious as demonstrated by parent satisfaction [117] and reduced readmissions [118]. On these bases, reoperation is acceptable when necessary. However, more than two or three failures may indicate other strategies like chronic PPIs or esophagogastric disconnection.

Children with respiratory symptoms of GERD respond well after operation when the problem is repeated aspiration (recurrent pneumonias and atelectasis) but less well when the respiratory disease is bronchoconstrictive like asthma or asthma-like bronchitis. In these cases, the patterns of nocturnal episodes of GER can orient the prediction of success of the operation [119]. In general, in the presence of "asthma" and GER, the surgical indications should be limited to cases refractory to all medical treatments with long nocturnal episodes of reflux [8].

The majority of children requiring surgery for GERD after repair of EA/TEF are improved by the creation of a new valve. However, in one third or more of them, the wrap fails after a few months due to the previously addressed unfavorable local conditions [116]. The proportion of wrap failures is particularly high, and this should be discussed prior to the operation. In this particular group of patients, however, there is increasing evidence of chronic esophagitis evolving into Barrett's esophagus, including some cases of intestinal dysplasia and even cancer. This has been observed even in cases with successful anti-reflux operations. Endoscopic surveillance for life is probably warranted in all them.

Babies operated upon for CDH and surgically treated for GERD have also a considerable proportion of wrap failures but certainly smaller than the neurologically impaired or EA/TEF ones. Babies who require fundoplication are usually the more severe cases in which respiratory, neurocognitive, or nutritional issues are predominant.

The experience with babies operated upon for AAWD and GER is limited, but it does not seem for the proportion of failures to be higher than in regular refluxers.

15.9 Conclusion

GERD is a serious problem during the first year of life in some patients without concurrent conditions and in many of those who suffer them. It would be naïf to believe that this complex phenomenon can be approached only by suppressing acid secretion. But it would be as naïf to believe that surgical creation of a new anti-reflux mechanism will suffice in all cases. A balanced approach is mandatory, and it should be taken into account that patients without comorbidities tend to improve during the first year of life. The use of medication at this particular age lacks evidence and so does anti-reflux surgery. Every effort should be made to design RCT to answer these uncertainties.

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16 Hypertrophic Pyloric Stenosis and Other Pyloric Affections

Mirko Bertozzi, Elisa Magrini, and Antonino Appignani

16.1 Hypertrophic Pyloric Stenosis

16.1.1 History

The history of what is referred to as infantile hypertrophic pyloric stenosis (IHPS) dates back to the 1600s. Hildanus (1627) [1] and Blair (1717) [2] have been attributed with earlier descriptions of HIPS.

Nevertheless our understanding of this condition comes largely from Hirschsprung's seminal work in 1888 [3].

Formerly, in order to release pyloric muscle spasm, gastric lavage, and electrical stimulation, dietary and drug treatments had been used. During this period, gastroenterostomy, which was performed as a desperate remedy, had a high mortality rate up to 50% [4].

In 1907, Henry Dufour and Pierre Fredet defined the surgical correction including splitting of pyloric muscle until submucosa with transverse closure of the muscle [4, 5].

In 1910, Fredet and Guillemot reported the clinical signs of pyloric stenosis enclosing pyloric tumor, increased gastric peristalsis, projectile vomiting, and weight loss, as well as the high frequency of the pyloric stenosis in boys. Additionally they recommended reducing oral intake, gastric lavage, and atropine usage for the initial treatment and suggested surgery for refractory disease [4].

In 1912, Conrad Ramstedt simplified the Fredet procedure by omitting the transverse suturing, leaving the mucosa exposed in the longitudinal subserosal defect. "Ramstedt" operation was successful, and its essential elements have remained virtually unmodified ever since [6, 7].

The operative approach to the pyloromyotomy has undergone to modifications in the last decades. Up until the 1990s, most of surgeons approached the pylorus through either by a right upper quadrant or upper midline incision. These approaches provide excellent access to the pylorus, but frequently the cosmetic result was unsatisfactory.

In 1986 Tan and Bianchi reported the use of circumumbilical incision [8].

Although cosmetically superior, the downside to this approach occurs when difficulty in delivering the pylorus is encountered. In some cases, there is a risk of serosal tear, and the incision may need to be extended.

Intracavitary pyloromyotomy has also been described and avoids the need to extend the skin incision to accommodate the pylorus [9, 10].

More recently, laparoscopic pyloromyotomy has been reported with a wide diffusion in many pediatric surgical units as well as other evolving techniques.

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16.1.2 Epidemiology

The incidence of IHPS ranges from 1.5 to 4 per 1000 live births in Caucasian infants [5] but is lower in African and Asian populations [1].

Males are more commonly affected than females with a ratio of at least 5: 1.4 although the explanation for this remains unclear [11]. Recently, a dramatic rise in incidence among male infants but not for females was reported, so that rates for the two sexes were 6.2 and 0.9 per 1000 infants per year [12, 13].

Mothers under the age of 20 have been reported to have 40% more risk of having a child with IHPS than the older ones [14]. The disorder often occurs in first-born boys [6]. Only 11% of the infants with IHPS are preterm, while most of infants with HIPS are term.

Additionally breast-feeding infants have been reported to have lower risk of IHPS [15].

IHPS strongly aggregates in families, even among distant relatives, and there is a high concordance between monozygotic twins [13] for that heredity is supposed to be polygenic [5, 14].

16.1.3 Etiology

Despite many researches were conducted about possible associated etiological factors and pathophysiological mechanisms, the etiology of IHPS is still unclear.

The pylorus has an elevated high-pressure zone that relaxes with the peristalsis of antrum and contracts as a response to duodenal stimulation. This mechanism prevents retrograde movement of duodenal contents back to stomach.

It is well known that pyloric sphincter functions are under control of some kind of hormones such as gastrin, cholecystokinin, and secretin. Formerly numerous gastrointestinal peptides or grow factors have been implicated as having a causal relationship with pyloric hypertrophy such as high gastrin levels, substance P, epidermal grow factor (EGF), transforming growth factor-alpha (TGF-alpha), somatostatin, enteroglucagon, and neurotensin. However, their role has not been substantiated [5].

Levels of vasoactive intestinal polypeptide and neuropeptide Y which are responsible for peptidergic innervation, as well as nitric oxide (NO) synthase which produces the nitrergic innervation mediator NO that all have relaxation effect on pyloric muscle, are found to be decreased in patients with IHPS. This inability of pyloric muscle relaxation and subsequent pylorospasm is supposed to be effective on IHPS development [16, 17].

Also expression of neural cell adhesion molecule that has an important role in the initial conduct, between neural and muscle cells, has been significantly found low in IHPS [5, 18].

In case of IHPS, a defect of intramuscular innervations has been demonstrated. Nerve-supporting cells of enteric neuronal system between hypertrophied circular and longitudinal muscle fibers of pylorus are absent or extremely rare. Nerve-supporting cells are responsible for a good order and arrangement among processes of neurons and cell bodies, essential for a good neuron function. Decrease of neuron-supporting cells corresponds to the absence or reduction of peptidergic, nitrergic, cholinergic, and adrenergic neural fibers.

Interstitial cells of Cajal (ICC) are the pacemaker of gastrointestinal smooth muscles, providing effective distribution of electrical activities and mediating neurotransmission. ICC helps inhibitory neurotransmission also by producing NO. Absence or deficiency of ICC within IHPS resulting in abnormal motility, secondary to decrease in slow wave occurrence, has been reported [19–21].

In the case of IHPS, an increase of an extracellular matrix protein synthesis (type I procollagen) within circular muscle fibers and connective tissue septa between fibers has been demonstrated, suggesting that the hypertrophied circular muscle of HIPS is actively synthesizing collagen [22, 23]. This composition appears to be responsible of the characteristic structure of pyloric tumor. Furthermore, smooth muscle cell abnormalities were found in IHPS [19].

In the recent years, some authors demonstrated the increasing of some kind of growth factors in IHPS such as insulin-like growth factor I, platelet-derived growth factor-BB, and transforming growth factor-β. Growth factors have been thought to be responsible for smooth muscle hypertrophy [18, 24, 25].

The possibility of an infectious etiology for IHPS has also been discussed [26].

Since there is a strong familial trend in developing IHPS, genetic factors have been implicated in its etiology: regions on chromosomes 2, 3, 5, 7, 11, and 12 have been investigated and implicated [27–30], and several susceptible loci have been identified [31]. Nevertheless a specific gene responsible for IHPS has not yet been discovered.

Variations in the incidence of IHPS and various environmental and mechanical factors suggest that it could be an acquired condition rather than congenital. Maternal smoking increase doubles the risk for IHPS [32].

Young maternal age has been related to IHPS as risk factor [13] as well as breast milk feeding in early pyloric stenosis [33].

Another extrinsic factor such as the usage of erythromycin which is a motilin agonist inducing gastric and pyloric contractions has been blamed to increase the risk for IHPS [34] as well as a neonatal transpyloric feeding [35].

16.1.4 Pathology

Muscular tunica of the stomach is composed of three-layer muscle fibers with different directions. In peripheral layer, muscular fibers are distributed longitudinal, circular in middle, and oblique in the inner layer. Commonly circular muscular fibers thicken at the pyloric level forming the pyloric sphincter. In IHPS the muscle complex becomes hypertrophied causing narrowing of the lumen. Furthermore in addition to muscle hypertrophy, a worsening of the narrowing of pylorus is caused by submucosal edema and lymphocyte infiltration [18, 21]. All these conditions are cause of a progressive obstruction of gastric outlet.

16.1.5 Clinical Presentation

The typical onset of symptoms occurs at 2–8 weeks of age with a peek occurrence at 3–5 weeks [5]. In a study conducted by Schärli et al. on 1215 patients with IHPS, they have revealed the initiation of vomiting after delivery in 20%, 1–2 weeks of age in 60%, and after 4 weeks of age in 20% of the patients [36, 37].

Commonly non-bilious vomiting is the first clinical sign. At first there is only regurgitation of feed, but over a period of several days, it becomes characteristically projectile at almost every feeding. In a little percent of patient, the vomitus may contain fresh or altered blood as a result of gastritis or esophagitis.

Owing to inadequate fluid and calorie intake and in addition to a delay of diagnosis, dehydration and weight loss become apparent [19].

In some patients with a significant delay in diagnosis, a lethargic condition may be present together with disappearance of subcutaneous fat and wrinkled skin.

Usually stools become infrequent, scanty, dry, and firm. However, some infants have diarrhea.

Jaundice is encountered in 2–5% of infants with IHPS and characterized with indirect hyperbilirubinemia due to glucuronyl transferase deficiency [5, 37].

Severe hypokalemic, hypochloremic metabolic alkalosis caused by vomiting in IHPS may result in apnea-like events [38].

16.1.6 Physiopathology

In the case of IHPS, continuous vomiting results in dehydration and metabolic disorders. Gastric fluid includes sodium, chloride, and potassium. Prolonged vomiting causes electrolyte loss rich in hydrogen and chloride and poor in sodium and potassium, and then a hypochloremic metabolic alkalosis develops. As a response to metabolic alkalosis, renal tubules excrete sodium and potassium to ensure the maintenance of hydrogen ions within the body. If the vomiting goes

on, hypovolemia activates renin-angiotensin system resulting in aldosterone secretion that provides sodium and water absorption through renal tubules and stimulates potassium and hydrogen excretion. Because of decrease of chloride via gastric fluid loss resulting in bicarbonate absorption from renal tubules with sodium, metabolic alkalosis gets worse. A hypokalemic, hypochloremic metabolic alkalosis is established. When hypokalemia is increased, renal tubules tend to keep potassium and excrete hydrogen ion from renal tubules. Thus, development of paradoxical aciduria is an indicator of deepened hypokalemia. In case of delayed diagnosis, hypoglycemia and hypoalbuminemia may also be encountered [39, 40].

16.1.7 Differential Diagnosis and Associated Anomalies

Pylorospasm and gastroesophageal reflux may be difficult to differentiate from IHPS without further imaging evaluation. Other medical and surgical conditions causing non-bilious vomiting described below are to be considered [5, 31]:

Surgical conditions to be considered in differential diagnosis of IHPS are:

- Gastric volvulus
- Antral web
- Preampullar duodenal stenosis
- Duplication cyst of the antropyloric region
- Ectopic pancreatic tissue within the antropyloric muscle

Medical conditions to be considered in differential diagnosis of IHPS are:

- Pylorospasm
- Gastroesophageal reflux
- Gastroenteritis
- Increased intracranial pressure
- Metabolic disorders
- Food allergy
- Adrenogenital syndrome

Associated anomalies are found in 6–20% of patients [41, 42]. Anomalies associated with IHPS are:

- Esophageal atresia
- Malrotation of the bowel
- Hirschsprung's disease
- Anorectal anomalies
- Cleft lip and palate
- Urological anomalies

16.1.8 Diagnosis

Infants having weight loss with non-bilious projectile vomiting with a hypokalemic, hypochloremic metabolic alkalosis should be considered for IHPS. On physical examination, abdominal distention and gastric peristaltic waves due to gastric outlet obstruction may be visible on left upper quadrant.

Palpation of the hypertrophied pyloric muscle ("olive") just above the umbilicus at the lateral border of the rectus muscle below the liver edge is deemed diagnostic and has been previously reported as having a 99% positive predictive value [43].

When the clinical findings are equivocal, the diagnosis can be confirmed by ultrasonography (US) or barium meal. Nevertheless US has become the most common and standard technique for the diagnosis of IHPS. The US sensitivity and specificity approach 100% in experienced hands [44].

The generally accepted criteria for a diagnosis of IHPS using US study are a pyloric muscle thickness $\geq$3.5–4 mm and a pyloric channel length $\geq$15 mm [5, 44] (Fig. 16.1).

For the infants younger than 30 days, 3 mm pyloric muscle thickness is assumed as boundary value [45].

Contrast meal study is still a highly sensitive examination for the diagnosis of IHPS. UGI may be used following a non-diagnostic US in a patient with a non-palpable "olive." Water-soluble contrast is generally preferred compared with barium to avoid the chemical pneumonitis should aspiration occur [5].

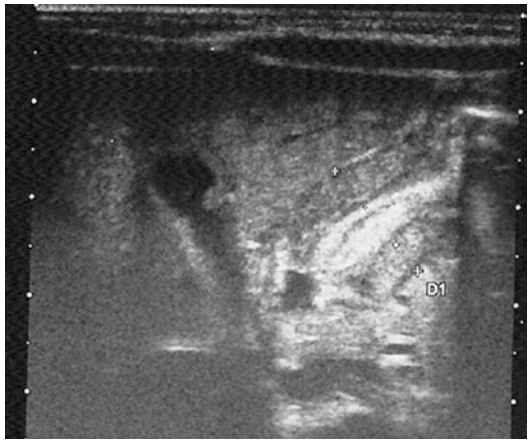

Fig. 16.1 Elongated and narrowed pyloric channel on US

To have a diagnosis of IHPS by contrast meal, it is necessary for the contrast to pass through the pyloric channel. In this case, contrast meal study may demonstrate elongation and narrowing of pyloric channel giving "string" or "double track" caused by compressed invaginated folds of mucosa in the pyloric canal [19]. If contrast does not leave the stomach, it is not possible to confirm the diagnosis of IHPS because pylorospasm can also produce transient complete gastric outlet obstruction [5]. However, it is possible to differentiate the two entities by taking sufficient time during an intermittent fluoroscopy [5].

16.1.9 Management

16.1.9.1 Preoperative Preparation

The surgical management of HPS is not an emergency and should be deferred until the infant is appropriately resuscitated because persistent vomiting in these patients results in chloride depletion and metabolic alkalosis. The length of preparation depends on the severity of the fluid and electrolyte abnormalities. Most infants with IHPS should be able to be resuscitated within 24-h period [5]. Intravenous administration of 0.45% or 0.9% sodium chloride with 5% dextrose and 10–20 mmol/L of potassium chloride at a rate of 150 mL/kg/day may be an optimal resuscitation regimen for fluid and electrolyte replacement [46].

Bicarbonate values higher than 30 mEq/L may cause myocardial dysfunction and central respiratory depression. Respiratory depression and/or apnea due to metabolic alkalosis in IHPS has been reported [38].

Fluid treatment is performed under control of urine output and serum electrolyte values of the infant. The aims of fluid treatment are improving dehydration and achieving potassium and chloride values close to normal [5, 40]. Usage of H2-receptor antagonists has been reported to improve metabolic alkalosis more quickly in IHPS [47, 48].

Decreasing of serum bicarbonate value less than 30 mEq/L represents improvement of alkalosis [5].

Nevertheless in the case of IHPS, thanks to early suspect and fast hospitalization nowadays, many babies with pyloric stenosis do not show any clinical evidence of dehydration on admission, and their serum electrolyte levels are usually normal [19].

Oral feeding should be discontinued. Generally, there is no complete obstruction in IHPS; thus, infant may tolerate its own gastric secretion. The placement of a nasogastric tube may cause additional fluid and hydrochloric acid loss; thus, nasogastric tube is not needed whether infants with IHPS that do not vomit following oral intake is stopped [5]. Usually a nasogastric tube is passed to keep the stomach empty immediately prior to the general anesthetic, to reduce the risk of aspiration of gastric contents. Being not an emergency, the operation for pyloric stenosis should never be undertaken until serum electrolyte levels have returned to normal.

16.1.10 Operative Treatment

16.1.10.1 Open Procedure

Pyloromyotomy for IHPS is one of the most important operations of the twentieth century. For the first time in 1907, Pierre Fredet who was a French surgeon from Paris performed Heineke-

Mikulicz pyloroplasty (a longitudinal cut through both muscle and mucosa that was then sutured in a horizontal fashion) on an infant suffering from vomiting for 1-month period. The infant died due to abundant hematemesis 1 day after operation; thus, later he performed pyloroplasty by extramucosal fashion. In 1912, Conrad Ramstedt performed extramucosal pyloroplasty on an infant with IHPS, but did not close the muscular layer, and left it open [7].

This technique is still in use for the surgical treatment of IHPS and called as Fredet-Ramstedt pyloromyotomy. Although the approach to the abdomen has continued to evolve, the pyloromyotomy itself has remained relatively unchanged over the past century.

In the case of open surgical approach, many types of incisions have been described:

- Lateral oblique muscle-splitting incision
- Transverse right upper quadrant incision
- Upper midline incision
- Right semicircular umbilical incision
- Supraumbilical semicircular incision

Once the hypertrophic pylorus is delivered from the abdominal incision (Fig. 16.2), it is possible to point out the vein of Mayo that marks the distal extent of the tumor. There is a relatively avascular plane in the middle of the anterior surface, and in this line, the serosal incision should be made. The incision should be extended as far as the pyloric vein of Mayo distally and onto the anterior surface of the antrum of the stomach proximally resulting in a 2–3 cm incision [6]. A gentle pressure with a blunt instrument into the incision allows splitting of the hypertrophied muscle fibers down to the submucosa that appears white and glistening. Twisting movements of the instrument cause a distal and proximal extension of the split, widening the incision [6]. To ensure that all muscle fibers have been divided throughout the length of the incision, the edges of the split muscle are spread apart with a pyloric spreader permitting to the submucosa to bulge into the incision [6] (Fig. 16.3). Special care must be taken at the pyloroduodenal junction, particularly vulnerable, to avoid perforation. At this point, a simple test to evaluate possible perforations is necessary. Via the nasogastric tube, an amount of 20 mL of air is introduced into the stomach. The air is then gently milked through the pylorus into the duodenum, and a gauze is placed on the incision to detect any bile staining. If there is no sign of bile leak, the intervention is considered completed. Any detected perforation of the mucosa should be closed by direct interrupted fine suture and a portion of omentum placed over this site [5]. Alternatively the pyloromyotomy is closed completely, and a redo myotomy on the opposite side of the pylorus may be performed [6]. At this point,

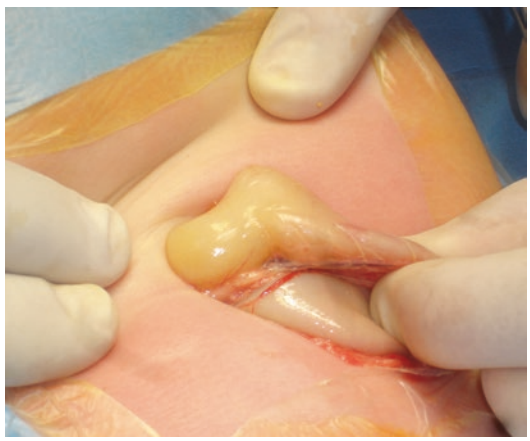

Fig. 16.2 Intraoperative appearance of "olive"

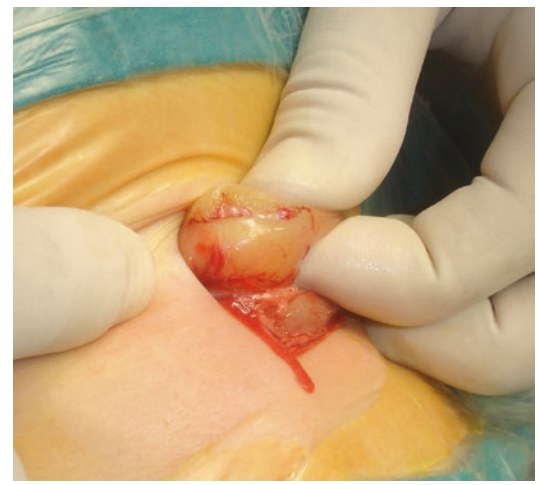

Fig. 16.3 Fredet-Ramstedt pyloromyotomy (hypertrophied muscle fibers are separated in midline to both sides in a fashion allowing for mucosal prolapse)

the pylorus is reintroduced in the abdominal cavity, and the fascial layers and the abdominal wall are closed with an interrupted or running suture. The skin is closed with subcuticular suture.

16.1.10.2 Laparoscopic Procedure

Laparoscopic pyloromyotomy was described for the first time by Alain et al., in 1991 [49].

LP has become increasingly popular over time, although the risks and benefits of this procedure, when compared with open pyloromyotomy, are still widely debated.

Usually, 5 mm laparoscopic port and laparoscope are placed in the umbilical fold. Pneumoperitoneum is established with CO2 at pressure of 6 mmHg. Two additional ports are placed in the left and right mid-clavicular line just below the costal margin under direct vision with the camera. The duodenum is grasped with atraumatic forceps just distal to the pylorus olive to stabilize it. A 3 mm diathermy hook is passed into the abdomen to initiate the pyloromyotomy. Some prefer to use a retractable, arthroscopic knife instead. The muscular layer is then separated with an endoscopic spreader. A satisfactory pyloromyotomy is evidenced by ballooning of the intact mucosa. The absence of mucosal perforation is checked by insufflations of air in the nasogastric tube; if the absence of perforation is seen, the instruments and ports are removed. The umbilical fascia is closed with absorbable suture, and the skin of all the wound is reapproximated with subcuticular absorbable sutures [31].

16.1.10.3 Evolving Techniques

Endoscopic pyloromyotomy, single-incision laparoscopic pyloromyotomy, and microlaparoscopic pyloromyotomy have been described. The data regarding endoscopic pyloromyotomy is limited to several case series [50, 51].

Data concerning single-incision laparoscopic pyloromyotomy is limited to small sample retrospective analyses; nevertheless it appears similar to traditional laparoscopic pyloromyotomy outcomes [52, 53].

Microlaparoscopic pyloromyotomy is performed using 2 mm instruments and 1.7–2.4 mm laparoscopes. Data regarding this technique is also limited to small, retrospective case series [54]. Modifications of the single-incision laparoscopic pyloromyotomy technique have also been reported in the literature with the aim of reducing complications and operating times [51] such as the single-port laparoscopic-assisted pyloromyotomy, where a laparoscope is used to facilitate delivery of the pylorus through an umbilical wound [55, 56].

16.1.10.4 Single-Port Laparoscopic-Assisted Pyloromyotomy: Operative Technique [55]

A prophylactic dose of intravenous antibiotic (ceftriaxone, 50 mg/kg) is administered 30 min before surgery. A roll is positioned under the baby's back to expose the high quadrants of the abdomen. Umbilical cleansing with povidone-iodine is provided before the surgical procedure. The infant is placed in anti-Trendelenburg position. The access to the abdominal cavity is performed according to Alberti et al. [57] with a right semicircular umbilical skinfold incision.

Once the peritoneum is opened, a 10–12 mm Hasson trocar with pneumostatic anchorage is inserted. After establishing a pneumoperitoneum (to a pressure of 6 mmHg—flow 0.5 L/min), an operative telescope is introduced, and a complete exploration of the abdominal cavity is performed. After the pylorus is spotted (Fig. 16.4), using an atraumatic instrument

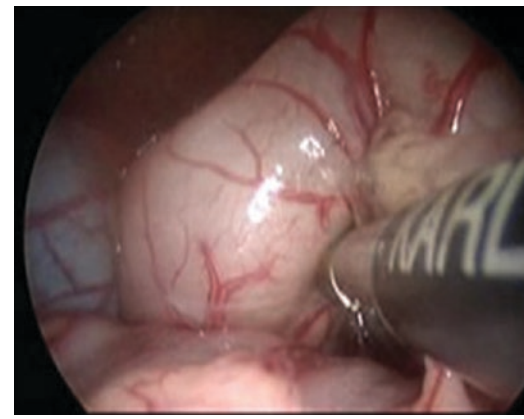

Fig. 16.4 The "olive" is spotted during the single-port laparoscopic-assisted pyloromyotomy

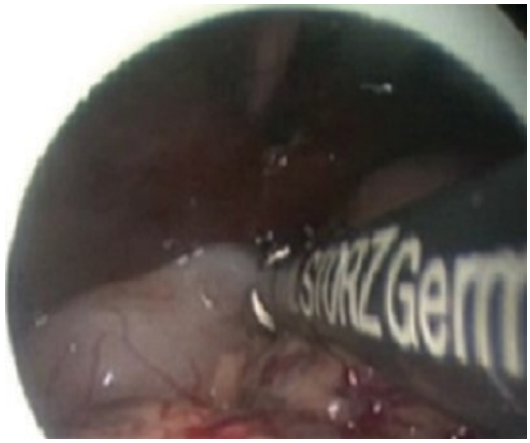

Fig. 16.5 The stomach is grasped laparoscopically proximal to the pyloric tumor during the single-port laparoscopic-assisted pyloromyotomy intervention for IHPS

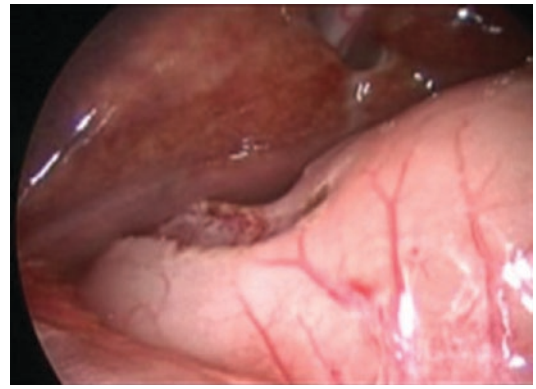

Fig. 16.6 The air test performed during the single-port laparoscopic-assisted pyloromyotomy to check perforation

introduced through the operative channel of the laparoscope, the stomach is gently grasped laparoscopically proximal to the pyloric tumor (Fig. 16.5) and exteriorized through the right umbilical incision; the trocar is removed. With this simple maneuver, often the tumor is exteriorized from the abdominal wall. In case of difficulty, taking the stomach in two fingers, a gentle traction is performed to pull out the hypertrophic pylorus from the umbilical incision; then a Ramstedt's pyloromyotomy is performed. Once conventional intervention is done, the pylorus is reintroduced in the abdomen. A reintroduction of the 12 mm trocar is performed, and a new pneumoperitoneum is created. After the individuation of the pyloromyotomy, a minimal irrigation with a Nelaton catheter 14 ch introduced in the operative channel of the telescope is done, and an air test by insufflating 50 ml of air through a previously placed nasogastric tube is performed to exclude any mucosal leakage (Fig. 16.6). If no perforation is detected, after a careful control of the hemostasis, the trocar is removed.

The wound is closed meticulously: 4-0 Vicryl interrupted fascia sutures are used, and skin suture is performed using 2-octyl cyanoacrylate [55, 58, 59].

16.1.11 Postoperative Care

The timing of reintroduction of feeds continues to be controversial [60–62]. Nevertheless in the majority of infants, feeding can be started within 4–6 h after surgical procedure, and complete oral intake can be achieved within 24 h. First oral feeding may be delayed to 12 h for the infants having hematemesis during preoperative course due to gastritis. Usually the authors of this chapter prefer to reintroduce nutrition 6 h after the intervention following an increasing scheme, discharging the patients only 24 h later the first full meal.

16.1.12 Nonoperative Treatment

Although this treatment to IHPS has been applied in the past, the only nonoperative treatment for HPS currently available is atropine sulfate [46]. The atropine suppresses muscular contraction and gastric peristalsis which potentially reduces the muscular spasm reputed to be the cause of IHPS. Despite some authors have reported a success rate in resolving the IHPS ranging from 75% to 88%, nowadays this way of treatment is only considered for extremely high-risk infants who cannot be operated due to other medical conditions or should be reserved only for the treatment of or for parts of the world where it is not safe to perform neonatal surgery [63–67].

Balloon dilatation of pyloric channel has been tried for nonoperative treatment of IHPS. The first reported study with balloon dilatation that has been tried on six patients with IHPS, only one dilatation of pyloric channel resolved the problem, but a mucosal rupture occurred [68]. Afterward, an infant who had developed IHPS following closure of a giant omphalocele was reported to be improved after two pyloric dilatations [69]. There are some articles suggesting balloon dilatation of pyloric channel for recurrent pyloric stenosis after IHPS operation [70] and for the hypertrophic pyloric stenosis that has late onset [71].

16.1.13 Complications

Nowadays, mortality after pyloromyotomy is almost not encountered, and morbidity is also extremely rare [4, 5].

Perforation of duodenal mucosa is the most severe surgical complication during pyloromyotomy. The risk perforation is reported to range from 0.4% to 10% in laparoscopic surgery and from 0% to 6% in open surgery [5, 72].

During postoperative 24 h, vomiting may be encountered caused by gastric atony, and vomiting caused by pyloric edema may be prolonged to several days. For vomiting continuing after two postoperative days, incomplete myotomy should be considered. Incomplete myotomy is generally caused by insufficient splitting of muscle fibers of pylorus on gastric side. In this case, endoscopic balloon dilatation of pylorus could be tried, or pyloromyotomy should be performed [70, 71].

The ratio of postoperative wound infection is reported ranging from 0% to 6% in laparoscopic group and from 0% to 7% in open surgical approach [5, 73, 74].

Postoperative hemorrhage, wound dehiscence, and incisional hernia are rare complications [73, 74]. A recent meta-analysis concerning complications of pyloromyotomy has indicated major complication rates 4.9% for laparoscopic and 2% for open surgery, respectively [75].

16.2 Pyloric Atresia

16.2.1 Introduction

Congenital pyloric atresia (CPA) is a very rare condition, representing less than 1% of all atresias of the gastrointestinal tract [76] with an incidence of 1:100.000 live births [77]. The first author describing CPA has been Calder in 1749 [78]. CPA may occur as isolated lesion or in association with other congenital hereditary anomalies: aplasia cutis congenita and multiple gastrointestinal tract atresias. Nevertheless the most common hereditary anomaly associated with CPA is the epidermolysis bullosa [79–83].

16.2.2 Etiology

Etiology is not exactly known. Vascular theory and failure of canalization theory have been proposed, but there is inadequate embryological evidence in support of either. CPA is thought to result from developmental arrest between the 5th and 12th weeks of intrauterine life. Mucosal desquamation has been suggested to play a role, mainly in patients with associated epidermolysis bullosa [84]. Mutations in the genes encoding the subunit polypeptides integrin alpha 6 beta 4 (ITGA6 and ITGB4) have been identified in several patients with epidermolysis bullosa and pyloric atresia. [85] There is no sexual predilection but most CPA can be associated with low birth weight.

16.2.3 Pathology

Three recognized varieties of CPA are known [76]:

- Type A, membranous pyloric obstruction (57%)
- Type B, longitudinal segmental atresia (34%)
- Type C, pyloric aplasia (9%)

16.2.4 History and Physical Examination

Oligohydramnios, large gastric bubble, and the presence of echogenic material in amniotic fluid (elevated alpha-fetoprotein and acetylcholinesterase) [86] on antenatal ultrasonography in the second trimester may be predictive signs of pyloric atresia [87]. Prenatal diagnosis of pyloric atresia and epidermolysis bullosa can be performed in pregnancies at risk for recurrence of this syndrome. Prenatal magnetic resonance imaging has been used to confirm the diagnosis, but its utility remains unclear [88].

16.2.5 Presentation

The typical presentation of CPA is non-bilious vomiting soon after birth with upper abdominal distention. Scaling and blistering of the skin are found if epidermolysis bullosa is associated. Respiratory symptoms such as dyspnea, tachypnea, cyanosis, and excessive salivation are often associated. CPA is common in infant with low birth weight [89]. In the case of associated colonic atresia on account of accumulation of bile in the bowel between pyloric and distal atresia, the abdomen can be distended [90].

16.2.6 Diagnosis

The diagnosis of CPA is suggested by an abdominal X-ray which shows a large single gastric air bubble and gasless non-distended abdomen [91]. Contrast study or endoscopy can confirm the diagnosis. There are three important radiological signs: (1) the single gas bubble sign, (2) the absence of beak sign, and (3) the presence of the pyloric dimple sign on a contrast study. The ultrasonographic examination may be helpful for differential diagnosis with hypertrophic pyloric stenosis [92].

16.2.7 Management

The treatment of CPA is surgical and depends on the anatomical type [93]:

Type A (membranous pyloric obstruction): excision of diaphragm and Heineke-Mikulicz pyloroplasty.

Type B (longitudinal segmental atresia): when the atresia is short, a Finney pyloroplasty can be carried out [92]. For longer atresias, the procedure is the same with type C.

Type C (pyloric aplasia): gastroduodenal end-to-end anastomosis. Gastrojejunostomy should be avoided.

16.2.8 Operative Technique

After a preoperative preparation (insertion of nasogastric tube, i.v. infusion, central line for parenteral nutrition, and medical treatment), the patient is ready for surgery. Surgery can be performed either with open or laparoscopic technique.

A supraumbilical right transverse incision is made. The abdominal cavity is opened, and careful exploration and search for other intestinal atresias are performed.

During the procedure, a gastrostomy can be helpful to identify the exact disease. Another way to find the exact location of the web avoiding a gastrostomy can be achieved by placing a 12–14 ch nasogastric tube, to be advanced up to the region of the obstruction [92].

This procedure is indicated for membranous pyloric obstruction (type A) and short atresia (type B).

After identification of the pylorus, a longitudinal incision is made with cutting diathermy or scissors, starting from the gastric side of the pylorus to the duodenum. The total length of the incision should be 1.5–2 cm, extending approximately 1 cm on the gastric side and 1.5–1 cm on the duodenal side of the pylorus; it should be performed on the midline between the greater and lesser curvatures of the stomach and superior and inferior borders of the duodenum. The membrane is excised circumferentially and the mucosa approximately with 5–0 absorbable sutures. The duodenal lumen is inspected, and a catheter is pushed down to exclude further distal atresias. The longitudinal incision is then closed transversely in two layers [92].

Gastrostomy is generally not necessary. The abdomen is closed and a nasogastric tube is left in the stomach.

Laparoscopic approach to pyloric atresia could be an alternative option to the conventional open procedure. However, the procedure should not significantly differ from that performed with the conventional laparotomic approach [92].

16.2.9 Prognosis

The prognosis of isolated CPA is excellent. The mortality depends on the postoperative care of neonates and co-existing morbidities and anomalies. In these last cases, mortality may be up to 50% [78, 82, 94].

16.3 Prepyloric Antral Diaphragm

16.3.1 Definition

Antral web represents about 1% of all gastrointestinal tract obstruction [94]. There is a male predominance. It is a thin septum, composed of mucosa and sottomucosa, soft and pliable with a thickness of 2–4 mm, located 1–3 cm from the pylorus [95].

It typically projects into the gastric lumen perpendicular to long axis of the antrum [96, 97].

The etiology of the antral web is still controversial. It may originate from incomplete canalization of the foregut during the 5–6 weeks of the embryonic age, as an incomplete form of membranous atresia [96–98].

Associated abnormalities are noted in 30% of children, including the gastrointestinal tract and cardiovascular system.

16.3.2 Presentation

The age of onset and clinical presentations of antral web depend on the degree of obstruction and the size of its aperture, from 2 to 30 mm [99]. We have three groups of patients: a neonatal group, childhood group, and adult group [97].

The most important symptom in neonatal group is non-bilious vomiting with apnea, cyanosis, and no weight gain.

In the childhood group: vomiting, abdominal pain, fullness after eating and bloating.

In adult group: episodic cramping, epigastric pain, fullness following meals, intermittent vomiting.

16.3.3 Diagnosis

The diagnosis of pyloric obstruction is made by a plain radiograph which reveals a large distended stomach with no air distal to it.

Contrast meal study allows accurate diagnosis of an antral web in 90% of cases [100].

Diagnosis of an antral web can also be established with ultrasound when performed by a skilled operator. Another diagnostic technique described in literature is endoscopy that can confirm the presence of an antral web or other gastric pathologies such as peptic diseases or adhesion [97].

16.3.4 Management

In the case of symptomatic antral web, gastric outlet obstruction surgery remains the primary treatment method [100].

It can be managed with an incision to excise the web. Endoscopic transection or laser lysis of the web has also been described [101]. In addition to resection of the web, antropyloroplasty was also necessitated. Complications are similar to pyloric atresia.

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Gastric Volvulus

17

Ascanio Martino, Francesca Mariscoli, and Fabiano Nino

17.1 History

Gastric volvulus (GV) consists in the rotation of at least 180° of the stomach on itself, resulting in partial or total foregut obstruction.

The first autoptic description of an adult case of GV was reported in 1866 by Berti [1]; in 1897 Berg [2] performed the first surgical correction; in 1899 Oltman [3] described the first pediatric case and in 1904 Borchardt [4] defined the classic triad presentation of acute gastric volvulus: violent nonproductive retching, severe epigastric distension, and inability to pass a nasogastric tube. In 1940 Singleton [5] classified the disorder on the basis of type, degree, and direction of rotation and on the basis of the etiology and of the mode of presentation.

17.2 Classification

The GV can be classified in several ways [6–10]. By the axis on which the rotation takes place, if the revolution is realized according to the longitudinal axis joining the gastroesophageal junction with the pylorus, volvulus is termed *organoaxial*, the most frequent form (Fig. 17.1a); if instead the rotation axis is the line joining the greater with the lesser gastric curvature, volvulus is called *mesentericoaxial* (Fig. 17.1b); the rarest form is *combined or mixed volvulus,* that is defined when there is a biplanar rotation.

Based on the etiology, GV may be *primary or idiopathic*, due to failure of gastric fixation (absence or laxity of one or more gastric anchors: the gastrophrenic, gastrosplenic, gastrohepatic, and gastrocolic ligaments). Volvulus is defined *secondary* when it is associated with anatomical or functional gastric disorders (e.g., hourglass stomach, gastric outlet obstruction) or with defects of adjacent organs (diaphragmatic hernia, hiatal hernia, wandering spleen, asplenia, intestinal malrotation).

According to its location, GV can be classified in *abdominal* and *intrathoracic*; in the majority of cases, the stomach remains in the abdomen cavity, whereas, more rarely, in presence of diaphragmatic defects, it can migrate and rotate into the chest. GV associated with hiatal herniation of the entire stomach into the chest has been called *upside-down stomach* [10].

Depending on its mode of presentation, GV may be *acute*, *intermittent* or *chronic* and *acute-on-chronic.*

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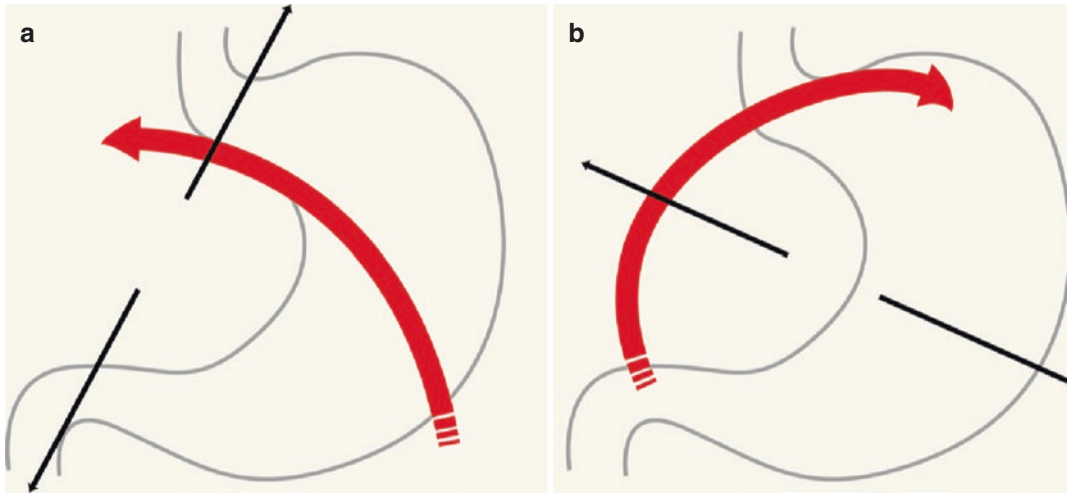

Fig. 17.1 (**a**) organoaxial gastric volvulus. (**b**) mesentericoaxial gastric volvulus

17.3 Incidence

GV is an uncommon disorder in pediatric age, although more frequent than reported, because the less serious forms can be misdiagnosed as gastroesophageal reflux, just sometimes concomitant.

The most extensive literature review [6] on GV in pediatric age refers to 581 cases of infants and children; of these, 252 (43%) were acute cases, of which 69% secondary and 54% organoaxial type, while 329 (57%) were chronic cases, of which 74% primary and 85% organoaxial cases. 381 cases (66%) were children aged ≤12 months; of these, 166 (38%) were acute, of which 54 (37%) were neonates and 40 (27%) were acute-on-chronic cases.

17.4 Clinical Presentation

Clinical features depend on the degree of rotation and obstruction and may range from asymptomatic to life-threatening. *Acute GV* is a surgical emergency, in relation to the evidence of vascular, ischemic disorders of the stomach.

Symptoms are crying because of postprandial abdominal pain, epigastric distension, persistent nonbilious vomiting, and, less often, cyanosis, acute respiratory distress, hematemesis, apnea, and acute neurovegetative crisis (pallor, hypotonia, ocular revulsion, up to cardiorespiratory arrest).

Intermittent or chronic GV may cause nonbilious emesis, feeding problems or failure to thrive, sleep problems, and, less often, dyspnea or gastroesophageal reflux disease, so that the differential diagnosis can be difficult, because of the similar clinical findings. *Acute-on-chronic volvulus* [10] represents the acute form of infants and children with a history of symptoms suggestive of chronic disorder.

17.5 Radiological Features

Although radiologic investigation must include a plain x-ray film of the chest and the abdomen, the diagnosis of GV is performed by repeated upper gastrointestinal contrast studies [6, 11]. Radiologic evaluation should be done in supine as well as in upright position; the diagnosis is possible after the first contrast study up to 83% of cases [12]. The radiological signs of organoaxial volvulus are horizontalness of the stomach with the greater curvature above the lesser curvature, in front of the lower esophagus, and pylorus pointing downward (Fig.17.2). In mesentericoaxial volvulus, the stomach may show double air-fluid levels (Fig. 17.3) and lies in an upright position, with

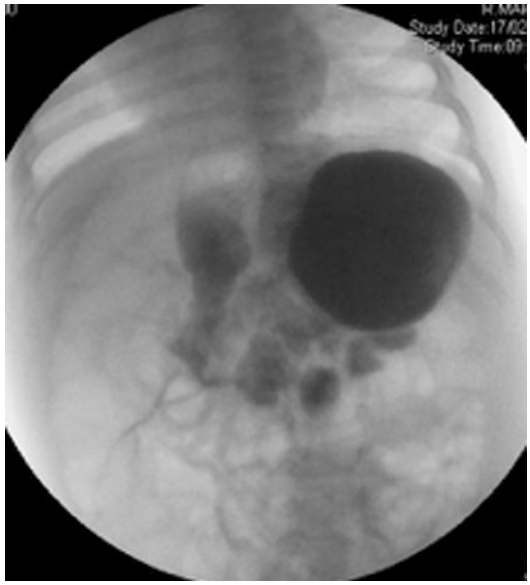

Fig. 17.2 Upper gastrointestinal series, organoaxial volvulus, the pylorus is pointing downward, and the greater curvature lies superiorly

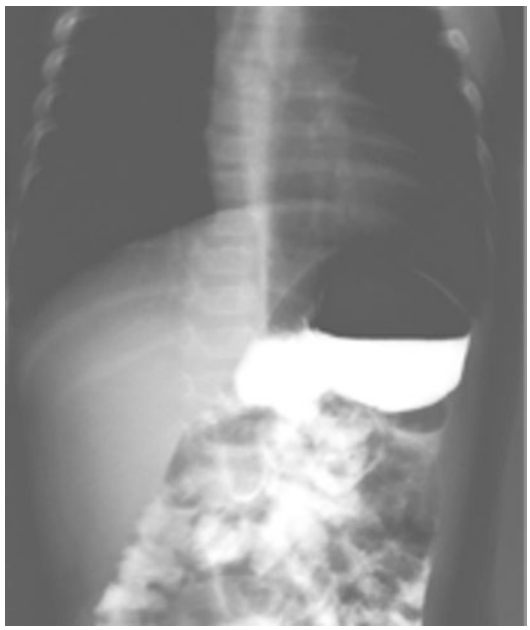

Fig. 17.3 Upper gastrointestinal series, gastric volvulus with double air-fluid levels

pylorus above the gastroesophageal junction. In the intermittent volvulus, radiologic examination may be normal, due to its spontaneous reduction.

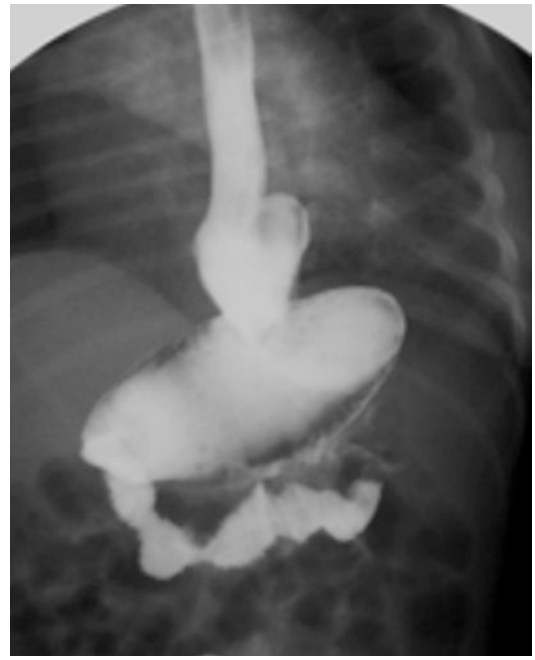

Fig. 17.4 Upper gastrointestinal series, gastric volvulus with hiatal paraesophageal hernia

In the secondary GV imaging studies may show the associated anomalies (e.g., diaphragmatic hernia, deviation of the spleen) (Fig. 17.4).

Gastroesophageal reflux is detected in 12–23% of cases [6, 12].

17.6 Treatment

The individualized treatment depends on the type of GV, on the underlying etiology, and on the presence of comorbidity. The management may be medical or surgical.

17.6.1 Medical Treatment [12–14]

Conservative management is advocated in patients with intermittent or chronic volvulus; it consists on diet modification (small amounts of thickened meals) and keeping the patient in a prone or in a right recumbent position with the head raised 30–45° for at least an hour after feeding. The advised positions allow rapid gastric emptying

and prevent the torsion of the stomach. In fact in chronic GV the gastric contents are retained in the fundus, while large amounts of air can pass through the pylorus, causing an intestinal distension, which can aggravate the volvulus pushing up the greater curvature. By keeping the patient as already mentioned, the air will fill the fundus, and this will reduce the intestinal distension, preventing the milk regurgitation into the esophagus.

Drug therapy (prokinetics and anti-secretory agents) may be useful.

Worsening of symptoms or their persistence resulting in failure to thrive represents indication for surgical approach.

17.6.2 Surgical Treatment [10, 12, 15–18]

Acute GV is a surgical emergency, because it can be life-threatening for children.

The delay in its recognition and management can cause strangulation and ischemic perforation of the stomach.

The surgical approach is recommended in volvulus secondary to pathology of adjacent organs as well as failure of conservative treatment of primary chronic type.

The goals of operative treatment are volvulus reduction, recurrence prevention, and any associated anomaly correction. Prompt gastric decompression with a nasogastric tube can facilitate the reduction of the volvulus (the Borchardt's triad is very rare in pediatric age) improving the clinical condition.

The surgical treatment of GV is still controversial; several procedures have been proposed: simple reduction, gastrostomy for neonatal cases, anterior gastropexy, and double and triple gastropexy, performed by open or laparoscopic approach.

Gastric fixation may prevent the recurrence and can be achieved by gastrostomy tube placement (open, laparoscopic, or endoscopic technique) or by anterior gastropexy; both of the previous procedures can cause or worsen a gastroesophageal reflux.

Fundal fixation and esocardiopexy may be associated with anterior gastropexy in order to eliminate any concomitant reflux, by reforming and stabilizing the angle of His.

Hiatal repair may be associated in patients with hiatal hernia. An additional antireflux procedure (fundoplication) may be performed in case of persisting reflux disease.

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Bowel Atresia and Stenosis

18

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Congenital anomalies of the bowel can affect any portion of the gastrointestinal tract. Bowel atresia and stenosis concern abnormal closure, discontinuity or narrowing from the duodenum to sigmoid colon, and the incidence is about 2/10,000 live births. The pathogenesis was previously believed to be an embryologic trouble of bowel recanalization or a disruption compromising small bowel vascular supply, but new genetic hypothesis emerges since a few years to explain the occurrence of bowel atresia and stenosis.

Prenatal diagnosis is common but remains difficult. The management of bowel atresia and stenosis depends on many criteria such as birth weight, the type and level of the atresia, the length of the remaining bowel, associated malformations, and the type of surgery. The results have improved dramatically since several decades due to enhanced medical support including intensive care management, total parenteral nutrition (TPN), and new surgical procedures.

18.1 Epidemiology

The reported incidence of small bowel atresia (SBA), i.e., concerning the duodenum, jejunum, and ileum, ranges from 1.3 to 2.8/10,000 live births [1]. However wide variations have been noticed according to the country, from 0.57 in Spain to 6.6/10,000 in Japan [2]. The European Surveillance of Congenital Anomalies system (EUROCAT) collected 1133 SBA out of 5,126,164 live births during a 16 years period (1990–2006) after exclusion of the cases associated with gastroschisis and teratogenic syndrome which represent an overall incidence of 1.6/10,000 in Europe. Associated malformations with SBA are frequent. Chromosomal and genetic syndromes are encountered in up to 20.6%. Among them Down's syndrome is far more frequent in association with duodenal atresia than with jejunoileal one. Other nonchromosomal malformations associated with SBA include all components of VACTERL and are significantly more frequent with duodenal atresia. Details can be found in Table 18.1 [3].

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Table 18.1 Most common associated malformations with small bowel atresia [3]

Associated anomalies	Duodenal atresia (%)	Jejunoileal atresia (%)
Cardiac	12.3	6.6
Intestinal (other than SIA)	8	2.6
Esophageal atresia	3.8	0.3
Anorectal malformations	3.8	1
Urinary system	6.5	2.4
Cleft (lip and/or palate)	1.3	0.5
Limb	6.9	1.3

18.2 Pathogenesis

The etiology of intestinal atresia remains unclear. For Tandler a SBA was a lack of revacuolization of the solid cord stage during intestinal development which occurs by Day 44–46 [4]. Against this hypothesis were evidences of bowel contents appearing later during the organogenesis and found below the atresia or in the intermediate parts of multiple SBA inconsistent with the revacuolization concept [5]. As early as 1904, Clogg, in reporting two cases of SBA, postulated that torsion of the intestine could account for some of these cases [6]. Louw and Barnard suggested a mesenteric vascular accident could be the cause of most jejunoileal and colonic atresias [7, 8]. However these theories do not explain how a duodenal atresia occurs in Down's syndrome, for instance.

With the improvement of prenatal ultrasounds, more than 30 cases of intussusceptions have been adequately documented in fetus, causing ischemia and subsequent SBA [9–13]. Let's mention that it has been hypothesized by Chiari as early as in 1888 [14], about a case in which intussusception of the fetal intestine was thought to be the cause.

Hereditary multiple intestinal atresia, first reported by Guttman et al. in 1973 [15] and then by Puri in 1988, is a very rare form of multiple atresia that suggests a malformative process could be involved rather than an ischemic one [16–18]. It has been proposed to be an autosomal recessive inheritance. They involve atresia from the stomach to rectum and have a very poor prognosis. Familial distal foregut atresia due to an autosomal dominant inheritance was also described by Robinson [19]. Experimentally Fourcade and Puri created multiple gastrointestinal atresia using Adriamycin in rats demonstrating that an ischemic process was not involved [20].

Many genes and the downstream morphogenetic events have been studied as possible causes of bowel atresia. Cheng reported possible duodenal atresia in mouse by mutation of gene fibroblast growth factor 2IIIb (Fgfr2IIIb) or its ligand (Fgf10) leading to an increase in cell death and a decrease proliferation specifically, and exclusively, in the endoderm [21]. These endodermal cellular events precede any changes in the vasculature by at least a full day in the mouse, leading to atresia formation [22, 23]. Furthermore these studies showed the mutation of Fgfr2IIIb and Fgf10 resulted in both colonic and duodenal atresia, suggesting that the mechanism of formation of this atresia is the same. Other genetic disruptions of endoderm development were described with disruption of hedgehog in mice leading to duodenal stenosis and anorectal malformation [24], or mutation of gene encoding Cdx2 transcription factor expressed exclusively in the colonic endoderm after D12 in mice, resulting also in intestinal atresia [25]. Johnson and Meyers reported 28 patients with SBA and increased association in the allelic frequency factor V Leiden or R353R mutation of factor VII [26]. More recently, Gupta studied 32 single nucleotide polymorphisms (SNPs): two had increased risk of SBA (ITGA2 873 G/A and NPPA 2238 T/C), and three had reduced risk of SBA (SERPINE1 11,053 T/G, MMP3 (-1171) A6/A5, and ADRB2 gln27glu) [27]. If genes and morphogenetic events are concerned in the occurrence of bowel atresias, the questions raised are when do they occur, the number and the type of genes involved, and what do these defects reveal about the normal processes of intestinal growth and development [2].

Besides experimental use of chemotherapy, maternal smoking and cocaine use have been associated with intestinal atresia [28].

Fetal movements associated with feeding have been described in fetuses as early as 12–14 weeks of gestational age (WGA) [29]. Should an obstacle occur on the bowel, swallowing became impossible to the fetus impeding clearance of amniotic fluid thus accumulating in the uterine cavity and leading to polyhydramnios. The more proximal the obstacle is, the more important will be the polyhydramnios. Hence any hydramnios should cast suspicion of an obstacle on the bowel.

18.3 Duodenal Atresia and Stenosis

Duodenal atresias and stenosis are usually evidenced on routine ultrasounds (US). As a result of fetal swallowing impairment, polyhydramnios is present in about 40% and leads to 6% of death in utero. Up to 40–50% of children are born prematurely. The prevalence of associated anomalies is higher in duodenal atresia than in any other type of intestinal defect [3]. They involve chromosomal anomalies, syndromes, and associated structural malformations.

18.3.1 Prenatal Diagnosis

Duodenum is never visualized on normal prenatal ultrasounds. A "double bubble sign" is typically observed in the second trimester, although it has been described since 20 WGA. This appearance results from a distended stomach and duodenal bulb that are separated by a hypoechoic gastric antrum. The word "bubble" has originated from postnatal X-ray findings and is misleading in the context of prenatal diagnosis as all fetal cavities are filled with fluid and not with air. It is often associated with a collapsed small bowel and colon and maternal polyhydramnios [30]. The "double bubble" sign in prenatal diagnosis is most often associated with duodenal atresia. However patent communication between the stomach and duodenum (Figs. 18.1 and 18.2) must be proven. Without communication, other diagnoses should be evocated such as duodenal duplication or retroperitoneal cyst (Fig. 18.3).

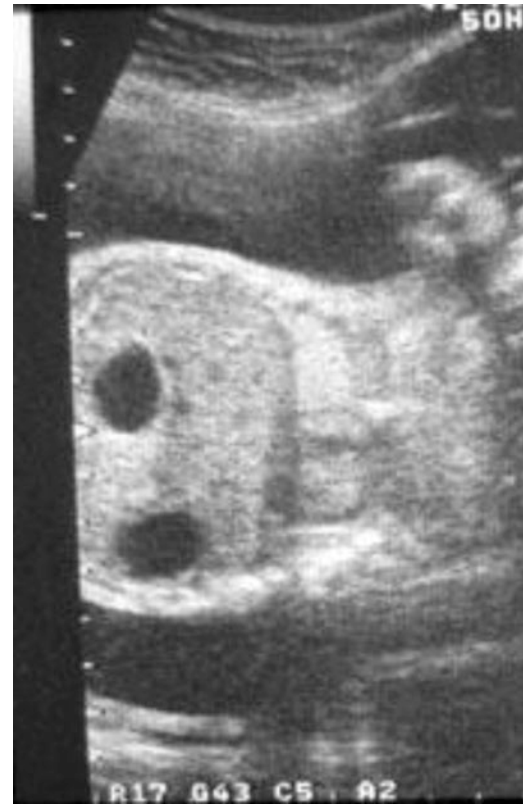

Fig. 18.1 Double bubble sign

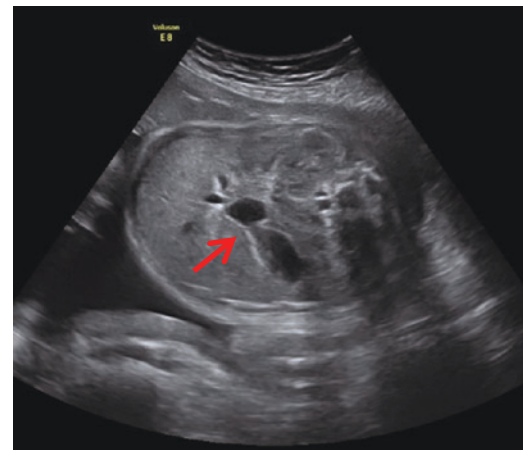

Fig. 18.2 Communication between the stomach and duodenum (arrow)

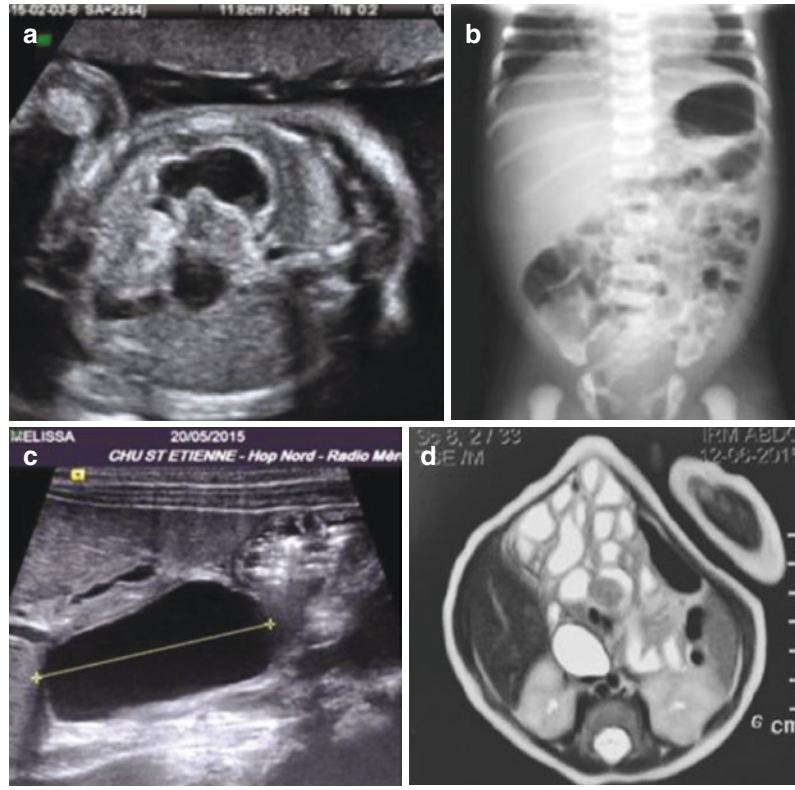

Fig. 18.3 (**a**) Double bubble sign at 20 WGA and prenatal suspicion of duodenal atresia (normal karyotype). (**b**) Normal neonatal appearance on X-rays. (**c**–**d**) Retropancreatic cyst on sonography and MRI. Finally diagnosis was a mature pancreatic teratoma

18.4 Classifications

Difference should be done between duodenal atresia and SBA. Mainly due to the fixation of the duodenal frame and to the jejunoileal meso, the forms of atresia differ and need for different classifications.

Three types of duodenal lesions were described by Gray and Skandalakis [31]:

Type I: occlusion by a mucosal web with normal muscular wall
Type II: defect with a short fibrous cord bridging the two blind ends of the duodenum
Type III: complete gap between the atretic ends

18.5 Diagnosis at Birth

Prenatal ultrasonographic findings of a polyhydramnios of variable severity associated with a double bubble sign raise the suspicion of an obstacle above the Treitz ligament and must be subsequently investigated at birth using conventional X-rays. Should a double bubble sign appear similar to that on prenatal diagnosis (Fig. 18.4), no further exam is needed. A gastric suction tube and appropriate IV hydration and nutrition are required awaiting for surgical treatment.

Without prenatal diagnosis, the baby vomits, usually bilious, but sometimes water-like if the obstruction is above the ampulla of Vater. The abdomen is depressed, except in the epigastric area if the diagnosis is delayed. Plain abdominal X-ray films are performed. If the double bubble is isolated without air below (Fig. 18.4a), the obstruction is total. The presence of small bubbles on the lower abdomen (Fig. 18.4b) is related to partial obstruction, i.e., to a diaphragm or a web with hole, a stenosis with or without annular pancreas.

Unlike duodenal atresia, duodenal stenosis is compatible with partial or total oral feeding. Thus the age of discovery is extremely variable from first week of life to adult's age according to the

severity and symptoms of duodenal obstruction, mainly chronic vomitings. Duodenal stenosis occurs in about 20% of congenital duodenal obstruction [32, 33]. Upper gastrointestinal contrast study shows the duodenal stenosis (Fig. 18.5) and leads to do endoscopy.

18.5.1 Associated Malformations

Associated malformations are common with duodenal atresia and stenosis. Down's syndrome occurs in 25%. Other malformations are listed in Table 18.1. Among digestive anomalies, the association with annular pancreas (Fig. 18.6) and malrotation (Fig. 18.7) must be highlighted as it is encountered from 11.5 to 35% [33–35].

Other associated digestive malformations are less common: esophageal atresia represents 3–9% and anorectal malformation 2–5%. A second low intestinal atresia does not appear in more than 0.5% of cases, according to a recent review of 408 patients [36]; subsequently, systematic extensive exploration of the lower bowel during the cure of a duodenal atresia is no more required.

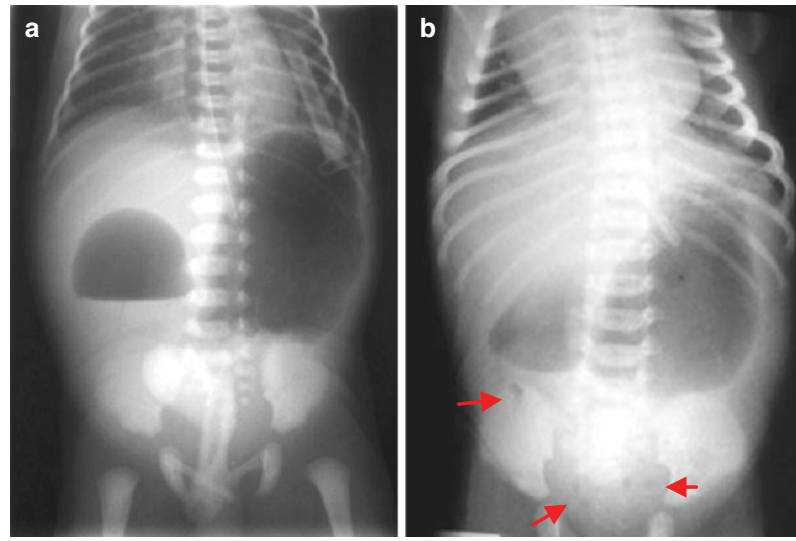

Fig. 18.4 (**a**) Total obstruction with isolated double bubble. (**b**) Partial duodenal obstruction with associated small bubbles (arrows)

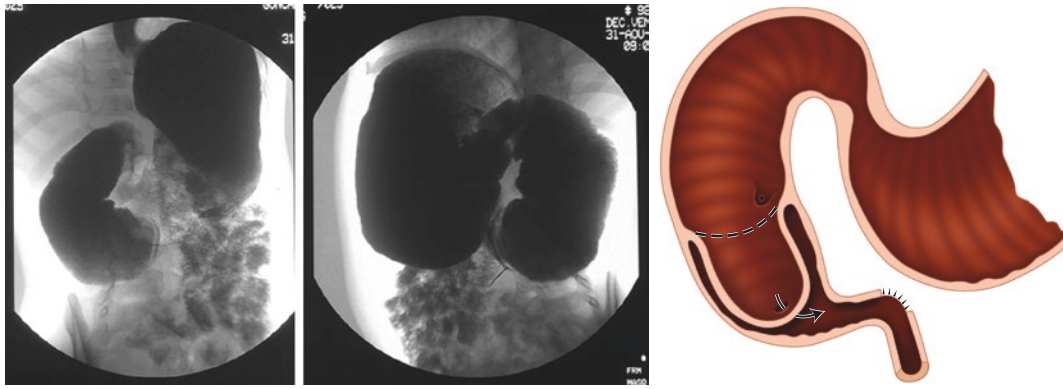

Fig. 18.5 3-year-old girl. Vomits since birth sometimes what she ate the day before. UGI and related drawing. Partial duodenal diaphragm can be seen as a negative print below the second bubble

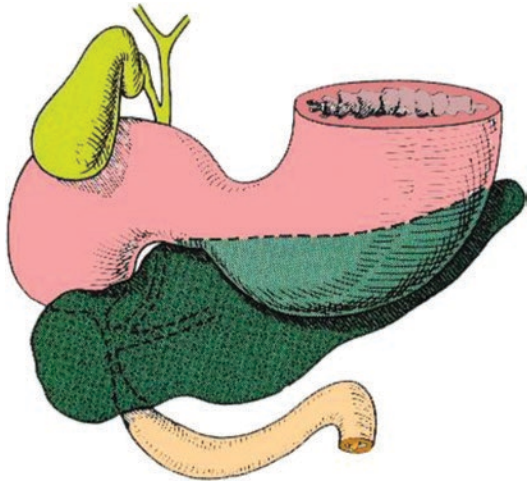

Fig. 18.6 Annular pancreas

18.5.2 Surgical Treatment

Initially, duodenojejunostomies were performed to cure duodenal atresia but were associated with delayed anastomotic functional impairment and sometimes with blind loop syndrome [33]. Today the procedure of choice is a duodeno-duodenostomy with an evolution from a side-to-side anastomosis (Fig. 18.8) to a proximal transverse to distal longitudinal ("diamond-shaped") anastomosis as described by Kimura in 1990 [37] whose geometrical design enlarges the anastomosis (Fig. 18.9). This can be achieved through an upper transversal laparotomy or a laparoscopy. Today the laparoscopic approach has become a gold standard for those teams experienced with neonatal minimally invasive surgery (MIS).

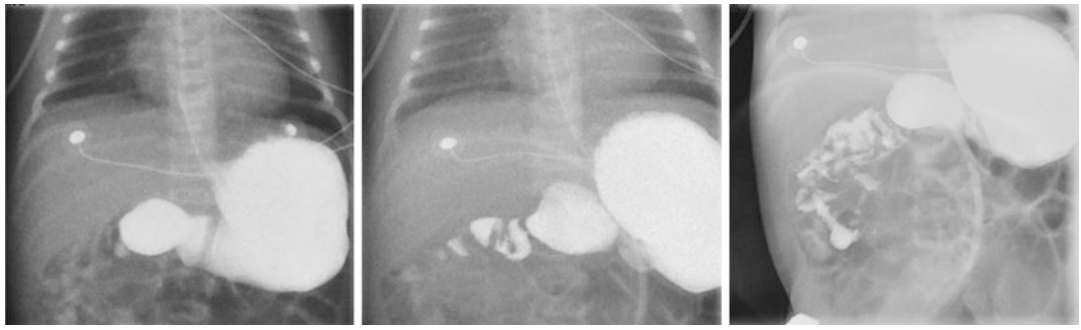

Fig. 18.7 Upper GI contrast study showing duodenal stenosis with malrotation (small bowel on the right)

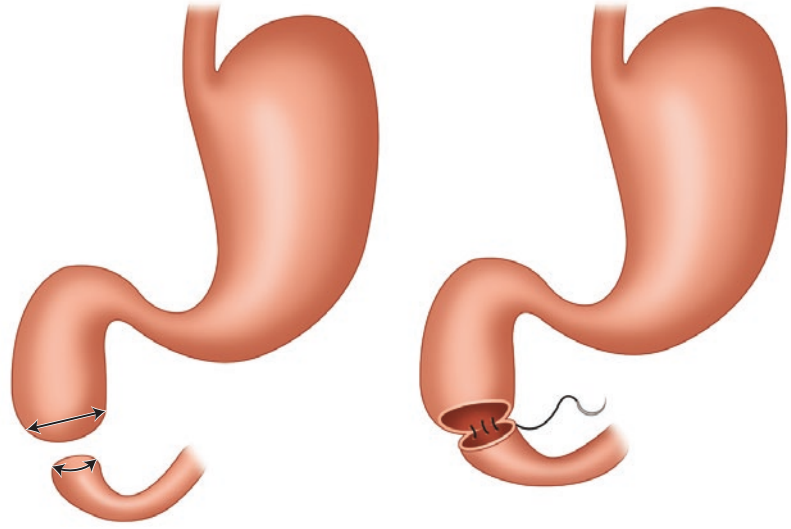

Fig. 18.8 Side-to-side anastomosis

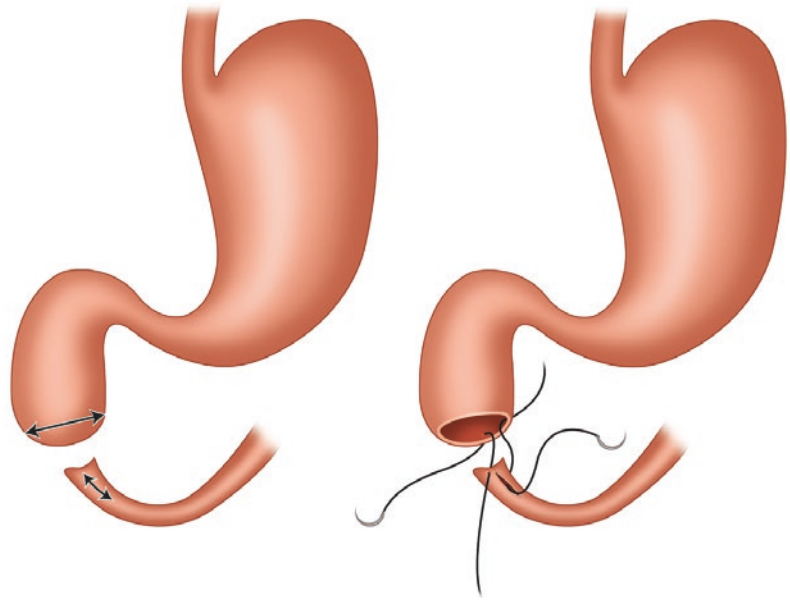

Fig. 18.9 Diamond-shaped anastomosis

Kimura's anastomosis requires a large mobilization of the duodenum using the Kocher maneuver to approximate the two edges of the anastomosis without tension. The bilious leak appearing at the opening of the duodenum gives the position of the ampulla above or below the stenosis or atresia. Thereafter, the surgeon must identify the ampulla without touching it and note its relationship to the web or to the gap because the medial portion of most of the defects is located close to the ampulla. In case of a web, its excision should proceed from the lateral duodenal wall, leaving the medial third of the web alone to avoid damaging the sphincter of Oddi or the ampulla. In patients with an annular pancreas, pancreatic tissue should not be divided for fear of pancreatic fistula. Patients who present with associated malrotation should undergo Ladd's procedure at the time of duodenal repair. Gastrostomy tubes were often used in the past with associated complications such as induced gastroesophageal reflux. However it might be performed in some circumstances (infants with trisomy 21 or neurological impairment or in some complex congenital heart disease). According to the surgeon's preferences, a small transanastomotic feeding tube (5F Silastic® nasojejunal feeding tube) can be placed to facilitate early postoperative enteral feeding with or without an orogastric tube for gastric decompression. We avoid placing peripheral intravenous central catheters (PICC) or central intravenous catheter as a parenteral nutrition is almost never required.

Many patients have a very dilated proximal duodenum at the time of initial repair. In patients with an extensively floppy and distended duodenum, an antimesenteric tapering duodenoplasty can be used to improve duodenal motility. However in most cases, the proximal dilatation of the duodenum resolves spontaneously with time as long as the anastomosis remains competent.

A web excision and duodenoplasty is also feasible (Fig. 18.10).

Recently, neonatal MIS developed dramatically and laparoscopic diamond-shaped anastomosis can be performed safely and successfully [38]. Three or four trocars are required, using 3 mm instruments and a 5 mm–30° telescope. The fourth trocar is mandatory with an enlarged liver in front of the duodenum. As through an open approach, the first step is to release the right colon to visualize the duodenum. The atresia is easily seen if an annular pancreas is present. A transparietal suspension of the first duodenum is done, giving a good exposure of the surgical area. It stabilizes and facilitates the

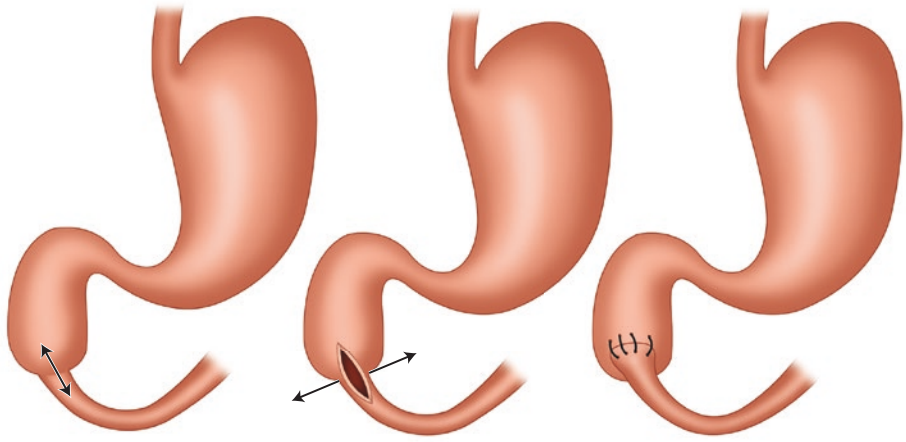

Fig. 18.10 Web resection and transverse suture

suture as well. The proximal transverse and longitudinal distal incisions are done. Then it is possible to check for the patency of the distal duodenum and proximal jejunum using a stent or a probe, even though the rate of distal web or atresia is very uncommon [36]. The diamond-shaped anastomosis is performed with interrupted or running resorbable sutures. Drainage is not mandatory but often performed. In the literature, most laparoscopies were done in neonates above 2000 g birth weight, but it has been proven possible from 1350 g [39]. The median time to initiate oral feeding was around 8 days (Tables 18.2 and 18.3) [40, 41], and the length of stay after MIS does not differ from that after open surgery [42–44].

A few reports described endoscopic treatment of congenital duodenal web in infants or

Table 18.2 Reported experiences comparing open and laparoscopic neonatal procedure [40, 41]

Authors	N	Open	Laparoscopy
Spilde 2008 [45]	29	14	15
Hill 2011 [46]	58	36	22
Jensen 2013 [47]	64	44	20
Parmentier 2015 [44]	29	19	10
Chiarenza 2017 [41]	18	10	8
	198	123	75

Table 18.3 Meta-analysis employed to compare laparoscopic and open repair of duodenal atresia [40], added by Chiarenza's study [41]

	Open = 123	Laparoscopy = 75	*p*
Median weight	2810 g	2590 g	NS
Smallest weight	1100 g	1200 g	NS
Down syndrome	23/60 (38%)	21/55 (38.2%)	NS
Cardiac abnormality	24/60 (40%)	15/45 (33%)	NS
Malrotation	10/46 (21.7%)	10/40 (25%)	NS
Operative time	**105 minutes**	**151 minutes**	***p* < 0.0001**
Fistula	1/123 (0.8%)	0/65	NS
Stenosis	2/123 (1.6%)	3/65 (4.6%)	NS
Death	1 sepsis	1 sepsis	NS
Time to initial feeding	Day 9.6	Day 6.8	NS
Time to full oral intake	Day 17	Day 17	NS
Length hospitalization	Day 22.2	Day 24.2	NS
Duodenal dysmotility >20 days	10/36 (27.7%)	4/22 (18.2%)	NS

later. In 1989 Okamatsu was the first to report the endoscopic treatment of duodenal stenosis in a 2-month-old baby with Down's syndrome, using balloon dilatations and high-frequency wave cutter on the web; the postoperative course was uneventful, and the child was doing well after 9 months [48]. In 1992, Ziegler reported the second case of endoscopic treatment of duodenal diaphragm by YAG laser in 5-month-old baby but with recurrence of vomitings a few days after the procedure; surgery showed an annular pancreas explaining the failure [49]. After 2006 several publications reported the endoscopic treatment of duodenal stenosis, and now 26 cases have been published (Table 18.4). Only three failures occurred, and 23 duodenal webs could be treated successfully. Annular pancreas seems to be a cause of failure, occurring in two cases. The procedures were variable from balloon dilatation to resection by knife, cauterization, or laser.

18.6 Complications

The postoperative complications are frequent (Table 18.5), especially when cardiac malformations are associated, with a high rate of death due to cardiac failure [33, 34]. Escobar et al. reported 5.9% deaths related to cardiac failures vs. 2.9% from cerebral bleedings, anastomotic leaks, pneumonia, respiratory distress, and biliary atresia [33].

Anastomotic leaks may occur. The question raised is whether they are related to the MIS procedure. Van der Zee et al. experienced leaks at the beginning of their MIS procedures and stopped doing duodenal atresia laparoscopically. After 3 years of appropriate training, they restarted MIS anastomosis without leaks proving they were related to their learning curve [42]. Anastomotic strictures and dysmotilites can occur after laparoscopic surgery, requiring redo procedures and sometimes taperings; laparoscopic tapering has not been described to date but seems feasible. No small bowel obstruction has been described after laparoscopy, unlike after open surgery (5.5%), but the follow-up is too short to conclude definitely. In a meta-analysis, Mentessidou and Saxena recently compared laparoscopic repair of duodenal atresia with the open approach (Tables 18.2 and 18.3), and Chiarenza et al. also published a comparative study between open and laparoscopic treatment. They concluded MIS shows comparable safety and efficacy with the open repair, although it is associated with significantly longer operative time [40, 41].

18.7 Prognosis

Finally, the prognosis of duodenal atresia depends from associated malformations, especially cardiac abnormalities and Down's syndrome. A surgical redo is sometimes required for stenosis or dysmotility. The rate of postoperative small bowel obstruction is an actual event, but it will decrease probably with the development of minimal invasive surgery.

18.8 Jejunoileal Atresia

Jejunoileal atresia occurs in approximately 0.7 per 10,000 live births [3]. They are equally divided between the jejunum and ileum. However associated congenital anomalies are less common with jejunoileal atresia than with duodenal atresia. Cystic fibrosis and malrotation are the most common associated malformations.

18.8.1 Prenatal Diagnosis

While duodenal atresia is commonly identified prenatally due to the presence of the "double bubble" sign, antenatal detection of jejunal and ileal atresia remains challenging. The discovery of small bowel atresia by prenatal ultrasound has been reported to be variable, and different sonographic criteria for diagnosis have been described, such as polyhydramnios, ascites, peritoneal calcifications, meconium pseudocysts, and dilated bowel (Fig. 18.11) and stomach. Virgone et al. reported in 2015 a meta-analysis with 640 fetuses from 16 studies, and a highly variable detection

Table 18.4 Endoscopic treatment of duodenal web in the literature

Author	N	Age	Technique	Number of endoscopic procedure	Results after endoscopic procedure	Follow-up (months)
Okamatsu 1989 [48]	1	2 months	Balloon + high-frequency wave cutter	1	Good	9
Ziegler 1992 [49]	1	5 months	YAG laser	1	Failure: annular pancreas at surgery	
Van Rijn 2006 [50]	4	8–28 days	Balloon dilatation	1 for 3 1 with 3 procedures	Good	15
Torroni 2006 [51]	4	8 days to 66 months	Sphincterotome: 3	1 for 3 1 impossible for annular pancreas	Good, 3 Surgery, 1	?
Barabino 2011–2012 [52]	2	1, 11 months 1, 20 months	Diathermic knife	1, 11 months 3, 20 months (1 bleeding and stop—2 recurrences)	Good, 1 Surgery, 1 (recurrence)	6
Bittencourt 2012 [53]	3	9–12 months	Balloon dilatation and membranectomy by papillotome	1	Good	48
Di Maio 2014 [54]	1	8 years	Knife + argon laser	1	Good	12
Bleve 2015 [55]	1	11 months	Electrosurgical knife	1	?	?
Huang 2015 [56]	6	7 days to 37 months	5/6 balloon dilatation 1/6 + electrocauterization	1	Good	24
Poddar 2016 [57]	3	2–9 years	Balloon dilatation (8–10 mm < 3 years and 18 mm > 3 years)	2–4	Good	6–9
Total	26	7 days to 9 years	Variable	1 = 21 2–4 = 5	Good, 23 Surgery, 3 (2 annular pancreas +1 bleeding)	21, 5

Table 18.5 Postoperative complications and deaths after open surgery

	N	Down syndrome	Complications	Treatment	Death (%)
Dalla Vecchia 1998 [34]	138	33	13, cardiac failure		14
			4, stenosis	4, redo	
			6, dysmotility	5, duodenal tapering	
			7, pneumonia		
			13, small bowel obstruction	13, laparotomy	
Escobar 2004 [33]	169	46	10, cardiac failure		5.9
			1, stenosis	1, redo	2.9
			7, dysmotility	3, duodenal tapering	
			2, fistula		
			4, small bowel obstruction	4, laparotomy	

was noted from 10 to 100%. The overall prediction of small bowel atresia was 50.6%, and the detection rates were 66.3% for jejunal atresia and 25.9% for ileal atresia [58], because the amount of amniotic fluid decreases progressively in the bowel due to intestinal reabsorption (Fig. 18.12). In case of suspicion of small bowel atresia before the third trimester, an ultrasound after 32 weeks

should be done, and John et al. demonstrated that the presence of both polyhydramnios and bowel dilatation upper than 17 mm has a sensitivity of 66% and specificity of 80% [59]. The bowel content is hypoechoic when it is a jejunoileal atresia contrary to a colonic one with hyperechoic content [60]. A volvulus can be suspected or proven if a whirlpool sign is seen close to the dilated bowel or mass, but this sign is difficult to find [61].

18.8.2 Pathology

The nature and the extent of damage to the smooth muscle in small bowel atresia have not been well characterized, but recently several studies showed lesions similar to intestinal neuronal dysplasia with an important decrease of the density of myenteric interstitial cells of Cajal in proximal *and* distal bowel [62, 63]. Wang et al. tested the expression of proteins in the atretic bowel wall, as calretinin, glial cell-derived neurotrophic factor (GDNF), bone morphogenetic protein 2 (BMP-2), c-kit, α-smooth muscle actin (α-SMA), and S-100 Protein. A significant decrease of these six proteins was noted with return to normal at 15 cm proximal and at 3 cm distal to the atresia site (Fig. 18.13) [64]. Then,

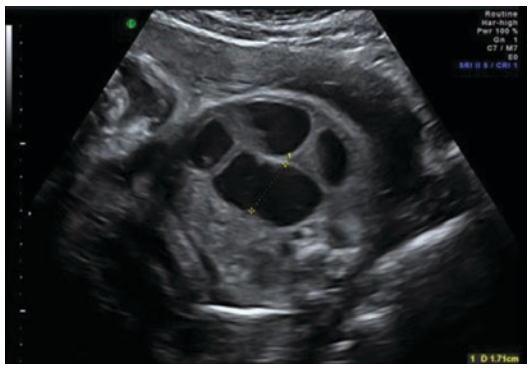

Fig. 18.11 Prenatal US (third trimester) of a jejunal atresia type IV. Note the bowel distension and the hypoechoic content

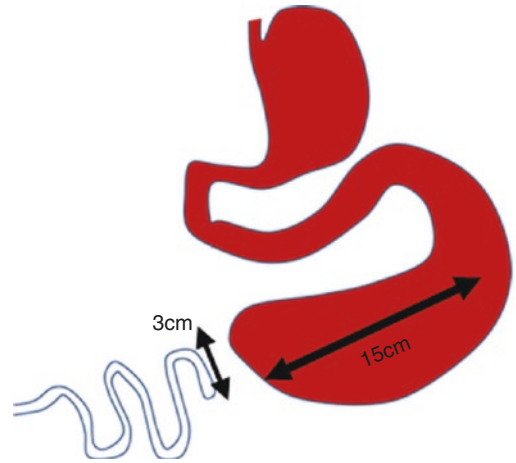

Fig. 18.13 Length of decreasing of expression of proteins [64]

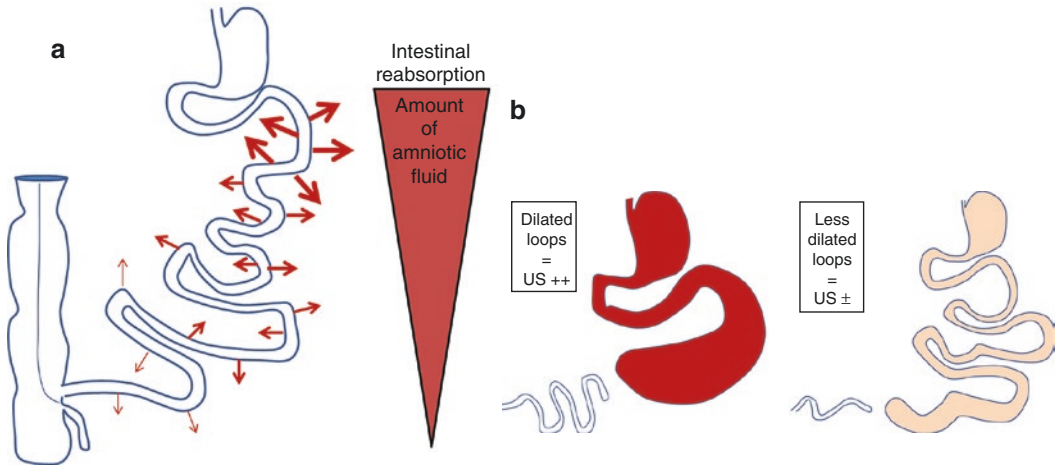

Fig. 18.12 (**a**) Amount of amniotic fluid in small bowel. (**b**) Huge dilatation in proximal jejunal atresia and slight one in ileal atresia (US ++, sonographic dilatation; US ±, no or slight sonographic dilatation)

the surgeon ideally should theoretically do a proximal resection of 15 cm and distal one of 3 cm before performing the anastomosis to avoid postoperative dysmotility. Furthermore, every newborn should be tested for cystic fibrosis because the incidence is about 10%.

18.9 Diagnosis at Birth

Bilious vomitings and abdominal distension are the main symptoms at birth. There is commonly no or grey meconium. Neonatal X-rays show one or multiple dilated bowel loops (Fig. 18.14) or calcifications due to prenatal perforation and meconial peritonitis. Ultrasonography helps to identify complications such as peritoneal effusion or bowel ischemia of the dilated loops and a whirlpool sign if a volvulus had occurred. Enema using nonionic hydrosoluble contrast is usually not necessary but, if done, can show an unused microcolon and the cecum location (Figs. 18.15 and 18.16).

18.9.1 Classification

The classification of jejunoileal atresia was initially proposed by Louw [65] and then later by Martin and Zerella [66]. The current classification of small bowel atresia is the Grosfeld modification (1979) [32] of the Louw Classification (1955) [7] to include the apple peel syndrome and multiple atresia. Four types are described (Figs. 18.17 and 18.18):

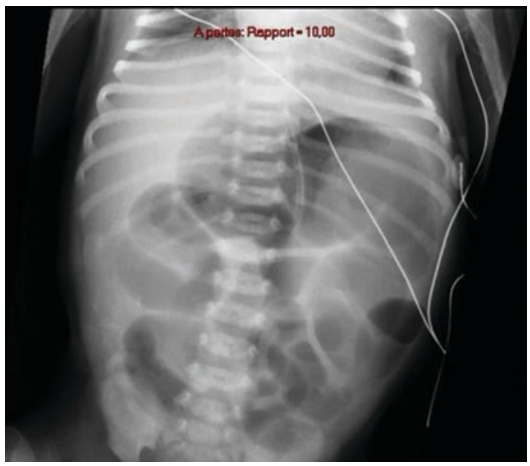

Fig. 18.14 Dilated bowel loops

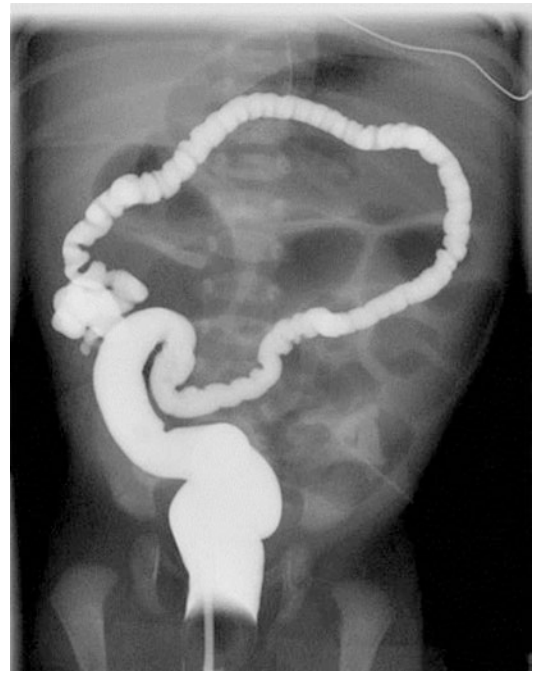

Fig. 18.15 Unused microcolon

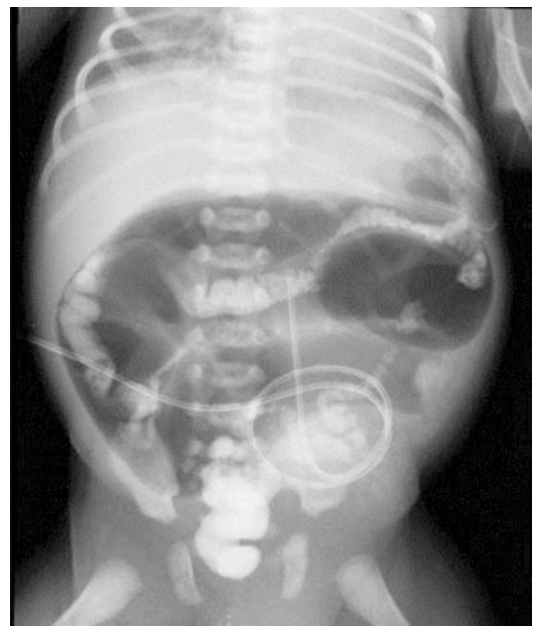

Fig. 18.16 Cecum location

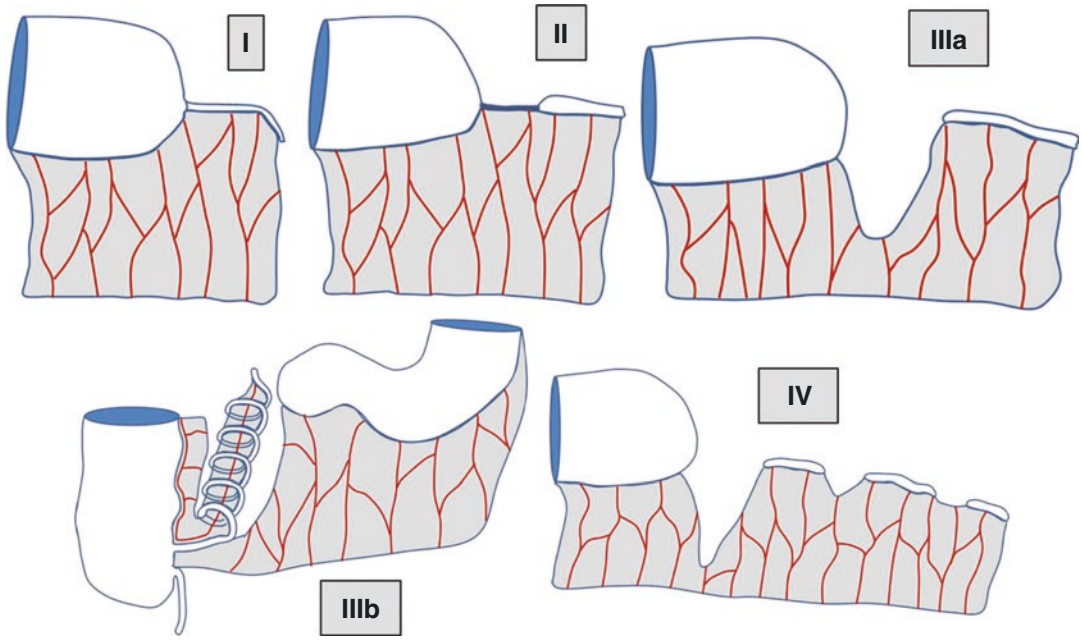

Fig. 18.17 Classification of small bowel atresia [32]

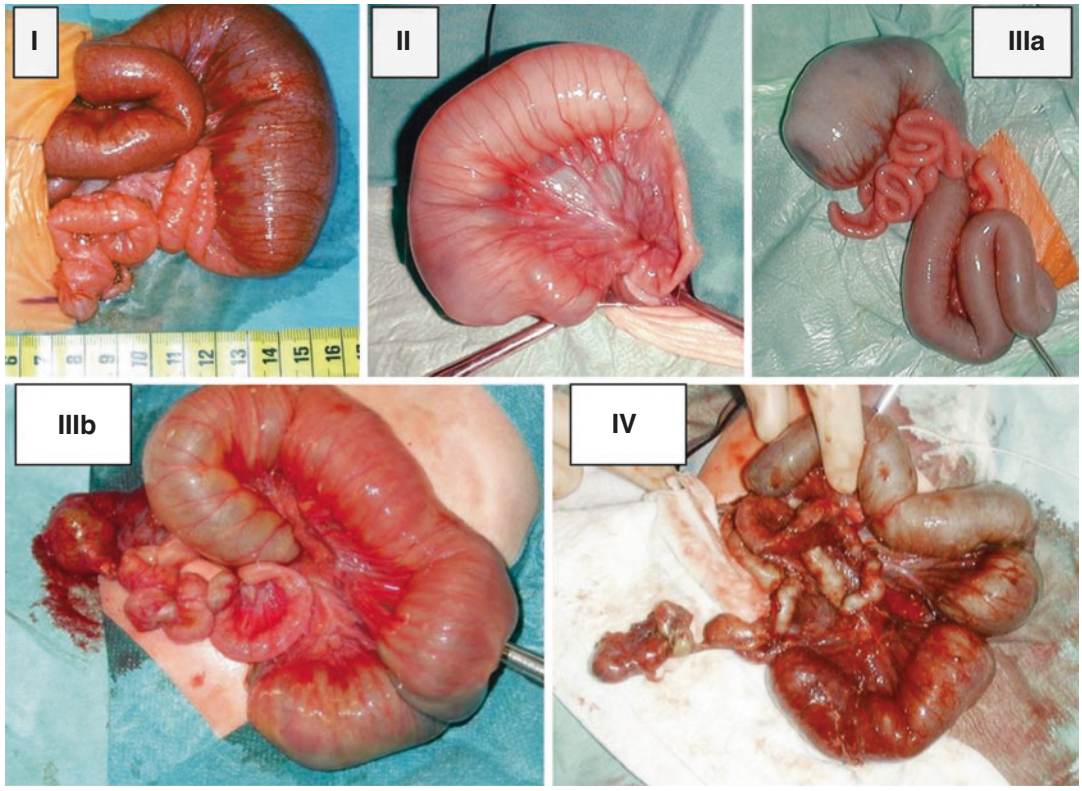

Fig. 18.18 (I) Atresia type I. No bowel interruption, but note a difference between the caliber of the proximal enlarged portion of the ileum and the small post-atretic one. (II) Atresia type II. Note the fibrous band between the pre- and the post-atretic bowel. (IIIa) Atresia type IIIa. Note the V-shaped mesenteric defect. (IIIb) Atresia type IIIb. Apple peel form: the ileum is wrapped around its vessel. (IV) Atresia type IV. At least five interrupted segments of bowel can be seen

Type I: occlusion by a mucosal web or diaphragm and an intact mesentery.
Type II: total defect with a bridge of fibrous cord between the two blind ends. No defect of the mesentery.
Type IIIa: total defect between the two blind ends. V-shaped mesenteric defect.
Type IIIb: the so-called apple peel syndrome in which there is a total defect between the two blind ends. The loop distal to the defect is twisted in a spiral around a single retrograde vessel.
Type IV: multiple atresia.

This classification system is also applied to colonic atresia.

From 233 cases of small bowel atresia, the rate of each type was 23% type I, 25% type II, 21% type IIIa, 8% type IIIb, and 23% type IV [34, 67]. The rate of stenosis should be about 5%, but it is not correctly specified in these papers.

18.9.2 Surgical Treatment

After intensive care unit preparation, surgery can be performed. The conventional approach is a transverse laparotomy. However, today MIS is proposed to decrease the size of the approach and minimize the effects of a large laparotomy on the neonatal abdominal content. Through a circular umbilical laparotomy, the umbilical vein and arteries are ligated and divided. Then the umbilical stalk is excised. A 2.5 cm sagittal mid-abdominal incision is created, which can be expanded by severing the linea alba cranially and caudally. It is always possible to enlarge the fascia or skin incision if the bowel exposure is not sufficient. At the end of the procedure, an umbilicoplasty is performed [68, 69]. Laparoscopy-assisted surgery was first described by Lima et al. in three cases in 2009. The procedure was an explorative laparoscopy to isolate the atretic bowel. Then in a second step, the resection and the anastomosis were performed outside the abdomen [70]. Since then, many authors [71, 72] including ourselves have proceeded using such laparoscopy-assisted surgery (Fig. 18.19).

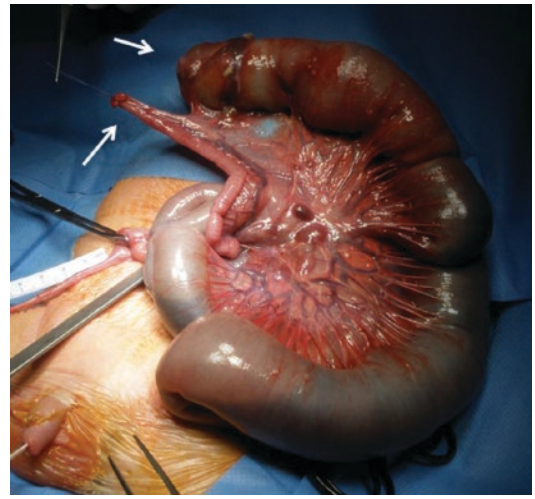

Fig. 18.19 Exteriorization of a small bowel atresia type IIIa (arrows) through the umbilical wound. Note the huge difference in diameters between the proximal enlarged bowel and the thin distal one

18.9.3 Anastomosis

The main challenge in an atresia is the approximation of the two ends of the bowel. Due to the lack of continuity, the bowel content is stopped at the level of the atresia. Thus the proximal part of the bowel enlarges, while the distal part does not develop resulting in a huge difference in their diameter. The surgical challenge is to establish the continuity between two tubes of different size. The ratio between the two parts can be up to 1:6. The first step is to resect the two edges of the atresia. A transverse section above the most dilated part of the proximal edge will reduce its diameter. Usually this dilated part does not recover normal movements and can be favorably resected. An oblique section of the distal end will enlarge the suturing line, the mesenteric side being longer than the antimesenteric (Fig. 18.20).

Unfortunately this may not be sufficient. An end-to-side anastomosis is not wise as it may impair the intestinal flow. A tapering of the dilated upper pouch gives better results (Fig. 18.21). It must be done on the antimesenteric side of the bowel.

18.9.4 Enterostomies

It is wiser to perform a temporary enterostomy followed by a second look than to spoil a segment of bowel that could have recovered. The more distal the enterostomy is placed, the better will be the enteric refeeding, i.e., an ileostomy carries a better outcome than a jejunostomy.

Several enterostomies and their modifications can been used according to the first priority (Fig. 18.22).

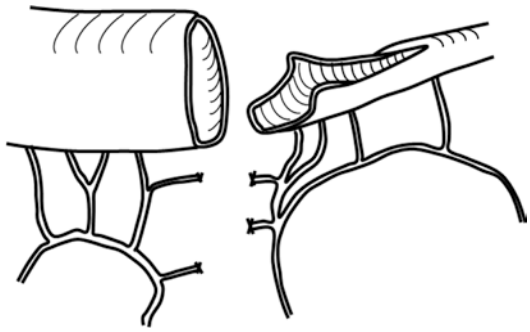

Fig. 18.20 Oblique section of the distal end to enlarge the suturing line

Historically the double barrel enterostomy as described by Mikulicz was used by Fockens who first successfully treated a case of SBA in 1911 (Fig. 18.22a) [73]. It can always be performed. The disadvantages are that the bowel content does not fill the distal limb to increase its diameter and that closure requires a laparotomy [74].

The problems related to small bowel enterostomies are the fluid and the electrolyte losses. The more proximal is the enterostomy, the more severe are the losses. As to allow partial refilling of the distal limb without impeding the proximal emptying, Gross and Willital have suggested modifications of Mikulicz's double barrel enterostomy. Initially Gross used a specially designed spur-crushing clamp that was applied to gradually cause necrosis of the common wall between the two limbs [30]. Willital has replaced the clamp by a stapler shot to sever the septum between the two barrels away from the vessels either when performing the stomy or later (Fig. 18.23) [75].

In 1956 Bishop and Koop described a "Roux-en-Y" anastomosis to be used in case of meconium ileus. Their purpose was to avoid spillage of

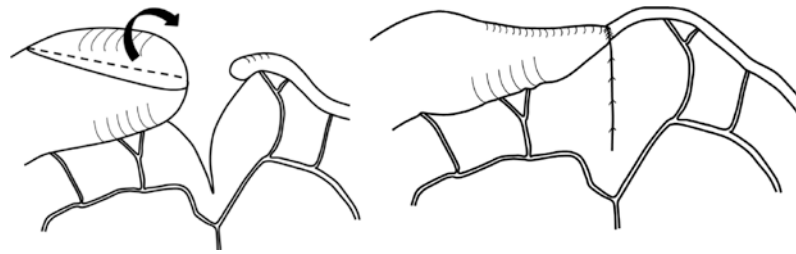

Fig. 18.21 Tapering of the dilated upper pouch

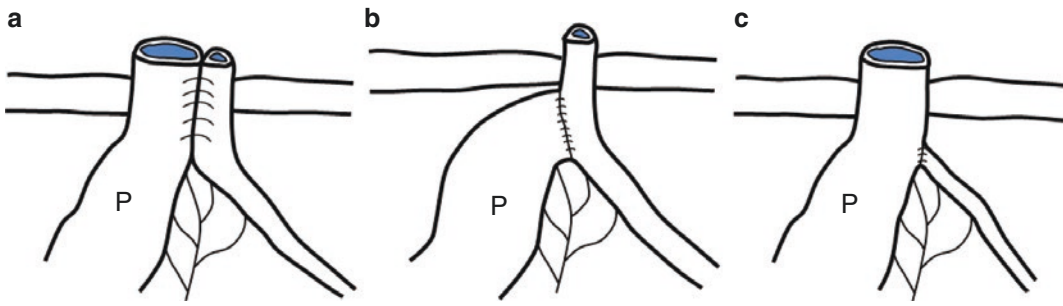

Fig. 18.22 Surgical options for SBA (P) for proximal limb. (**a**) Double barrel Mikulicz enterostomy. (**b**) Bishop-Koop enterostomy. (**c**) Santulli enterostomy

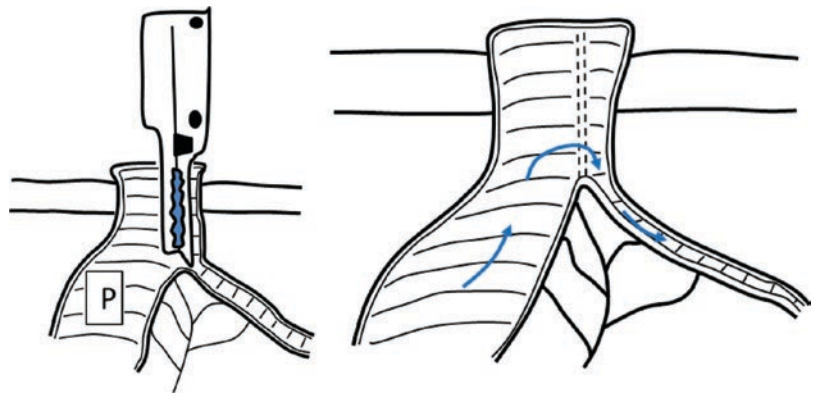

Fig. 18.23 The Willital technique to improve a double barrel Mikulicz enterostomy with staplers

pancreatic enzymes (Fig. 18.22b) [76]. Since then, this enterostomy has been widely used for bowel atresia as it allows distal refeeding as well. The thin distal loop is exteriorized in a single limb enterostomy, and the enlarged proximal one is anastomosed intraperitoneally very close to the stomy by 3–4 cm. It is expected that when the bowel distal to the anastomosis becomes patent, the ileostomy ceases to loose stools. If not, an easy extraperitoneal closure is performed later on. Nowadays the Bishop-Koop enterostomy has lost popularity. However it is still in use and has been proven safe and efficient especially when the stomy has to be performed proximally [77].

Using the Bishop-Koop procedure, Santulli and Blanc found too many anastomotic leaks in their series. They believed it was related to a poor passage through the distal bowel and look for an immediate relief of obstruction by a dependable and effective method. Then they described a new technique bringing the dilated proximal limb to the skin, the small distal one being anastomosed intraperitoneally by 3 cm above the level of the skin (Fig. 18.22c) [5]. At first the enterostomy is left open in order to decompress the proximal bowel, and then a nutriment can be instilled into the distal one through a catheter. This supplies fluid, electrolytes, and nutriments but also induces a progressive enlargement of the distal intestine. Once the baby's conditions have improved, a clamp is placed across the enterostomy to the edge of the indwelling catheter. This intermittent occlusion forces the passage through the anastomosis and can be used for weeks. Once the anastomosis becomes patent enough, the enterostomy can be closed extraperitoneally.

To summarize the differences between these techniques and to help with decision, let us say that the double barrel enterostomy according to Mikulicz is the simplest and the fastest procedure but may induce an important loss of fluids and of electrolytes. The modification brought by Willital partially solves the problem but with a vascular risk. The Bishop-Koop procedure favors refilling into the distal bowel but may fail to empty the proximal one, while the Santulli anastomosis is more efficient when proximal decompression is needed [78].

In case of high flow through the enterostomy (high-output stoma ≥50 mL/kg/d) and with a patent distal bowel, a reinfusion procedure should be initiated. It is known under various names: succus entericus reinfusion, continuous extracorporeal stool transport (CEST), and mucous fistula refeeding. This is not an easy technique, and one of the available protocols must be carefully followed in a PICU. But it is highly beneficial. The reinstillation of the proximal bowel content into the distal one diminishes per se the proximal flow by up to 30% [79]. Additionally it improves the bowel movements, increases the distal diameter, stimulates absorption of nutriments, and diminishes the risk of mucosal atrophy and of bacterial translocation [80, 81].

According to the patient's conditions, different procedures are performed to treat a small bowel atresia: resection and anastomosis, with or without proximal tapering, jejuno- or ileostomy, and delayed anastomosis [34, 64, 67, 82] (Table 18.6).

Table 18.6 Different procedures to treat a small bowel atresia

Author	N	A	RA	TA	WE	O	BK
Dalla Vecchia [34]	127	45		23	5	54	
Sato [82]	88	23	49 + 9 multiple	7			
Stollman [67]	114	70		9	5	30	
Wang [83]	81		37	11		8	25
Total	410	138 33.7%	95 23.2%	50 12.2%	10 2.4%	92 22.4%	25 6.1%

N number of cases, *A* anastomosis, *RA* resection and anastomosis, *TA* tapering and anastomosis, *WE* web excision, *O* jejuno or ileostomy, *BK* Bishop-Koop procedure

Table 18.7 Postoperative complications

Author	N	Fistula	Wound abscess	Sepsis	Stricture	Necrosis	Prolonged ileus
Dalla Vecchia [34]	127	5	6				11
Sato [82]	88	4			2		
Stollman [67]	114	8	4	9	1	3	
Wang [83]	81	1					12
Total	410	18	10	9	3	3	23

Postoperative complications are listed in Table 18.7 with their ratio. Prolonged ileus is reported only by two authors and raises the question of a redo procedure with tapering [34, 83]. The average of full oral intake without TPN is by 15 days (limits 12.5–17 days) and appears to be longer with TPN between 32.4 and 88 days [67, 82]. Late complications were represented by small bowel obstruction in 48 from 410 children (11.6%) and deaths in 51 (12.4%), especially due to short gut syndrome and TPN, but also by prematurity and infection.

18.10 Colonic Atresia

Colonic atresia and stenosis are extremely rare conditions with an approximate incidence of 1:20000 births [84, 85].

18.10.1 Prenatal Diagnosis

The prenatal detection of colonic atresia is uncommon, and three cases have been suspected because they were associated with small bowel atresia [85].

18.10.2 Diagnosis at Birth and Classification

All newborns with isolated colonic atresia develop delayed vomitings and huge abdominal distension. No patients pass meconium. Plain abdominal X-rays show bowel obstruction (Fig. 18.24). A contrast enema must be done to evidence the (micro) bowel distal to the obstruction and precisely state the level (Fig. 18.25). However, the diagnosis is most often done during surgery. The classification used for colonic atresia is that of small bowel (Grosfeld classification). Among 227 cases, the types of atresia reported are type I 14.5%, type II 12.8%, type IIIa 62.1%, and type IV 10.6%. The atresia is more frequently located on the right colon (71.7%) than on the left one (28.3%) [34, 86–88]. Colonic stenosis alone without atresia has been reported only in less than 20 cases [89–92].

18.10.3 Associated Malformations

Associated anomalies were found in 106 children from 227 cases found in the literature [34, 86–88]: 40 had gastroschisis, 37 jejunoileal atre-

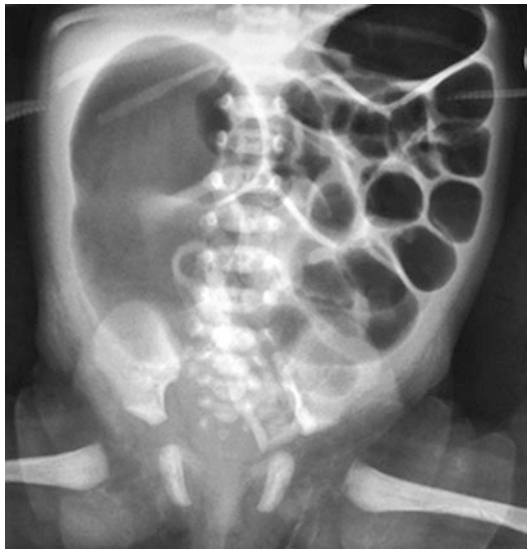

Fig. 18.24 Colonic atresia and neonatal X-rays

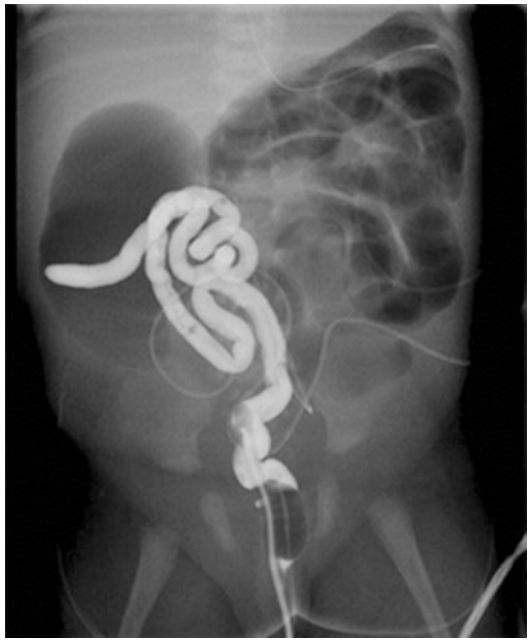

Fig. 18.25 Stop of contrast enema in right flank

sia, 36 malrotations, 19 Hirschsprung's diseases, and 19 multiple malformation syndromes. Subsequently, biopsies and immunohistochemistry for Hirschsprung's disease are mandatory during surgery.

18.10.4 Treatment

Due to this very unusual anomaly, there is no consensus to treat colonic atresia, and the same procedures as for jejunoileal atresia can be done. Classically, from the proximal right colon to the splenic flexure, primary anastomosis is indicated, sometimes protected by ileostomy, and beyond a colostomy is done followed by a delayed anastomosis after a few weeks. But the final decision must be taken according to the newborn's condition, presence of a sepsis or not, surgical school, and type of lesions found at surgery. The rate of death is significantly higher when the baby is managed beyond 72 h of obstruction, and the prognosis is also depending on associated small bowel atresia, the absence of ileocecal valve, bowel perforation, and associated Hirschsprung's disease [86]. Rectal and/or colonic biopsies during surgery seem to be an important step to improve the knowledge and the management of colonic atresia.

18.11 Conclusion

Duodenal and jejunoileal atresia rates differ according to the countries, but an incidence of 1.6/10,000 births seems to be accepted. Arguments for a genetic origin have become more important to explain the pathogenesis of atresia, even if the vascular origin remains a valid hypothesis. Minimal invasive surgery can treat numerous cases with less invasive procedures and good results. The associated malformations, such as cardiac anomalies, Down's syndrome, short gut syndrome or Hirschsprung's disease, play a significant role in the prognosis, the functional result, and the final outcome.

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Meconium Ileus

19

Philip Corbett and Amulya Saxena

19.1 Introduction

Meconium ileus (MI) is neonatal intestinal obstruction caused by protein-rich, inspissated meconium in the terminal ileum. This viscid meconium adheres to the bowel wall, causing an intra-luminal obstruction (sometimes referred to as obturator-type obstruction). Its incidence is approximately 1:10,000 live births [1] within the white population but lower in other races. Historically, MI has been almost exclusively associated with cystic fibrosis (CF); however this dogma has been challenged by some published series that report 21–46% of their cases did not have CF [2, 3]. 10–20% of children born with CF present as MI [4, 5].

MI is classified as 'simple' or 'complex' with roughly half of cases falling into each category. Simple MI is a pure obstruction with a distended terminal ileum filled with sticky meconium and unused distal bowel containing small pellets of grey stool. Complex cases have undergone a perforation in utero, often secondary to a segmental volvulus, resulting in bowel wall necrosis. This causes a sterile, chemical peritonitis, which either settles entirely with resorption of the damaged bowel and a type 3 atresia at birth, or it causes the peritoneum to thicken and in some cases calcify. The resulting fluid-filled cavity is called a meconium pseudocyst. Occasionally a perforation can heal without obstruction, and evidence of the previous injury is discovered incidentally as peritoneal calcification on x-ray much later (Fig. 19.1).

MI has been reported by some studies to be an indicator of poor growth and respiratory function later in life, suggesting that MI represents a more severe phenotype of CF [6, 7]. However, subsequent large multicentre retrospective studies and matched control studies have shown no difference in long-term outcomes [8, 9].

19.2 Cystic Fibrosis

CF is an inherited autosomal recessive disease with a carrier rate of up to 5% in the general population and an incidence of about 1:2500 live births amongst white babies in Europe and North America. Amongst black and Asian babies, the incidence is much lower [10]. The condition is caused by mutations in a gene which codes for a protein known as the cystic fibrosis transmembrane regulator (CFTR) and is situated on the long arm of chromosome 7 (7q31) [11]. CFTR regulates the passage of Cl^- and HCO_3^- ions across epithelial cell apical membranes. An abnormality results in abnormal electrolyte concentrations and desiccation of secretions which can block epithelial-lined tubes such as bronchi,

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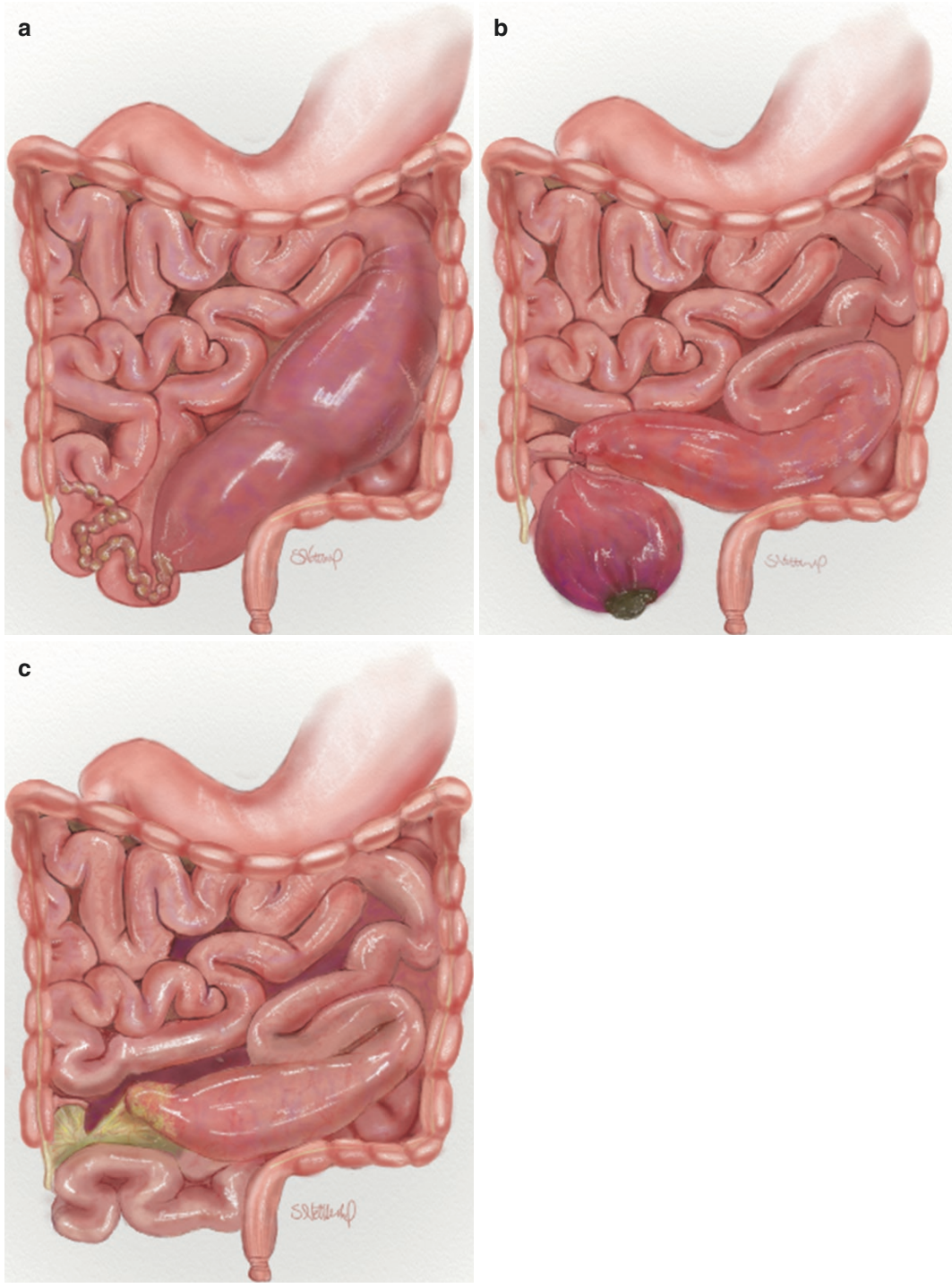

Fig. 19.1 (**a**) Meconium obstruction in terminal ileum. (**b**) Segmental volvulus secondary to obstruction with ischaemia and perforation. (**c**) The injured bowel is reabsorbed, resulting in type III atresia

vasa and pancreatic and biliary ducts. The defective excretion of HCO_3^- and its role in the pathogenesis of CF have only recently been discovered. Normally mucus is secreted into the bowel lumen in a tight matrix formation, held in place by Ca^+ ions. The ions are chelated in a process involving the HCO_3^- which allows the matrix to spring open, absorb water and become normal mucus [12, 13]. The failure of this mechanism is now thought to be the cause of the obstruction which affects neonates. Previously it was believed that pancreatic insufficiency played a role in this process, but since 1992, numerous animal models have shown that obstruction can occur with a normally functioning pancreas [14].

There are currently more than 2000 documented mutations in the CFTR gene although not all of these result in CF [15]. The most common mutation worldwide is F508del, which is identified in up to 66% of CF sufferers (although the incidence is over 80% in Northern American and Northern European whites). Less than 20 other mutations are responsible for the vast number of cases of CF, but they vary depending on the location and ethnicity of the carrier meaning screening for 'common' mutations must be tailored accordingly [16]. Interestingly, the F508del mutation predisposes to meconium ileus with homozygous carriers having a 25% chance of presenting with MI and those with other mutations having a 12.5% chance [17]. Furthermore it appears that genes other than CFTR affect the phenotype, with one study showing an 82% concordance for MI in monozygotic twins which dropped to 22% in dizygotic twins [18].

There are various methods of testing for CF. In some countries (e.g. the UK), routine blood spot screening is employed. A neonate with CF cannot readily excrete pancreatic trypsinogen via the duct and so it builds up in the blood. This rise in 'immunoreactive trypsin' (IRT) can be detected in the first 8 weeks of life by a heel-prick test. A level greater than 80 μg/L is indicative and should be confirmed by further investigation. Increasingly, genetic testing for the most common mutations has become commonplace, but it should be noted that a negative result does not necessarily exclude the diagnosis. The gold standard test for cystic fibrosis remains the sweat test. To ensure an adequate sample is obtained (100 μg), the test is performed on children over 2 kg and 2 weeks of age. Sweating is induced by placing electrodes on an area of skin and running a very small electrical current through them (iontophoresis). One of the electrodes contains pilocarpine, a muscarinic agonist. The current draws the drug into the skin, stimulating perspiration. The sweat is collected on a piece of gauze and sent for analysis; a concentration of sodium in excess of 60 mmol/L is considered diagnostic, whilst concentrations below 30 mmol/L are expected in a child under 6 months [19]. A result between these two values is non-diagnostic and needs repeating.

19.3 Prenatal Diagnosis

Hyperechoic bowel contents, dilated bowel and non-visualisation of the gall bladder have all been reported as suggesting MI, but they are extremely insensitive and nonspecific. In a series of 289 cases of hyperechoic bowel identified at the second trimester scan, only 7.6% had CF, whilst 24.6% had other pathologies including trisomy-21 and cytomegalovirus infections. 67.8% had no pathology at all [20]. If hyperechoic bowel is identified, its relevance can be determined by testing parents for common CF mutations. If one or both parents are carriers, the pregnancy is considered 'high risk', and the positive predictive value of this sonographic sign jumps to 52% from 6.4% in pregnancies where neither parent is a carrier [21].

Dilated bowel and absent gall bladder also suggest a wide range of diagnoses including normal pregnancy. In short, antenatal ultrasound scan is only helpful when both parents are identified as CF carriers. In this instance, the parents may be offered amniocentesis with counselling as a positive diagnosis would mean considering termination or referral to a tertiary centre.

19.4 Presentation, Initial Management and Investigation

Simple MI presents as abdominal distension within the first with bilious vomiting and non-passage of meconium. Complicated MI may present identically or have the addition of an

inflamed, tender abdomen if the meconium peritonitis is still active. In most cases, the presentation will be difficult to differentiate from other causes of distal bowel obstruction such as Hirschsprung's disease or distal ileal atresia. Examination should include assessment of the child's breathing, perfusion, temperature and glycaemic control with immediate correction as needed. A detailed examination of the abdomen should identify palpable bowel loops, exclude incarcerated hernias and ensure that the sacrum and anus are normal. A per rectal examination should exclude atresia and presacral mass. A limited rectal washout with 20 mL/kg of warm 0.9% saline introduced with a soft rubber catheter may be both therapeutic and diagnostic as most cases of Hirschsprung's disease will see some decompression of the abdomen with effective rectal washouts but usually MI will not.

The immediate priorities are as with any neonatal obstruction, i.e. intravenous hydration, nasogastric tube decompression and appropriate antibiotic cover. In addition to blood tests which are needed to direct fluid management and exclude clotting problems, blood should also be taken and stored for future genetic analysis (should the child receive a blood transfusion, subsequent genetic tests may be unreliable because of the presence of the donor's genetic material).

After initial resuscitation, plain abdominal x-ray is a useful first-line imaging request. Simple MI appears as unequal distension of proximal bowel loops containing swallowed air and meconium with a characteristic 'soap bubbling' appearance (Fig. 19.2). This feature is due to the presence of small air bubbles trapped in the exceptionally viscid meconium which also means that air-fluid levels are usually absent. Complex MI can be distinguished from simple by the presence of a large intra-abdominal mass displacing bowel loops and sometimes containing an air-fluid level. This 'meconium pseudocyst' mentioned previously may also show visible calcification varying from faint flecks to a clear curvilinear rim, delineating the edge of the lesion. Whilst evidence of a pseudocyst on plain x-ray is an indication for laparotomy, the absence of signs does not rule out complex meconium ileus. In 1 series of 58 neonates, 27 (47%) required laparotomy and resections for complex MI, but only 8 (30%) of those had radiographic evidence of calcification preoperatively [22].

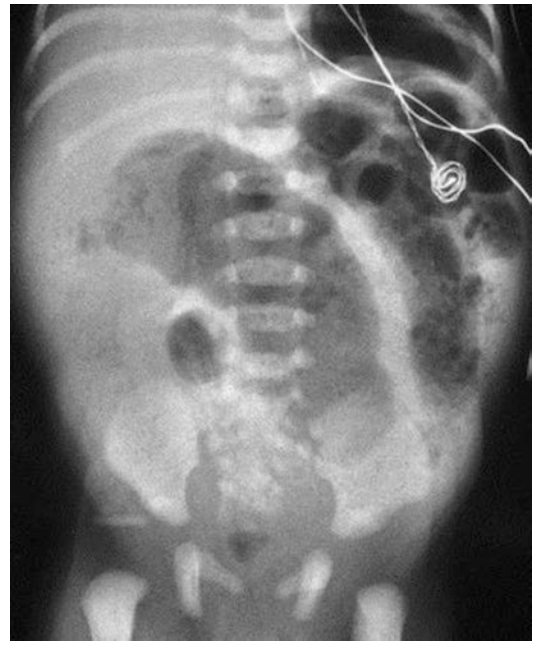

Fig. 19.2 Plain abdominal radiograph showing 'soap bubbling', also known as Neuhauser's sign

19.5 Conservative Management

Whilst clinical or radiological suspicion of complex MI mandates surgery, simple MI can potentially be relieved conservatively. Since Noblett first described its use in 1969, per rectal administration of Gastrografin enema under fluoroscopic control has been the most popular method of relieving obstruction caused by inspissated meconium [23].

Although there is no uniformity of practice, typically, a soft catheter is passed rectally, and contrast medium is introduced slowly, whilst its progress is monitored by intermittent x-ray screening. The goal of this process is to observe contrast passing from the unused 'micro-colon' (Fig. 19.3) and terminal ileum to distended small bowel. If this is achieved, passage of the obstruct-

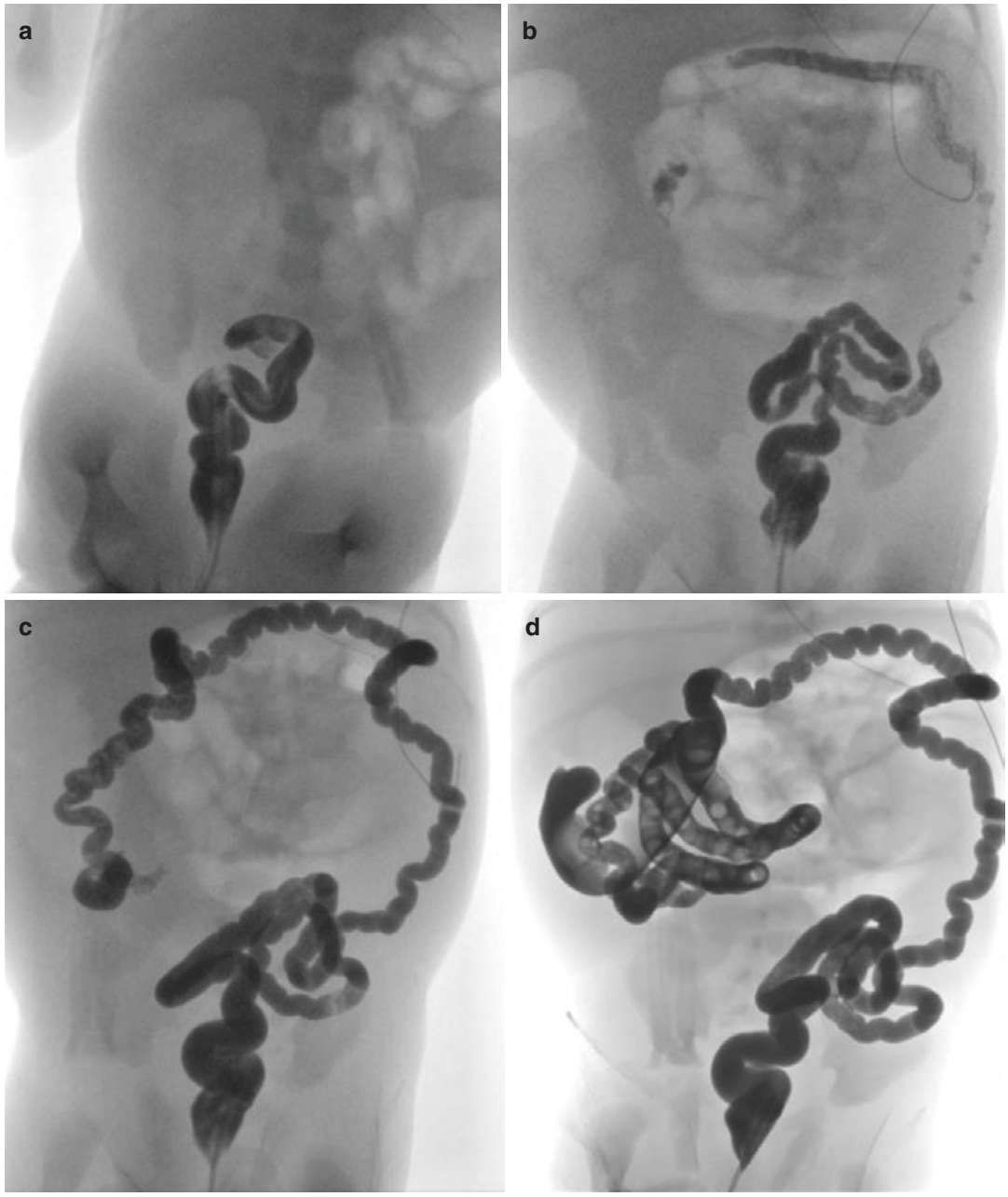

Fig. 19.3 (**a**) Instillation of contrast enema under fluoroscopic control. (**b**) Passage of the meconium through the colon which has a 'nonused' appearance. (**c**) Successful instillation of contrast enema beyond the ileo-caecal valve and entry of the contrast media in the small bowel. (**d**) Contrast enema reaching the ileal loops of bowel which is filled with impacted meconium

ing meconium is almost always observed shortly thereafter. If one treatment does not relieve obstruction and no adverse effects are observed, some clinicians advocate repeated attempts separated by intervals of a few hours [24]. Failure to relieve obstruction may result from the inability of contrast to reach the distended bowel or because the patient has an unrecognised complex MI.

Gastrografin is a water-soluble, iodine-containing contrast agent designed to be given enterally. Its active ingredients are sodium amidotrizoate and meglumine amidotrizoate in water with flavourings and an emulsifying agent, polysorbate 80 (Tween 80). It has an osmolarity of 1900 mOsm/L, which is approximately six times that of extracellular fluid [25]. The rate of successful decompression has been reported in older series to be between 50 and 66% of neonates with simple MI [24, 26]. However, the most recent series published in 2009 reported a success rate of only 22% [27]. The success of Gastrografin has been attributed to two of its physical characteristics:

1. Its high osmolarity draws large quantities of water from the bowel wall into the lumen, hydrating and liquefying the meconium resulting in an osmotic diarrhoea.
2. The polysorbate 80's action as an emulsifier is presumed to reduce the viscosity of the meconium directly.

A survey of the American Society of Pediatric Radiology in 1993 demonstrated that Gastrografin was more effective than other contrast media but revealed no significant difference in success rates between those who used pure Gastrografin to those who diluted the contrast to serum osmolarity [28]. The same survey showed a statistically higher success rate for radiologists who included additives (like extra polysorbate 80) to their Gastrografin, but more recently, animal and in vitro studies of human meconium have shown no advantage of polysorbate 80 over normal saline in relieving constipation or reducing viscosity [29]. Therefore, whilst Gastrografin is shown to be effective, exactly why it is remains a matter of debate.

Failure to relieve obstruction is not the only complication of Gastrografin enema. Perforation of the bowel occurs in approximately 3% of enemata although there is significant variation in this from series to series. The majority of perforations are identified at the time of the study [27, 28]. The mechanism is almost certainly mechanical over distension of bowel either causing immediate injury or mural necrosis resulting in delayed perforation. Type of contrast and size of catheter have no influence on perforation rates, but anecdotal evidence suggests the use of inflated balloon catheters in the rectum increases the risk [28]. Studies assessing the toxic effects of meglumine amidotrizoate and polysorbate 80 on colonic mucosa in animal models have produced strongly conflicting results, but in the experience of the authors, there is no direct irritant effect observed [29, 30]. The osmotic diarrhoea caused by undiluted contrast can result in distributive shock secondary to third space fluid losses. Experienced radiologists will either dilute the contrast with water or ensure that the child is receiving appropriate replacement for the expected losses during the procedure.

19.6 Operative Management: Simple Meconium Ileus

The indications for surgery are:

1. Failure of conservative measures to relieve the obstruction
2. Complication of conservative measures, e.g. perforation
3. Evidence of complicated MI, suggesting an atresia

Since 1948, the simplest method of surgical relief of obstruction has been laparotomy and meconium disimpaction using saline via a tube enterostomy at the site of obstruction coupled with a limited bowel resection as necessary [31].

Typically, a right-sided supra-umbilical transverse abdominal incision is made, and the peritoneum is entered safely. The midgut can then be gently expressed through the wound and inspected for signs of injury or atresia. Such exposure of the viscera will result in rapid loss of heat and fluid, requiring the surgeon to be quick in their inspection before returning the majority of the bowel to the abdominal cavity. In simple MI, the site of intra-luminal obstruction is usually quite clear with a marked change in bowel diameter somewhere in the terminal ileum. The

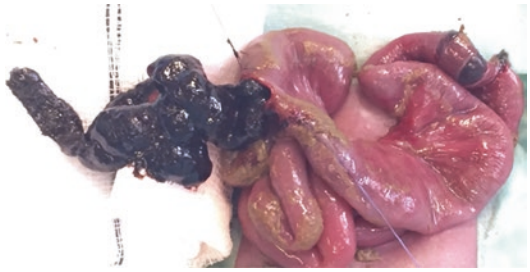

Fig. 19.4 Enterotomy is used to remove the highly viscous meconium from the intestinal loop, as manual milking of the meconium through the intestine can lead to serosal tears of the bowel loops (see right top loops in image)

upstream small intestine is grossly distended due to the long-standing nature of the obstruction, whilst the distal bowel is collapsed and firm, containing puttylike pellets of meconium which can be indented with pressure. An enterotomy is made on the anti-mesenteric border through which a soft tube can be passed and manoeuvred both proximal and distal to the site of obstruction (Fig. 19.4). Some authors advocate the placement of a purse-string suture to prevent spillage of bowel contents and peritoneal contamination, but in our experience, the enterotomy needs to remain open and be large enough to allow expression of the abnormally viscid bowel contents [32]. An irrigation solution can then be instilled to dilute the inspissated meconium and gently distend the bowel which has the action of freeing the sticky substance from the mucosa. The irrigation solution and meconium are then gently expressed along the bowel lumen to the enterotomy and removed. This process must be repeated until the proximal bowel is free of thick meconium and the distal bowel contents have been clearly irrigated into the colon to exclude the possibility of distal ileal obstruction. Ideally, some of the irrigation fluid and pellets of grey meconium are discharged from the anus during the operation to demonstrate patency throughout. However, it is well recognised that many neonates exhibit continuing symptoms of obstruction post-operatively even when full decompression is achieved at the time of surgery. Whether this is due to a prolonged post-operative ileus or the reaccumulation of viscid secretions is not clear, but there may be benefit from doses of mucolytics (administered orally and rectally) post-operatively until they start opening bowels for themselves.

Many irrigation solutions have been used from 0.9% saline to Gastrografin [33] and even hydrogen peroxide [34]. N-Acetylcysteine (NAC) has been used as an intraoperative irrigant since the early 1960s [35]. It depolymerises glycoproteins in mucus by hydrolysing the disulphide bonds that link the mucin monomers [36]. Despite its widespread use and successes reported anecdotally in the literature, there is relatively little evidence that it is more effective than saline. An in vitro study of normal human meconium showed that, saline is superior to 4% NAC at immediately reducing viscosity (84% reduction versus 69% reduction) [29]. The same study did note a 99% drop in viscosity with NAC after 6 h of incubation, suggesting that it has a place as an effective mucolytic but perhaps not in the operating theatre.

Once decompression has been achieved, the surgeon faces a choice as to how to complete the operation, and on this, there is no consensus. The decision should be made based on the condition of the bowel, the patient and the experience of the surgeon.

1. **Closure of enterotomy** can be performed if the proximal bowel is minimally distended and the surgeon is very confident that she has completely cleared all trace of meconium obstruction distally.
2. **Resection and anastomosis** is possible if there is a segment of small bowel that the surgeon feels is too dilated to recover its propulsive ability. This too relies on complete clearance of the meconium obstruction as a high distal intra-luminal pressure will result in anastomotic leak. Proponents of primary anastomosis point out that no further anaesthetics are needed for stoma closure and the risks of anastomotic leak are acceptable [37].
3. **Formation of a tube enterotomy**. By bringing the enterotomy to the skin and leaving a tube in situ, it is possible to continue washouts of the distal bowel until such time that the baby achieves normal bowel transit. Some

authors have proposed creating an appendicostomy for the same purpose. One centre that routinely uses this technique reported completed decompression in all eight reported cases, allowing the tube to be removed 12–14 days later on the ward. All enterotomies closed spontaneously within 24 h of tube removal [38].

4. **Formation of a stoma**. Concerns about anastomotic leak have led many surgeons to opt for an ileostomy. Many types of stoma have been used over the years with some now confined to the history books (see also Chap. 18.9.4).
   (a) **Mikulicz stoma**. This technique, popularised by Gross in 1953, involved bringing the distended loop to the wound and suturing its afferent and efferent limbs to the abdominal wall as for a stoma. When the abdomen was closed, the distended loop was resected just above the skin, leaving a double-barrelled stoma which was converted to a single orifice by the application of a crushing clamp to the common wall [39]. This procedure has largely been superseded by others.
   (b) **Bishop-Koop stoma.** In 1957 these two doctors proposed performing an end-to-side anastomosis of the proximal bowel to the distal and then bringing a 'chimney' of distal bowel to the skin as a stoma and catheterisable channel through which irrigation could be performed [40]. When the distal bowel had recovered sufficiently, the faecal stream would start to pass preferentially towards the terminal ileum and colon, and the stoma output would drop.
   (c) **Santulli stoma.** Four years after Bishop and Koop, Santulli suggested an adaptation of their stoma in which it was the proximal limb which was brought to the skin rather than the distal [41]. He felt this configuration would improve proximal bowel decompression.
   (d) **Simple divided ileostomy.** This has the advantage of being relatively simple to form, has no internal anastomosis and still provides a catheterisable channel to irrigate the distal bowel.

Credible arguments can be made for most of the options outlined above, and it is essentially a balance of risk between the formation of an anastomosis in a system where some element of distal obstruction may remain and the complications and extra anaesthetics associated with stomas. We identified six large retrospective reviews of MI management from single centres since 1990 in the world literature [42–47]. Collectively, they reported the results of the operative management of 79 cases of simple MI (they also reported outcomes for use of Gastrografin enema and complicated MI separately). None of the papers had sufficient numbers for statistical analysis, and in their conclusions, two favoured simple enterotomy [42, 43], washout and closure, two favoured stoma's in all cases [44, 45], one paper was non-committal [46] and the last concluded that it would no longer use Bishop-Koop or Santulli stomas due to three of their ten stomas developing problems at the end-to-side anastomosis requiring re-laparotomy [47].

19.7 Complex Meconium Ileus

As stated previously, a diagnosis of complicated meconium ileus is an indication for laparotomy, but the intra-abdominal findings will influence the rest of the operation. If active peritonitis is found from a recent perforation, lavage and formation of a stoma is the simplest, safest management. Similarly, the presence of an established, thick-walled pseudocyst will necessitate decortication and stoma.

However, if the obstruction is due to a segmental volvulus which has not perforated, resection of the volved segment and primary anastomosis can be considered. If the volvulus has resulted in a pure atresia (3a or 3b) but no evidence of chemical peritonitis remains, anastomosis could also be attempted then. Whenever anastomosis is attempted, the relative discrepancy in size between the huge proximal segment and the collapsed distal segment will have to be resolved. If sufficient small bowel is present that some might be excised without compromising absorption, then the most distal, distended part of

the proximal bowel may be excised to make the anastomosis simpler. Alternatively, a discrepancy may be reduced by opening the distal bowel at an oblique angle, increasing its circumference. Various methods for tapering the proximal side of the anastomosis are also described.

We, like other authors [32, 48], feel that in the majority of cases of complicated MI, a stoma is appropriate. Only one retrospective series in the last 10 years has treated all the cases of complicated MI with resection and anastomosis [49]. In a series of 13 patients, 4 (31%) had surgical complications requiring a repeat laparotomy, and 1 of those died. The authors concluded that primary anastomosis was still their favoured method for managing complicated MI.

19.8 Post-Operative Management

Fluid and electrolyte homeostasis is the primary goal of management in the immediate post-operative period. Ileus secondary to the surgery will exacerbate the pre-existing gut hypomotility caused by a long period of obstruction. Therefore, third space and nasogastric losses will have to be replaced in addition to maintenance fluids. If the child has a stoma, this is also a potential source of fluid and electrolyte loss and should be considered in fluid balance calculations.

Four percent NAC can be instilled via nasogastric tube (or via stoma, if present) to help break down any residual meconium. 5 mL given three times per day is recommended by the British National Formulary [50] and can be continued until ileus resolves. Most surgeons would prescribe a short post-operative course of antibiotics, but prophylaxis beyond this is not required. Stomas are typically closed early at approximately 6 weeks to limit nutrition, fluid and electrolyte difficulties.

19.9 Nutrition

The importance of nutrition to life expectancy in cystic fibrosis sufferers has been known for decades. A major cross-sectional study published in 1988 comparing CF Centres in Toronto and Boston showed median survival was 30 years in Toronto, but 21 years in Boston. The only significant difference between the groups was nutritional status—the Canadian patients were taller and weighed more than their American counterparts [51]. More recently a prospective, observational study of 3142 children demonstrated that those with weight at or above the 50th centile early in life had significantly better pulmonary function and survival rates than those below the 10th centile [52]. Based on such evidence, guidelines issued by the Cystic Fibrosis Foundation recommend that the target weight for any CF infant should be above the 50th centile [53]. Neonates not reaching this centile should have their calorific intake increased from 100 kcal/Kg/day to 115–130 kcal/Kg/day. Nutritional guidelines published by the CF Foundation [54] and the European Consensus on Nutrition in Patients with CF [55] recommend human milk feeding but accept that the evidence for this is not strong. A prospective cohort study found no difference in weight or length between exclusively human milk-fed infants with CF and those who were exclusively formula-fed [56].

There are several challenges common amongst babies presenting with meconium ileus that make adequate weight gain difficult. If bowel resection or a stoma has left the child with short gut, a normal enteral feeding regime will be insufficient. Continuous enteral feeding with a predigested formula is recommended until such time as a routine feed is tolerated. However, if sufficient enteral feeds cannot be absorbed, parenteral nutrition must be employed.

Neonates with MI should be assumed to have pancreatic insufficiency until it can be confirmed by measurement of faecal elastase levels (<100ug/g is diagnostic) which is now considered the ‘gold standard’ [57]. Since this test cannot be performed on ileostomy effluent, children with a stoma can only be tested after closure. Whenever enteral feeds are started, pancreatic enzyme replacement therapy (PERT) should commence. This includes feeding with predigested formulas [58]. Dosing of PERT is based on historical precedent as no formal studies have

been undertaken to determine optimal dosing [59]. A widely recommended dosing regimen is 2500 lipase units per kilogramme per feed (assuming a feed of about 120 mL) with a maximum daily dose of 10,000 lipase units per kg per day [60]. Although PERT contains protease and amylase, dosing is always based on lipase units. PERT needs to be tailored to each patient based on response; too low a dose can result in malabsorption, failure to thrive and constipation, whereas excessively high dosing has been shown to cause fibrosing colonopathy, a condition presenting as obstruction due to multiple colonic strictures [61–63].

Infants with cystic fibrosis secrete large amounts of sodium in their sweat, and this can lead to a total body deficit which is not reflected by the serum sodium [64]. A urine sodium concentration of less than 20 mEq/L suggests that the child's kidneys are actively retaining sodium because of sodium depletion. These losses are exacerbated by the presence of a stoma. 2–4 mmol of sodium chloride can be added to each feed [50]. Babies with meconium ileus can also have deficiencies of fat-soluble micronutrients, i.e. vitamins A, D, E and K and zinc. For this reason, it is recommended that they receive vitamin supplementation as standard and zinc supplementation if there is unexplained poor weight gain [54].

Gastroesophageal reflux disease (GERD) has an increased prevalence in infants with CF with up to 50% displaying symptoms and having abnormal pH studies [65]. Proton pump inhibitors or histamine-2 receptor antagonists can be used as a first line if the child is symptomatic. In addition, they can be given empirically as an adjunct to PERT which is inactivated if the stomach's pH is very low.

19.10 Respiratory Support

Although respiratory symptoms tend not to manifest in the first year of life, it is perceived that commencing airway clearance therapy as soon as possible reduces complications later in life. Therefore, respiratory bodies recommend commencing daily percussion and postural drainage in the first few months of life [66, 67]. The addition of a bronchodilator (albuterol) has been shown to enhance the effect of the physical therapy [68, 69]. They only caveat is that head down posture may exacerbate GERD and so is to be avoided [70, 71].

19.11 Other Complications of Cystic Fibrosis

Distal intestinal obstruction syndrome (DIOS), formerly known as meconium ileus equivalent, is caused by increased viscosity of intestinal contents and occurs most commonly in teenagers and young adults. The aetiology is unclear, but some cases are certainly due to poor compliance with pancreatic enzyme replacement therapy which is a problem in this age group. Presenting symptoms are most commonly abdominal pain and distension, which can cause some diagnostic difficulty as other pathologies associated with CF also present similarly in this age group, i.e. intussusception, appendicitis and fibrosing colonopathy. Cross-sectional imaging is sometimes required to clarify the diagnosis. Treatment is hydration and administration of a strong osmotic laxative containing polyethylene glycol (Klean-Prep®, Golytely®). Failure of this therapy would mean surgery, but this is a rare outcome [72].

In addition to intussusception, viscous stool increases the possibility of rectal prolapse although there is very little concerning this in the literature. A single retrospective review suggests there is a 3–4% incidence of CF in children presenting with rectal prolapse [73]. Biliary disease resulting in hepatic failure is a very serious but thankfully rare complication of CF. End-stage liver disease requiring transplant does occur but usually in adulthood [74]. Fertility is severely impacted in men with 98% being infertile due to occlusion or absence of the vasa. Epididymal sperm aspiration is possible but only rarely practised [75].

19.12 Prognosis

Prior to 1948 when Hiatt and Wilson reported their results with enterotomy and irrigation, meconium ileus was a fatal condition. Numerous new techniques developed in the 1950s and 1960s saw increasing successes in surgical and nonsurgical management. Although few advances in surgery have taken place since, infant survival continued to improve due to a greater understanding of the supportive care required. Today, infant survival rates for MI of all types approaches 100% [26, 46, 76, 77]. Current trends suggest that average life expectancy for children born with CF today is in the 1950s [1].

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Gastrointestinal Tract Duplications

20

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20.1 Introduction

Gatrointestinal tract duplications (GTDs) are rare congenital anomalies that can occur in any portion of the gastrointestinal tract from mouth to anus but are more commonly encountered in the small intestine. The term intestinal duplication was first used by Calder in 1733 and later by Fitz in 1884 but was not widely used until it was popularized by Ladd in 1937, with further classifications by Gross in 1953 [1–3].

Gastrointestinal tract duplications have an incidence of 4500–12,500 live births [4], and recent studies report that duplications are more common in males than in females [5]. They can present at any age, but 80% of cases present within the first 2 years and the majority within the first 3 months of life, with antenatal diagnosis made in a significant number of cases [6, 7].

The distribution of alimentary tract duplications shows that the most common location is in the midgut (more than 64%). It is reported in the literature that most of these duplications are located in the terminal ileum, but recently Rattan et al., reporting their case histories regarding 17 neonates, found that the major site involved in intestinal duplications was the mid-ileum rather than the terminal ileum [5].

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20.2 Pathogenesis

Various theories have been proposed to explain the origin of these lesions, but none adequately explains all intestinal duplications. The primitive foregut gives rise to the pharynx and its derivatives, the respiratory tract (the trachea and lungs), esophagus, stomach, and duodenum to the level of the ampulla of Vater. No single embryological theory explains the spectrum of anomalies covered by the heading "foregut duplications." The split notochord theory is an attractive explanation for some alimentary tract and spinal anomalies, e.g., neurenteric canal, but does not explain the full spectrum of lesions observed. The notochord appears to have a pivotal role to play in foregut development as the organizer of paraxial organogenesis. There is some evidence emerging that altered expression of the sonic hedgehog gene by the notochord affects the Shh-GLi signaling pathway and may contribute to a spectrum of bronchopulmonary, alimentary tract, and associated anomalies [8]. It would appear that the cystic duplications develop secondary to an altered split notochord mechanism, and instead, tubular duplications could develop secondary to a partial twinning of the fetus. According to the *split notochord theory*, early in embryonic life, the neurenteric canal is formed connecting the primitive neural tube with the developing intestine. During closure of the neurenteric canal, remnants of developing intestine may be left anywhere from the intraspinal space to the chest and abdominal cavities.

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According to the theory of *incomplete twinning*, the type of duplication that occurs most commonly involves the hindgut causing duplications of the colon, rectum, and anus. Bremer's theory of *incomplete recanalization* has also been considered; according to this the error occurs during the recanalization phase of the intestine with formation of a long continuous tube. Errors in this process can leave cystic structures composed of intestinal remnants in addition to the normal gut. These duplications are usually of the cystic type [9]. Finally, the literature reports on environmental stress on the fetus, even during different gestational times, and in this regard, Mellish and Koop hypothesized that traumas and hypoxia could lead to the formation of duplications.

Cystic duplications may be associated with spinal cord and vertebral anomalies, and tubular duplications may be associated with urinary tract, spine, and central nervous system anomalies. Foregut duplications probably occur during the normal division of the foregut into respiratory and esophageal structures and may therefore contain elements of respiratory tract, such as cartilage and bronchial epithelium (bronchogenic cyst), elements of the esophagus such as smooth or striated muscle and squamous epithelium (esophageal duplication), or elements of both (foregut duplication) [7].

20.3 Pathology

Gastrointestinal tract duplications may be single, multiple, or complex and can be classified according to morphology into cystic or tubular masses with the presence of an intimate attachment to the GI tract, a layer of smooth muscle in the wall and an epithelial lining resembling some part of the GI tract (islets of gastric mucosa, pancreatic tissue, and respiratory ciliary epithelium). These are located on the mesenteric board of the intestinal canal with which they share the muscular layer and vascular axis but with a mucosal lining. Duplications may be communicating or noncommunicating with the intestinal lumen, although most duplications do not communicate with the adjacent bowel [10].

The most common duplication is usually cystic (80%) and is located on the mesenteric aspect of the small or large intestine (midgut 64%).

Esophageal duplication cysts have a double layer of surrounding smooth muscle, are lined by alimentary (squamous or enteric) epithelium and are attached to the esophagus in either a paraesophageal or an intramural fashion [11].

Gastric duplication cysts are usually single and, in general, do not communicate with the gastric lumen. Histologically, the cyst wall can consist of mucosa, subepithelial connective tissue, a layer of smooth muscle and an outer fibrous capsule. The mucosa is typically lined by gastric foveolar epithelium, but most of the cystic wall is lined with a pseudostratified columnar ciliated epithelium. Sometimes, small intestinal or colonic mucosa can be also found. Gastric duplication cysts may also contain ciliated cells, proteinaceous debris, crystal formations or engulfed histiocytes. Bronchogenic duplication cysts are lined with respiratory epithelium (which is usually ciliated pseudostratified columnar in nature) and may contain cartilage/bronchial glands in their wall. Bronchogenic duplication cysts can also contain one or more layers of smooth muscle. Most are located in the mediastinum around the tracheobronchial tree or within the pulmonary parenchyma.

Small bowel duplication cysts can be associated with all three small bowel subtypes: duodenal, jejunal, and ileal. In general, the wall of small bowel duplication cysts can contain two mucosal layers sharing a common muscle layer. More specifically, duodenal duplication cysts consist of submucosa, muscularis propria, a duodenal epithelial lining, and intimate attachment to the GI tract. Jejunal duplication cysts consist of submucosa and muscularis propria and are lined with jejunal mucus glands. Similarly, ileal duplication cysts consist of submucosa and muscularis propria and are lined with ileal mucous glands and can contain heterotopic gastric mucosae.

In 33% of colonic duplication cysts heterotopic gastric mucosa may be found; these cysts can contain multiple layers of the bowel wall including mucosa, submucosa, and muscularis propria. They can contain at least one outer muscular layer with an inner gastrointestinal mucosal lining. Colonic duplication cysts can also contain well-organized layers of smooth muscle with intimate attachment of the common wall to the

colon and fibrosis, inflammatory cells, lymphoid aggregates, necrosis, and calcification.

Multiple duplications are seen in about 10% of patients. As many as 30% of patients with thoracic or thoracoabdominal duplications have additional duplications below the diaphragm.

Some cases lack anatomical association with the normal GI tract, and they are called isolated enteric duplication cysts (IEDCs). Prenatal vascular accidents, torsion, and heterotopic tumors may be considered the etiological mechanism of IEDCs. This type of tumor has been reported in locations including the tongue, pleural space, liver, pancreas, biliary tree, and retroperitoneum. Only 17 cases of retroperitoneal IEDCs have been described in the literature, many of which have a unilocular or multilocular shape [12].

20.4 Clinical Presentation

Symptoms are usually related to age, site, size, presence of ectopic mucosa and communications with the native bowel; in fact, the clinical presentation is quite diverse and often mimics other intra-abdominal conditions, thus posing a great challenge for pediatric surgeons to arrive at a clinical diagnosis preoperatively.

Oral and esophageal lesions may cause rashes, respiratory distress due to pressure on the bronchi or lung, cough, cyanosis, retrosternal pain, and a mass effect with dysphagia, and also hemorrhage and peptic ulceration when an ectopic gastric mucosa is present. Mediastinal enteric cysts are often associated with vertebral anomalies such as vertebral fusion, scoliosis, anterior and posterior spina bifida, diastomyelia, and the absence of vertebra [13]. Gastrointestinal duplications may lead to nausea, vomiting, obstruction, hemorrhage, or perforation [14, 15]. In ileal and jejunal duplications, the most common symptoms were palpable mass, abdominal distension, pain, and bleeding. Colonic and rectal duplications are mostly accompanied by constipation and bleeding [4]. In a few cases intussusceptions and volvulus may occur in which the adjacent cystic mass would represent the lead point. Jehangir et al. have also described some peculiar presentations, such as unexplained persistent metabolic acidosis in a neonate with a perforated ileal duplication; dysuria and hematuria syndrome, attributed to the presence of gastric mucosa in the cyst in an infant with retroperitoneal duplication; and vaginal bleeding in an unusual anterior tubular rectal duplication [16].

20.5 Diagnosis

The imaging modalities commonly used to investigate duplication cysts are ultrasound, abdominal X-ray, barium studies, CT, and magnetic resonance imaging (MRI) as they are helpful in defining the anatomical borders of a duplication [17].

The characterization of enteric duplications is not simple given that there is a large range of anatomical variability. The differential diagnosis to be considered in a fetus with an intra-abdominal cyst includes neurenteric cyst, anterior myelomeningocele, mesenteric cyst, choledochal cyst, and ovarian cyst. The first prenatal detection of an enteric duplication was reported by Van Dam in 1984 at 20 weeks' gestation by ultrasound [18]. Since then, large ultrasound surveys have shown that there are two sonographic signs highly suggestive of enteric duplication: the "double-wall" sign and the presence of peristalsis [19, 20].

Indeed, enteric duplication cysts may be suspected on sonographic demonstration of an intra-abdominal cystic mass in the second or third trimester of gestation [21], with the typical "double-wall" sign characterized by a hyperechoic inner mucosal layer correlating with the mucosa-submucosa and an outer surrounding hypoechoic layer reflecting muscularis propria. Duplication cysts may contain thick mucinous material, septations, fluid levels, and debris, and they may also contain detached ciliary tufts, which could be diagnostic. In addition, duplication cysts can have peristalsis, which appears as ring contractions with a concentric contraction of the cystic wall. Peristalsis in a juxta-enteric cyst is specific for a duplication cyst and can be a diagnostic feature [11]. However, prenatal diagnosis is often difficult, and ultrasound identifies only 20–30% of lesions [22]. When an enteric duplication (or any other malformation) is found in a fetus on a surveillance ultrasound, a prenatal

MRI and echocardiogram are indicated. As fetal MRI technology has advanced, MRI is more accurate than ultrasound in delineating many aspects of fetal anatomy [23]. On fetal MRI, enteric duplications appear hyperintense on T2-weighted images and hypointense on T1-weighted images. Despite this, ultrasound is considered the first-choice imaging modality that allows a fast postnatal treatment strategy, reducing the risk for potential complications [24, 25].

Contrast study demonstrates a submucosal mass with mass effect extending into the lumen of the GI tract. CT and MRI are not used routinely, but are quite helpful in difficult cases such as esophageal, duodenal, and rectal duplications. Radionuclide scanning with technetium-99 m sodium pertechnetate can be used in cases in which the presence of heterotopic gastric mucosa is suspected [5].

20.6 Treatment

In asymptomatic patients, surgical resection is controversial. Although some authors advocate a resection owing to possible malignant degeneration of the duplication cyst, others have advocated active observation. As there have been case reports of stable duplication cysts on endoscopic ultrasound surveillance, this may be a suitable method of outpatient follow-up and surgical resection can be considered if the patient develops symptoms. In any case, surgical versus nonsurgical management of asymptomatic duplication cysts is likely to remain controversial until we understand more about the time course and risk factors associated with their malignant degeneration.

The surgical approach varies according to the localization and type of the duplication, rather than on the duplication size. From a treatment perspective, surgical removal/enucleation is the treatment of choice in most symptomatic cases. In asymptomatic patients, surgical treatment should be performed to avoid complications such as ulcers or perforations or neoplastic degeneration, although some authors prefer conservative attitudes and clinical-instrumental monitoring. Surgical treatment involves open and minimally invasive techniques depending on surgeon experience, lesion localization, and resilience criteria.

To begin with, laparoscopy and thoracoscopy played merely an explorative role aimed at the definition of the location and nature of the lesions; nowadays, the lesions can be resected or enucleated with a purely laparoscopic/thoracoscopic or a laparo-/thoracic-assisted approach [26]. Should an enucleation compromise the vascularization of the remaining bowel, a resection followed by an end-to-end anastomosis is recommended.

20.7 Esophageal Duplication Cysts

Faced with a mediastinal enteric cyst, thoracoscopic surgical excision of the cyst is the mainstay of treatment with comprehensive supportive care. But when esophageal or vertebral connections or large cysts are present or expertise in thoracoscopy is not available, a thoracotomy is the approach to follow; in particular, large esophageal duplications can be resected, leaving the esophageal mucosa intact and closing the left muscular defect (Fig. 20.1). Another treatment strategy is observation in asymptomatic individuals. Indeed, some authors, such as Versleijen, argue that removing an asymptomatic cystic lesion can lead to long-term complications, such as heartburn and gastroesophageal reflux with esophagitis and can lead to mortality in up to 1%. Versleijen et al. described a case in which a patient with an asymptomatic esophageal duplication cyst with a diameter of 1.1–4.1 cm was followed for 13 years and routine endoscopic ultrasound did not show cyst growth [27].

20.8 Gastric Duplication Cysts

Gastric duplication cysts make up between 4 and 9% of all intestinal duplication cysts [28]. Unlike other duplications, a female predilection is seen. They are usually single and in general do not communicate with the gastric lumen. Most cystic

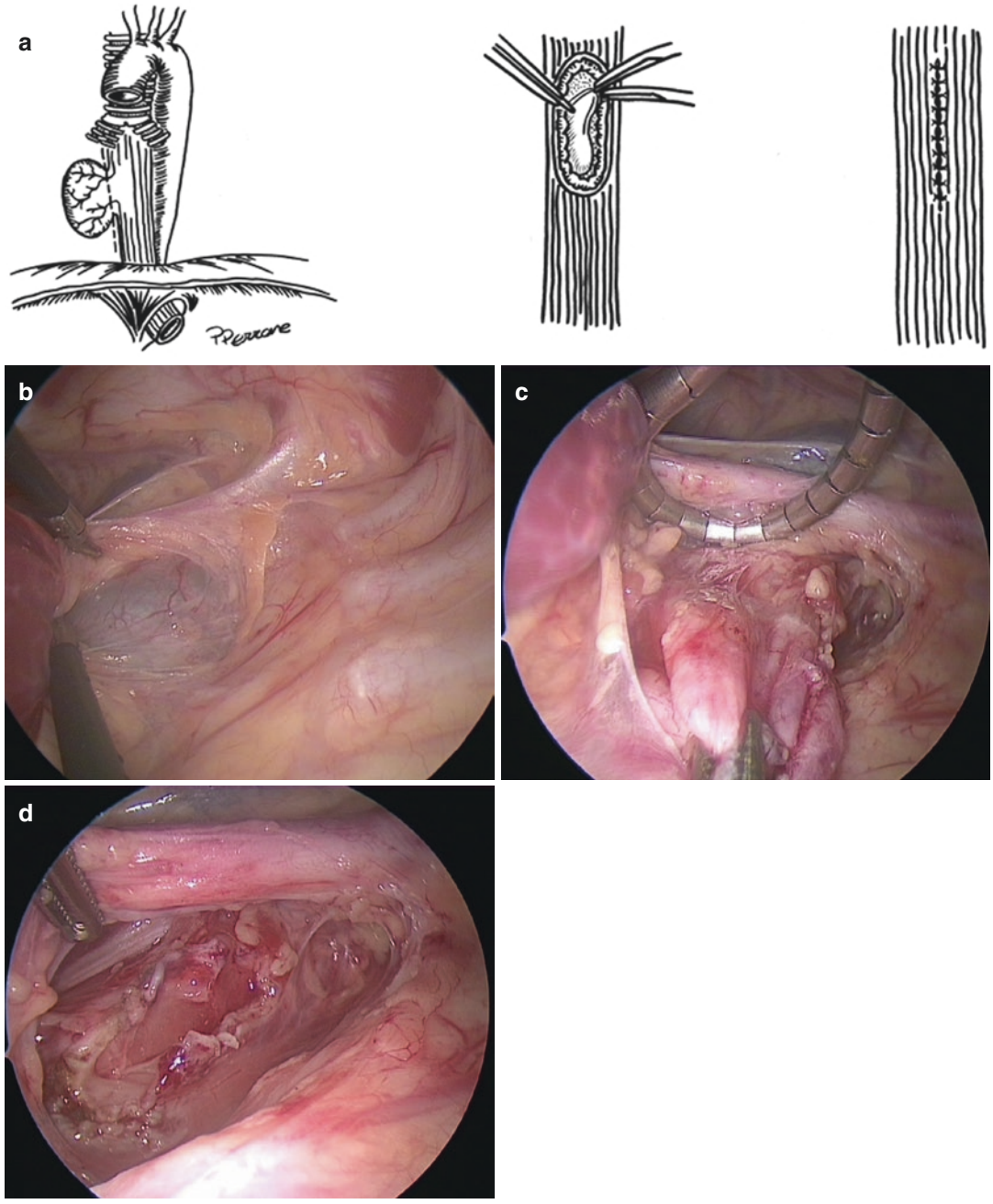

Fig. 20.1 Esophageal duplication. (**a**) Scheme of surgical treatment. (**b**–**d**) Intraoperative thoracoscopic view

duplications of the gastric or pyloric curvature can be completely removed by subtracting the cysts with subsequent repair of the seromuscular defect. Small gastric duplications can be simply removed by resection of a stomach margin followed by a double-layer gastric suture (Fig. 20.2); large or complex duplications may require partial gastrectomy.

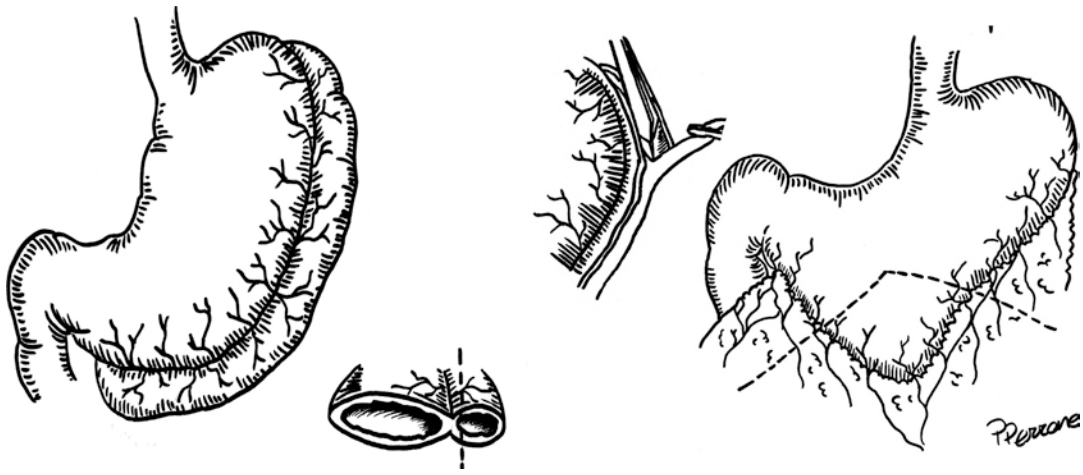

Fig. 20.2 Gastric duplication (scheme of surgical treatment)

20.9 Bronchogenic Duplication Cysts

Most bronchogenic duplication cysts are located in the mediastinum around the tracheobronchial tree or within the pulmonary parenchyma. With regard to treatment, surgical enucleation is the treatment of choice in symptomatic cases. In asymptomatic cases, surgical resection has been suggested owing to the rare development of complications or malignancy, but many of these lesions can be safely observed [29].

20.10 Pancreatic Duplications

The rarest form of alimentary tract duplications is pancreatic, with only a few cases reported in the literature. Anatomically, the pancreatic head is the most common location (51%), with the remainder equally distributed in the body and tail. At operation, the presence of a smooth muscle lining on frozen section distinguishes pancreatic duplications from pseudocysts. Treatment ranges from cystectomy to more complex procedures, including cystojejunostomy, pancreaticoduodenectomy, or partial pancreatectomy, depending on the location.

20.11 Small Bowel Duplication Cysts

Small cystic intestinal duplications can be simply removed via a laparoscopic approach with the adjacent bowel (Fig. 20.3). As intestinal duplications are situated on the mesenteric side of the intestine, it is not possible to resect them without compromising the blood supply of the adjacent normal bowel. Long tubular duplications can also be removed, unless the amount of adjacent bowel that has to be sacrificed is considered too much for the welfare of the patient. In these cases, the seromuscular layer of the duplication can be opened, and the mucosa can be stripped from the entire length of the duplication (Fig. 20.4).

The seromuscular cuff can be resected and closed over the area of denuded epithelium. Resection can be limited to the area where the duplication communicates with the intestine. Alternatively, the duplication and adjoining bowel can be anastomosed over a long length to ensure free drainage.

The principles of management include bowel preservation, mucosectomy, internal drainage, and staged operations where indicated to achieve the best possible outcome for each individual child.

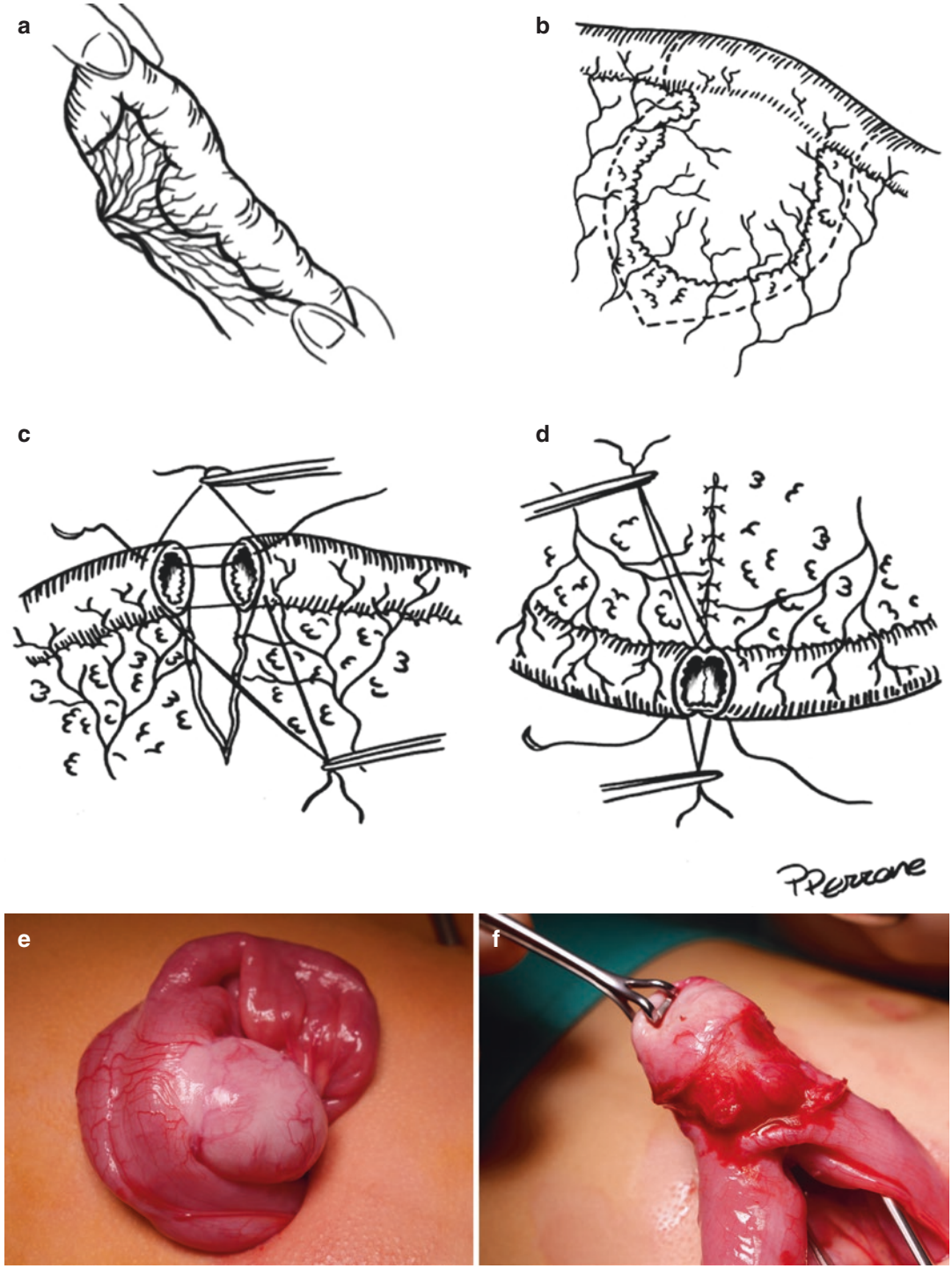

Fig. 20.3 Small bowel cystic duplications. (**a**–**d**) Scheme of surgical treatment. (**e**, **f**) Intraoperative view

20.12 Colonic Duplications

The treatment of colonic duplications varies depending on the type and extent. Cystic duplications are managed with resection and anastomosis (Fig. 20.5). Small cystic duplications can sometimes be enucleated. Tubular duplications are usually more challenging. For symptomatic tubular duplications, resection is preferred, if possible. If resection is considered too aggressive, a distal communication between the duplication and the native colon can be created to relieve the obstruction. For large tubular duplications that are asymptomatic and with a distal communication, conservative management with stool softeners is appropriate.

20.13 Rectal Duplications

Treatment varies from marsupialization through a transanal approach, division of the septum between the duplication and the rectum, or excision using a posterior sagittal approach. An initial colostomy may be needed in some patients. Ileal and colonic tubular duplications vary in length and complexity [30].

20.14 Complications

The potential complications of an intra-abdominal enteric duplication are numerous and can be fatal. Pain is one of the most frequent forms of

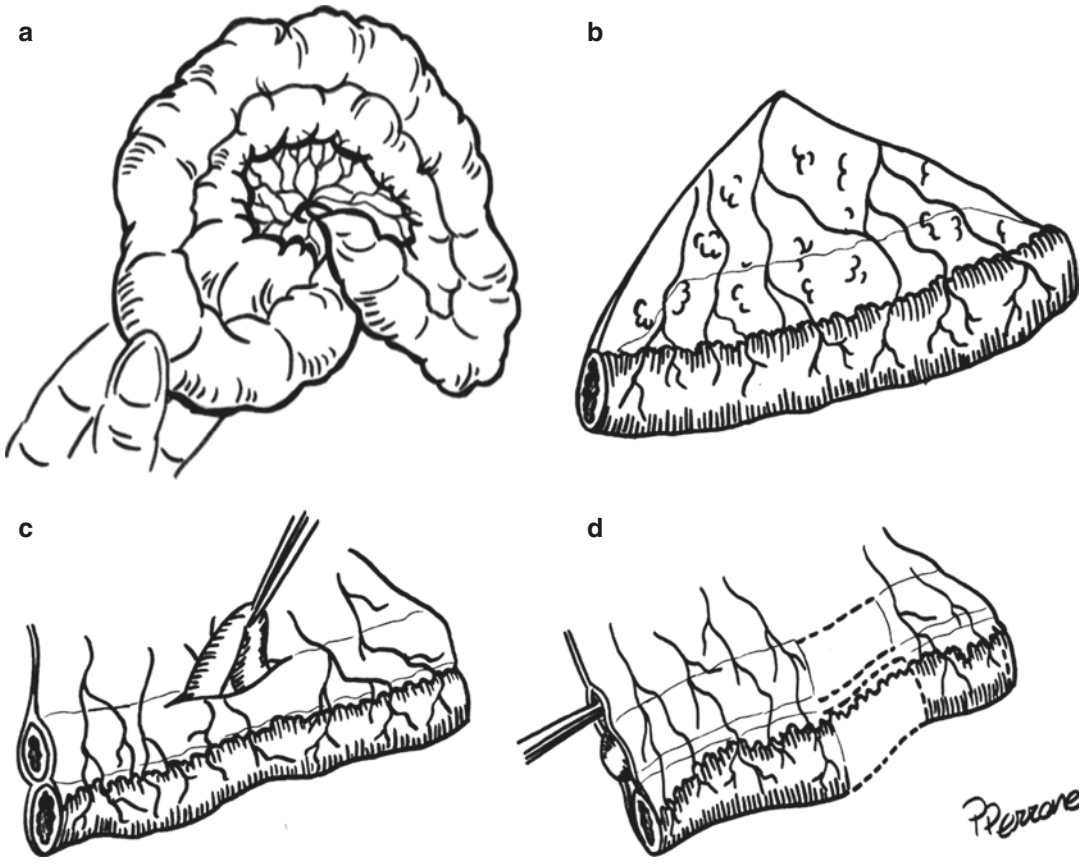

Fig. 20.4 Long tubular bowel duplications. (**a**–**d**) Scheme of surgical treatment. (**e**–**h**) Intraoperative view

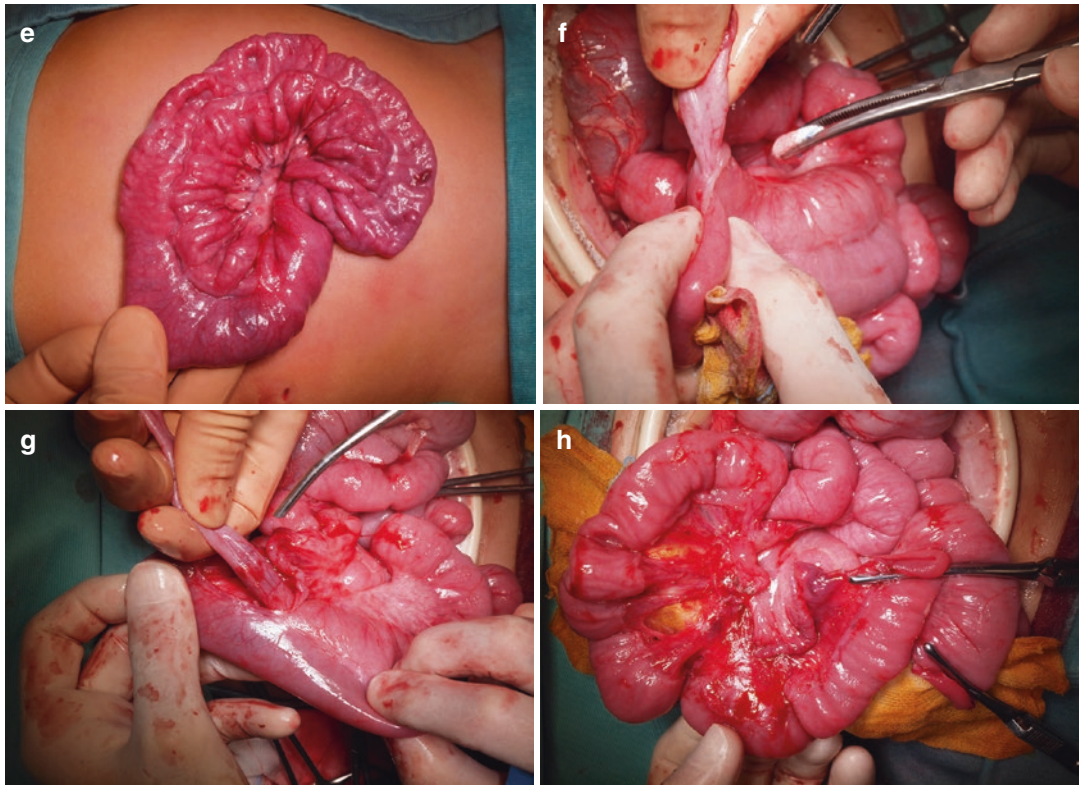

Fig. 20.4 (Continued)

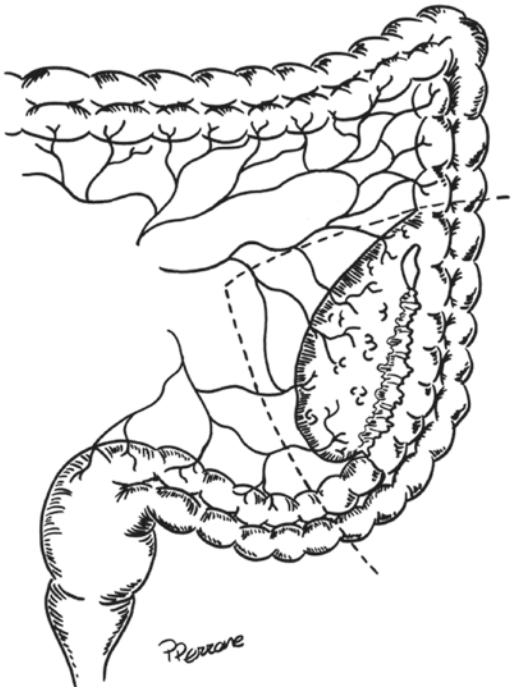

Fig. 20.5 Colonic duplications (scheme of treatment)

presentation and is usually attributed to high pressure inside the duplication because of the accumulation of secretions. Intussusception is another complication in which the duplication serves as a lead point. Intestinal obstruction because of the extrinsic compression of the adjacent bowel has been reported as well. However, perhaps the most dangerous complications are those associated with the presence of gastric mucosa, such as ulceration, perforation, and hemorrhage. Finally, malignant changes can occur in the mucosa of an enteric duplication, regardless of the mucosal type and the anatomical location [31].

In the literature, from 1955 to 2012, 67 cases of malignancies have been reported arising from alimentary tract duplications near the esophagus (n=6), stomach (n=10), small intestine (n=19) [duodenal (n=3), jejunum (n=3), ileum (n=12), not described (n=1)], appendix (n=1), and large intestine (n=31) [cecum (n=5), colon (n=13), and rectum (n=13)]; of these, 39 occurred between 1990 and 2012. The age of presentation ranged

from 12 to 88 years, but most patients were between the ages of 40 and 60 [32]. Although enteric duplications occur most often in the small bowel, a higher incidence of the tumor arising from a large intestine duplication was noted compared with other sites, especially the colorectum [33]. There are also reports about carcinomas arising in duplications of the duodenum and the stomach. Female predominance of 3:1 is found in the colorectum site. Malignant transformation should be suspected if any abnormal solid component is found within the duplication or if the serum carcinoembryonic antigen (CEA) or carbohydrate antigen 19e9 (CA19e9) level is elevated. Indeed, although CA19e9 is not clearly associated with malignancy, the prognostic value of CA19e9 levels in colorectal cancer has been reported and could be of interest in the diagnosis and management of intestinal duplications. More authors think that serum levels of CEA may serve as a valuable index for predicting tumor progress arising from GI duplication.

Carcinomas arising in duplication cysts include carcinoid tumors, squamous cell carcinomas, and common adenocarcinomas. Owing to the rare presentation with unspecific symptoms, tumors are commonly diagnosed when the they are greater than 4 cm and so more invasive and at an advanced stage with metastatic disease [32]. If malignant change is found in small bowel duplications, the high rate of lymph node metastases should be considered. Curative resections are rarely performed. The prognosis is generally poor once malignant change has occurred (Tables 20.1, 20.2, and 20.3) [25].

Table 20.1 Case series of gastrointestinal tract duplication in the last 25 years (1990–2015)

Author	Year	Number of patients
Rattan et al.	2017	17 (2001–2015)
Erginel et al.	2016	40 (1990–2015)
Jehangir et al.	2015	35 (2003–2014)
Okur et al.	2014	32 (2000–2013)
Haifen et al.	2012	39/67 (1990–2012)
Lima et al.	2012	22 (1995–2010)
Laje et al.	2010	18 (2001–2009)
Schalamon et al.	2000	12 (1989–1999)

Table 20.2 Characteristics of the numerical prevalence of duplications for sex, site, and morphology

First author	n.D–n.Pz	F-M	T-A	Esophagus	Stomach	Duodenum	Jejunum–ileum	Cecum	Colon	Rectum	Morphology
Rattan, 2017 [5]	18–17	4–13		/	1	2	0–13	1	1	/	18 cystic
Erginel, 2016 [34]	40	12–28		2	2	3	3–21	4	5	/	40 cystic
Jehangir, 2015 [16]	38–35	11–24	3 + 1[a]	6[b]	3	1	0–17	/	6	1	22 cystic–16 tubular
Okur, 2014 [4]	32	23–9	2	1	2	5	3–11	2 + 2[d]	3	1	25 cystic–7 tubular
Haifen, 2012 [32]	39	24–15		4	5	2	3–10[c]	3	6	6	6 tubular–33 cystic
Lima, 2012 [35, 36]	22	6–16		6	3	/	0–10	/	2	1	20 cystic–2 tubular
Laje, 2010 [10]	18	8–10		/	3	4	0–10	/	/	/	Cystic
Schalamon, 2000 [14]	13–12	Nd		/	3	1	2–6	/	/	1	Nd

Case series of gastrointestinal tract duplications in the last 25 years (1990–2015)[b]
n.D number of duplications, *n.Pz* number of patients, *T-A* thoracoabdominal, *Nd* not described
[a]Other site
[b]Six are mediastinic
[c]One of the ten described was localized in the appendix, one in the small intestine
[d]Two duplications were localized in the appendix

Table 20.3 Prevalence as a percentage of duplications for morphology, sex, and localization

Total cases	**Cystic**	**Tubular**	**Morphology Nd**
220	80%	14%	6%
Total cases	**F**	**M**	**Sex Nd**
220	40%	52%	8%
Total cases	**Foregut**	**Midgut**	**Hindgut**
220	25, 45%	64, 10%	10, 45%

Nd not described

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Mesenteric and Omental Cysts

21

Mario Lima and Neil Di Salvo

21.1 Introduction

A mesenteric cyst is defined as any cyst that is located in the mesentery and may or may not extend into the retroperitoneum; histologically, the inner surface of the cystic wall presents a recognizable lining of epithelium (cuboidal/columnar), endothelial or mesothelial, depending on the embryologic origin of the cyst. According to this definition, intestinal duplications, being most commonly cystic and located on the mesenteric aspect of the small or large intestine, may be part of this group. However, we will consider them in this chapter only for the differential diagnosis. Furthermore, in this chapter we will only consider cysts that interest the neonatal or infancy period, that is, the congenital ones. In older children and adults, other cysts of an acquired nature do exist. These have an infectious (e.g. hydatid cyst) and neoplastic (e.g. teratoma) etiology and are excluded from this context.

Mesenteric cysts are located anywhere in the mesentery; more commonly they are localized close to or even adjacently to the intestine. They may also extend from the base of the mesentery into the retroperitoneum. The most common localization is small bowel mesentery (ileal mesentery more frequently), followed by large bowel mesentery (especially sigmoid mesentery) and retroperitoneum. The fluid contained inside the cyst can be serous, chylous, haemorrhagic or purulent (if infected). The fluid is generally chylous when the cyst is located in the proximal small bowel mesentery and serous when it involves the ileal mesentery or the mesocolon. This could be related to a possible communication of these cysts with the absorption system of the intestinal wall. Another aspect that confirms this idea is the progressive dimensional increase that is often observed in the natural history of these cysts.

Since the first description of a mesenteric cyst reported by an Italian anatomist in 1507, Benevieni, many authors have tried to classify these lesions on the basis of different criteria: etiology, histology or origin. Because these cysts share common characteristics, thus the evaluation and therapeutic objectives are the same, and a simple classification is the one that refers to origin. There are then cysts of lymphatic origin (lymphangioma, simple lymphatic cyst), mesothelial origin (mesothelial cysts) and enteric origin (bowel duplication cysts or simple enteric cysts). Mesenteric and omental cysts are considered similar in origin and histological structure. The most common type of mesenteric or omental cyst is lymphangioma, followed by intestinal duplication cysts, mesothelial cysts and enteric cysts [1, 2].

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Lymphangiomas are very well known vascular congenital malformations of the lymphatic system. Their volume can increase all of a sudden, so as related symptoms, usually after viral infective episodes or traumas. Pathologically, lymphangiomas are large, thin-walled, cystic masses that are usually multiloculated. The fluid contents are predominantly chylous but may be serous or haemorrhagic. Lymphangiomas can be closely attached to the bowel wall. They have an endothelial cell lining, foam cells and thin walls that contain lymphatic spaces, lymphoid tissue and smooth cells. Mesenteric lymphangiomas are usually localized within the leaves of the mesentery, but they can also be pedicle (in this case very easy to resect).

Simple lymphatic cysts presumably originate from benign proliferation of ectopic lymphatics in the mesentery; they have a recognizable lining of endothelial cells and lack smooth muscle cells.

Cystic intestinal duplications present a thick wall composed of all the normal intestinal wall layers; part of the muscle layer is shared with the adjacent intestinal tract to which the duplicated part is intimately attached, in the mesenteric side of the bowel. They are therefore localized within the mesentery; the inner surface presents a gastrointestinal mucosa, not necessarily of the same type to the adjacent normal bowel. Contents are usually serous.

Enteric cysts are lined with gastrointestinal mucosa (hence enteric). They differ from duplication cysts because there is no reduplication of all the intestinal wall layers. Enteric cysts result from migration of a small bowel or colonic diverticulum into the mesentery. Pathologically, they are thin, smooth-walled cysts, usually unilocular, with serous contents. They are lined with enteric epithelium and have a thin fibrous wall without muscle layers.

Mesothelial cysts are thin-walled unilocular cysts with a mesothelial cell line on the inner surface. They usually contain serous material [2, 3].

21.2 Symptoms

Mesenteric and omental cysts have a wide range of clinical presentations; they are often asymptomatic and can be discovered as an incidental finding during a radiological study such as an ultrasound, a CT or MRI done for other purposes; they can also be incidentally noticed during a surgical procedure (laparotomy or laparoscopy) for another condition. Nowadays, these cysts in the majority of cases are discovered, thanks to routine screening ultrasounds, during pregnancy; the prenatal suspicion is then frequently confirmed at birth by ultrasonography. Depending on the data from the study, the clinician will decide whether to start a sonographic follow-up of the cyst or undertake a second-line imaging study such as an MRI or proceed with surgery. Even if mesenteric and omental cysts can pass as asymptomatic during a whole lifetime, it is also true they may manifest as a life-threatening acute abdomen. The most common symptom, related to complications of the cyst, is abdominal pain; this can be secondary to intestinal obstruction with or without volvulus. In the first case, compression of adjacent bowel will cause abdominal distension, vomiting and constipation; if a volvulus occurs, besides the abovementioned symptoms, bloody stool, bowel perforation due to necrosis and a rapid decay of general clinical conditions will progressively take place. Abdominal pain can also set in with no obstruction or volvulus. In these cases, pain is due to torsion, rupture of the cyst or the quick increase of cystic dimension for intracystic bleeding. These conditions rarely occur following an abdominal trauma (the so-called detector trauma). Other extremely rare complications reported in literature are infection of the cyst or anaemia from intracystic bleeding. The cyst can be so enormous to give an abdominal distension (with no obstruction); sometimes the mass can simulate ascites. An older patient can even perceive the presence of

an abdominal mass even with no pain associated; in these cases, the mass can also be palpated by the patient or by a physician during an examination; when palpable the mass is usually movable in the abdomen [3, 4].

21.3 Diagnosis

As said in the previous paragraph, the cysts can be found as an incidental finding in an ultrasound. Nowadays it is very common to detect these cysts during routine prenatal screening ultrasounds. In the prenatal period, it is very difficult to distinguish the nature of these cysts, and therefore a differential diagnosis will have to be undertaken in the postnatal phase: ovarian cysts including cystic teratomas, intestinal duplications, dilated bowel for other types of intestinal obstructions (intestinal atresia, for instance) and huge hydronephrosis. Before describing the different contributions that imaging studies can give when dealing with a prenatally suspected abdominal cyst, we want to express our conviction that a precise preoperative diagnosis is not generally possible neither actually necessary. Any abdominal cyst with a diameter superior to 5 cm, independently of its origin or anatomic attachment, must be explored for its associated risk of complications, being an intestinal volvulus or an ovarian torsion in the worst hypothesis. In this case performing an MRI in a newborn in order to have a better anatomic definition would only mean giving an extra general anaesthesia for something that will have to be surgically explored anyway. Different is the case of a cyst <5 cm or in case of older children. We suggest anyways dosing, in the preoperative assessment, oncologic markers for ovarian tumours in the unlikely event of finding a cystic ovarian teratoma. This is done only for post-operative follow-up purposes. Abdominal ultrasonography is the first-line imaging study in these cases: it shows the cystic nature of the lesion and gives information on dimension (Fig 21.1). Contents can be anechoic or hypoechoic. Cysts can present hyperechoic material in the inside; this aspect is probably determined by haemorrhage and/or infection residuals and cyst debris. Ultrasounds can also help determine if the mass is actually movable or not in the abdomen, considering, for differential diagnosis, movable cysts are more likely to be mesenteric and not movable when of ovarian origin. The differentiation between intestinal duplication cysts and mesenteric cysts may be problematic because both are often intimately attached to the normal bowel wall. The former share a common blood supply and muscular layer with the adjacent bowel and have a well-defined mucosal layer that mesothelial or simple enteric cysts lack. Therefore, sonographically intestinal duplications are anechoic with a thick wall composed of multiple layers, resembling a normal bowel wall. While lymphangiomas appear as cystic and multiseptated masses with lobules, enteric and mesothelial cysts only occasionally are seen with septations. A plain abdominal radiograph shows a gasless, homogeneous, water-dense mass that displaces bowel loops around it. Omental cysts may compress bowel loops posteriorly, whereas mesenteric cysts may be surrounded by bowel loops. Fine calcifications can sometimes be seen. MRI and CT add minimal additional information, although they can reveal that a cyst is not arising from another organ such as the kidney, pancreas or ovary. They can also give more detailed information of the cystic wall and contents. For instance if this imaging reveals a cystic mass with a thick wall that enhances after contrast material is injected, we are more likely dealing with an intestinal duplication and not a simple lymphatic, enteric or mesothelial cyst where the wall is not really discernible. Differences can also be noted with regard to the cystic content [2, 5] (Fig. 21.2).

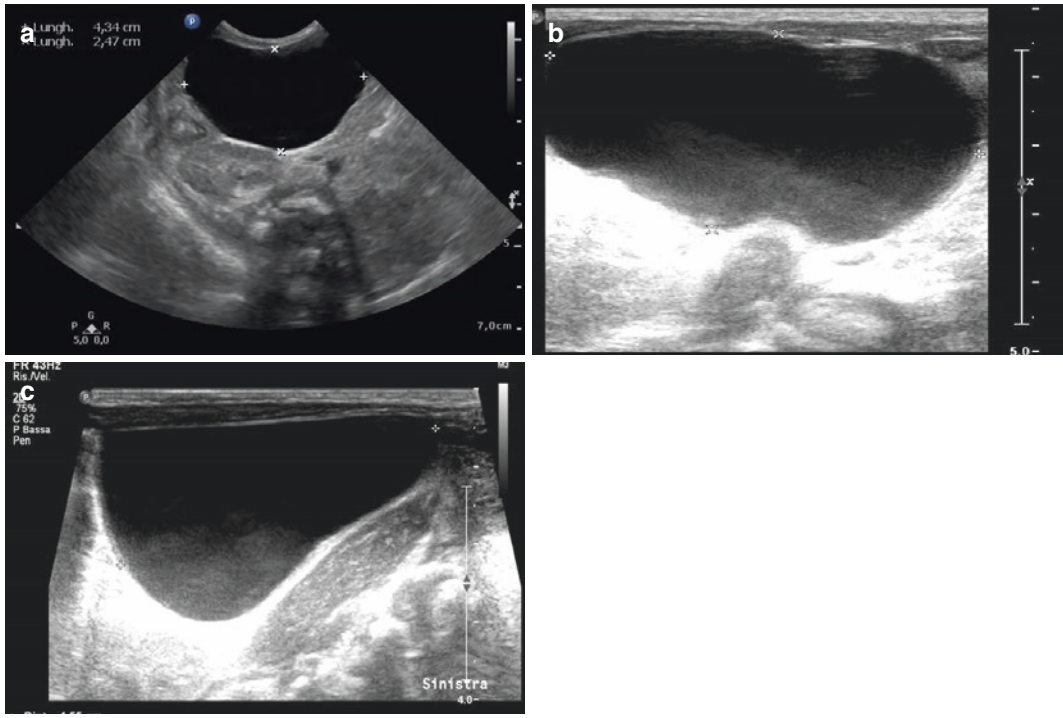

Fig. 21.1 Abdominal ultrasounds in a newborn with prenatal suspicion of intraabdominal cyst. Postnatal ultrasound confirmed the presence of the 4.6 cm cyst, anechoic, uniloculated, thin-walled, in the right abdomen (**a**). One week later, the cyst moved to the left; furthermore, some declivous sedimentations could be noticed (**b**, **c**). Surgical exploration later demonstrated a simple enteric cyst of the mesentery

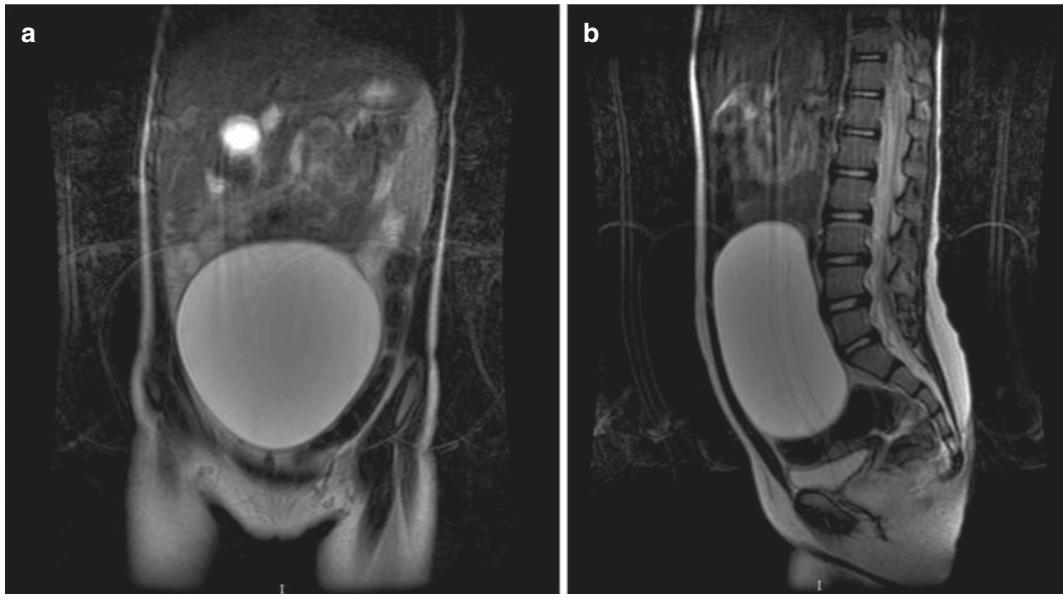

Fig. 21.2 MRI showing fluid-filled and thin-walled enormous mass (12 × 13 × 6.5 cm) extending from the hypogastrium to the pelvis (**a**, **b**, **c**); a mesenteric cyst was suspected

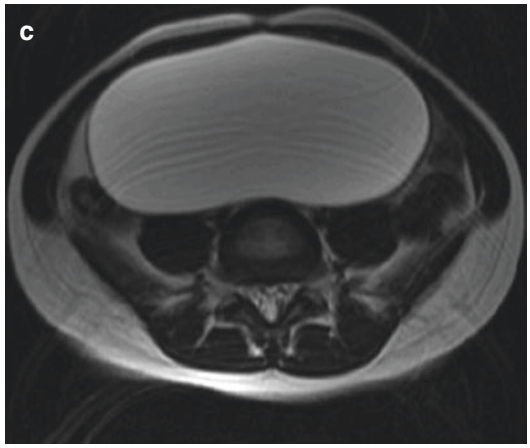

Fig. 21.2 (Continued)

21.4 Treatment

With increasing awareness of the potentiality these cysts have in leading to severe complications such as bowel obstruction or, worse, intestinal volvulus with loss of vital intestine, once the suspicion of a mesenteric cyst is confirmed postnatally, indication for surgical intervention has to be given. It is not possible to determine the exact timing, but it is our opinion to proceed as soon as possible during early infancy. They can be removed with no bowel resection by shelling them out from between the two leaves of the mesentery (enucleation). Any resulting mesenteric defect must be closed to prevent an internal hernia. If mesenteric vessels are damaged with impairment of intestinal blood supply, a concomitant bowel resection with a primary end-to-end anastomosis is required. Obviously, this principle does not apply to omental cysts, which can therefore be removed without resecting the adjacent transverse colon or the stomach. All of the above-mentioned surgical procedures can now be performed even in the newborn with a laparoscopy-assisted approach. The cyst can be localized laparoscopically, and the affected mesentery with the intestine is brought out through a small laparotomy or via an extended umbilical incision (Fig. 21.3). Enucleation or resection and anastomosis are then performed with an open approach. Whether to drain the cyst during the laparoscopic phase because the excessive size of the cyst does not allow the passage through the abdominal incision is still debated because the surgeon could be in front of a bowel duplication with possible communication with bowel lumen and eventual spillage of intestinal content in the abdominal cavity. A laparoscopic intracorporeal technique has been described but not in neonatal cases; the small working space and the long duration of pneumoperitoneum are the major limits in newborns for such technique. If enucleation or resection is not feasible, basically due to a retroperitoneal extension of the cyst, an option is partial excision with marsupialization of the remaining cyst into the abdominal cavity. The remaining cystic surface in this case should be sclerosed; different sclerosing agents have been used: 10% glucose solution, electrocautery or tincture of iodine. Recurrence is a possibility; it happens in patients who undergo only partial excision, eventuality that occurs often in cysts located deep from the root of the mesentery to the retroperitoneum [3, 5].

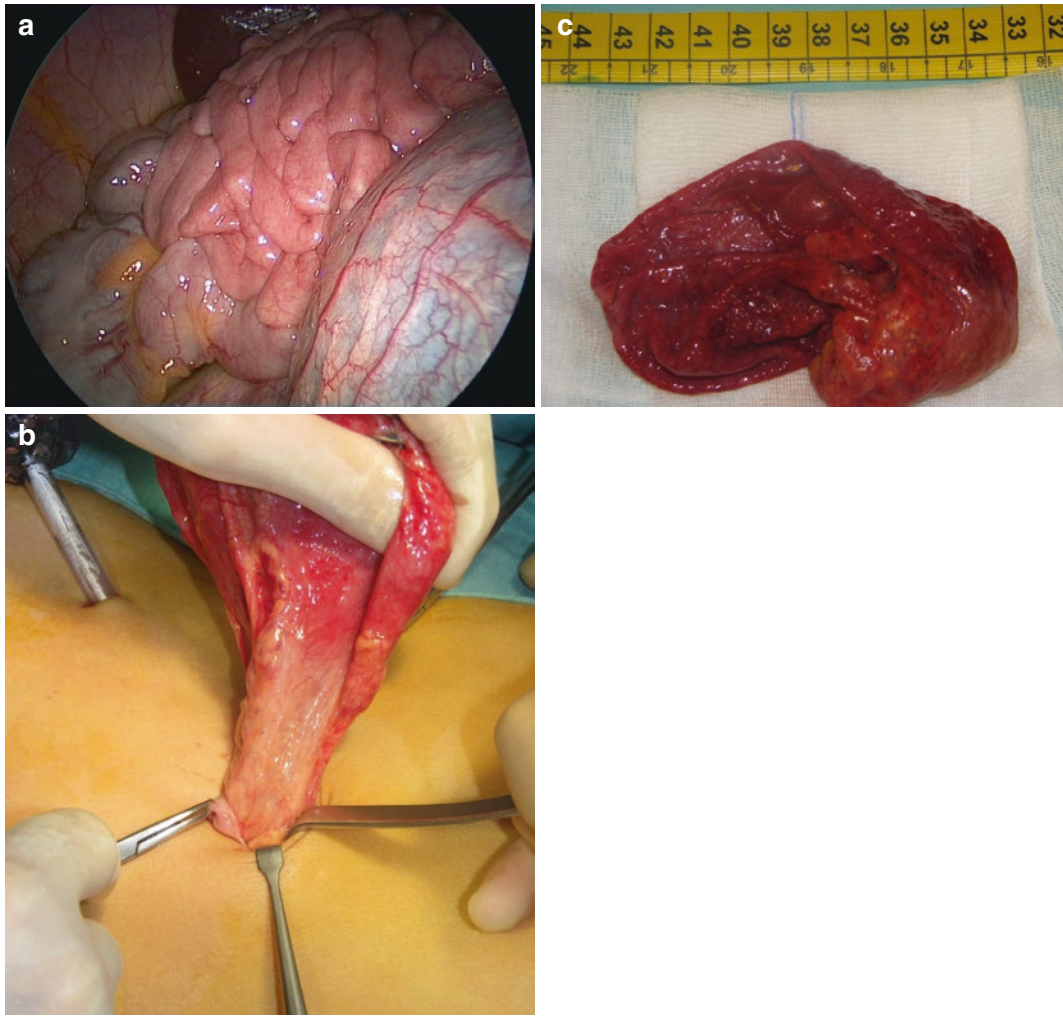

Fig. 21.3 (**a**–**c**). Laparoscopy-assisted transumbilical procedure on the cyst seen in Fig. 21.2. The cyst is seen during laparoscopic exploration (**a**), punctured, drained and then removed through the umbilical access (**b**, **c**)

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22 Surgical Necrotizing Enterocolitis: Early Surgery - The Key to Live Bowel and Quality Life

Adrian Bianchi

22.1 Introduction

The term necrotizing enterocolitis (NEC) has been used to cover diverse neonatal illnesses [1] of altogether different prognosis e.g. spontaneous ileal perforation, such that it has been difficult to accurately ascertain the true incidence, appropriate management, and long-term outcome. Better referred to as surgical necrotizing enterocolitis (SNEC), it is an acquired postnatal condition of considerable mortality and morbidity that affects primarily premature infants. The long-term prognosis for survivors is good, but the quality of life will depend on the complications of prematurity (chronic pulmonary dysplasia, blindness from retinal infiltration, ischaemic brain injury) and *on the absorptive and immunological capabilities of the residual bowel*. Management has been largely determined by Bell's criteria [2, 3] that were developed to stage the progress of the disease (Table 22.1). This essentially conservative approach with surgery figuring at a late stage is associated with 30–50% mortality from sepsis (abscess, peritonitis, perforation) and multiorgan failure, and with a significant risk of functionally damaged and/or short bowel in survivors. Indeed, along with midgut volvulus from malrotation and gastroschisis, SNEC is a major cause of the short bowel state that commits the child to long-term parenteral nutrition, autologous gastrointestinal reconstruction [4], and possible bowel or liver-bowel transplantation.

The extent of the residual functional bowel, so relevant to long-term survival with good quality life, depends not only on the severity of the disease but also on the *timing and nature of surgical interventions as determined by the child's medical carers*. The increasing number of very premature infants requires a dedicated 'specialist neonatal team' that includes at its core a neonatologist, a neonatal surgeon, and a committed anaesthetist for early, better, and co-ordinated management. Bell's Staging (Table 22.1) has been a poor guide for determining the timing of surgery. Most importantly the surgeon should not alter the proven accepted surgical criteria for management of the acute abdomen and should not be deterred by prematurity or the size and weight of the child from early and effective intervention, while the child is still in relatively good condition and before irreversible bowel injury has occurred.

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Table 22.1 NEC staging system

Stage I (suspect)
(a) Any one or more historical factors producing perinatal stress
(b) Systemic manifestations—temperature instability, lethargy, apnoea, bradycardia
(c) Gastrointestinal manifestations—poor feeding, increasing pre-gavage residuals, emesis (may be bilious or test positive for occult blood), mild abdominal distension, and occult blood may be present in stool (no fissures)
(d) Abdominal radiographs show distension with mild ileus
Stage II (definite)
(a) Any one or more historical factors
(b) Above signs and symptoms plus persistent occult or gross gastrointestinal bleeding, marked abdominal distension
(c) Abdominal radiographs show significant intestinal distension with ileus, small bowel separation (oedema in bowel wall or peritoneal fluid), unchanging or persistent 'rigid' bowel loops, pneumatosis intestinalis, and portal vein gas
Stage III (advanced)
(a) Any one or more historical factors
(b) Above signs and symptoms plus deterioration of vital signs, evidence of septic shock, or marked gastrointestinal haemorrhage
(c) Abdominal radiographs may show pneumoperitoneum in addition to others listed in IIc

Source: Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, Brotherton T. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Annals of Surgery 1978; 187(1): 1–7

22.2 Pathophysiology of NEC

Surgical NEC is an acquired postnatal condition affecting primarily premature infants <30 weeks' gestation with immature gut of reduced absorptive and immunological ability, but may affect also 'stressed' babies of greater gestation e.g. intrauterine growth retardation, babies of diabetic mothers, babies with congenital heart disease, and those given indomethacin therapy for closure of a patent ductus arteriosus. The cause of SNEC remains unclear, and it is not the intention of this chapter to discuss the diverse aetiological theories [5–7] but rather to concentrate on aspects of care that are immediately amenable to beneficial change. Although rare in unfed babies and less common in breast-fed infants, there is a significant association with formula-milk feeds, particularly of larger volume and administered at a rapid incremental rate. The natural chymotrypsin curdles the milk protein (casein) which the immature small bowel of the premature baby finds difficult to digest and to progress through the bowel. Curd stasis causes obstruction and eventual mucosal inflammation particularly in the lower ileum, at the ileocaecal valve, and in the right colon leading to reduced peristalsis and progressive small bowel gaseous distension (Fig. 22.1).

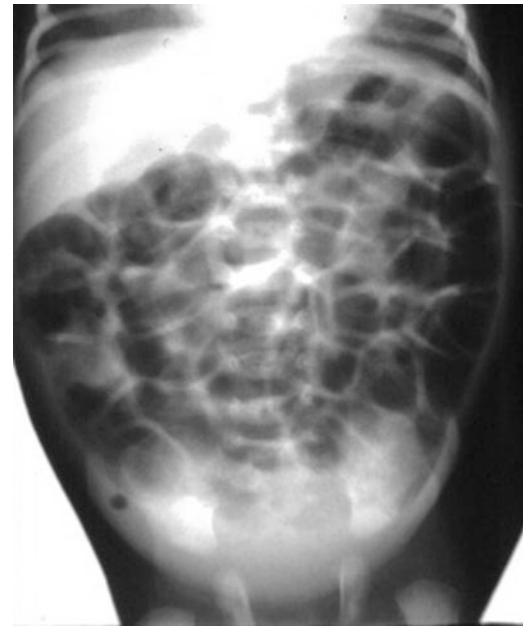

Fig. 22.1 NEC abdominal distension

Inflamed oedematous bowel is tender, is often palpable on abdominal examination, and is identifiable on Doppler ultrasound as a 'ring' hyperperfusion [8] (Fig. 22.2) of thickened often static loops that are typical of Bell Stage I–II [2, 9].

Eventually mucosal necrosis and bacterial infiltration are detectable radiologically and ultrasonologically as intramural (Fig. 22.3a) and intraportal gas (Fig. 22.3b) bubbles (Bell Stage II) [2, 9].

Increasing bowel gas from ingested air and from curd fermentation raises intraluminal pressure that impairs perfusion to the antemesenteric border (Fig. 22.4a) of the tightly distended loops that is detectable as the Y-sign (Fig. 22.4b) on Doppler ultrasound [8–12], causing ischaemic necrosis and eventual perforation.

Early accumulation of intraperitoneal fluid (Fig. 22.5a) and later local or general bowel

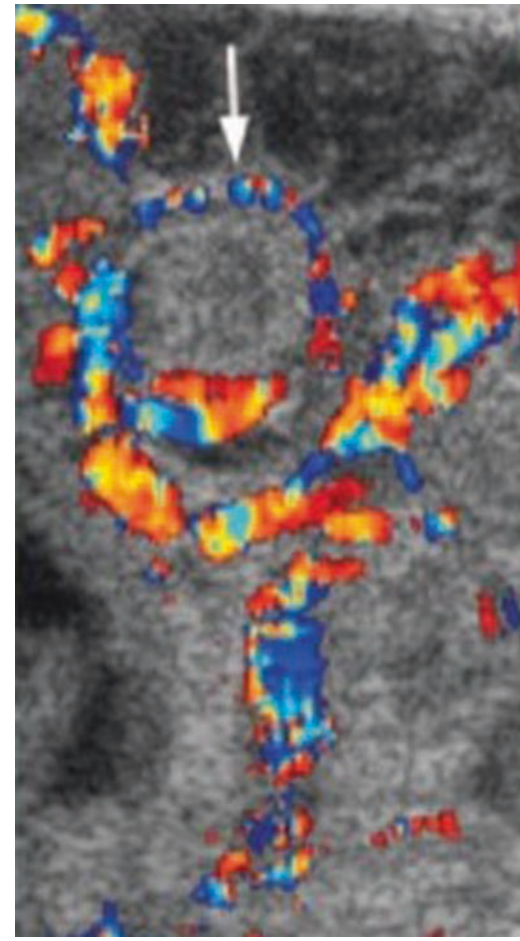

Fig. 22.2 US ring sign of hyperperfusion (Adapted from Epelman et al. [8])

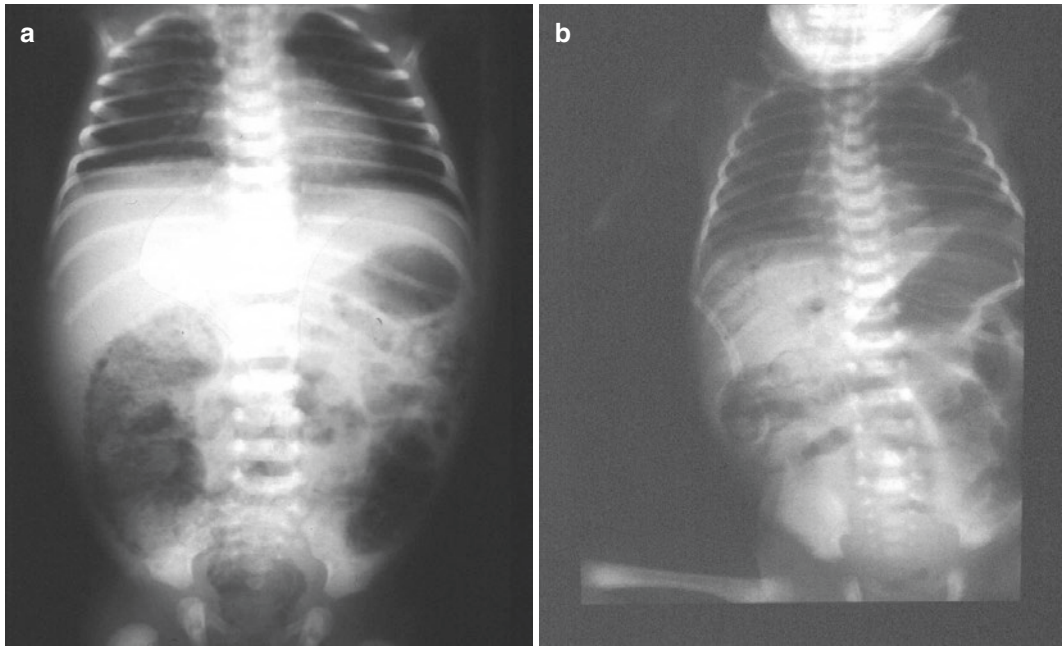

Fig. 22.3 (**a**) NEC intramural gas. (**b**) NEC static loops intraportal gas

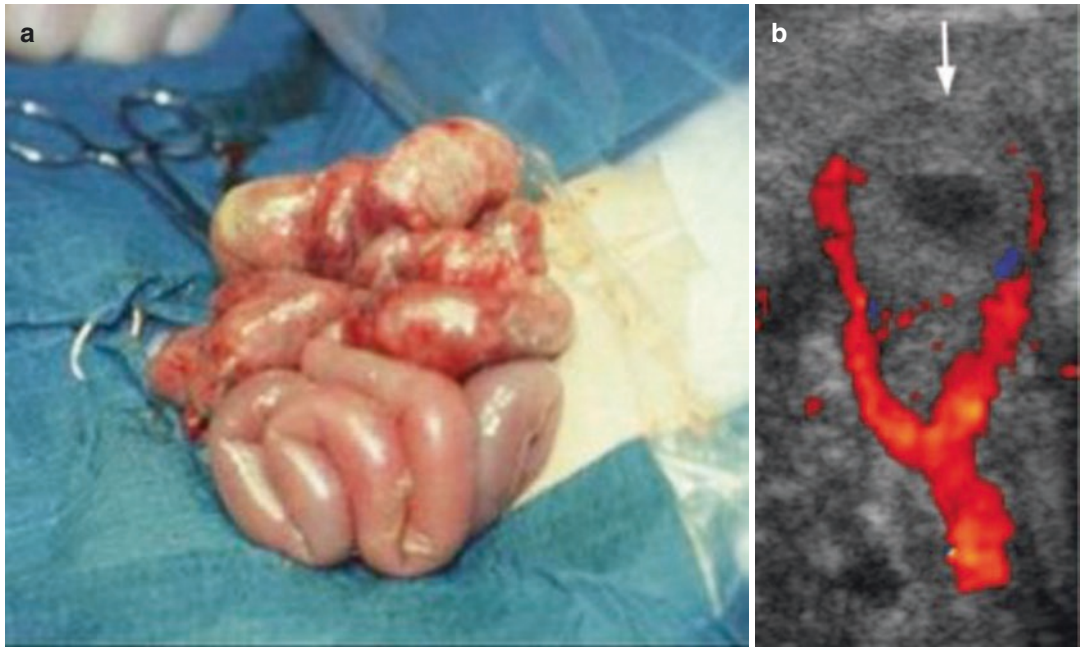

Fig. 22.4 (**a**) Necrotic loops—no perf. (**b**) US Y-sign of absent antemesenteric perfusion (Adapted from Epelman et al. [8])

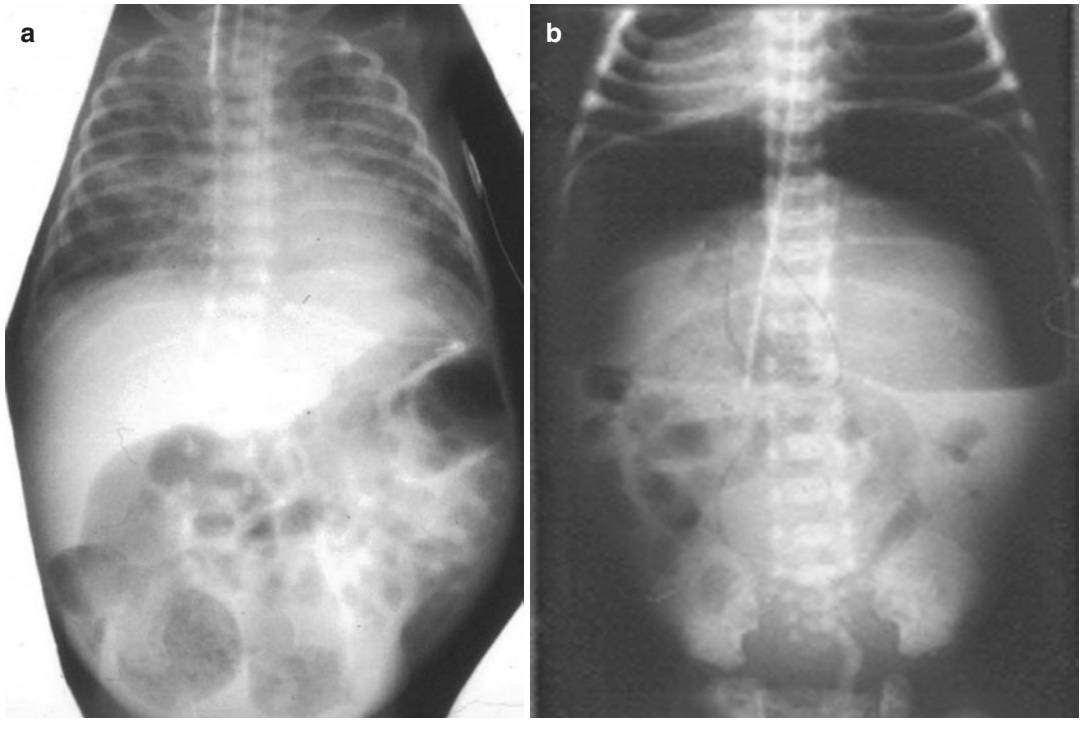

Fig. 22.5 (**a**) NEC fluid - ground-glass appearance. (**b**) NEC perforation with free gas

perforation with collection of free gas and bowel content (Fig. 22.5b) are clear ultrasonologically and on X-ray of the abdomen. Septic intraperitoneal fluid undergoes dialysis with the systemic circulation across the peritoneum and is associated with overwhelming septicaemia.

22.3 The Clinical Picture: Diagnostic Features

The baby, initially in good condition and active, develops non-specific features of ill-health. Carers often report that they are 'unhappy' with the child who is 'not as well as previously' demonstrating lethargy and reduced activity, an unstable temperature, and apnoeic spells (Bell Stage I [2]). Biochemical parameters and sepsis markers may not yet have altered; however the need for respiratory support is a significant deterioration. It is at this earliest stage of alteration in general health and developing abdominal signs that constant joint review by the core specialist neonatal team (neonatologist, neonatal surgeon, committed anaesthetist) is crucial to determining an integrated pre-, intra-, and postoperative management plan designed to optimize the timing and nature of surgery to ensure child survival and *specifically to limit bowel loss*.

A developing metabolic acidosis and a disturbance in the serum electrolyte profile with a reduction in serum sodium levels are of increasing relevance. Some babies will pass foul stools containing mucus and blood that, along with a drop in the platelet count, are ominous prognostic signs (Bell Stage I–II [2]). Abdominal features are initially minimal, and assessment demands expertise from clinicians (neonatologist *and neonatal surgeon*) of major experience. Progressive distension [13] and tenderness to palpation become increasingly evident. Palpable oedematous bowel loops or the presence of an abdominal mass is significant. As SNEC progresses, the child's general condition steadily deteriorates. With fluid accumulation within the peritoneal space, the abdominal X-ray shows a ground-glass appearance with loss of the normal definition of the muscle planes of the abdominal wall (Fig. 22.5a). The constant unaltered presence of gas within a static oedematous 'sentinel loop' (Fig. 22.3b) suggests serious inflammation if not a local perforation. Mucosal inflammation and hyperperfusion are followed by necrosis and bacterial infiltration, with intramural gas bubbles becoming increasingly evident (Fig. 22.3a). Ultrasonological findings of a reduction in bowel wall thickness and reduced perfusion, detectable by Doppler as the Y-sign, affect primarily the antemesenteric aspect of the bowel loops and indicate ischaemia and likely irreversible mucosal and bowel wall necrosis [8–10]. Intraportal gas may become evident within the liver. The child demonstrates all the clinical features of a generalized septicaemia with a significant drop in blood pressure requiring inotrope support of cardiac and renal function. A severely low platelet count from platelet consumption and marrow depression increases the risk of debilitating or fatal intracerebral bleeding. Blood, platelet, and clotting factor transfusions and difficult fluid and electrolyte management are necessary to manage anaemia, coagulation problems, metabolic acidosis, and severely disturbed electrolytes.

Abdominal wall discolouration and cellulitis (Fig. 22.6) and the presence of an abdominal mass, free fluid, and gas within the peritoneal cavity are late features related to intraperitoneal sepsis and perforation and are of poor prognosis for both the bowel and the child. Increasing intra-abdominal pressure with diaphragmatic splinting impairs ventilation even despite the child being paralysed and mechanically ventilated and, together with overwhelming septicaemia and eventual multiorgan failure, significantly compromises survival. Surgery, even at this late stage, may be successful in rescuing the dying child by helping to control sepsis but is usually far too late for salvage of sufficient functional bowel. Indeed, extensive removal of necrotic, autolysing, and irreversibly damaged bowel is unavoidably necessary for survival.

Even following aggressive-but-conservative surgery retaining all potentially viable bowel, surviving children face the prospects of bowel of

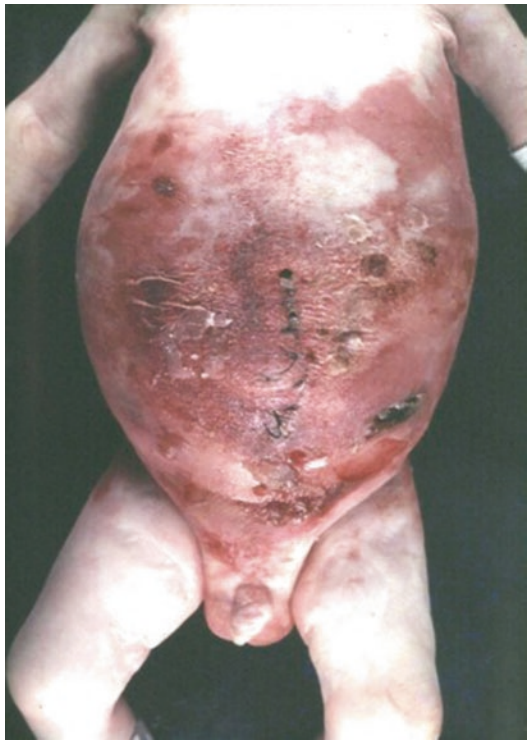

Fig. 22.6 Abdominal wall cellulitis

impaired absorptive and immunological function, of further resection of significant lengths of stenotic bowel (Fig. 22.7) and the short bowel state.

22.4 Management (Table 22.2)

Nutrition, for infants considered to be at risk of SNEC, should be largely provided parenterally with specific emphasis on replacement or limitation of soya-based lipids that contain high liver-toxic plant phytosterols, with omega-3 fish oil. Combinations such as SMOFlipid (Fresenius Kabi, Uppsala, Sweden) containing reduced soya lipids, medium-chain triglycerides, olive oil, and fish oil are also proving acceptable. Enteral feeding is commenced at minimal volumes and at a very slow incremental rate with low residue feeds that are preferably immunologically competent (derived from fresh breast milk). During the first days, freshly expressed maternal colostrum containing high levels of IgM is particularly valuable. Subsequently, low residue feeds supplemented with the whey after removal of the milk protein curds from chymotrypsin-treated *freshly expressed breast milk* may be the only means of providing a degree of immunological support as well as nutrition.

Any deterioration in the general condition of an 'at-risk' child, however non-specific, and particularly when associated with abdominal tenderness and distension, should alert the carers and the specialist neonatal team to the likelihood of SNEC. Enteral feeding is stopped, and free gastric drainage with frequent aspiration commenced through a large 8F naso-/oro-gastric tube, to avoid further small bowel distension from swallowed air. Positive pressure nasopharyngeal support is contraindicated since swallowed gas further distends the stomach and small bowel, and respiratory support should only be offered endotracheally. At this early stage, a colonic washout is usefully undertaken with a dilute 4% chlorhexidine gluconate solution (Hibiscrub, MediSupplies Ltd) and an equal volume of air, delivered through an 8F feeding tube that is slowly advanced through the anus. Concomitant abdominal massage along the course of the colon helps to clean out the whole colon through to the caecum. There should be no fear of perforation of live colon, and any suspicion of perforation is indicative of necrotic bowel for which urgent abdominal drainage and exploration are required. Routine sepsis investigations are undertaken, and conservative management commenced with blood and other factors (red cells, platelets, coagulation factors) and initially with broad-spectrum antibiotics, later guided by bacteriological evidence from stool and blood cultures.

At this early stage, abdominal radiology may be less helpful, showing only a generalized distension of bowel loops (Fig. 22.1) that on Bell's criteria is not considered to be a definitive sign of SNEC. Thus, it is *relevant to frequently serially assess perfusion in dilated bowel loops with Doppler ultrasound* [8]. Reduced or absent peristalsis, thickening of the bowel wall from oedema, and hyperperfusion, noted as a 'ring' pattern on Doppler sonography, indicate inflammation in bowel that is potentially still viable [8]. These findings, together with clinical deterioration and

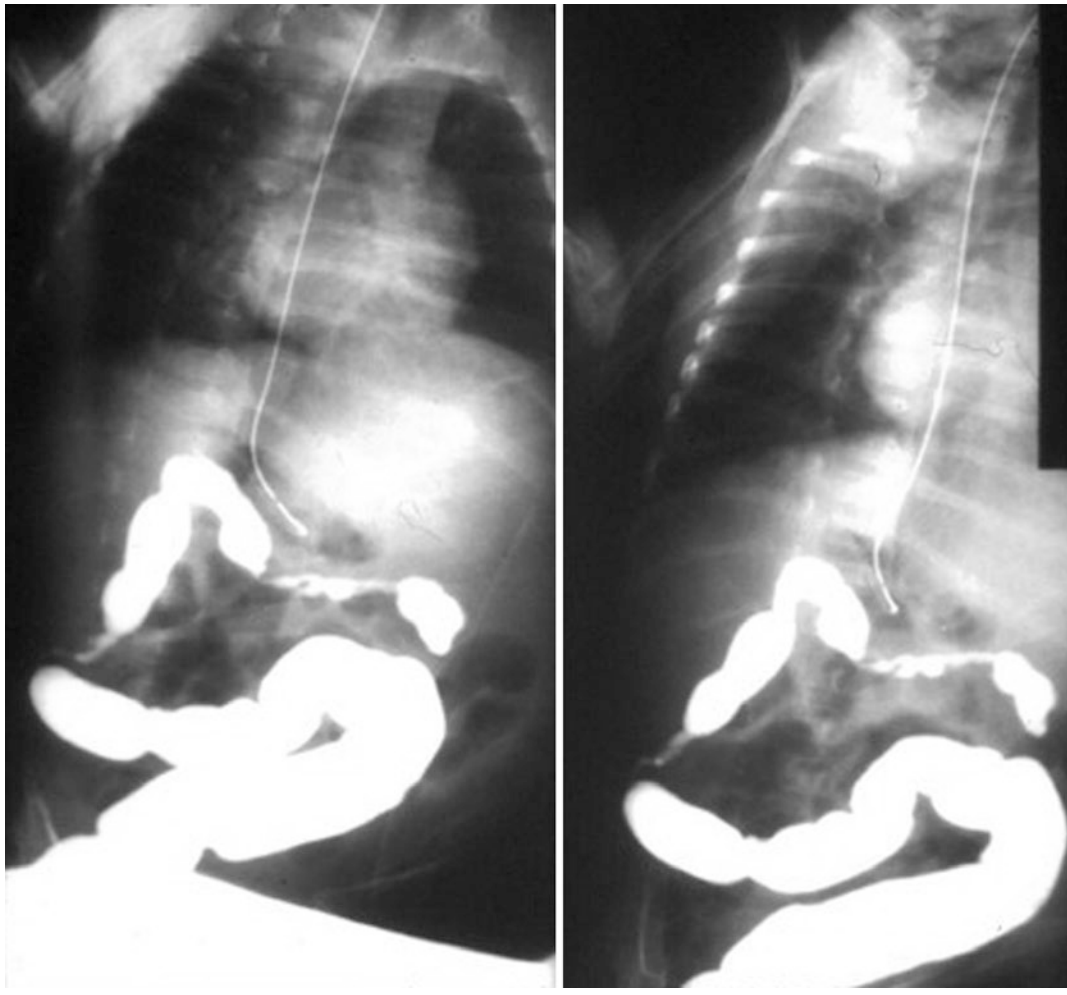

Fig. 22.7 Multiple stenoses and damaged bowel in a survivor

Table 22.2 SNEC management

Early SNEC
Large 8F nasogastric tube on free drainage and 15 min aspiration
Respiratory support only endotracheally
Blood products, fluids, and electrolytes
Antibiotics—broad spectrum, but later guided by blood and stool cultures
Ultrasound monitoring of bowel loops for perfusion —Ring and Y-sign
Progressive disease
Paralysis and ventilation
Inotropes
Large tube drain to peritoneal space —14F Argyle intercostal drain
Peritoneal wash and dialysis —1.36% normal sodium with 4 mmol/L KCL

features of an 'acute abdomen' (tenderness, palpable loops) in a child who is still in reasonable condition, *are definite indications for urgent early laparotomy for control of sepsis, and of particular relevance to limit the extent of bowel injury by deflating the distended bowel and improving loop perfusion*. There is nothing to be gained, and indeed it is contraindicated to wait for the appearance of intramural gas bubbles, localized or free gas in the peritoneal space, reduced bowel wall thickness, and poor or absent perfusion of the antemesenteric surface of the dilated loops, detectable as the '"Y" pattern' [8] on Doppler sonography, as these are late features indicative of ischaemia, mucosal loss, and severely damaged

bowel. Early rather than later surgery is indicated, and it is inappropriate to await these late 'definite indications for surgery'.

A tight abdomen from maximal fluid and gaseous distension that indeed cannot distend further, and paralysis for ventilatory support, make clinical abdominal assessment much more difficult and uncertain and tend to delay surgery! Other less specific features suggesting deterioration acquire greater relevance. These include unstable temperature, poor respiratory parameters, occult or manifest blood in the stools, disturbed electrolytes, metabolic acidosis, reducing platelet count, and the need for inotropes to support the circulation and maintain renal function. Such major deterioration and evidence of severe sepsis are very late stages in SNEC and are indications of a major intra-abdominal catastrophe requiring immediate surgical intervention for survival. It is unfortunately likely that the opportunity for bowel-sparing surgery will have been missed.

22.5 Indications for Surgical Intervention (Table 22.3)

On suspicion of SNEC and during the initial critical hours of conservative management and monitoring, the child deserves the immediate and constant attention of the specialist neonatal team. Prematurity is incidental, and surgical assessment should follow *the time-proven criteria for any patient presenting with deteriorating general health and a suspicion of intra-abdominal inflammation*.

Table 22.3 Indications for surgery

Early:	Tender distending abdomen
	Palpable bowel loops
	Foul, bloody stools
	Deteriorating general condition and biochemical parameters
	Doppler US 'Ring' sign — hyperperfusion of thickened bowel
	Increasing intraperitoneal fluid
Late:	Doppler US 'Y'-sign — absent perfusion
	Reduced bowel wall thickness and absent peristalsis
	Intramural gas bubbles
	Intraperitoneal fluid, especially with echogenic material
	Intra-abdominal mass
	Local or free gas in peritoneal space

Drainage: An unwell child with a tender abdomen, palpable bowel loops, and increasing abdominal distension from intraperitoneal fluid and gaseous loop distension should be regarded as suffering from SNEC, and is an indication for early surgical intervention while the child is still in an acceptable general condition. Radiological and ultrasound evidence of thickened bowel loops showing increased perfusion, and free fluid with hyperechoic debris within the peritoneal space (Fig. 22.5a), are strong indications for abdominal drainage and peritoneal lavage, to enhance the child's general condition in preparation for a laparotomy. A large bore tube, e.g. 12–16F Argyle intercostal tube drain (Medtronic/Covidien, UK), should be passed through the right iliac fossa along the peritoneal surface of the anterior abdominal wall towards the left hypochondrium (Fig. 22.8). There should be no

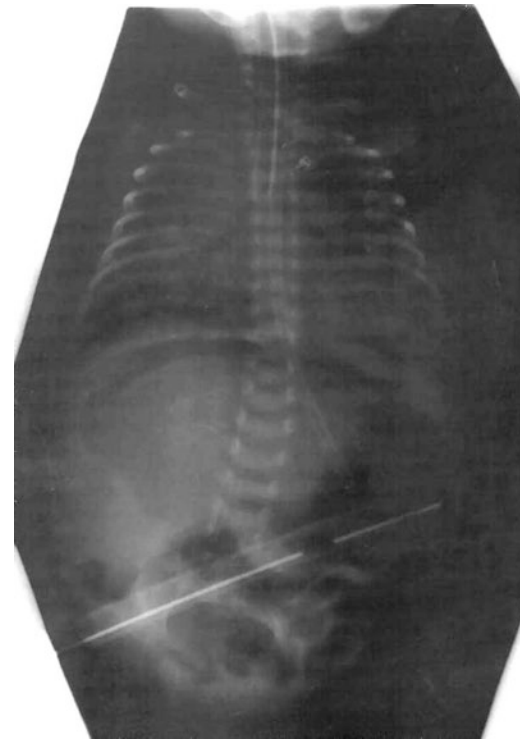

Fig. 22.8 NEC large abdominal drain

concern regarding possible loop perforation during drain insertion since laparotomy is likely to follow, and any iatrogenic perforation can be managed. Indeed, the reduction in intraluminal pressure following loop perforation can act favourably to enhance bowel salvage by reducing intraluminal pressure and allowing better loop perfusion. Peritoneal lavage is undertaken with a warm isotonic 1.36% normal sodium (136 mmol/L) solution (Baxter, UK) with added 4 mmol/L of potassium chloride, as is used for peritoneal dialysis. The fluid is infused to a volume that is tolerated without ventilatory or circulatory compromise, the abdomen gently massaged to help with peritoneal cleansing and decompression, and drainage allowed by gravity. The initial cleanout is followed by 20-min washout cycles with the dialysate infused over 5 mins, retained for 10 mins to allow equilibration with the circulation, and drained by gravity over 5 mins. Repeated cycles over a few hours help to improve the child's general condition, circulation, renal function, and electrolyte profile. Laparotomy is considered when the child's condition is maximally improved.

Abdominal Surgery: Even though SNEC is a life-threatening condition, the surgeon should remain conscious of the fact that 'it is the survivor who is interested in an aesthetic abdomen'. It is therefore relevant to consider an aesthetic approach with scars placed appropriately in skin creases when possible. Laparoscopic intervention has become more popular and has a place particularly in early SNEC when abdominal distension is less marked and bowel inflammation is limited and less severe. Peritoneal lavage and drainage, limited loop resection of irretrievably damaged (autolysing, necrotic) bowel, and small bowel deflation with consideration of a stoma, commonly a low ileostomy possibly placed at the umbilical port, form the basis of laparoscopic management.

More extensive disease and difficulties with laparoscopic intervention are stronger indications for open laparotomy that allows extensive peritoneal (subhepatic, subdiaphragmatic, pelvic) cleansing and careful inspection of all the bowel. An aesthetic Pfannenstiel incision, with the occasional addition of a second circumsupraumbilical incision, gives good access to the whole of the small and large bowel. Alternatively, a transverse supraumbilical incision is less aesthetic but practical. Distended loops are exteriorized and an enterotomy performed preferably in the lower ileum or as dictated by the necrotic process. An *intraluminal* bowel washout is undertaken with a mixture of air and 4% chlorhexidine gluconate solution (Hibiscrub, MediSupplies Ltd) diluted in warm 1.36% normal sodium dialysate (Baxter, UK) with added 4 mmol/L KCl, infused through an 8F catheter that is advanced distally towards the caecum until fluid and air exit through the anus, and retrogradely along the small bowel until aspirated from the stomach. Gentle bowel massage and suction ensure thorough cleansing and complete collapse of all the small and large bowel from necrotic material, with evident return of perfusion to live bowel. The enterotomy may be closed or brought out as a double-barrelled stoma, and there is little role for a widely split stoma that will later require an extensive laparotomy for closure. In the event of widespread or more severe disease, only obviously necrotic, irretrievably damaged bowel is resected, with emphasis on preserving all 'questionable' but potentially viable bowel. Several segmental resections and multiple anastomoses may be necessary. It is most important to appreciate that even short lengths of 1–5 cm of viable bowel are worth preserving, since the added total may be sufficient to avoid the short bowel state. The collapsed, better perfused bowel is more easily replaced and the abdomen closed without tension and with adequate drainage, or with a large tube drain if further washout/dialysis is contemplated postoperatively.

The child and stoma are carefully monitored, and further 'housekeeping' laparotomies should be liberally entertained for peritoneal cleansing and for bowel review and management. This is particularly relevant to those with bone marrow depression and a low white cell count who tolerate ongoing sepsis poorly. It is axiomatic at every stage to preserve as much bowel as possible. At this point, the immediate prognosis remains guarded. Even survivors may have sustained sufficient mucosal injury for the residual bowel to

have lost its absorptive and immunological functions, or to require extensive resection because of stenosis(es) (Fig. 22.7) culminating in the short bowel state.

22.6 Discussion

The adage 'prevention is better than cure' is particularly suitable to the premature 'at-risk' child, such that all factors known to increase the possibility of SNEC should be avoided. Nutrition is primarily parenteral, avoiding phytosterol liver toxicity from soya-based lipid solutions and favouring omega-3 fish oils or combinations with reduced soya such as SMOFlipid (Fresenius Kabi, Uppsala, Sweden). During the first days of bowel bacterial colonization, the child and bowel should be assisted immunologically with the mother's fresh colostrum. Small-volume no-residue enteral feeds should be introduced only very gradually and supplemented with immunologically competent expressed *fresh* breast milk or preferably the whey leftover following chymotrypsin coagulation of the breast milk protein. As enteral feeding progresses, great relevance should be given to alterations in the child's general state. Non-specific features such as temperature instability and apnoeic episodes, particularly if associated with abdominal tenderness and progressive distension, should alert the specialist neonatal team to the possibility of early SNEC. In addition to increased clinical review, frequent serial Doppler ultrasound monitoring of bowel motility, bowel wall thickness, and particularly bowel wall perfusion should be instituted. Palpable tender bowel loops, accumulating intraperitoneal fluid, and ultrasound evidence of hyperperfusion are indicative of inflammation of viable bowel and should lead to consideration of early surgery, while the child is in better condition, to drain the peritoneum and to deflate and clean out the bowel lumen *before the onset of severe bowel injury*.

Neonatal anaesthesia and neonatal surgery are now well-developed specialties, and the neonatal surgeon and committed anaesthetist together with the neonatologist form the core of the specialist neonatal team for the early management of the increasing number of very premature babies that are a high-risk cohort for SNEC.

It is worth noting that mortality and morbidity (short bowel state) in SNEC do not relate to the operative intervention, but rather to the *lack of essential surgery at an early enough stage when the bowel is still viable*. The high mortality and morbidity relate to the severity of the illness and the extreme condition of the child when surgery is undertaken, often as a last resort and when all other therapeutic options are failing. Surgical assessment should follow the time honoured and proven criteria for management of any ill patient with a tender 'acute' abdomen and a suspicion of intra-abdominal inflammation. The child's prematurity and size are incidental and should not influence or delay essential surgery. The traditional 'irrefutable indications for surgery' are far too late and, together with Bell's criteria, have been superseded and should no longer be used to determine the timing of operative intervention. Judicious early surgery before major bowel injury is crucial to maximal bowel salvage that avoids the short bowel state, to survival of the child, and to the quality of long-term life. It is time for change, and further prevarication can only lead to unnecessary additional child morbidity and mortality.

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Hirschsprung's Disease

23

Maria Grazia Faticato and Girolamo Mattioli

23.1 Introduction

The initial description of Hirschsprung's disease (HSCR) or the so-called congenital megacolon was attributed in 1691 to Frederik Ruysch, a Dutch anatomist who described a 5-year-old dying from an intestinal obstruction [1]. Similarly, Domenico Battini in Italy, in 1800, described a child affected by congenital megacolon [2].

In 1886 Sir Harald Hirschsprung, a Danish pediatrician, described for the first time two young patients who died of septic shock and turned out to have huge colonic dilatation at postmortem assessment. This was the first clinical description of congenital megacolon or rectosigmoid aganglionosis that was subsequently named Hirschsprung's disease [3]; however, Ehrenpreis first diagnosed the disease in a neonate later, in 1946, and realized that aganglionosis was the cause of congenital megacolon [4]. In 1948 the first successful operation for HSCR was performed by Swenson who understood that the clue of the disease was to resect the spastic and narrowed colon down to the anal canal with preservation of the sphincteric structures [5]. Since then, many other patients have been treated successfully, and a variety of surgical procedures have been described in an attempt to restore normal bowel in HSCR [6–11].

HSCR is a relatively common cause of intestinal obstruction in the newborn and has always been one of the most interesting topics for pediatric surgeons due to its intriguing features and challenging treatment.

23.2 Etiology and Pathogenesis

HSCR is a congenital rare disease which occurs in roughly 1 in 5000 live births; the incidence varies significantly among ethnic groups (e.g., higher in Asian population) [12] with a male to female ratio of roughly 4:1. The male preponderance is less evident in long-segment HRSC, where the male to female ratio is about 1.5–2:1. Recurrence risk to siblings depends on the child sex affected and also on the extent of aganglionosis. However, the risk is substantially higher in siblings of children with total intestinal aganglionosis.

HSCR is a congenital abnormality of the enteric nervous system (isolated neurocristopathy) characterized by distal bowel aganglionosis with variable proximal involvement in both submucosal and myenteric plexus of the hindgut [13]. The ganglion cells derived from the neural crest and coordinate muscular activity balancing the motor effects of the preganglionic cholinergic fibers and inhibitory influence of postganglionic adrenergic fibers. The disease is a consequence of

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premature arrest of craniocaudal migration of neural crest cells in the hindgut during 5th–12th gestational weeks.

The earlier the arrest of cells migration, the longer will be the aganglionosis segment. HSCR can be classified based on the length of the aganglionosis into four subgroups:

- Rectosigmoid: the aganglionic segment does not extend beyond the upper sigmoid (80%).
- Long-segment: aganglionosis extends to the splenic flexure or transverse colon (10%).
- Total colonic aganglionosis: the aganglionic segment extends to the colon and a short segment of terminal ileum (10%).
- Total intestinal aganglionosis: the absence of ganglion cells from duodenum to the rectum (extremely rare form of HSCR) [14].

A hypothesis to explain the obstruction caused by ganglionated dilated bowel is the role of the enteric nervous system (ENS), which is essential for normal propulsive intestinal motility. ENS is the intrinsic innervation of the bowel and named "gut mini brain"; ENS coordinates movements, immune functions, and secretion of the gut. ENS is independent and functioning in the absence of input from the brain or spinal cord and can mediate reflexes, even when it is isolated from the central nervous system. It is important to emphasize that the aganglionic bowel in HSCR is not denerved; in fact many authors suggested that aganglionic portion may be hyperinnervated by catecholaminergic and cholinergic nerve fibers [15, 16]. What is therefore essential for the mediation of reflexes are the cell bodies of ENS, not nerve fibers. There are also recent studies which suggest that the ganglionic bowel in patients with HSCR has abnormalities in innervation [17–22].

The classic pathological feature in HSCR is dilation and hypertrophy of the proximal colon with abrupt or gradual transition to normal or narrow distal bowel. Although the degree of dilation and hypertrophy increases with age, the cone-shaped transitional zone from dilated to narrow bowel is usually evident in the newborn.

HSCR is a complex genetic disease, and several genes have been identified as involved in the development of the enteric nervous system: in 1994, mutations affecting the RET proto-oncogene on chromosome 10q11.2 were identified in HSCR patients; this gene is also involved in different diseases such as multiple endocrine neoplasia types 2A and 2B and sporadic and familial medullary thyroid carcinoma. These mutations are detected in up to 50% of familiar and in 10–15% of sporadic cases [23–27]. A number of minor HSCR susceptibility genes have been identified to date, namely, GDNF, EDN3, EDNRB, NRTN, ECE1, PHOX2B, SOX10, and ZFHX1B.

The involvement of heterogeneous genetic pathways and pluripotent cell lineage explains why HSCR disease can be associated to malformations basically involving all organs and systems.

RET is crucial for the embryologic development also of other organs, including the kidneys and urinary tract [28], and this could explain why Hirschsprung's disease is also associated with a number of syndromes or diseases: Waardenburg-Shah syndrome, congenital central hypoventilation syndrome (Ondine syndrome), MEN 2B, Goldberg-Shprintzen syndrome, Smith-Lemli-Opitz syndrome, neurofibromatosis, neuroblastoma, pheochromocytoma, and a variety of other congenital anomalies.

23.3 Diagnosis

The diagnosis of HSCR is usually based on clinical aspects, radiological evaluation, and in particular on histological examination, histological and immuno-histochemical examination of the rectal wall biopsy specimens.

23.3.1 Clinical Aspects

The usual presentation of neonate affected by HSCR is an intestinal obstruction characterized by abdominal distension, bilious vomiting, and feeding intolerance suggestive of distal intestinal

obstruction during the first few days of life. Delayed passage of meconium beyond the first 24 h is characteristic, but it is evident only in approximately 64% of children with HSCR [29]. In many cases of neonates with abdominal distention, a rectal examination or rectal irrigation causes passage of meconium or may demonstrate a tight anal sphincter and explosive discharge of stool and gas [30, 31].

Approximately 10–25% of neonates with HSCR present with fever, abdominal distention, and diarrhea due to Hirschsprung-associated enterocolitis (HAEC), a serious complication which can basically occur from birth to adulthood, regardless of the length of aganglionosis. HAEC is an inflammatory colitis which can lead to bacterial translocation, sepsis, and death.

Though great advancements in HSCR treatment have been made in the past 20 years, due to early diagnosis, rectal decompression and appropriate vigorous resuscitation and antibiotic therapy, HAEC pathophysiology is largely unknown, and predisposing factors as well as specific prevention strategies have not been determined yet. Various hypotheses regarding the etiology have been postulated. Based on experimental and clinical studies, several contributory factors have been identified that may help to explain its development.

HAEC can occur either preoperatively or after radical surgery. Owing to improved and prompt diagnosis, the incidence of preoperative HAEC (ranging between 6 and 26% of cases) has decreased over the past decades [32, 33]. Also mortality rate has markedly decreased, thanks to the advancements in its recognition and prompt management. HAEC occurs postoperatively in between 5 and 42% of patients [33]. The risk of postoperative HAEC is significantly increased by mechanical factors related to anastomotic complications and intestinal obstruction [34]; other factors which may have an influence on postoperative HAEC is a previous (preoperative) episode of HAEC or associated anomalies such as Trisomy 21. Mortality rate decreased to nearly 10 to 0% though the average mortality rate in the last 20 years is around 3% [35]. The pathophysiology of HAEC remains poorly understood. HAEC represents a clinical entity determined by a combination of various dysfunctions and/or disruptions of intestinal homeostasis. The assessment of the histological abnormalities observed in the gut of patients suffering from HAEC has provided understanding regarding the pathogenesis of the disease. From a histological point of view, HAEC is characterized by the presence of cryptitis, with a huge inflammation and neutrophilic infiltration of the crypts. These findings have been described in both ganglionated and aganglionated bowel, suggesting a mechanism that goes beyond the simple absence of ganglia. One of the theories of pathogenesis of HAEC is partial obstruction, due to the aganglionosis itself or surgical issues that determine a persistent state of fecal and bacterial stasis. This lack of bowel emptying leads to bacterial overgrowth, bowel dilatation, bowel wall stretching, impaired blood flow to the mucosa, and subsequent increased permeability with bacterial translocation. The abnormal development of the enteric nervous system plays a pivotal role in the pathogenesis of HAEC. In fact, the ENS is of utmost importance in gut homeostasis and commensal microflora with a complex neuroimmune modulation effect. When ENS is compromised, the integrity of epithelial barrier is at risk; the neuroimmune dysfunction may thus lead to the propagation of the inflammatory vicious circle of HAEC.

Abnormalities in the intestinal microbiote have been also implicated in the development of HAEC [36–39]. *Clostridium difficile* and *Rotavirus* have been frequently detected in patients with HAEC, even if no specific organism has been found to consistently cause HAEC. In particular, a cytopathic toxin of *Clostridium difficile* has been found in the stools of a consistently high percentage of patients with HAEC. Although this toxin has been detected in patients with severe clinical manifestations of HAEC, the majority of healthy neonates and infants younger than 1 year of age carry *Clostridium difficile* in their stools. However, the relationship between Clostridium species and the development of HAEC remains controversial, but

this aspect suggests that the toxin itself is not enough to trigger an HAEC episode [39]. The knowledge of microflora before, during, and after and HAEC episode may help in establishing preventive and therapeutic strategies. Metagenomics studies have amply demonstrated the existence of an alteration and a predisposition microflora in patients with recurrent HAEC as well as the existence of similar protection microenvironments. These studies suggested that the occurrence and recurrence of enterocolitis may be associated with a specific distribution of intestinal flora, which is influenced by the use of antibiotics. The factors described above may create a dysfunctional environment in the "acceptable" gut microbiome, with a decreased colonization of bifidobacteria and lactobacilli, a probiotic organism that maintains a microbial equilibrium. Disruption of these mutually beneficial relationships could result in HAEC. However, the mechanism is still uncertain [40, 41].

The genetic of HSCR is complex, and it is possible that a genetic predisposition to HAEC may exist. Many investigators have identified certain *predisposing factors* associated with the development of HAEC:

- *Age at presentation*: early symptoms onset seems to correlate with HAEC severity and susceptibility.
- *Associated anomalies and syndromes*: Down syndrome, central nervous system anomalies, and congenital cardiac malformations have been considered strong risk factors by many authors.
- *Postoperative issues*: all complications or surgical issues leading to bowel obstruction or impaired bowel emptying increase the likelihood of HAEC development.
- *Personal history* (*previous HAEC episodes*): patients who previously developed HAEC are at higher risk of recurrence in a sort of predisposition/susceptibility.
- *Extent of aganglionosis*: patients with ultra-long HSCR (i.e., total colonic aganglionosis) have a higher likelihood of developing HAEC both preoperatively and postoperatively with an overall incidence approaching 50% [33].

The most reliable clinical grading system developed for HAEC is from Elhalaby that stratified HAEC severity into three major categories [33]:

- *Grade I*: mild explosive diarrhea, mild to moderate abdominal distension, and no significant systemic manifestations
- *Grade II*: moderately explosive diarrhea and moderate to severe abdominal distension associated with mild to moderate systemic manifestations (e.g., fever and tachycardia)
- *Grade III*: explosive diarrhea, marked abdominal distension, and shock or impending shock

The initial symptoms of HAEC may be indistinguishable from acquired infective gastroenteritis. Nonetheless, as HAEC can progress rapidly and even result in death, most pediatric surgeons will treat all patients regardless of univocal HAEC diagnosis, in order to avoid delayed treatment or misdiagnosis.

Conditions that can mimic HSCR in the neonatal period include cystic fibrosis, meconium plug syndrome, small left colon syndrome, hindgut atresia, anorectal malformations, ENS immaturity of the preterm, hypothyroidism, and chronic intestinal pseudo-obstruction [31, 42]. Hirschsprung's disease is associated with a variety of other congenital abnormalities like malrotation, genitourinary anomalies, ocular disorders, congenital heart disease, limb abnormalities, cleft lip and palate, hearing loss, mental retardation, and dysmorphic features. These conditions should increase suspect diagnostic. Other causes of intestinal neonatal occlusion should be considered, such as intestinal atresia, meconium ileus, meconium plug syndrome, and other less common conditions.

23.3.2 Rectal Biopsy

The gold standard for the diagnosis of HSCR is rectal suction biopsies (RSB) [43, 44] (Fig. 23.1). The development of histochemical and immunohistochemical staining techniques using rectal suction biopsies for the diagnosis of HSCR rep-

Fig. 23.1 Solo-rectal biopsy tool [44]

resents a considerable advance in the investigation of this disease, particularly in the newborn.

RSB is a safe and painless procedure that can be carried out at the bedside without the use of general anesthesia with an incidence of complications (bleeding, perforation) lower than 1% [44–46]. RSB is the standard method for collection rectal tissues; however, it often results in smaller tissue specimens compared with full-thickness biopsy; though larger tissue specimens may be obtained, full-thickness biopsy requires general anesthesia.

Because there is a usual paucity of ganglion cells in the area 0.5–1 cm above the pectinate line, the first biopsy should be taken at least 1 to 1.5–2 cm above it and should contain enough submucosa tissue that properly assess the ENS.

Ideally, an adequate biopsy is 3–4 mm in diameter and 1–2 mm deep with a minimum of a third of the biopsy represented by submucosa. Two or three adequate specimens all containing submucosa area are typically collected to enable the pathologist making a confident diagnosis.

Identification of ganglion cells excludes the diagnosis of HSCR. Lack of submucosal ganglion cells, particularly when accompanied with hypertrophic submucosal nerves and/or an abnormal acetylcholinesterase-staining pattern, is sufficient evidence to establish the diagnosis of HSCR. In aganglionic rectum, the density and thicknesses of AChE-positive nerves in the muscularis mucosa and typically also in the lamina propria are increased [47].

The diagnostic accuracy of RSB is close to 100% after 1 month of age but must be taken with care in the newborn or preterm who can only partially express all diagnostic features. Usually the rectal suction biopsy in a preterm is not recommended because first of all the ganglion cells should be difficult to detect for the pathologist due to their intrinsic immaturity and also because the pediatric surgeon could not obtain enough tissue to allow the diagnose without increasing the complications in a small baby. So, it is better to decompress the distal colon with multiple and daily irrigations and performed the diagnostic procedure when the child is closer to term. The rectal biopsy shows the absence of ganglion cells, but in many cases there are no hypertrophic nerves or abnormalities of acetylcholinesterase staining (long segment).

Worldwide, two approaches are currently used for the specimen evaluation: (1) analysis of hematoxylin eosin-stained paraffin sections with or without frozen sections stained for acetylcholinesterase (AChE)-enzyme histochemistry or (2) evaluation of frozen sections stained enzyme histochemically for neuronal markers including that to AChE.

Alternatively a single or multiple snap-frozen biopsies can be cut for hematoxylin eosin-stained frozen sections and AChE preparations. After completion of these, the remainder of the biopsy can be thawed, fixed in formalin, and processed into paraffin sections.

A potential alternative to the use of AChE is the Calretinin, an immunohistochemical marker. Calretinin is present normally in the perikarya and nerve processes of a subset of enteric ganglion cells, including small nerves in the superficial submucosa and muscularis propria. Immunoreactivity in the latter sites is lost in the aganglionic segment of HSCR.

Other types of techniques include alpha-naftylesterase, NADPH-diaphorase, succinic and lactic dehydrogenases, and nitric oxide synthase. However, AChE histochemistry is the most widely employed technique and has a very high reported accuracy rate in the detection of HRSC (greater than 99%) in laboratories with significant experience.

23.3.3 Radiological Evaluation

For the neonate with a strong suspect of HSCR, a plain abdominal radiograph may show a dilated small bowel or proximal colon and fluid levels. Subsequently, the first step in the radiological evaluation diagnostic pathway is contrast enema. This exam may demonstrate a transition zone or change in caliber, created by distention of the normally innervated bowel proximal to the narrowed and functionally obstructed aganglionic segment (Fig. 23.2). The transition zone is commonly a common absence in neonates (approximately 10%) though it may still be present due to a short aganglionic segment and indefinitely in patients with total colonic disease. However, the rectal transition zone is the most evident in the lateral radiologic view. Other findings on the contrast enema that are suggestive of Hirschsprung disease include a reversed rectosigmoid index and retention of contrast in the colon on a 24-h postevacuation film.

In the presence of enterocolitis complicating HSCR, contrast enema may demonstrate spasm and, in occasional cases, mucosal edema, and ulceration. A plain abdominal radiograph can show, in HAEC patient, the typical intestinal "cutoff sign" in the rectosigmoid colon with absent distal air, dilated loops of bowel, air fluid levels, and even free abdominal air in case of perforation.

In the presence of enterocolitis complicating HRSC, contrast enema may demonstrate spasm and in occasional cases mucosal edema, and ulceration. A plain abdominal radiograph can show, in HAEC patient, the typical intestinal "cutoff sign" in the rectosigmoid colon with absent distal air, dilated loops of bowel, air fluid levels, and even free abdominal air in case of perforation, indicating toxic megacolon. In some cases ultra-

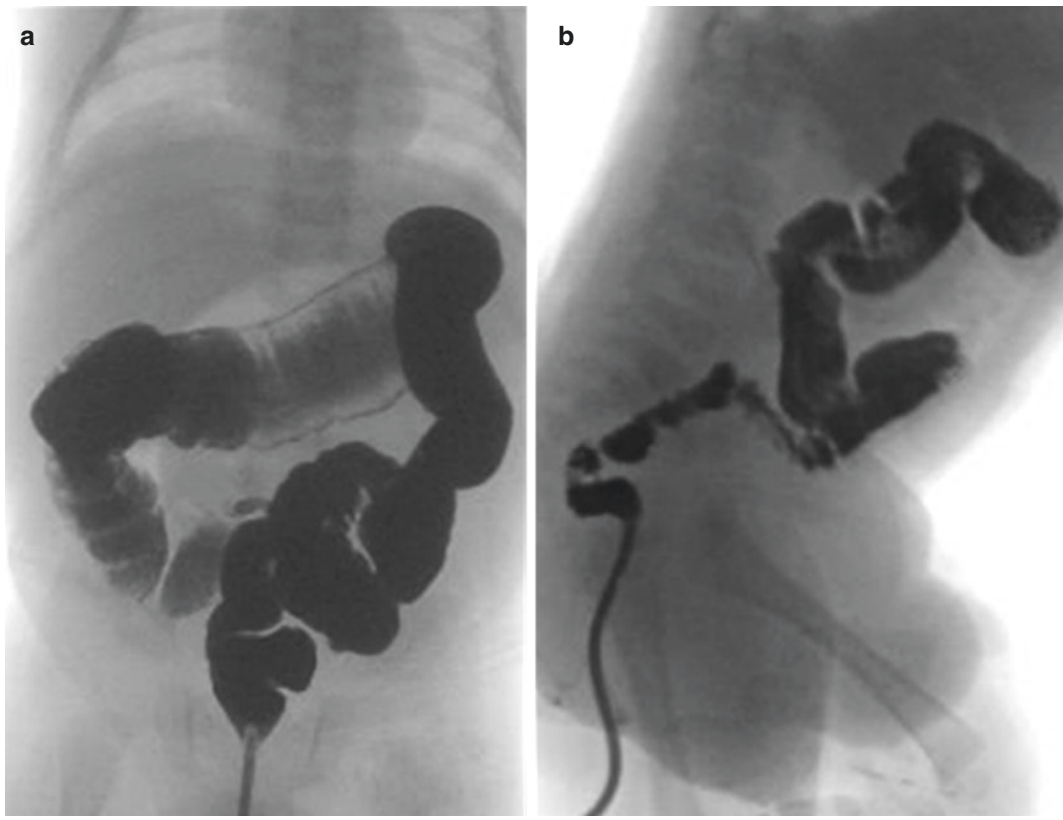

Fig. 23.2 (**a**) Contrast enema demonstrating a transition zone at the splenic flexure. (**b**) Lateral view

sonography can be used to identify peritoneal ascites or internal septations that are suggestive of peritonitis or intestinal inflammation.

Other suggested diagnostic tools include US of the kidney and urinary tract for the high percentage of CAKUT in HRSC patients [48]. Other investigations, like audiological evaluation, heart US, cerebral US, and ophthalmologic assessment should be performed basing on clinical features [49].

23.3.4 Anorectal Manometry

Anorectal manometry demonstrates the absence of recto-anal inhibitory reflex (reflex relaxation of the internal anal sphincter in response to rectal distension) present in normal children but absent in children with Hirschsprung disease. Contrast enema and anal manometry are similar in sensitivity and specificity, and it is necessary to consider that anorectal manometry is not widely available for neonates.

23.4 Treatment

Once the diagnosis of HSCR has been confirmed, the patient must be prepared for surgery. It is necessary to distinguish the preoperative management of healthy newborns from those with enterocolitis. Healthy newborns with undistended colon and rectosigmoid HSCR can benefit a primary surgery. Rectal irrigations must be performed daily prior to surgery in order to wash and empty the bowel.

The treatment of newborn with HAEC is:

1. Resuscitation in case of impending shock
2. Decompression of the gastrointestinal tract
3. Antibiotics, directed mostly against Gram-negative and anaerobic species

A key aspect in the management of an acute HAEC episode is a good fluid resuscitation, close hemodynamic monitoring, and in some severe case, ventilatory support and admission to intensive care unit. In case of prolonged disease, a parenteral nutrition support may be indicated. Rectal washouts, flatus tubes, and bowel decompression should be performed as soon as possible, with 2–4 times daily irrigations with saline until the effluent is clear. Usually it is possible to continue twice daily until symptoms settle. At the beginning of HAEC treatment, the patients should be kept fasting. Feeding should be allowed once symptoms improve. Depending on the severity of the disease, in particular when *Clostridium difficile* is detected in the stools, HAEC can be effectively treated with oral or intravenous metronidazole.

Inability to adequately decompress the bowel or severe and uncontrolled septic shock may be an indication for urgent bowel diversion with a levelling colostomy (or ileostomy in patients with total colonic aganglionosis) fashioned proximally to the transitional zone (intraoperative histochemistry) [50].

Ideally, the best treatment for HAEC is the prevention. The main foresight is rectal washout, especially preoperatively in the newborn. Immediate diversion should be strongly considered for patients presenting with sepsis or severe HAEC, especially in newborn when this is the initial presentation.

Radical surgery (pull-through) should be performed as soon as possible. In fact, most of the severe cases of HAEC do occur preoperatively being surgery mostly event-free. Preoperative and postoperative probiotics use recently failed to demonstrate a beneficial or protective role over HAEC likelihood and severity.

Severe and fatal HAEC are more likely to occur in patients with syndromes or congenital heart diseases. On the ground of these considerations, patients with congenital heart disease should undergo prophylactic stoma fashioning in order to minimize the risk of HAEC and consequently possible fatal complications [29, 35]. Nonetheless, although enterostomy could consider protective toward the development of HAEC, it cannot prevent cardiocirculatory problems or issues related to pre-existing syndromes, and HAEC could potentially occur also after stoma formation.

The main goal in the treatment of patients with Hirschsprung's disease is to remove aganglionic bowel radically and to identify normoganglionic

bowel with intraoperative seromuscular biopsies for intraoperative assessment in order to identify the correct site of anastomosis.

The radical resection of the aganglionic bowel can be performed either with an endorectal (Soave), retrorectal (Duhamel), or perirectal (Swenson) approach. For many times, surgical treatment of HSCR involved staged procedures, but in recent years many surgeons are now performing one-stage pull-through operations in the newborn with minimal morbidity rates and encouraging results [51–54].

Swenson provided the first description of a surgical approach to Hirschsprung disease in the late 1940s. The procedure involves the mobilization and resection of aganglionic bowel with end-to-end anastomosis of normal colon to the anal canal. The operation was originally done through a laparotomy, with the anastomosis being performed from a perineal approach after eversion of the aganglionic rectum.

The Duhamel procedure (first reported in 1960) [7, 55] implicates bringing the normal colon down through the bloodless plane between the rectum and the sacrum and joining the two walls to create a the rectum instead of removing it with less pelvic dissection and the presence of a "reservoir" makes it the rectum instead of removing it with less pelvic dissection and the presence of a "reservoir" makes it appealing for patient with longer aganglionic segments.

Rehbein's procedure is one of the techniques mostly used in Europe for the past 25 years [56]. The procedure provides resection of the aganglionic colon only up to the upper rectum (2 cm below the peritoneal reflection) followed by dilatation of the remaining rectum and anus, after performing colostomy immediately proximal to the aganglionic segment.

In 1964, Soave described an endorectal pull-through procedure doing a submucosal endorectal dissection and placing the pull-through bowel within a "cuff" consisting of aganglionic muscle an excised exteriorized bowel; the anastomosis is done at a second operation several weeks later. Subsequently Boley modified this procedure performed in a single stage. The concept of the Soave procedure is to prevent extensive pelvic dissection outside the rectum [57].

De la Torre-Mondragón and Ortega [11], in 1998, reported a modified Soave procedure, a single-stage transanal endorectal pull-through performed totally through a transanal approach. This technique reduces the risk of complications like damage to pelvic nerves.

The advent of minimally invasive surgery has modified the surgical approach, and HSCR and classic pull-through techniques were modified and improved with laparoscopy, leading to the advantages of reduced pain and improved cosmesis [9, 10, 55, 58–61]. As a result of the obvious advantages of laparoscopic-assisted pull-through operations, the Soave-Georgeson technique [10], which embraces the advantages of the endorectal pull-through and those of the minimally invasive surgery, has gained much popularity [62].

The Soave-Georgeson procedure involving laparoscopic biopsy to identify the transition zone, laparoscopic mobilization of the rectum below the peritoneal reflection, and a short mucosal dissection through a perineal approach.

Preoperative intravenous antibiotic is given on call in the operating room. The patient is positioned on the operating table in the lithotomy position to allow for access to both the abdomen for trocar placement and the perineum for the transanal dissection. Biopsy site is selected by observing the apparent transitional zone; a seromuscular biopsy is taken along the antimesenteric surface; the sample is promptly sent to pathologist for examination. In the meantime the colon is isolated, and the peritoneum is divided around its lateral and anterior reflection from the rectum, exposing the muscle coat of the rectum. Once the endoscopic dissection has been completed, the perineal dissection is started. The rectal mucosa is circumferentially incised using the cautery, approximately 5 mm from the pectinate line; the rectal muscle is then incised circumferentially, and the endorectal dissection is carried to a point above the peritoneal reflection. The entire rectum and part of the sigmoid colon can be delivered through the anus. When the transition zone is reached, the anastomosis is done from below (after histopathological confirmation of ganglionic specimen).

A transanal approach can also be used if the patient has already had a colostomy, by using the

stoma as the end of the pull-through bowel and performing the rectal excision using the transanal technique. In patients with a more proximal transition zone, laparoscopy can be used to mobilize the left colon and/or splenic flexure to achieve adequate length.

This procedure is associated with excellent clinical results and permits early postoperative feeding, early hospital discharge, and no visible scars.

Recently, robotic surgery was introduced in the pediatric surgery but may play a role in the treatment of older patients with HSCR [63].

23.5 Postoperative Management and Outcome

Patients undergoing a laparoscopic approach for HSCR can be fed immediately, and most can be discharged within 24–48 h. It is important to calibrate the anastomosis with an appropriately sized dilator or finger 1–2 weeks after the procedure.

Postoperative complications including anastomotic stricture, rectal obstruction due to long rectal cuff in endorectal procedure, or long spur in Duhamel intervention, enterocolitis, adhesions, leakage, and residual anal achalasia have been described for different procedures [64, 65]. Most patients will have perineal skin problems, but this problem tends to resolve spontaneously with time. The most common cause of mechanical obstruction after a pull-through is a stricture. The treatment for this problem consists of repeated dilatation, and only in sporadic cases, when the stricture cannot be successfully dilated, is revision of the pull-through necessary.

Enterocolitis, constipation, failure to thrive, fecal soiling, and incontinence are the most frequent complaints after surgery [59, 66]. In particular soiling and incontinence have an important impact on quality of life [67, 68]. Furthermore, the outcome of the bowel function could be influenced by the age of the patients; if a patient is less than 4 years of age, he may not be considered continent.

Persistent obstructive symptoms following a pull-through may be due to a mechanical obstruction, recurrent or acquired aganglionosis, disordered motility in the proximal colon or small bowel, internal sphincter achalasia, or functional megacolon caused by stool-holding behavior.

Mortality rate for HSCR is relatively low; the patients died preoperatively due to complications, like enterocolitis or associated anomalies, like congenital heart disease, but rarely died postoperatively.

The family should be educated about the signs and symptoms of enterocolitis, and the family must be told to bring the child to the hospital if there are any signs suggestive of this problem because children can become very sick and even die from enterocolitis.

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Anorectal Malformations

24

Kristiina Kyrklund and Risto Rintala

24.1 Introduction

Anorectal malformations (ARMs) comprise a spectrum of congenital defects with an incidence of 1:2500 that range in severity from mild anal stenosis alone to complex malformations involving the anorectum and urogenital tract. Both males and females are equally affected, and a detailed understanding of the anatomy of these defects is essential for the provision of optimal surgical care during the neonatal period. Improvements in neonatal and surgical care over the past decades have reduced mortality in ARM patients to around 3% in units with modern technology [1], and mortality is usually the result of uncorrectable associated anomalies rather than the ARM. Apart from cloacal abnormalities, prenatal suspicion of ARMs is uncommon, and the diagnosis is usually made shortly after birth. Because associated defects affect over half of patients, management in the neonatal period involves prompt screening based on a set algorithm. The modern operative management of ARMs involves anatomical reconstruction of the defect with minimal disturbance to the existing continence mechanisms. As ARMs represent relatively rare disorders, definitive repair should be performed in experienced tertiary units to ensure optimal healthcare outcomes.

24.2 Embryology of ARMs

In early embryology, the caudal region of the normal hindgut is called the cloaca. During the 7th week of gestation, cloacal division into ventral and dorsal components occurs with descent of the urorectal fold, forming the urogenital tract ventrally and the anorectal tract dorsally. The urorectal fold ultimately forms the perineal body between them. The dorsal part of the cloacal membrane (CM) ends at the position of the future anal opening at a fixed point near the tail groove in the normal rat model (Fig. 24.1) [2]. In ARMs, the critical factor for development may be an abnormally shortened cloacal membrane (Fig. 24.2) [2], which could lead to aberrant siting of the bowel termination during cloacal subdivision in ARMs, including urogenital connections. The site where the anal orifice should be, as marked by the location of the external sphincter apparatus in humans, is already established at a fixed point in the mouse model prior to cloacal subdivision [2]. In normal development, the cloacal membrane disintegrates where it meets the tip of the descending urorectal fold posteriorly, forming the anal ori-

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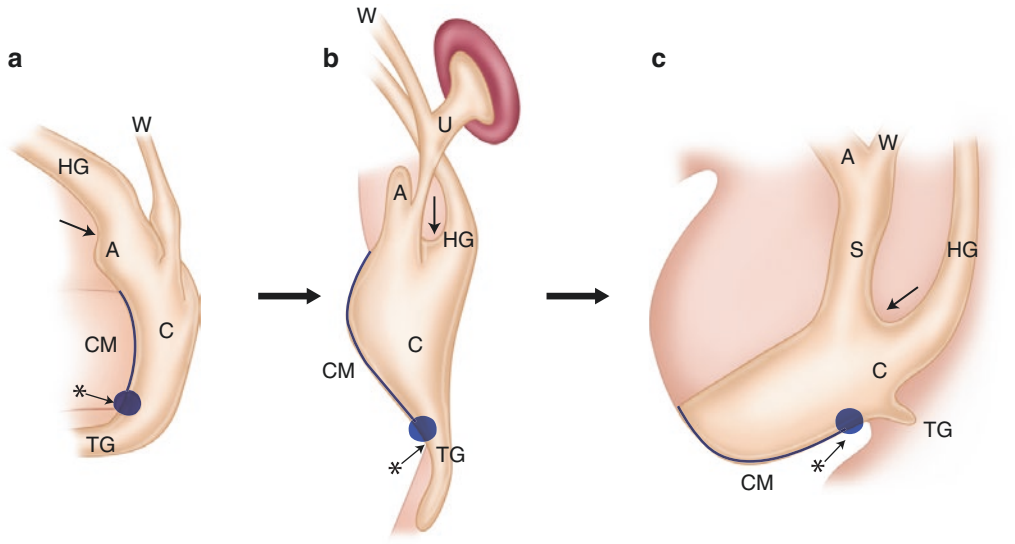

Fig. 24.1 Normal cloacal development in the rat model. Schematic diagram of a normal (**a** and **b**) and an abnormal (**c**) cloaca

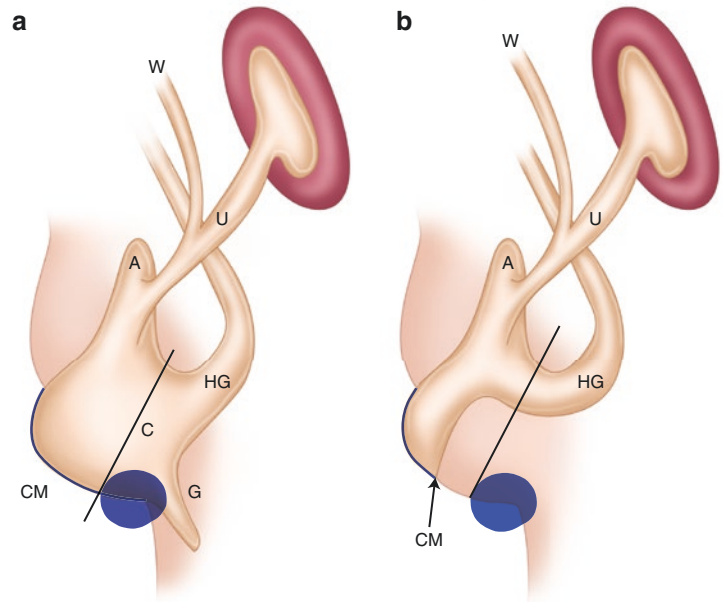

Fig. 24.2 Model of abnormal cloacal development. Schematic diagram of a normal (**a**) and an abnormal (**b**) cloaca. In the abnormal embryo, the cloacal membrane (CM) is too short (arrow). The cloacal membrane does not extend to the region of the tail groove (grey area). The dorsal cloaca is missing. In the normal embryo (**a**), the cloacal membrane is of normal length and extends to the region of the tail groove (grey area). Reproduced from Fig. 7 in Kluth [2]. Embryology of anorectal malformations. Semin Pediatr Surg 2010, 19: 201-208 and reproduced with kind permission from Elsevier

fice [3]. This initially closes with the ectoderm and is recanalized 2 weeks later. Abnormalities of recanalization of the anal orifice during the 9th week of gestation could assist to explain mild ARMs, including stenotic and membranous defects [3].

24.3 Etiologic Factors

The etiologic basis of ARMs is based on genetic and environmental influences. The most frequent chromosomal associations involve micro-

deletion of chromosome 22q11.2 (also known as DiGeorge or CATCH-22 syndrome) and Down syndrome (trisomy 21). A chromosomal abnormality is observed in approximately 10% of cases [3]. Townes-Brocks, Pallister-Hall, Opitz-Kaveggia, Johanson-Blizzard, Kaufman-McKusick, Lowe, oculo-auricular-vertebral (Goldenhar), fragile X and trisomy 8 syndromes are other reported associations [4]. A genetic aetiology is supported by a familial occurrence in up to 8% of cases [5] and among monozygotic twins. Autosomal dominant inheritance of mutations in *HLXB9* is responsible for 50% of patients with Currarino syndrome. Environmental risk factors for ARMs include prenatal exposure to caffeine, alcohol or drugs as well as maternal factors such as diabetes and epilepsy. Assisted reproductive techniques, primiparity, pre-eclampsia and maternal fever in early gestation have also been implicated [6].

24.3.1 Associated Anomalies

Malformations of the VACTERL (vertebral, anal, cardiac, tracheo-esophageal, renal, limb) and CHARGE (choanal atresia/coloboma, anal, renal, gastrointestinal and ear/hearing) sequence are recognized, non-random associations of ARMs. Over half of all patients with ARMs have at least one other associated congenital malformation, and these may affect over 90% of patients with severe ARMs. Approximately 10–15% fulfil the criteria for VACTERL association [6–8], having three or more anomalies from this sequence. A recent epidemiological survey identified a prevalence of 13% for cardiac defects (mainly atrial septal defect, ventricular septal defects and tetralogy of Fallot), 15% for skeletal defects, 10% for tracheo-oesophageal fistula, 25% for urologic abnormalities (most commonly vesicoureteric reflux, renal agenesis and dysplastic kidney), 13% for limb defects and 13% for genital anomalies [4, 7]. Uterine and vaginal abnormalities are common in cloaca patients and occur less frequently in females with milder types of ARMs. Additionally, craniofacial abnormalities including cleft palate are present in approximately 5% of patients.

24.3.2 Normal Anatomy of the Pelvic Floor

Knowledge of the normal anatomy of the pelvic floor and anal canal is necessary for understanding the pathologic anatomy of ARMs. The pelvic floor comprises a sheetlike diaphragm of striated muscles that support the pelvic organs and abdominal viscera. These muscles insert into the pubic bone anteriorly, the most inferior part of the sacrum posteriorly and the obturator membrane, ischium and ischial spine laterally. The ventromedial aspect forms a funnel-like sling around the urethra, vagina and anorectum, with fibres fusing medially at the perineal body and serving to close the urogenital and anorectal hiatuses by contraction [9]. The superior part of this muscle funnel is called the levator muscle, and its inferior fibres are continuous with the deep fibres of the external anal sphincter. Contraction of the puborectalis sling fibres of the levator complex maintains the anorectal angle (Fig. 24.3), preventing faecal descent during sudden increases in intra-abdominal pressure [10].

24.3.3 Anatomy of the Anal Canal

The voluntary or external anal sphincter (EAS) muscles of the anal canal are continuous superiorly with the fibres of the levator muscles, forming a striated funnel comprising of deep, superficial and subcutaneous components (Fig. 24.4). The EAS provides approximately 15% of resting continence but becomes activated during physical activities that increase the intra-abdominal pressure. It receives its motor and sensory supply from the inferior rectal branches of the pudendal nerve and the perineal branch of S4, which is also sensory to the skin of the anal canal to approximately 1 cm proximal to the dentate line [10]. The internal anal sphincter (IAS) fibres provide the remaining 80–85% of resting anal canal pressure and represent a thickened continuation of the inner smooth (visceral) muscle of the rectum [10]. The tone of the IAS is maintained by sympathetic pathways from the hypogastric plexus. The rectoanal inhibitory reflex of the IAS is principally intramural and

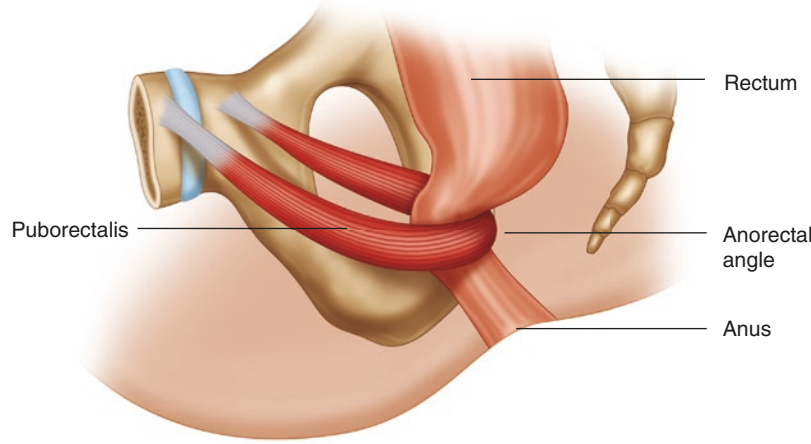

Fig. 24.3 The normal anorectal angle, formed by the puborectalis sling, which is part of the levator muscle complex

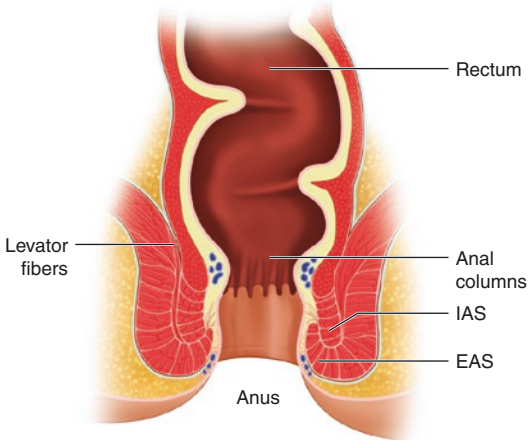

Fig. 24.4 Normal anatomy of the anal canal: the levator fibres are continuous with the deep portion of the external anal sphincter (EAS); the internal anal sphincter (IAS) is a thickened continuation of the smooth muscle of the rectum

mediated by nitric oxide synthase-containing neurons [11].

24.3.4 Pathologic Anatomy in Anorectal Malformations

Most of the structures observed in normal infants are present in anorectal malformations, but the anatomical relationships between structures involved in continence are displaced to varying degrees. In all ARMs, the levator muscles and external sphincter apparatus are more or less normally sited, but the bowel termination is increasingly displaced with increasing severity of malformation. Higher malformations are also associated with greater hypoplasia of the structures involved in faecal continence. Functional IAS tissue is present in the bowel termination of all ARMs, and the fistula contains all components of a normal anal canal, including stratified columnar epithelium, anal glands and anal columns [12]. In mild or 'low' malformations, the bowel termination is at least partially within the voluntary sphincter funnel, and the levator muscles are nearly normally developed.

24.3.5 Classification of ARMs

The main purpose of classification systems in ARMs has been to provide a platform for describing the anatomy, operative treatment and functional outcomes for different types of malformations. Several systems have been used over the past decades (Table 24.1), of which the most recent is the clinically oriented Holschneider (2005) [13] classification. This is a simplification of earlier models that divides

Table 24.1 Classification systems for ARMs

Holschneider (2005) [13]		Peña (1995) [14]		Stephens (1986) [15]	
Major clinical groups	Rare/regional variants	Males	Females	Males	Females
Perineal (cutaneous) fistula Rectourethral fistula: Bulbar Prostatic Bladder neck Vestibular fistula Cloaca No fistula Anal stenosis	Pouch colon Rectal atresia/ stenosis Rectovaginal fistula H-type fistula Others	Perineal fistula Rectourethral fistula: Bulbar Prostatic Rectovesical (bladder neck) Imperforate anus without fistula Rectal atresia	Perineal fistula Vestibular fistula Persistent cloaca: <3 cm common channel >3 cm common channel Imperforate anus without fistula Rectal atresia	*High* Anorectal agenesis Rectoprostatic fistula No fistula Rectal atresia *Intermediate* Bulbar fistula Anal agenesis *Low* Anocutaneous fistula Anal stenosis Rare malformations	*High* Anorectal agenesis Rectovaginal fistula No fistula Rectal atresia *Intermediate* Rectovaginal fistula Rectovestibular fistula Anal agenesis *Low* Anovestibular fistula Anocutaneous fistula Anal stenosis Cloaca Rare malformations

ARMs into major clinical groups and rare/regional variants. The preceding Peña [14] classification was based on the surgical approach and included division of ARMs into male and female groups. The Wingspread classification (1986) [15] considered anomalies based on the location of the rectal termination in relation to the levator plate. The major clinical groups described in the Krickenbeck classification are covered herein; the rare and regional types are uncommon, but the principles of surgical treatment are the same as for other types of ARMs.

24.3.6 Clinical Features of ARMs

In this communication, ARMs from the Krickenbeck classification with a bowel termination mostly *within* the external sphincter complex are considered *mild* types, and those with a bowel termination *outside* the EAS are considered *severe* anomalies.

24.3.7 Mild ARMs

24.3.7.1 Anterior Anus with or Without Anal Stenosis

Present exclusively in females, anterior anus represents the mildest type of ARM and is characterized by a normal-looking anus that is anteriorly sited (Fig. 24.5). In approximately half of patients, mild anal stenosis may be present. The bowel terminates natively mostly *within* (≥70%) the external sphincter complex. Anterior anus may be associated with a perineal groove, which is a mucosa-lined median cleft between the vestibulum and anus (Fig. 24.5) [16]. A perineal groove may also be present in the absence of an anorectal anomaly and in itself requires no treatment. The mucosal surface epithelializes gradually over time.

24.3.7.2 Perineal Fistula and Anal Stenosis in Males

In males, perineal fistula (Fig. 24.6) and anal stenosis essentially constitute variants of the same type of mild ARM [17]. In a male perineal fistula, there is a

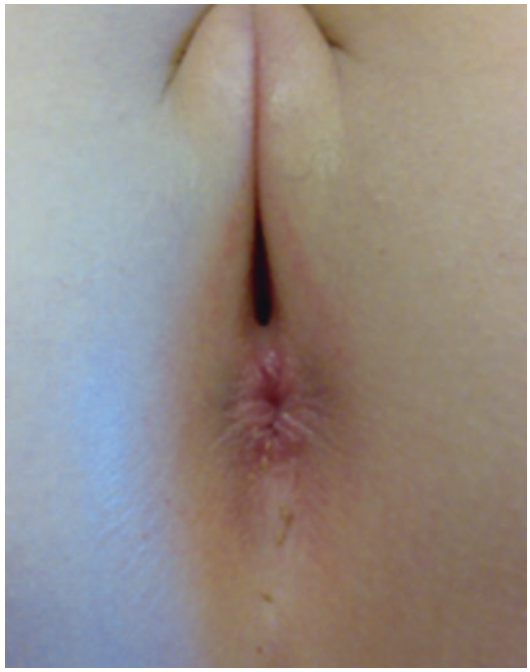

Fig. 24.5 Anterior anus with perineal groove. Reprinted from Fig. 3 Pakarinen and Rintala [16], with kind permission from Springer Science & Business Media

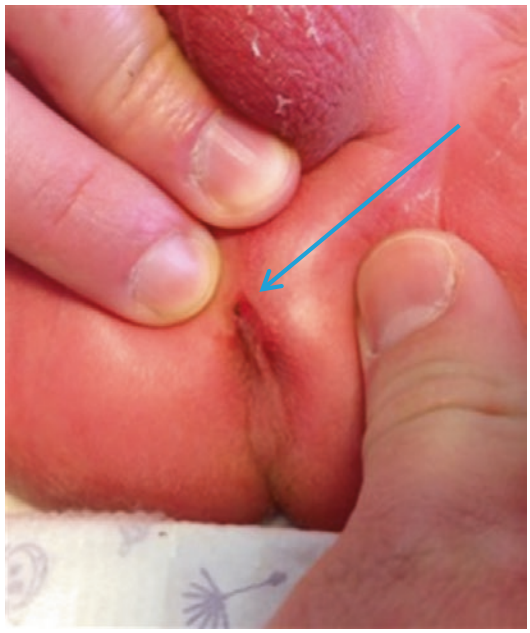

Fig. 24.6 Perineal fistula in a male (arrowed). There is a subcutaneous tract from the site of the bowel termination within the external sphincter complex

superficial subcutaneous tract in the midline for a variable distance along the perineum or scrotal raphe through which meconium extrudes (arrowed). The bowel termination is natively mostly *within* the external sphincter funnel, for which reason a perineal fistula in a male is considered to be a mild ARM. The bowel termination may be covered by a median bar or an anal membrane that is usually situated at the level of the dentate line [16]. Complete anal membranes are uncommon (2% of cases) and could also represent the least severe form of imperforate anus without a fistula [18].

24.3.8 Severe ARMs

24.3.8.1 Perineal or Vestibular Fistula in a Female

In contrast to a perineal fistula in a male, in females with a perineal or vestibular fistula, the bowel termination is anterior to and *outside* the support of the external sphincter funnel on the perineum (Figs. 24.7 and 24.8) [16, 19] or vestibulum (Fig. 24.9 and 24.10) [20]. Therefore, these are not considered mild ARMs. Rectovaginal fistula is a very rare variant, and most cases in which this is suspected are actually vestibular fistulas on careful clinical examination. In perineal and vestibular fistula, there are separate and usually normal openings for the urethra and vagina.

24.3.8.2 Cloaca

The most severe form of ARM in females is cloaca, which is characterized by a single perineal opening (Figs. 24.11 and 24.12). The urethra, vagina and anorectum terminate into a single common channel of variable length. Flat buttocks and natal cleft are suggestive of a longer common channel. Prenatal diagnosis of cloaca may be suspected in the presence of significant hydrometrocolpos. Nearly all cases of cloaca have associated anomalies.

24.3.8.3 Rectourethral Fistula

In males with no opening on the perineum (Fig. 24.13), the diagnosis is usually a rectourethral fistula, which is the most severe form of ARM in males. The fistulous connection of the terminal anorectum is most often at the level of

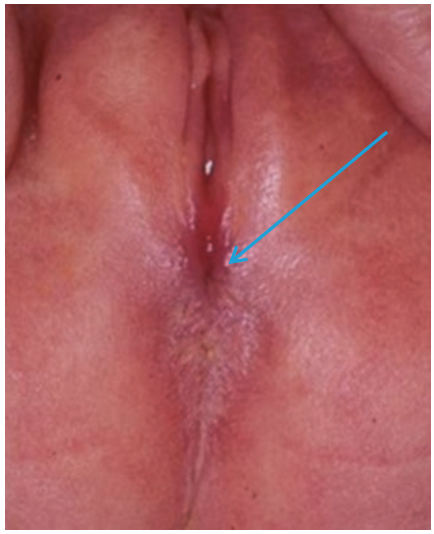

Fig. 24.7 Perineal fistula in a female (arrowed) reprinted from Pakarinen and Rintala [16], with kind permission from Springer Science & Business media

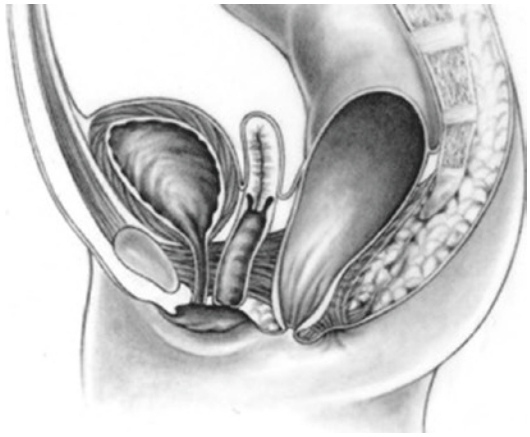

Fig. 24.8 Perineal fistula in a female; The diagram (black and white) from Levitt and Pena [19], with kind permission from BioMed Central

the bulbar or prostatic urethra but may be as high as the bladder neck (Fig. 24.14). Some patients may pass meconium via the urethra, which is diagnostic. Higher rectal terminations are associated with more significant hypoplasia of the native continence mechanisms, which is clinically apparent from a relatively flat and featureless bottom as with females with cloaca. The differential diagnosis when there is no perineal opening in males is imperforate anus without a fistula. Nearly all males with rectourethral fistula have associated anomalies.

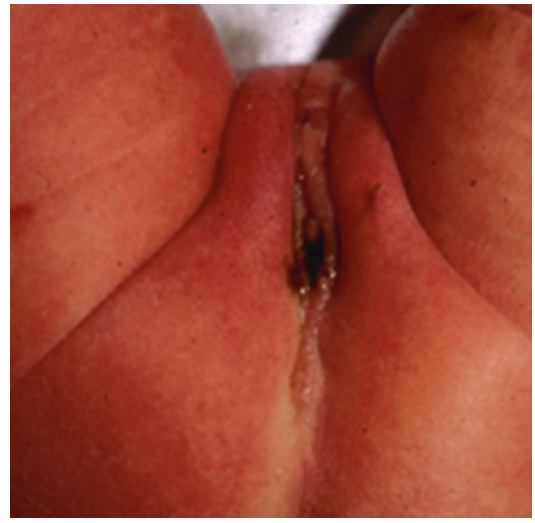

Fig. 24.9 Vestibular fistula in a female.

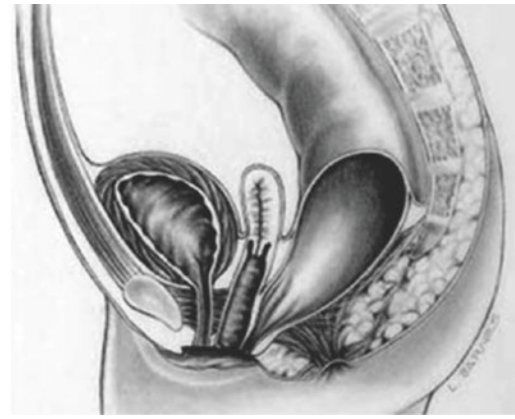

Fig. 24.10 Vestibular fistula in a female; Reprinted from Fig. 5 in Levitt and Pena [20], with kind permission from BioMed Central

24.3.8.4 Imperforate Anus Without a Fistula

Imperforate anus without a fistula is usually associated with well-developed sphincters, and this type of ARM occurs in males and females and is the most common type of ARM present in patients with Down syndrome. When the rectal termination is below the dentate line and immediately subcutaneous to the anal pit, the anomaly is termed anal agenesis. Less commonly, the anus may be normal-looking but terminates blindly at 1–3 cm of depth. In this type of ARM, termed rectal atresia, the rectal pouch commonly terminates above the levator plate [21].

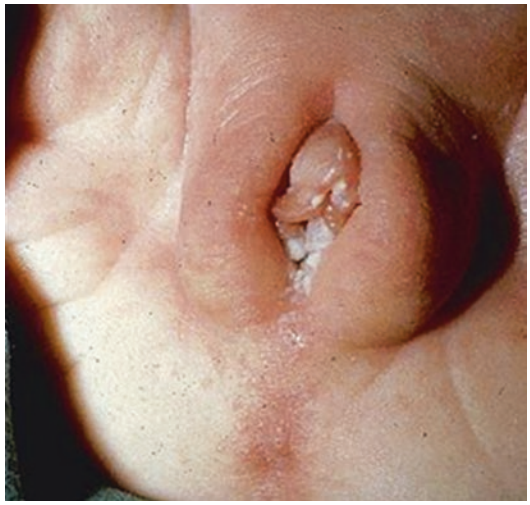

Fig. 24.11 Single channel cloaca.

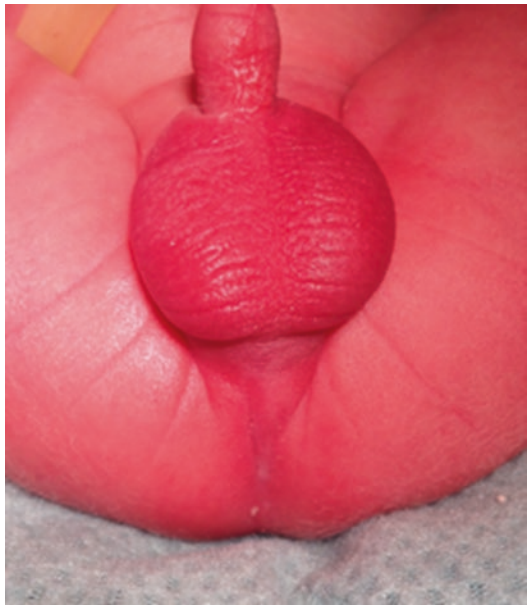

Fig. 24.13 No perineal opening in a male is usually a rectourethral fistula

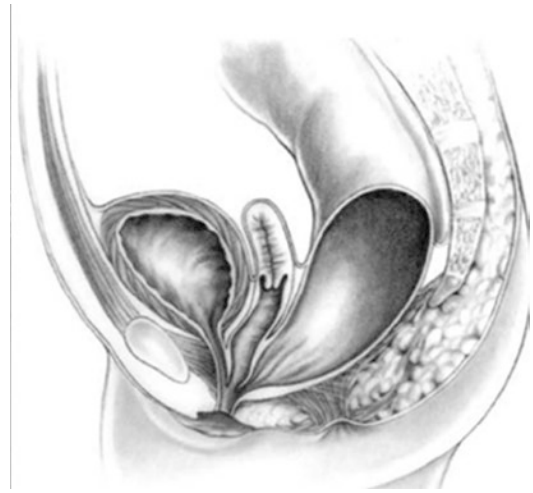

Fig. 24.12 Cloaca, single perineal opening; Reprinted from Fig. 7 in Levitt and Peña [19], with kind permission from BioMed Central

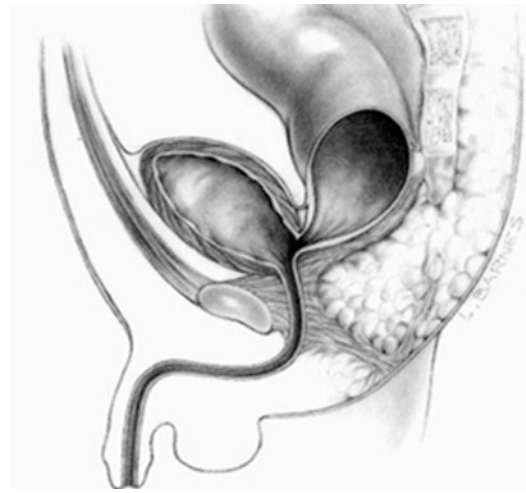

Fig. 24.14 No perineal opening in a male: usually rectobladder neck or rectourethral fistula. Reprinted from Fig. 6 in Levitt and Peña [19], with kind permission from BioMed Central

24.3.9 Initial Assessment

Clinical examination is often sufficient to make a provisional diagnosis of the severity of the ARM. In females, the diagnosis can be made from careful examination of the perineum to demonstrate the site of the termination of the anal canal: within the external sphincter complex in anterior anus, or fistulously on the perineum or vestibulum, or as a single channel cloaca. If there is any uncertainty in distinguishing an anterior anus from a perineal fistula in a female, electrical muscle stimulation under anaesthesia can clarify this [16]. In anterior anus, the anus is calibrated using Hegars (normal in a full-term neonate is Hegar 12–14). In males, meconium extruding onto the perineum indicates a mild ARM with a low rectal termination. If no fistula is appar-

ent, a nasogastric tube is passed, and the patient is kept nil by mouth. If there is still no meconium after 24–48 h of observation and gentle probing, it is safer to assume a high ARM as the working diagnosis and to proceed with a double-barrelled colostomy. Cross-table lateral X-rays and perineal ultrasound have limitations in their diagnostic sensitivity with regard to the level of the defect. Antimicrobial prophylaxis is appropriate in suspected urogenital connections or if there is vesicoureteric reflux.

24.3.10 Screening for Associated Anomalies

It is important to rule out serious associated malformations as part of the initial management. Normal passage of a nasogastric tube rules out oesophageal atresia, which is not uncommon in ARM patients. Cardiac and renal tract ultrasound and a chest/abdominal X-ray should be performed promptly for high anomalies. Screening investigations, during the hospitalization period include a micturating cystourethrogram, spinal column radiography (Fig. 24.15) and spinal ultrasound to assess for tethering. Chromosomal assessment and genetic consultation is indicated if a syndrome is suspected. Spinal cord magnetic resonance imaging can be performed at a later stage to rule out intraspinal anomalies.

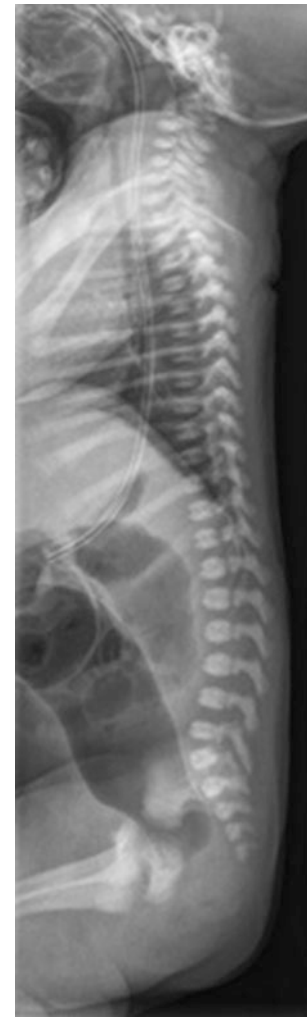

Fig. 24.15 Spinal column radiograph of a patient with a rectourethral fistula showing an extra vertebra with rudimentary ribs between T12 and L1 and four sacral segments

24.4 Initial Surgical Management

24.4.1 Mild ARMS

24.4.1.1 Anterior Anus

No operative management is indicated for patients with anterior anus because the anal canal terminates natively mostly within the external sphincter funnel. If anal stenosis is present, this usually responds well to serial Hegar dilatations up to Hegar 14, increasing the Hegar size at weekly intervals. Parents are taught to perform Hegar dilatations twice a day at home, attending outpatients for Hegar changes by a paediatric surgeon. In the absence of anal stenosis, observant, expectant management is sufficient. The long-term continence outlook with appropriate aftercare is good/normal in most cases [22].

24.4.1.2 Perineal Fistula, Anal Stenosis or Incomplete Anal Membranes in Males

In mild ARMs in males, the anal canal is usually located mostly within the external sphincter complex, and patients have a nearly normally developed anal canal [16]. In males with perineal fistula, the skin overlying the subcutaneous tract can be laid open over a thin probe inserted from the tip of the fistula to the centre of the sphincter complex to uncover the anus proper under general anaesthesia (Fig. 24.16), usually on the first day of life. Anal sphincter fibres are not divided

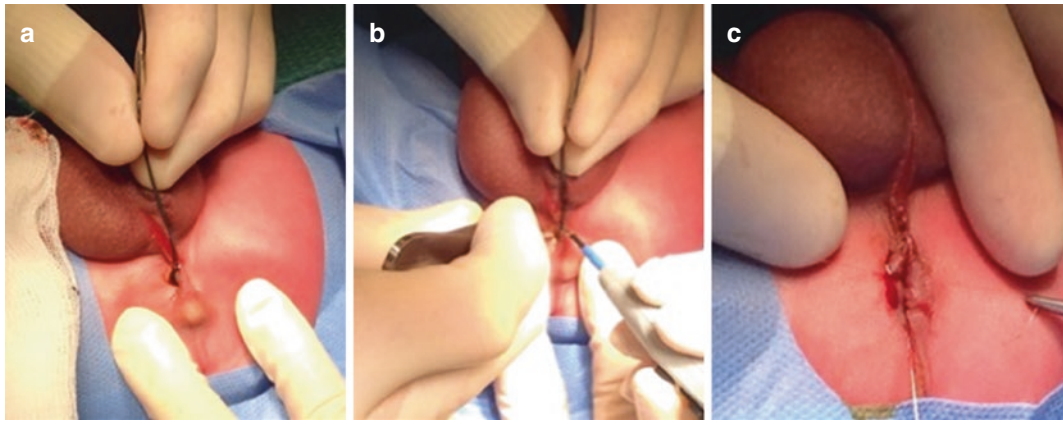

Fig. 24.16 Minimally invasive management of a perineal fistula in a male: (**a**) introduction of a thin probe through the subcutaneous fistula tract; (**b**) the skin overlying the fistula canal is laid open using diathermy up to the centre of the external sphincter complex; (**c**) anoplasty of the bowel terminus to the skin edges with a few absorbable interrupted sutures

during this procedure. The centre of the external sphincter complex may be delineated with electrostimulation. Standard anoplasty to suture the bowel termination to the skin edges is performed using a few interrupted absorbable sutures. Posterior sagittal anorectoplasty is also practised for males with perineal fistula, but there is no evidence to suggest superior outcomes compared to simply laying open the fistula tract. Urologic injuries should also be completely avoided with this minimally invasive approach.

If a mild ARM in a male is associated with a median bar or 'bucket handle' defect that interferes with faecal outflow, this should be excised. Males with anal stenosis and/or partial anal membranes can be treated with gradual Hegar dilatations, which can usually be performed without general anaesthesia. Complete anal membranes require surgical incision. If the patient has undergone a primary colostomy due to initial suspicion of a higher ARM, it is possible to incise the membrane under endoscopy control through the distal colostomy to transluminate the skin over the membrane [16]. The colostomy can be closed during the same procedure. Following anoplasty for perineal fistula, the anus usually approximates to Hegar 7–8 immediately post-operatively. Males with mild ARMs undergo a standard Hegar dilatation programme over 6 weeks up to Hegar 14, beginning 2 weeks post-operatively.

24.4.1.3 Anal Dilatation Programme

Parents are taught to perform twice daily dilatations with weekly outpatient visits for Hegar changes. Upon reaching Hegar size 14, a "2 + 2 + 2" programme is subsequently followed, comprising dilatations twice a day for the first 2 weeks, then every other day for 2 weeks and twice a week for the last 2 weeks. Anal strictures after a successful dilatation programme occur in only 2% of cases, and the likelihood requiring other anorectal surgery is low [17]. Funnel anus, a distinct type of anal stenosis characterized by a deep skin-lined funnel up to a stenotic ring (Fig. 24.17), is an exception [16]. As late presentation is common and although these patients may also be treated with serial dilatations, many go on to require excision of a megarectum. Funnel anus is most commonly associated with Currarino syndrome.

24.4.2 Severe ARMs

24.4.2.1 Perineal and Vestibular Fistulas in Females

The principles of surgical management of ARMs with an anal canal termination outside the external sphincter comprise restoration of the normal anatomical relationships between structures with minimal interference to existing continence mechanisms. Anterior sagittal anorectoplasty

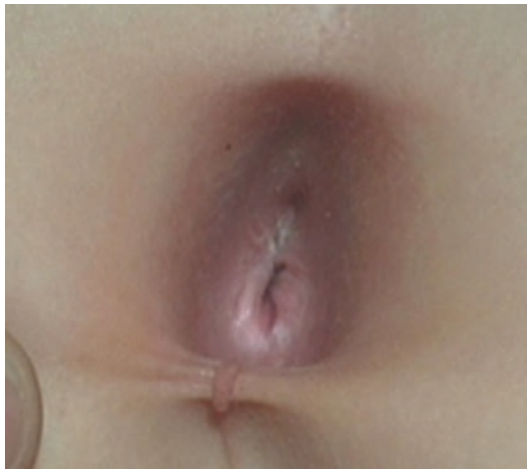

Fig. 24.17 Funnel anus. Reprinted from Fig. 2 in Pakarinen and Rintala [16], with kind permission from Springer Science & Business Media

(ASARP), also termed limited posterior sagittal anorectoplasty, is a well-established and minimally invasive operation for both perineal and vestibular fistulas in females [23]. In ASARP, a squash-racket incision is made around the fistula, extending this in the midline up to the centre of the external sphincter complex as marked pre-operatively by electrostimulation. The terminal anorectum is then carefully mobilized from its surrounding structures, taking particular care not to injure the posterior vaginal wall. Conservation of the fistula canal, which contains internal anal sphincter tissue in ARMs, is practised by the authors.

In ASARP, sufficient mobilization of the terminal anorectum to enable tension-free anastomosis to the centre of the external sphincter complex is technically important. The perineal body is then reconstructed in layers using absorbable sutures. ASARP may be safely performed as a single-stage procedure in otherwise well infants during the neonatal period [24, 25]. A covering sigmoid colostomy is currently advisable for older patients. Intravenous antibiotic prophylaxis is advisable during the immediate post-operative period. Most wound complications relating to ASARP are superficial infections that respond well to local hygiene and antibiotics. Patients undergo a standard anal dilatation programme up to Hegar 14 beginning 2 weeks post-operatively as for males with perineal fistula.

Posterior sagittal anorectoplasty is also practised for females with perineal and vestibular fistulas with comparable results to ASARP. Anal cutback has also been used to treat females with perineal fistula, but this does not equate to an anatomical repair as it leaves the external sphincter complex anteriorly deficient and the perineal body greatly shortened. Other procedures used in the past have been largely superseded by sagittal repairs.

24.4.2.2 Rectourethral Fistula

The current 'gold standard' approach to high urogenital connections including rectourethral fistula is posterior sagittal anorectoplasty (PSARP), which was first introduced by De Vries and Peña in 1982 [26]. PSARP largely modernized the safety and technical standards of the repair of severe ARMs by introducing an operative technique for anatomical reconstruction under direct vision. Serious operative complications reduced from 10 to 30% in classical operations of the past to 2% after PSARP [27]. Following a primary double-barrelled sigmoid colostomy in the immediate neonatal period, PSARP may be performed electively for rectourethral fistula at approximately 2–3 months of age but later if other congenital anomalies require repair first. The colostomy should be proximal enough to the retroperitoneal connections of the descending colon to reduce the risk of prolapse but most importantly so that enough length of distal bowel is left to reach the perineum during the definitive repair [20].

The level of the defect is ascertained pre-operatively as precisely as possible. The micturating cystourethrogram can demonstrate the fistula and its level of entry into the urogenital tract (Fig. 24.18), and a distal colostogram is complementary to this purpose. Filling the bowel with sufficient pressure to permit passage of contrast into the bladder through the fistula is technically important. Failure to demonstrate a urethral connection, however, does not completely rule out the possibility of one.

Classical PSARP involves a strict midline sagittal approach through the levator muscles and external sphincter with the patient in the prone position to access the bowel termination. Although nearly all urethral fistulas are acces-

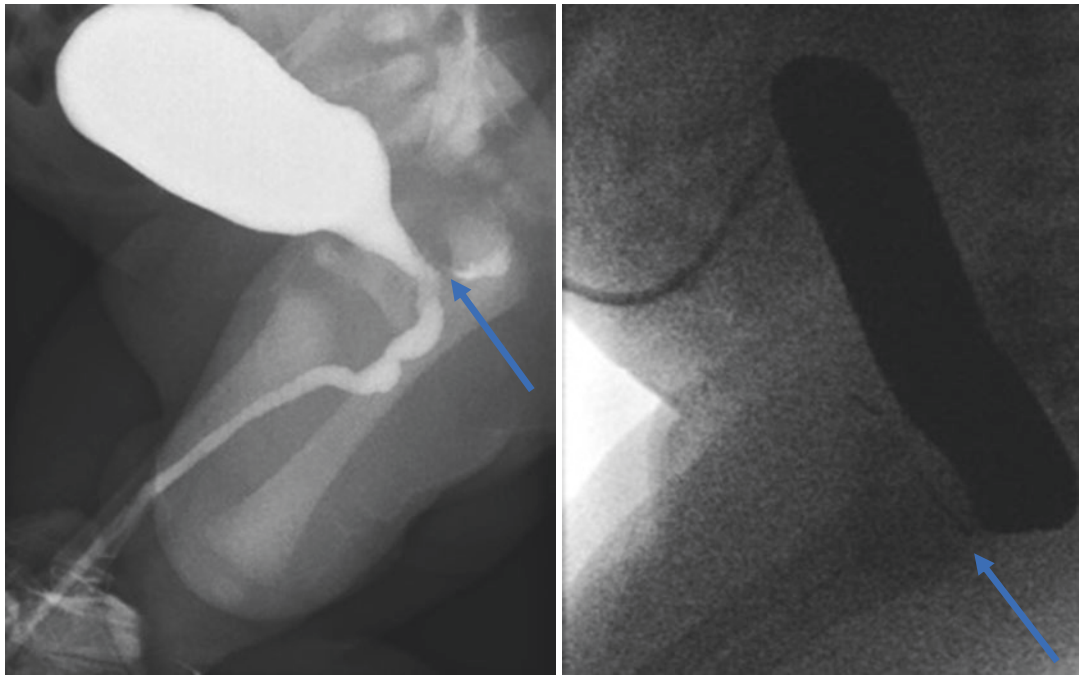

Fig. 24.18 Micturating cystourethrogram showing a rectourethral fistula at the level of the prostatic urethra (**a**) and the distal colostogram of the same patient (**b**) demonstrating the entry of contrast into the bladder through the fistula (arrowed)

sible through the posterior sagittal approach alone [20], laparoscopy is an attractive option for accessing high urogenital connections and permits excellent visualization of the fistula (Fig. 24.19). A combined technique, involving laparoscopic ligation of the fistula and a posterior sagittal incision for anastomosis of the bowel in the centre of the external sphincter complex, represents our current practice for patients' recto-prostatic or recto-bladder neck fistulas. In rectourethral bulbar fistulas, the posterior sagittal incision alone provides optimal access. Laparoscopic division are both anatomically challenging in these cases and may be complicated by a posterior urethral diverticulum due to incomplete excision of the fistula. As a limited modification of PSARP, the most distal part of the external sphincter may be conserved during posterior sagittal incisions. As with vestibular and perineal fistulas, an internal anal sphincter-saving technique that preserves the entire fistula canal is practised [27]. The recto-anal inhibitory reflex, indicative of functional

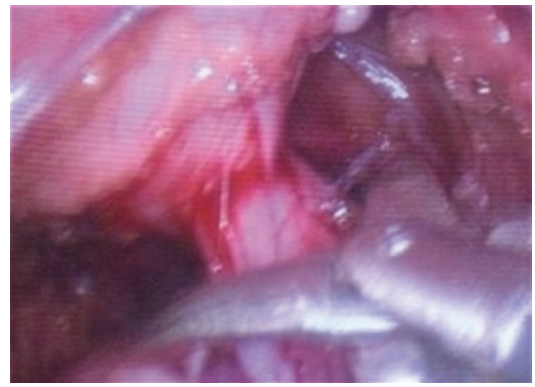

Fig. 24.19 Laparoscopic ligation of a high rectourethral (prostatic) fistula

internal anal sphincter tissue, has been demonstrated to be present in most patients post-operatively with this technique [28]. After PSARP, a standard anal dilatation programme is followed up to Hegar 14, after which colostomies can be closed.

Almost fully laparoscopic repairs for urethral fistula are also practised in some centres [29].

This technique involves laparoscopic dissection of the fistula and pull-through of the bowel via a small 1 cm incision at the centre of the external sphincter complex. Although minimally invasive, laparoscopic pull-throughs continue to be complicated by a high rate of rectal prolapse, and there are no long-term studies to suggest improved functional results. A benefit of the posterior sagittal incision is that it enables reconstruction of the normal anorectal angle through anatomical positioning of the bowel within the support of the sling muscles, which may be important for preventing rectal prolapse. Minor anal mucosal ectopy, which occurs in a few patients in the mid to long term after PSARP, is usually amenable to local corrective surgery.

24.4.2.3 Imperforate Anus Without a Fistula

The posterior sagittal approach is appropriate for patients with an imperforate anus without a fistula. In rectal atresia, the principles of operative management are otherwise the same as for urethral fistula. However, if a complete anal membrane is present (anal agenesis), this can be treated minimally invasively by incision as described previously. Colostomy closure can be performed at the same time. In imperforate anus without a fistula, the sphincter muscles are usually quite well developed, and the continence outcomes are mostly favourable.

24.4.3 Cloaca

Cloaca is a rare and complex type of anorectal malformation that requires considerable experience in its surgical management. In the immediate neonatal period, other life-threatening anomalies, including obstructive uropathy, cardiac anomalies and tracheo-oesophageal fistula, should be ruled out. Pre-operative investigations of the cloacal malformation should aim to establish the length of the rectourogenital confluence and the urethra and the anatomy of the bladder and gynaecologic structures for planning the reconstruction. Ultrasound of the urinary tract and imaging with contrast through the perineal opening may assist in this purpose (Fig. 24.20). However, not all structures may be visualized, and accurate interpretation of the findings is dependent on the experience of the radiologist.

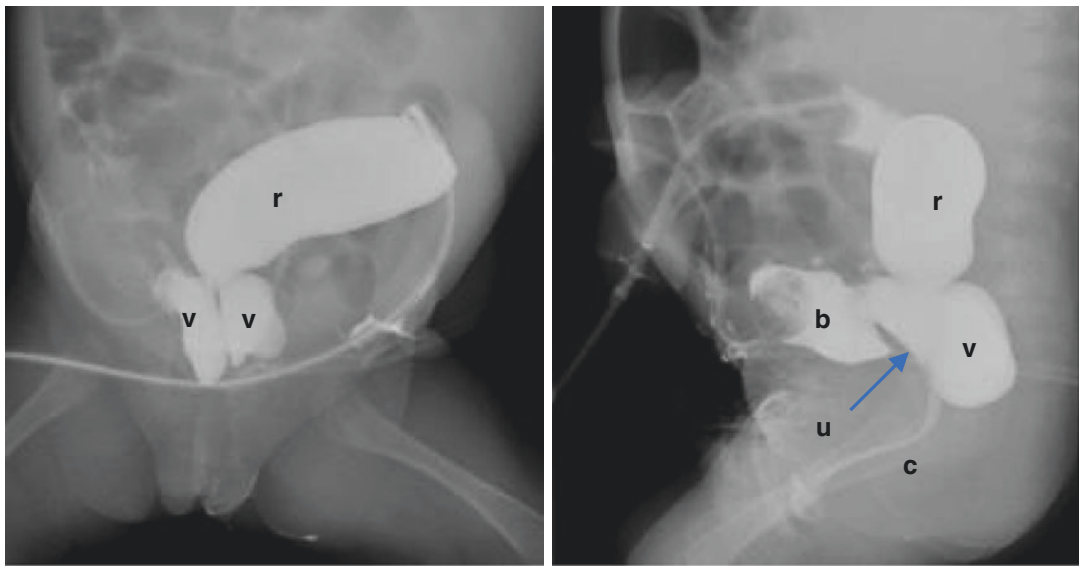

Fig. 24.20 Contrast study of a patient with a cloaca showing the rectum (r), duplex vagina (v), bladder (b), urethra (u) and urogenital confluence (c)

Endoscopy through the cloacal common channel using a paediatric cystoscope and warm flushing fluid is performed to measure the length of the common channel and urethra and visualize the number and size of vagina(s) and the position of the rectourogenital connection. A high-confluence cloaca is considered one with a common channel length in excess of 3 cm.

With regard to the initial colostomy, if there is (1) clear anatomy and (2) a patent vagina with no expectation of a possible need for vaginal reconstruction, a double-barrelled sigmoid colostomy may be performed. The colostomy should aim to leave as much distal bowel as possible for the definitive repair, so that the bowel can reach the perineum without tension. If there is (1) a very high confluence and (2) uncertainty of the need for sigmoid vaginal augmentation or (3) the anatomy is simply unclear, a transverse colostomy should be performed. A transverse colostomy does not preclude the later use of the sigmoid colon for vaginal reconstruction or hinder the subsequent pull-through. A contrast study of the distal bowel prior to the definitive repair should be performed and combined with the results of neonatal imaging when planning the definitive surgery.

Hydrometrocolpos is commonly present in cloaca patients, because urine may first pass into the vagina before being evacuated via the common channel [30]. Catheterization of the bladder is usually not possible without endoscopic aid, as the junction of the proximal urethra with the common channel is sharply angulated towards the pubic bone [30]. Catheter decompression of the hydrometrocolpos should be attempted as it can relieve urinary obstruction and prevent sepsis. If intermittent catheterization of either the bladder or vagina for urinary drainage is not feasible and severe urinary outflow obstruction or upper tract dysfunction is present, a vesicostomy is indicated. A colpostomy is only indicated in large hydrometrocolpos and often decompresses the upper urinary tract. However, a colpostomy may also preclude a posterior sagittal approach and total urogenital mobilization for vaginal pull-through.

24.4.4 Definitive Reconstruction

The timing and nature of the definitive reconstruction in cloaca patients are based on the clinical judgement and experience of the surgeon. The objectives include enabling faecal continence, urinary continence and a functional genital tract. Patients should be stable from a cardiovascular and urologic perspective, >5 kg of weight and over 6 weeks of post-gestational age. Through a posterior sagittal approach, the first structure to be opened in cloaca is the rectum, which is split in the midline; the vaginal and urethral communications are identified through the rectal opening. In high rectal communications, a laparotomy may be required. If there is a long common channel and a short proximal urethra, it may be opted to retain the common channel as the urethra, particularly if it is not too wide. The rectum and vagina are separated from their surrounding structures and pulled down to their anatomical positions on the perineum. The rectum is transected flush to the vaginal wall. The most difficult part of a cloacal repair this way is separation of the vagina from the urethra. Total urogenital mobilization, which was first introduced in 1996 [31], is an attractive option for cases with a short common channel for this reason. It involves mobilization of the urethrovaginal junction en bloc and bringing this down to the perineal skin, thereby only requiring separation of the rectum. In low confluences, posterolateral mobilization of these structures is sufficient, but in higher confluences, anterior retropubic dissection is also required. When required, vaginal reconstruction may be performed using bowel segment transposition with the (1) sigmoid colon or (2) ileum.

24.4.5 Basic Principles of Aftercare During the First Year of Life

Adequate aftercare of patients with ARMs is at least as important in securing optimal functional outcomes as a successful primary repair. Patients should be cared for in centres that are also able to provide high-quality, multidisciplinary manage-

ment of both the ARM and associated anomalies. In terms of bowel function, a tendency to constipation is a central feature that affects all types of ARMs. The aetiology may relate to developmental factors or to corrective surgery. The onset is commonly around the time the child begins to take solids, around 3–6 months of age. After surgical repair, patients should be reviewed in outpatients at regular intervals to ensure satisfactory stooling, and parents should be educated on the importance of attending to constipation. Most constipation in ARMs responds well to oral laxatives that include bulking agents (macrogols), lactulose and stimulant laxatives (natrium picosulphate). Treatment should be continued until the tendency to constipation completely resolves, which may not be for several years in some cases. Failure to address constipation can lead to severe complications, including megarectosigmoid from faecal impaction and secondary overflow incontinence [19]. Apart from an increasing level of the malformation, other negative prognostic factors for bowel function in ARMs are severe sacral defects, meningomyelocele and significant cognitive impairment. The families of patients with complex ARMs may benefit from additional psychological support to ensure appropriate adjustment to the child's condition and other disease-related stressors.

24.4.6 Long-Term Bowel Function

Parental counselling and open dialogue with regard to the functional outlook and possible problems can serve to establish a good foundation for the future years of follow-up. In mild ARMs, the functional outcomes are likely to become comparable to normal with adequate management of constipation, and toilet training from diapers can also be expected to occur at the normal age [17, 22]. In females with perineal or vestibular fistulas, at least 2/3 achieve normal bowel function over time, although minor continence disturbances may affect a proportion beyond the growth period [23]. In urethral fistula, the continence outcomes reduce with increasing level of fistula. They are good in approximately 40%, with the remainder reporting varying degrees of residual symptoms. Although the majority of patients with high bladder neck fistulas achieve social continence with modern care, secondary measures for bowel management such as an antegrade continence enema (ACE) conduits are likely to be required [27]. Secondary interventions aim to enable weaning from diapers before primary school and to ensure normal social integration during childhood. In cloaca, approximately half of patients attain faecal and urinary continence, and the remainder stay clean or dry by adjunctive measures, including bowel management, continent urinary diversion or intermittent catheterization [32]. However, most patients with ARMs report a normal quality of life after contemporary treatments in the long term [32, 33].

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Congenital Pouch Colon

25

Devendra K. Gupta, Shilpa Sharma, and Kashish Khanna

25.1 Introduction

Congenital pouch colon (CPC) is a type of anorectal anomaly where a pouch-like dilated and shortened colon is associated with the anorectal malformation (ARM). It is reported widely from the South Asian subcontinental countries India, Pakistan and Bangladesh with anecdotal cases from other parts of the world [1, 2].

CPC comprises of around 5–15% of all cases of ARM in Northern India, 8–10% in Pakistan and 1.7% in Bangladesh. Its incidence is as higher in tertiary centres especially in high ARM to the tune of one fifth to one sixth of the cases [3]. It is more common in males than in females (3:1–7:1) [2, 4].

25.2 Definition

Pouch colon is a type of anorectal agenesis in which the whole or a part of the colon is replaced by a pouch-like dilatation that communicates distally with the urogenital tract by a large fistula. This supralevator anomaly is associated with a colonic pouch of variable length and diameter. It has a short and poorly developed mesentery, absent taenia coli and no appendices epiploicae or haustrations and usually has a very thick wall.

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25.3 Anatomical Criteria

CPC most commonly fits in the following anatomical criteria [1, 2]:

1. There is anorectal agenesis.
2. The total length of the colon is short.
3. The colon has a pouch of varying length (5–15 cm) and form (saccular or diverticular) with collected meconium or faecal matter.
4. The pouch has an abnormal blood supply. It is usually supplied by the branches from the superior mesenteric artery, which form a leash of vessels around the pouch.
5. It has a uniformly thick and muscular colonic wall with hypertrophied mucosa.
6. In females, the pouch opens into the genitourinary tract via a wide, long and muscular fistula, closely adherent to the bladder wall either open into the vaginal wall, the vaginal septum between two hemi-vaginae, bladder or rarely in the perineum. In males, there is a short fistula that communicates with the bladder usually opening in the dome or posterior wall of the bladder.
7. There is no transitional zone between the pouch colon and the normal bowel, and the bowel pattern changes suddenly and abruptly.
8. CPC frequently has other associated major anomalies especially the genitourinary anomalies.

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25.4 Classification

In 1984 Narasimharao et al. suggested the name CPC syndrome and classified it into types I–IV based on the length of the normal colon proximal to the colonic pouch [5]. Wakhlu et al. (1996) classified it into types A and B based on the need for coloplasty [6]. It was in 2005 that Gupta and Sharma modified this classification based on the management of CPC into incomplete and complete varieties and CPC was recognized as rare/regional anomalies in the Krickenbeck classification of ARM [1, 7, 8]. The classification was based on the feasibility to use the remaining colon while performing the pull-through.

The Gupta and Sharma (2005) classification has been described (Fig. 25.1) as:

Complete: There is either none or little normal colon left that is insufficient for performing the pull-through.

Incomplete: The length of the normal colon is adequate enough to perform the pull-through without the need for doing a coloplasty.

25.4.1 Characteristics of Subtypes

Complete CPC: A large, dilated, thick-walled pouch occupies most of the left side of the abdomen. Cecum, if present, almost always opens into the sac from the right side. It may be associated with an absent, rudimentary or double appendix. The pouch is usually supplied by the superior mesenteric artery on the superior and right side and an arcuate extension of superior mesenteric artery on the left side [9].

Incomplete CPC: The pouch usually occupies the left half of the abdomen with adequate length of the normal colon which opens into the pouch from the right. Apart from the branches of superior mesenteric artery, the pouch in its lower half may be supplied by the inferior mesenteric artery [1].

With growing awareness of the anomaly, incomplete pouch colon is more commonly recognized [2].

The genitourinary fistula opens at various levels in males and females (Fig. 25.2).

In female newborns with CPC often mucosal folds radiating inwards and upwards from the margins of the vestibule may be seen (Fig. 25.3).They may usually have a short wide urethra, deficient bladder neck, small bladder, poorly developed trigone and laterally placed ureteric orifices [10, 11]. These features may be responsible for the higher incidence of urinary incontinence (around 85%) seen in these patients [10].

Rarer varieties of pouch colon have been described with double pouch with associated rectal atresia, pseudoexstrophy bladder and associated duplicated exstrophy bladder [12–14]. The embryologic basis of the association of pouch colon with duplicate bladder exstrophy has been proposed as malposition of allantoic diverticulum with the yolk sac resulting in anorectal malformation or sequestration of a part of the allantois, infraumbilically and improper mesodermal progression giving rise to duplicate bladder exstrophy [14].

Gupta and Sharma operated a newborn with a patent pouch colon opening at the umbilicus and connected to the bladder via a fistula with no normal intervening colon. The ileum opened into the pouch-like structure. The baby had an associated bifid scrotum and meningomyelocele [15]. Short colon has been described by Chiba as a shortened length and a narrow calibre of left colon without associated ARM in babies usually born to diabetic mothers [16].

25.5 Embryopathogenesis and Aetiology

CPC is a complex congenital anomaly thought to have resulted due to error during the partitioning of cloaca at around 4–6 weeks. During development, a coronal wedge or ridge of mesenchyme, the urorectal septum (URS), forms in the angle between the allantois and the hindgut. As the URS grows caudal towards the cloacal membrane, it divides the cloaca into an anterior portion, the primitive urogenital sinus, and a posterior part, the anorectal canal. By 7 weeks of age, the URS reaches the cloacal membrane and fuses with it. Thus, the failure of rostrocaudal growth of the

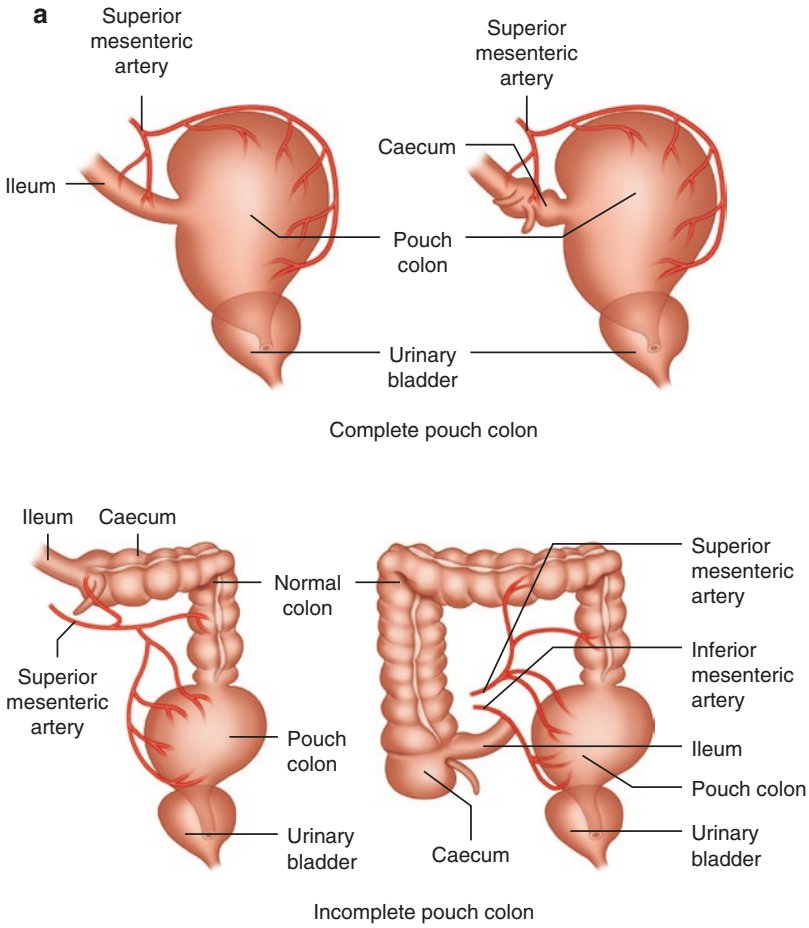


Fig. 25.1 (**a**–**c**): (**a**) Modified classification of congenital pouch colon (incomplete and complete CPC). (**b**) Operative photograph of incomplete pouch colon showing sufficient length of the normal colon. (**c**) Operative photograph of complete pouch colon with the ileum seen entering into the pouch from the right side

URS would cause an arrest of cloacal septation with hindgut opening above the level of Wolffian duct in males and at a similar level in females. The earlier the timing of arrest, the more are the chances of complete pouch. Various theories have been proposed for the same [15] (Table 25.1).

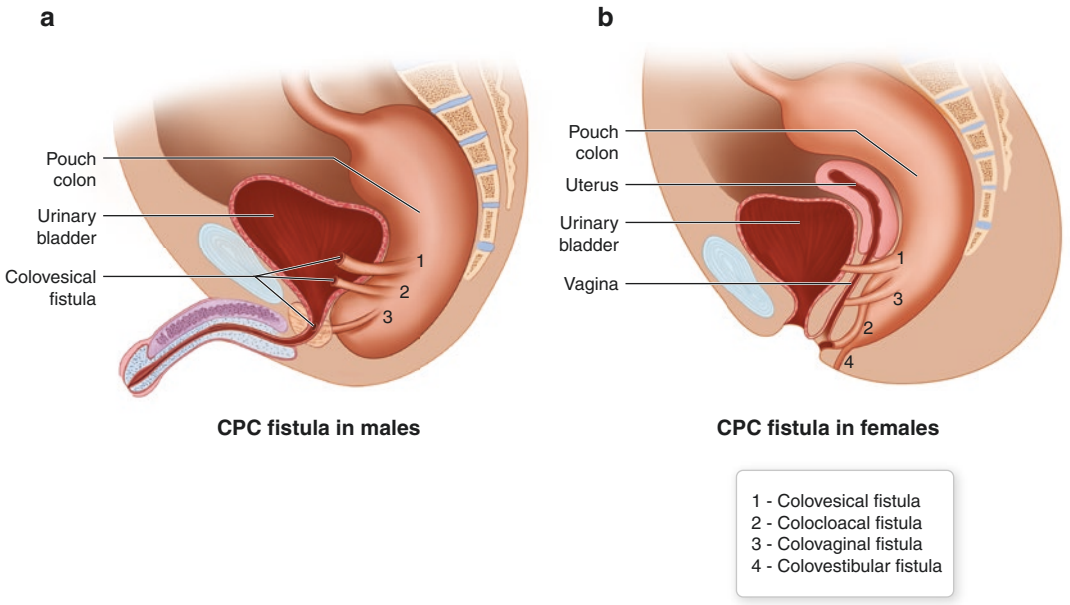


Fig. 25.2 (**a**, **b**): Showing site of fistula. (**a**) In males, colovesical fistula in males opens either in the posterior wall of the bladder (1), near the bladder base (2) or just above the bladder neck (3). (**b**) In females, common sites of fistula are colovesical (1), colocloacal (2), colovaginal (3) and colovestibular (4)

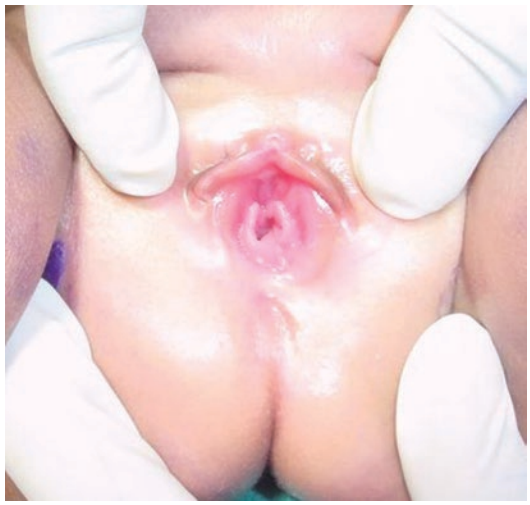


Fig. 25.3 External examination of a girl with common cloaca and incomplete CPC, showing wide vestibule with folds radiating inwards

The major aetiological factors currently proposed to be involved are [15]:

- *Vascular*: The blood supply to the pouch is always abnormal and is mainly from the branches of the superior mesenteric artery.

Table 25.1 Theories of faulty embryogenesis in CPC

	Proposed by	Theory
I	Dickinson	Aborted hindgut development following obliteration of the inferior mesenteric artery early in foetal life [17]
II	Chatterjee	Improper development of the postaxial midgut or presplenic gut due to a primary disorder of the proximal end of the hindgut or postsplenic gut [18]
III	Wu	Faulty rotation and fixation of the colon leads consequently to a disturbed longitudinal growth [19]
IV	Wakhlu	The anomaly is a stage in the development of cloacal exstrophy and is the combined effect of defective development of the splanchnic layer of the caudal fold and failure of rotation of the gut causing defective longitudinal growth of the colon [9]
V	Gupta and Sharma [2007]	Role of pesticides, micronutrients or the vitamin deficiency in a largely vegetarian community with poor socioeconomic status, affecting the vascular supply in the growing hindgut of the foetus at a critical window period of gestation [2]. Any genetic link, though suggestive of a strong geographical distribution, still needs to be confirmed

The absence of inferior mesenteric artery in 50% of the cases points towards early vascular insult during the foetal period.

- *Environmental*: The high density of cases in the northern parts of the Indian subcontinent strongly suggests a possible association with deficiency of micronutrients (iodine, vitamin B and zinc) and the liberal use of pesticides and fungicides which may affect the pregnant mother during organogenesis.
- *Genetic*: Recent reports in the literature have shown that germline mutations/deletions of genes encoding the proteins of signalling pathways (NOTCH, Wnt gene and Hedgehog) of the normal colon result in its malformation. Maudar et al. reported an immunohistochemical study of colonic pouch tissue that revealed an enhanced expression of beta-catenin, Ihh, Notch1 and HMGA1 and commented on the expression of molecules from all three embryonic signalling pathways [20]. However, more biochemical and molecular studies are still required.

25.6 Histopathology

Various studies have revealed abnormal histopathological changes in the pouch. Gupta and Sharma found disorganization of the muscle coat in an arborizing manner as a salient feature [1]. It is not clearly differentiated into inner circular and outer longitudinal muscles but is disarranged in a decussating pattern. The circular muscle may be incomplete in 50% cases [15]. In the nerve plexus, the ganglion cells are mature and present in all cases with the presence of normal or occasionally hypertrophic nerve bundles. The pouch wall consists of normal ganglion cells though these maybe reduced in number and smaller in size [2]. However, giant ganglia are also seen in 10% cases [15]. Nerve bundle hypertrophy has also been reported [8]. Varying degrees of submucosal fibrosis may be present [21–23]. Mucosal congestion and focal haemorrhages are seen commonly. Occasionally, heterotopic epithelium (gastric/pancreatic/small intestinal) has been reported [21].

The typical histology of pouch and the mechanics of a grossly dilated colon with abnormal peristaltic activity mandate its removal for a better functional outcome when feasible, especially in incomplete pouch colon. Gangopadhyaya et al. concluded from their study on histopathologic evaluation that the pouch is an abnormally developed tissue and needs to be resected for better functional outcome of the remaining gut [23].

25.7 Clinical Presentation

Most cases present early within the first 7 days of life with an absent anal opening and gross abdominal distension [1]. Meconuria may be present in up to half of the cases. There may be associated bilious vomiting. In case the pouch perforates, the newborn may present with pneumoperitoneum, peritonitis and sepsis. Abdominal distension may not be marked in incomplete pouch and in female patients decompressing well via colocloacal fistula. Such patients may present late.

25.8 Investigations

In addition to the clinical examination and the endemic disease pattern, an erect anteroposterior skiagram helps to clinch the diagnosis in suspected cases of CPC. In cases of complete pouch colon, a large bowel loop with a single air-fluid level occupying more than 50% of the abdominal width ending at a supralevatoric level with its apex positioned in the left hypochondrium is usually seen. In cases of incomplete pouch, the apex of the pouch may be in the right hypochondrium or variable in position [24]. On an invertogram, the pouch is proximal to the pubococcygeal line (Fig. 25.4a, b). In case of perforated pouch, pneumoperitoneum may confound the diagnosis of CPC. Similarly in very wide CVF, the gas may escape into the urinary bladder, and a cross-table prone/lateral film will help to differentiate.

Before the child undergoes a definitive surgery, an ultrasound of the abdomen, an intravenous urogram and voiding cystourethrography and an echocardiography should be done to rule out other associated anomalies. Examination under anaesthesia (EUA) and cystourethroscopy may help to confirm diagnosis in females. In

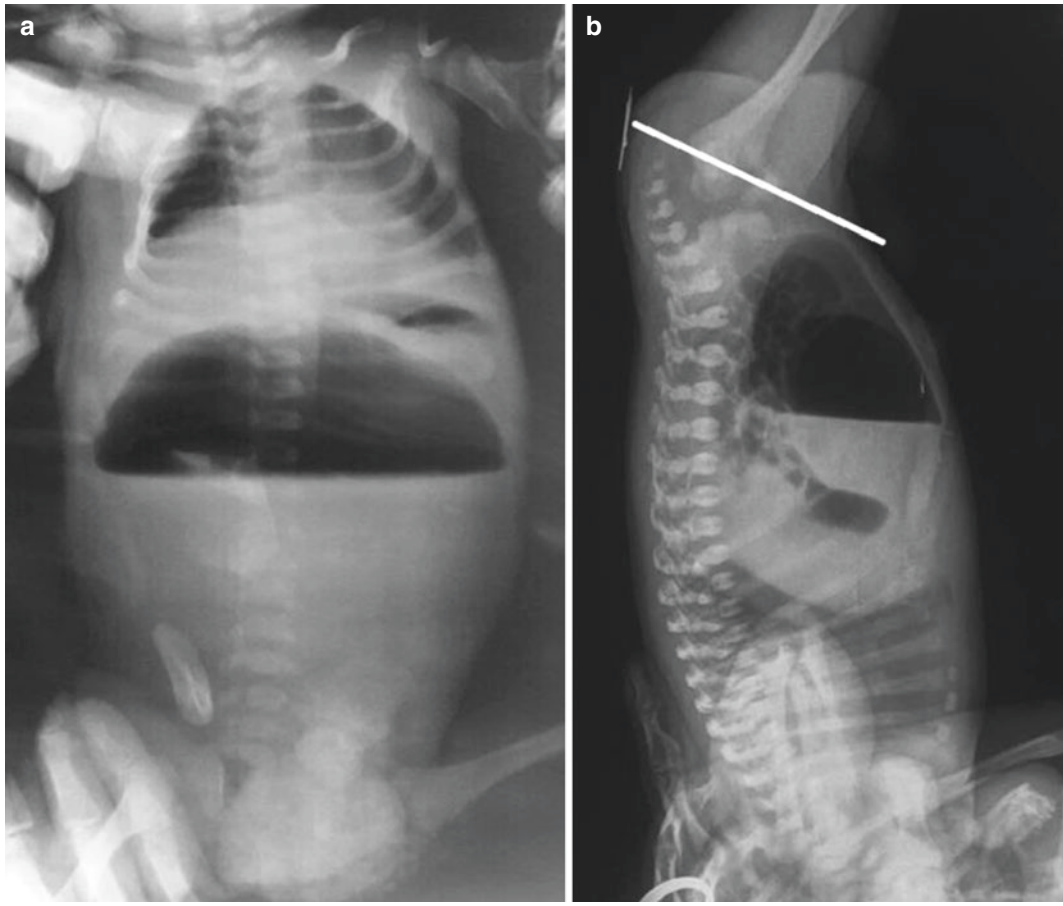


Fig. 25.4 (**a**) X-ray abdomen erect (AP view) showing a large air-fluid level occupying more than 50% of the abdomen suggestive of a pouch. (**b**) Invertogram with a large air-fluid level ending above the PC (pubococcygeal) line

males, cystourethroscopic examination shows that the CPC fistula usually ends above the bladder neck [10]. However, in endemic regions, the diagnosis is almost confirmed on the anteroposterior film, and an abdominal exploration is indicated directly without cystoscopic confirmation. In females, endoscopy may help to prognosticate about the urinary incontinence.

Other causes which may mimic the diagnosis of CPC include:

- ARM with hugely dilated rectosigmoid
- ARM with hydrometrocolpos
- ARM with a rectouterine fistula
- Localized pneumoperitoneum due to a sealed perforation

25.9 Associated Anomalies

The genitourinary anomalies like vesicoureteric reflux, renal agenesis and bicornuate uterus, followed by gastrointestinal anomalies like absent appendix or double appendix are most commonly associated with CPC. Table 25.2 summarizes the other associated anomalies.

Table 25.2 Common associated anomalies reported in literature [2, 15]

Type	System	Anomalies
I	Genitourinary system	Vesicoureteric reflux Hydronephrosis Renal dysplasia/agenesis/ectopia Pseudoexstrophy bladder Cryptorchidism Hypospadias Urethral anomalies—diverticulum, duplication, megalourethra, stricture Prune belly syndrome Bicornuate uterus Double uterus/vagina Septate vagina
II	Gastrointestinal system	Absent appendix Double appendix Malrotation Meckel's diverticulum Duplication of colon Oesophageal atresia
III	Vertebral and limb anomalies	Sacral agenesis (partial/complete) Hemivertebrae Meningomyelocele Congenital talipes equinovarus
IV	Cardiovascular system	Congenital heart disease

25.10 Management

25.10.1 Preoperative Resuscitation

Initial management includes nasogastric tube decompression, dehydration and electrolyte correction, temperature maintenance, bladder catheterization and proper antibiotic coverage. Surgery should be aimed at preserving the available length of the colon for ensuring adequate absorption, faecal storage and continence postoperatively. A staged management has been widely accepted for CPC. Single-staged surgery is not routinely advocated due to unacceptably high mortality rate [1, 2, 22].

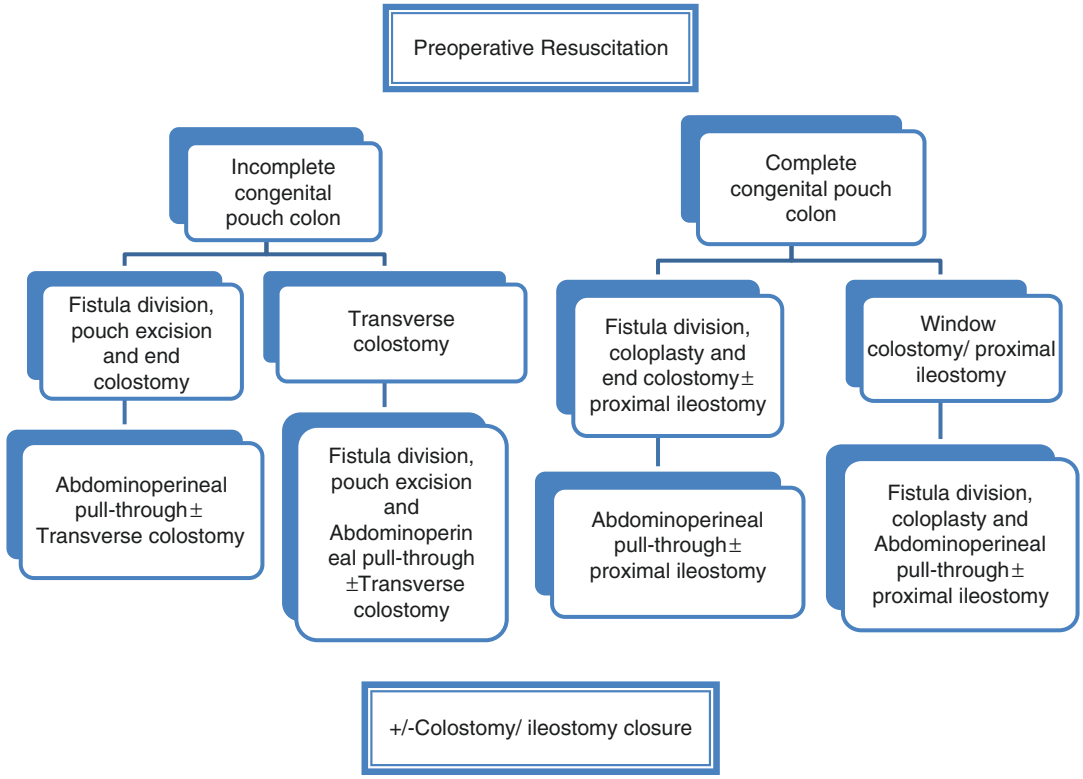
25.10.2 Incomplete Pouch

In incomplete pouch, the preferred approach consists of fistula division, pouch excision and end colostomy followed later by abdominoperineal pull-through. The other option is initial window colostomy or a transverse colostomy followed by fistula division, pouch excision and abdominoperineal pull-through later at 6–18 months with or without a protecting transverse colostomy.

25.10.3 Complete Pouch

In complete CPC, tubularization of pouch till about 15 cm length is essential to preserve the function of the colon [1, 2]. Hence fistula division, coloplasty, end colostomy and a proximal ileostomy followed by an abdominoperineal pull-through of the tubularized colon later are the preferred approach. Alternately a window colostomy/proximal ileostomy can be done as an initial procedure depending upon the condition of the baby, technical skills of the surgeon and the available facilities.

25.10.3.1 Management Algorithm of CPC



Window colostomy: An opening made in the anterior surface of the pouch. Fistula is not ligated.

Advantages

- Simple procedure
- Minimum anaesthesia required
- Less operative time
- Provides adequate decompression
- Can be done in a sick neonate

Disadvantages

- Complications: massive pouch prolapse, bleeding from prolapsed pouch, pouch recession and stenosis
- Incomplete decompression requiring regular washouts
- Recurrent urinary tract infection and enterocolitis due to persistent fistula
- Pouchitis
- Adhesive obstructions
- Septicaemia and failure to thrive
- High mortality (15–20%) [15]

End colostomy is the preferred procedure. Stoma-related complications like stomal retraction, prolapse, peristomal excoriation, bleeding, anaemia, stomal diarrhoea and poor weight gain are seen more in ileostomy and transverse colostomy than in end colostomy.

Coloplasty: In complete CPC, the pouch first mobilized completely by dividing the inferior mesenteric artery (if present). Thereafter, the pouch is incised on the anti-mesenteric border, preserving the vascularity, and a tube is fashioned over a red rubber catheter to obtain a uniform calibre. This coloplasty may be brought out as an end colostomy on the abdominal wall for a staged procedure and can be pulled down later during definitive procedure. In neonates though, a primary pull-through is possible, but it is associated with high morbidity and even mortality [1] (Fig. 25.5).

Advantages

- Preserves adequate length of the colon for functional purposes (about 15 cm)
- Less faecal incontinence and diarrhoea later as compared to ileal pull-through cases

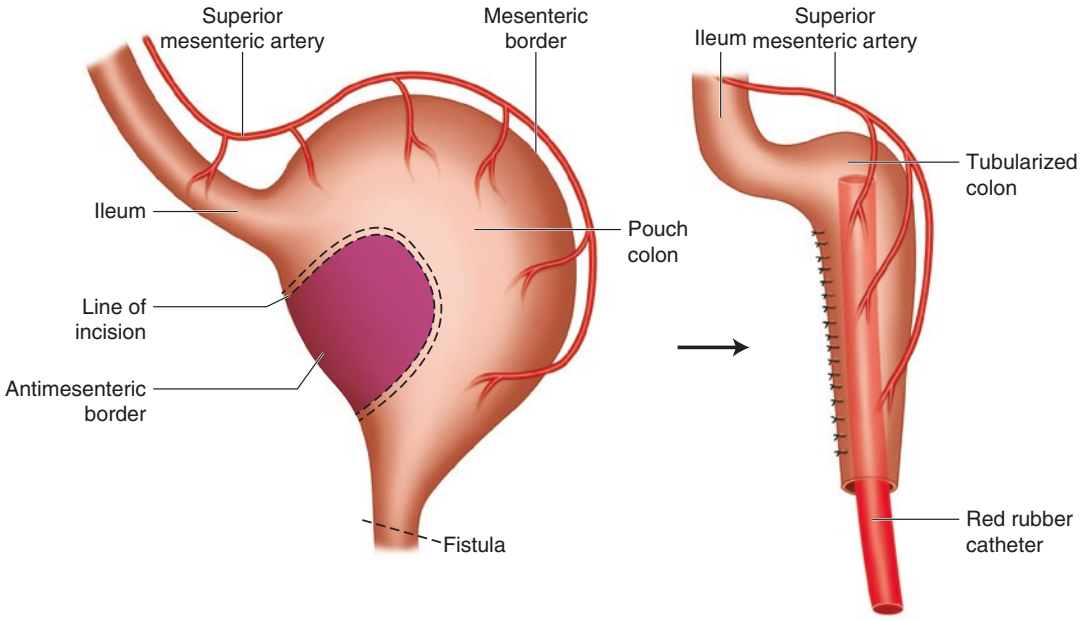


Fig. 25.5 Coloplasty is performed while preserving the vascular arcade to the pouch

Disadvantages

- Suture line leak
- Wound dehiscence
- Constipation
- Re-dilatation
- High mortality if not performed as a staged procedure
- Increases operative time during initial surgery

In case if the child presents with a severely ischaemic/gangrenous pouch or a pouch with multiple perforations, then pouch excision, fistula ligation and a proximal ileostomy remain the safest option.

Definitive surgery: It is usually performed after 6–18 months when the child has gained enough weight and has been evaluated completely for other associated anomalies. In incomplete pouch, the abdomino-posterior sagittal anorectoplasty approach (abdomino-PSARP)/abdominoperineal pull-through (APPT) is performed with the child in supine lithotomy position. In complete pouch, the tubularized colon is pulled down to create a neoanus by APPT. The complications and the appropriate management of pull-through surgery are given in Table 25.3.

Table 25.3 Complications related to pull-through surgery in CPC

	Complications	Management
I	Mucosal prolapse	Mucosal excision
II	Anal stenosis	Regular anal dilatation starting 3 weeks after pull-through
III	Colonic re-dilatation of the coloplasty segment	Redo surgery using shorter pouch length for retubularization is required sometimes
IV	Shortened colon length leading to recurrent watery diarrhoea and poor weight gain	Adequate vitamin, mineral and dietary fibre supplementation
V	Faecal incontinence	Bowel management and dietary modifications

A protective stoma (ileostomy/transverse colostomy) is preferred during a pull-through surgery. This could later be closed after 3–6 months.

Use of pouch in common cloaca: The pouch can be used to reconstruct the vagina and the anorectum both at the same time by splitting it longitudinally into two while preserving the blood supply of either segments [25].

25.11 Follow-Up

Initial follow-up examination is performed after 2 weeks and then after 1 month. Then 3-monthly follow-up for the first year and 6-monthly follow-up for the next 3 years are required. Thereafter the child can be followed up once in 2 years till adulthood to assess for long-term results.

Initially the baby passes frequent liquid stools, but subsequently, the frequency decreases and the consistency changes to semisolid and over months to solid. Perineal excoriations and bacterial and fungal infections are common in the initial period. The colon on follow-up examination shows normal calibre in most of the cases; however, dilatation of the tube coloplasty is rare but a serious problem [1, 23].

25.12 Outcome and Prognosis

The mortality in patients of CPC has decreased from 30–40% to 10–20% with the growing awareness and improved management of this disease [3]. Prognosis and results depend upon various factors:

- The age at presentation
- The weight of the child
- Presence of sepsis and perforation
- Associated congenital anomalies
- Complete/incomplete pouch colon
- Type of perineum and the muscle complex
- Surgical expertise and NICU care
- Nutritional management
- Compliance to follow-up

Babies with incomplete pouch colon fair better than those with complete pouch colon.

Faecal continence: Most patients have fairly good continence results by puberty. However, around 60% of children with complete pouch colon may have faecal incontinence in the initial few years after pull-through surgery. Oral loperamide/diphenoxylate, daily colonic washes may improve the dry interval.

Urinary incontinence: Though not a common problem, it may persist in females with CPC associated with wide bladder neck or in those with associated sacral anomalies and poor pelvic musculature.

Growth and development: In a study on functional outcomes of CPC patients, Puri et al. found that all 13/22 (59.1%) patients with an ileal pull-through had height and weight less than the 50th percentile of the expected value for age [26]. However, 9/22 (40.9%) patients with types III/IV CPC or type I/II CPC with pull-through after coloplasty had near-normal growth patterns or parameters between the 50th and 80th percentile.

Nutritional outcomes: These patients require monitoring of nutritional status. Anaemia and malnutrition are common in complete CPC patients, and hence early dietary modification, high-protein consumption and micronutrient supplementation are important.

Colonic re-dilatation: Incidence reported varies. This occurs primarily because the colonic pouch has an abnormal histology and a tendency to dilate. Hence, the use of a shorter segment of pouch for tubularization is now recommended.

25.13 Future

Leads from the past will lead to the work in the future in the field of CPC. The exact aetiopathogenic factors responsible for CPC still need to be explored. A genetic link though pointed by the typical geographic distribution of CPC needs to be studied further. Environmental association with micronutrient deficiency may provide a scope for prevention of this disease. Management of faecal incontinence and urinary incontinence especially in girls still remains a challenge. Long-term follow-up studies of these patients till adulthood are required to form a proper management protocol and improve the quality of life of these patients [27].

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Inguinal Hernia and Hydrocele

26

Ciro Esposito, Maria Escolino, Alessandro Settimi, and Giuseppe Cortese

26.1 Introduction

The incidence of inguinal hernia (IH) varies between 1 and 5% in the pediatric population with a strong male preponderance [1]. Preterm babies have a higher likelihood to develop inguinal hernia with an incidence that has been reported to be as high as 30% [2, 3]. The incidence of incarceration in untreated hernias in young children has been reported to vary between 6 and 18%, but it can exceed 60% during the first 6 months of life [4]. Bilateral inguinal hernia is significantly more common in younger patients with an incidence of about 50% if patients are less than 1-year-old [5].

As a consequence, inguinal hernia repair is one of the most common surgical procedures performed by pediatric surgeons [6, 7]. In pediatric population, the traditional inguinal approach is an excellent method for hernia repair [8]. However, it has the potential risk of injury of the spermatic cord and vas deferens, hematoma, wound infection, iatrogenic cryptorchidism, testicular atrophy, and recurrence of hernia [9, 10].

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In particular, in small babies, this can be a daunting procedure, due to the fragile hernia sac, small anatomic region, and possible comorbidities, so frequent in ex-preterms [11]. Similarly, the incidence of postoperative issues (recurrence and testicular atrophy) has a higher incidence in infants compared to the general pediatric population [12–14].

Open herniotomy (OH) has always been the standard procedure for this group of patients over years. During the last decade, laparoscopic IH repair (or herniorrhaphy) (LH) has become a routine procedure in older children, but its use in neonates and premature babies is still limited [15–20]. Reported advantages of laparoscopic hernia repair include excellent visual exposure, minimal dissection of vas deferens and spermatic vessels, fewer complications, comparable recurrence rates, and improved cosmetic results compared to the traditional open approach [21, 22]. In addition, laparoscopic approach allows diagnosis and repair of contralateral patent processus vaginalis (CPPV), uncommon types of hernias (femoral, direct, combined hernia), and recurrent or complicated hernias [4, 23]. During the first year of life, the probability of finding a patent processus vaginalis (PPV) on the contralateral side may be up to 50% of cases [24], and the incidence of metachronous hernia ranges from 1 to 38% as reported in different studies [25]. Recently, few authors have reported successful treatment of these infants through laparoscopy. Controversy remains about a possible increase in length of

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operative time, costs, indications, and contraindications and the need of orotracheal intubation for anesthesia [26–28]. Difficulty in operative technique, comorbid conditions, and high anesthetic risk in premature babies may be still the reasons for the preference of open repair in many centers [15]. Furthermore, the timing of IH repair in infants – early or delayed – still remains a matter of debate.

26.2 General Considerations

26.2.1 Diagnosis

As for the diagnosis of inguinal hernia, it is a clinical diagnosis. In general, patients with hernia are assessed by history and clinical examination [29]. Their history often reveals a sudden, intermittent appearance of a bulge in the inguinal region or in the scrotum during diaper change or after bathing. This is also usually seen during crying or defecation [30]. In cases of hernia incarceration, it can cause an intestinal obstruction, and the child may have vomiting and abdominal distention. If the hernia is incarcerated at the time of examination, a mass is usually palpated in the inguinal region [31] (Fig. 26.1). In girls, a small mobile mass often appears in the groin or labia, which usually represents an ovary [32]. The differential diagnosis of hernia from a hydrocele is important. In case of a hydrocele, there is a painless swelling within the scrotum. It is larger in the evening than in the morning. Clinical examination reveals a fluctuant painless swelling, which may or may not be reducible. Transillumination reveals a fluid-filled scrotum, which may be bilateral above all in infants [33] (Fig. 26.2).

26.2.2 Anesthesia

The vast majority of infants and children undergoing surgical treatment of inguinal hernia require pre-anesthetic medication and general anesthesia [34].

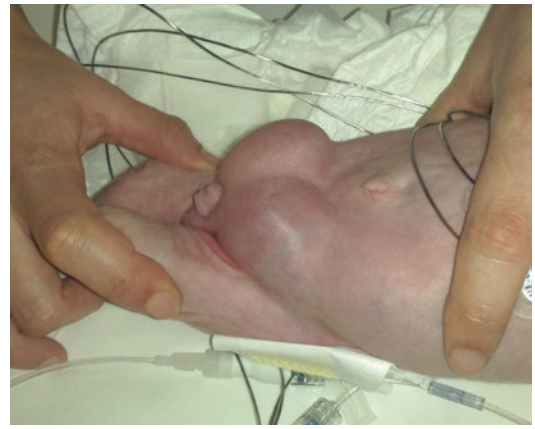

Fig. 26.1 A giant bilateral inguinal hernia in a newborn

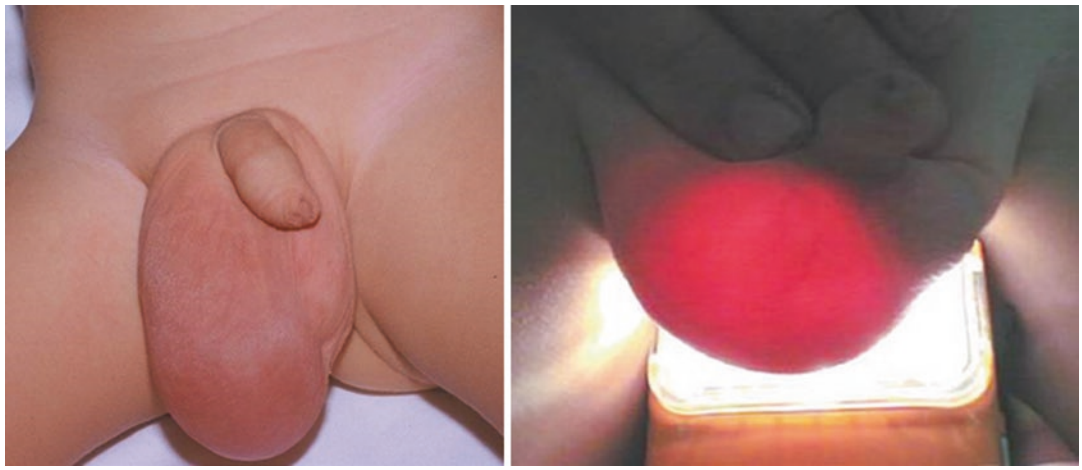

Fig. 26.2 Transillumination, revealing a fluid-filled scrotum, confirms the diagnosis of hydrocele

The anxiety of separation is enormously experienced. The inherited, the personality, the previous experiences, and the anxiety of parents are the factors involved in the severity of the children anxiety. Recalling the early phases of anesthesia which begins with the placement of anesthesia mask and follows with the smelling of the anesthetic gas is an unpleasant experience. Some medications such as benzodiazepines are used as pre-anesthetic tranquilizers. Midazolam, in the oral route, is a common pre-anesthetic medication. Some studies reported the doses of 0.25 mg to 1.0 mg/kg for midazolam, when employed as a pre-anesthetic tranquilizer. In regard to the general anesthesia, it can be accomplished in many ways depending on the experience and preference of the anesthesiologist.

At the arrival in the operating room, in each patient, pulse oximetry, heart rate, and noninvasive arterial blood pressure are monitored. Anesthesia is induced with sevoflurane 8% in oxygen 6 L/min via face mask. Sevoflurane is currently one of the volatile agents of choice in pediatric anesthesia because of its acceptance for inhalation induction. It is suitable because it has a pleasant smell, it does not irritate the airways, and its blood-gas partition coefficient is slightly greater than that of desflurane or nitrous oxide. A vascular access is taken (22 or 24 gauge) after loss of the eyelash reflex, and opioid is given to maintain a suitable depth of anesthesia.

Airway management using laryngeal mask or endotracheal tube is an acceptable alternative [35]. The relative ease of insertion and lower rate of airway complications compared to endotracheal intubation make laryngeal mask use a logical choice, but the use of an endotracheal tube is the safest strategy for the patient with a full stomach and an irreducible inguinal hernia and for laparoscopic surgery.

Anesthetics produce dose-dependent and drug-specific changes in the mechanics and in the central control of the respiratory center. Inhaled anesthetics decrease muscle tone within the airways, chest wall, and diaphragm, in addition to inhibiting central respiratory drive and responsiveness to ventilatory stimulants such as carbon dioxide. Intravenous anesthetics may also alter respiratory function, while opioids produce a dose-dependent depression of medullary respiratory centers, also resulting in decreased responsiveness to partial pressure of carbon dioxide (PaCO2). For these reasons regional anesthesia is often used in combination with general anesthesia for pediatric surgery and has been shown to reduce general anesthetic requirements, opioid use, postoperative nausea and vomiting, and pain [36, 37].

Pain is of the utmost concern in patient recovery. By providing optimal pain management, providers can improve patient and parents' satisfaction, mobility, compliance, hemodynamic alterations from stress responses, and potentially even wound healing.

So the regional anesthesia is often used to supplement general anesthesia and provide postoperative analgesia. The most common forms used are regional nerve block or caudal anesthesia performed after the induction of general anesthesia [38].

As for the regional nerve block, the local anesthetic is introduced at a puncture site 1 cm medial to the anterior superior iliac spine. Because the nerves most commonly run below the external oblique, the needle is advanced until a "click" is felt as the needle passes through the external oblique, and the local anesthetic is injected. Caudal block is performed by injecting local anesthetic into the epidural space via the sacral hiatus. Standard dosing provides neuraxial blockade of sensory input at and below the T10/umbilical dermatome [39].

Finally, the intranasal use of clonidine to awakening is interesting [40].

Clonidine acts as an agonist at a2 adrenoceptors. The locus ceruleus (LC) is the site of action for the sedative effect of clonidine. The LC contains a high density of a2 adrenoceptors. Following binding of clonidine to a2 adrenoceptors, hyperpolarization of noradrenergic signaling to the ventrolateral preoptic area (VLPO) occurs, thus producing sedation.

The drug is rapidly absorbed by the nasal route and peak plasma levels are reached within 10 min. No sign of irritation or edema in the nasal cavity has been observed after a single dose. Intranasal

administration of drugs is an easy and minimally invasive alternative route of administration: a relatively large surface area is available for drug absorption, and a thin, very vascularized epithelium ensures rapid absorption and onset of therapeutic action by avoiding the first-pass effect.

26.2.3 Anesthetic Risks in Premature Infants

Premature infants are at a higher risk for developing postoperative respiratory complications compared with full-term and even older premature infants [29]. Steward reported that 33% of premature infants undergoing hernia repair developed respiratory complications, most commonly apnea [41]. All of the infants with apnea weighed less than 3 kg at the time of surgery and were under 10 weeks of age.

Allen and coworkers reported an association with the use of intraoperative narcotics and muscle relaxants and the incidence of postoperative apnea-bradycardia episodes in ex-premature infants with a postconceptual age of <60 weeks [42]. Warner and coworkers found that a history of apnea or respiratory distress syndrome significantly increased the chance of a postoperative respiratory event in premature infants undergoing herniorrhaphy [43]. A history of bradycardia or ventilatory support for 24 hours or more after birth was also a significant risk factor.

The anesthetic risk for former preterm infants is inversely proportional to the postconceptual age. However, there is still some controversy about the minimum postconceptual age that reduces the chance of a postoperative anesthetic event. Several studies have attempted to address this question, leading to recommendations ranging from 40 to 60 weeks postconceptual age [44, 45]. Although the postconceptual age has been shown to be the major risk factor, the presence or absence of a history of preoperative apnea or the need for ventilatory support also influences the safety of performing an outpatient procedure. Some studies also show that the presence of anemia is an independent risk factor for a postoperative apneic event [44, 45]. Recent literature has suggested that the use of regional anesthesia (spinal, epidural, or caudal) has a role in decreasing the risk of a postoperative respiratory complication as compared with general anesthesia [36, 46]. Perhaps this decreased risk may lead to a decreased need for inpatient postoperative monitoring in the ex-premature infant after an inguinal hernia repair.

26.2.4 Timing of Repair

Surgery is indicated for all pediatric patients where a diagnosis of inguinal hernia has been made [6, 7]. However, the timing of surgical repair in premature infants is controversial [13, 29]. In a small premature infant, the operation is technically more difficult and associated with a higher morbidity, including an increased incidence of testicular atrophy and recurrent hernias [14]. Furthermore, the anesthetic risk is higher in a premature infant. Some debate exists about the optimal time to repair the asymptomatic hernia found in a premature infant in the neonatal intensive care unit (NICU). The factors that must be considered in making the decision when to operate include the technical difficulties of a fragile hernia sac and higher risk of injury to the vas deferens or the testicular vessels, the presence of comorbid conditions associated with prematurity, and the anesthetic risks in a premature infant. Because of the risks of surgery in the premature infant, many surgeons used to discharge patients home from the neonatal intensive care unit (NICU) and repair their hernia once they reached a certain age or weight. With recent advances in anesthesiology and neonatal care, many surgeons have moved toward performing an early hernia repair before discharge from the NICU [3, 47, 48]. Proponents of immediate repair [31] justify the risk of an early operation based on an increased risk of incarceration with a longer waiting period before surgical repair. Others advocate waiting until an arbitrary weight or age criteria has been met, thereby optimizing some of the associated morbidities [49].

Vaos in 2010 and Uemura in 1999 demonstrated that the sooner the patients are operated on upon diagnosis, the lower is the risk of complications [50, 51]. Conversely, Lautz and colleagues

recently stated that delaying surgery of newborns and ex-preterms after discharge from the hospital does not increase the risk of complications [52].

Pini Prato et al. strongly recommended to perform herniotomies before discharge for neonates diagnosed during hospital stay and to schedule as soon as possible (within a month) those who present to the outpatient clinic [3].

In our practice, we typically repair neonatal inguinal hernias before discharge from the NICU. If the family is reliable, however, and the repair cannot be easily scheduled without prolonging the hospital stay, we perform the operation soon after the discharge.

26.3 Operative Techniques

Inguinal hernia in children can be treated through either an open or laparoscopic approach.

26.3.1 Open Inguinal Approach

Open technique of *inguinal hernia* repair requires an inguinal approach. An inguinal incision of about 3–4 cm is made on the ipsilateral side to the symptomatic inguinal hernia. The procedure involves the separation of the hernia sac from the surrounding cord structures, including cremaster muscle, vas deferens, and the testicular vessels or round ligament. This must be done using atraumatic dissection without seizing the vas and/or vessels as to avoid vas occlusion or testicular atrophy. A ligature is usually applied to the separated sac, and the distal sac is divided. There is no evidence in the literature if it is preferable to adopt a resorbable or a non-resorbable suture (Fig. 26.3). In general during the open repair of a unilateral inguinal hernia, there is no check of contralateral patency. In the 1980s French pediatric surgeons described the tech-

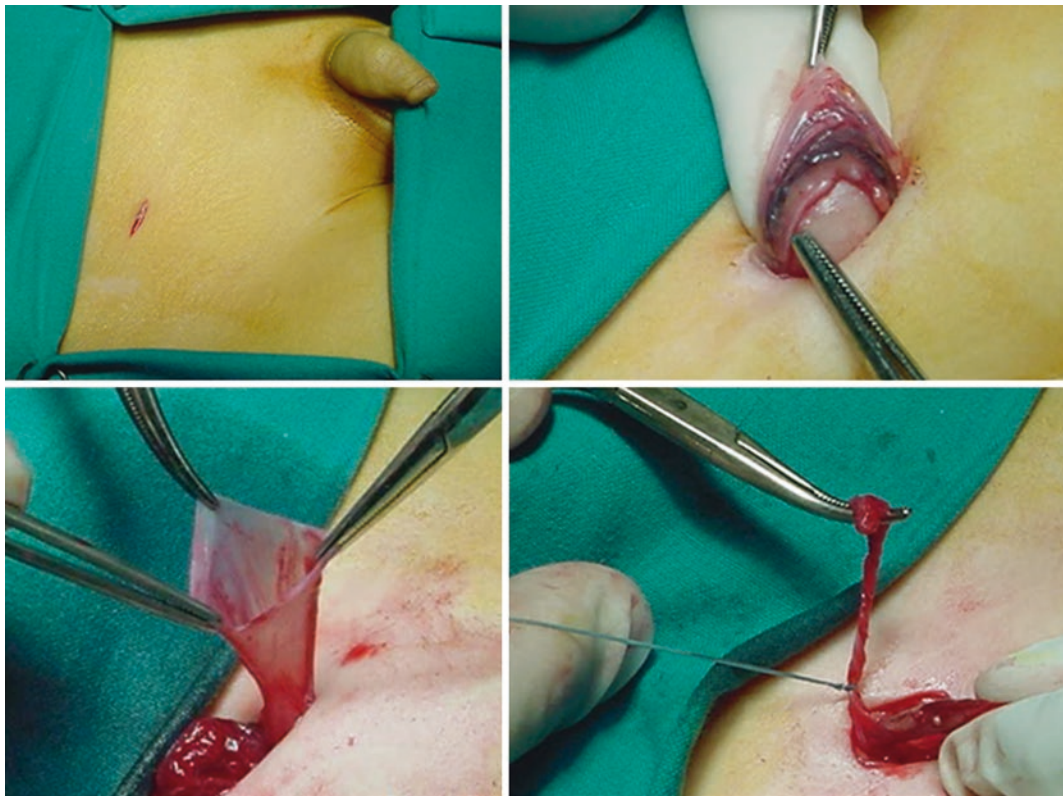

Fig. 26.3 Open inguinal hernia repair requires an inguinal incision, separation of the hernia sac from the surrounding cord structures, ligature, and division of the hernia sac

nique to check the presence of a contralateral peritoneal vaginal duct or hernia consisting in the passage of a 45- or 70-degree angled telescope through the hernia sac prior to ligation (hernioscopy) [53]. This technique of contralateral video control requires the use of the laparoscopic video column, the creation of the pneumoperitoneum, and the use of the optic and all laparoscopic equipment; for this reason this procedure is rarely adopted in the clinical practice.

26.3.2 Laparoscopic Approach

Laparoscopic inguinal hernia repair (or herniorrhaphy) (LH) in children has been introduced as an alternative method to conventional open herniotomy (OH) and first described by Montupet in 1993 [26–28, 54]. Regarding the technical point of view, there are many techniques now described for LH repair [55, 56]. The different repair options can be categorized as either intracorporeal or extracorporeal/percutaneous. In regard to intracorporeal repairs, in 1993 Montupet firstly described the technique, consisting in a purse-string suture performed on the periorificial peritoneum at the level of the internal inguinal ring [26–28]. In 1998, Schier introduced his technique, consisting in an "N"-shaped suture on the periorificial peritoneum [54]. In 2004, Becmeur and coworkers described the laparoscopic division and resection of the hernia sac at the level of the internal ring with subsequent closure of the peritoneal edges [57].

The extracorporeal techniques all involve the placement of a suture circumferentially around the internal ring and tying the knot using percutaneous techniques [58]. Loads of variations of this approach have been described. Recently, Ostlie and Ponsky stated that there is no sufficient evidence to support one approach or another [56]. However, the addition of the peritoneal incision intentionally created at the level of the internal inguinal ring, as reported by Esposito, seems to result in a more durable repair [6, 7, 59].

The laparoscopic approach can be performed either transperitoneally or through a preperitoneal approach (using special needles) with transperitoneal visualization [60].

The laparoscopic technique that we commonly adopt is the classic transperitoneal approach using three ports. The patient is always placed in supine position with a 15°–20° Trendelenburg inclination of the operative table to reduce the intra-abdominal pressure (IAP) and abdominal contents. The surgeon is positioned at the head of the patient and the camera operator contralaterally to the side of pathology, and the screen is placed at the feet of the patient. Average IAP is 6–8 mmHg in patients under 1 year of age. The emptying of the bladder using a Nelaton catheter is performed before surgery.

A 0° telescope of 5–10 mm through an umbilical port is used, allowing direct visualization of the deep inguinal rings, followed by the use of two 3-mm trocars in triangulation to keep a good ergonomics. As for the optic, the use of a 5- or 10-mm optic gives the same invisible scar in the navel; for this reason the use of a 5- or 10-mm optic depends on the instruments' availability. As for the operative 3-mm trocars, the majority of authors prefer to adopt screw trocars. The advantage of using screw trocars is fundamental above all in infants under 10 kg; in fact, in these categories of patients, the tissues and the skin are very thin, and the smooth trocars tend to slip out easily creating a subcutaneous emphysema. Screw trocars are more stable, and in addition you can change instruments rapidly, without dislodgement of the trocars and without gas leaks (Fig. 26.4). In case you have only smooth trocars, you can put a piece of Nelaton catheter around the cannula and then fix the piece of Nelaton catheter to the skin to stabilize the trocar (Fig. 26.4).

Some surgeons prefer to use instruments without the assistance of trocars (stub incision); also if using this technique, it may be difficult to change instruments.

The first step of the laparoscopic procedure consists of checking the patency of the peritoneal

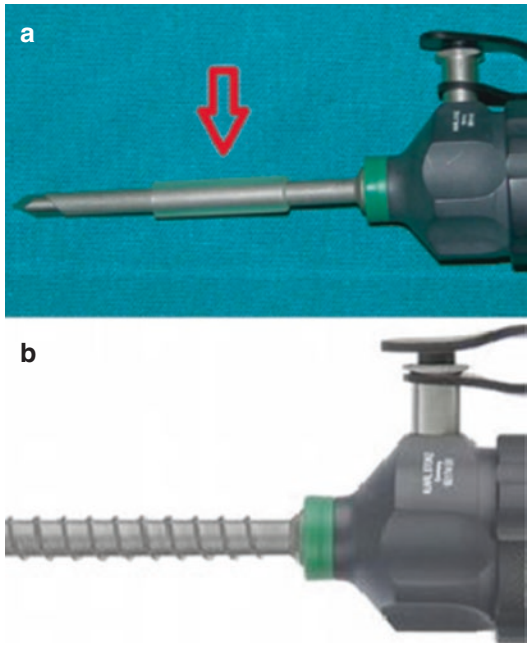

Fig. 26.4 Trocars used for laparoscopic hernia repair: (**a**) smooth trocar with a piece of Nelaton catheter around the cannula to be fixed to the skin to stabilize the trocar; (**b**) screw trocar

vaginal duct as well as the inspection of the contralateral side for the presence of a contralateral patent processus vaginalis (CPPV). In case of incarcerated hernia, before closing the defect, it is necessary to reduce the hernia by releasing incarcerated elements like epiploon, intestinal loops, appendix, or ovaries. The next step consists in circumferentially cutting the periorificial peritoneum, distally to the internal inguinal ring, by using a monopolar hook. We consider the section of the periorificial peritoneum a key point of the technique, because using this expedient there is the collapse of the distal part of the sac and consequently there is no tension on the suture line in closing the internal ring. The deep ring is then closed, after sectioning the periorificial peritoneum, with a resorbable or non-resorbable suture, performing either a purse-string suture as described by Montupet (Fig. 26.5) or an N suture as described by Schier (Fig. 26.6). In general, if the diameter of the inguinal orifice is of about 10 mm or larger, it is preferable to perform a purse-string suture according to Montupet's technique, whereas in orifices of about 5 mm or smaller, an N-shaped suture according to Schier's technique or a purse-string suture may be adopted as well.

It is also important to well close the medial part of the ring, in particular the peritoneum between the inner spermatic vessels and the vas, because this is the most frequent location of recurrences.

As for technical point of view, the needle has to be introduced into the abdominal cavity transparietally and then removed transparietally or transumbilically. The preferred needle to use is 3/8 of circle with a 20–22-mm needle. To perform a unilateral closure, the length of suture has to be 13–15 cm; for a bilateral repair, it has to be 15–20 cm, according to the surgeon's preference. The trocar orifice is closed with stitches or glue.

Percutaneous internal inguinal ring (PIRS) technique is the most common percutaneous method for inguinal hernia repair, and it was firstly described by Patkowski in 2006 [61]. In this method, after induction of pneumoperitoneum and visualization of internal inguinal ring, a 2-mm stab incision is made to correspond to above the internal ring. An 18-G angiocath needle with a 2/0 nonabsorbable monofilament suture loaded as a loop is passed on one side of the internal ring, entering and leaving the peritoneal cavity several times. The loop is introduced into the peritoneal cavity at the farthest opposite aspect that the needle allows. The 18-G angiocath is then introduced on the other side of the internal ring, entering and leaving the peritoneal cavity several times, once again passing to the farthest opposite side the needle allowed. The needle is then passed through the previously introduced loop. A 2/0 nonabsorbable monofilament suture is then passed through the needle. After removal of the needle, the loop is withdrawn, catching the second suture and passing it out of the stab incision. After manual reduction of gas from the hernia sac, the suture is then tied, obliterating the internal ring (Fig. 26.7).

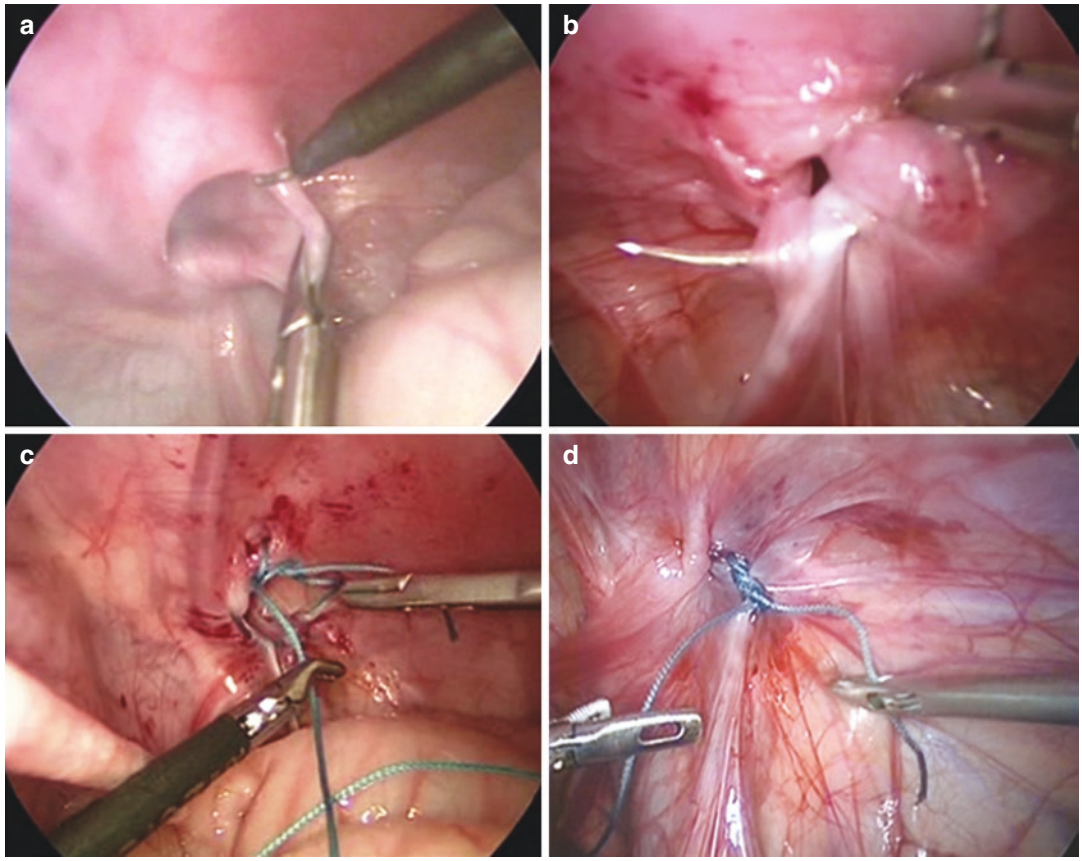

Fig. 26.5 Laparoscopic hernia repair according to Montupet's technique: (**a**) the periorificial peritoneum is sectioned; (**b**) the needle is introduced transparietally; (**c**) a purse-string suture is placed on the periorificial peritoneum; (**d**) the hernia defect is closed

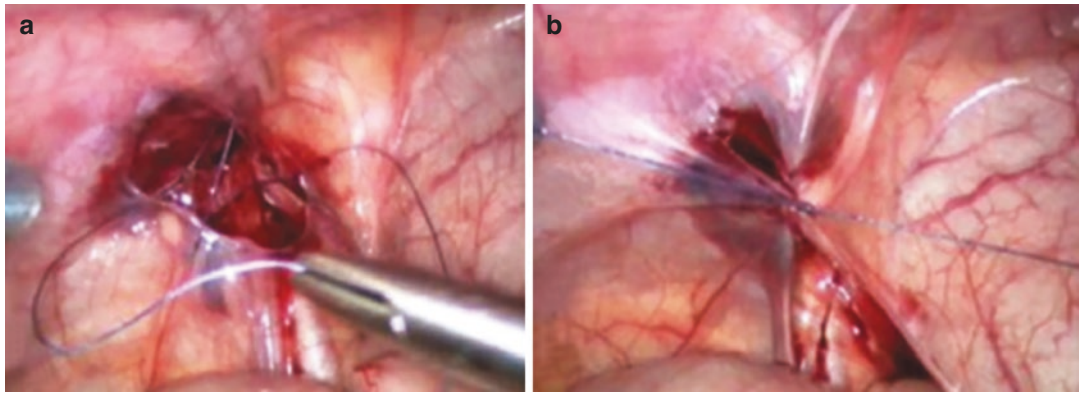

Fig. 26.6 Laparoscopic hernia repair according to Schier's technique: (**a**) an N-shaped suture is placed on the periorificial peritoneum; (**b**) the hernia defect is closed

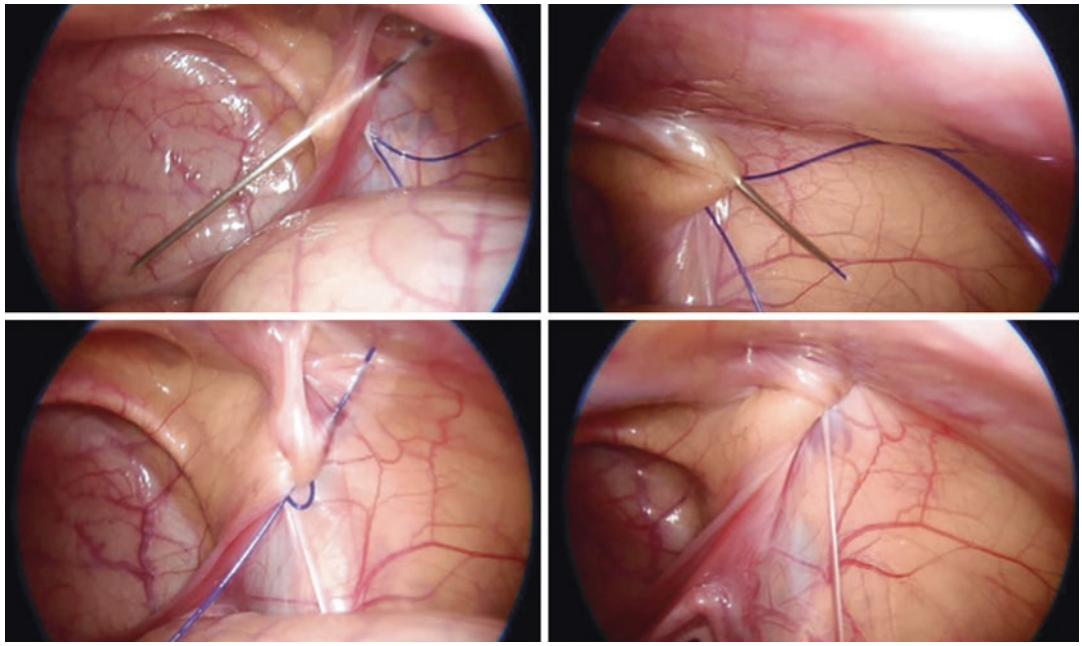

Fig. 26.7 Percutaneous internal ring suturing (PIRS) technique

26.3.3 Tips and Tricks of Laparoscopic Repair in Infants

From a technical point of view, the laparoscopic repair is more technically demanding in infants because of the visual restriction and the very small working space available, due to bowel distension. For this reason, it is useful to perform a bowel preparation the day before operation in such patients, with one or two enemas and simethicone per os in order to empty the intestinal loops of gas and to allow the creation of a larger working space into the abdominal cavity [26–28].

In regard to port position, in small infants, we do not have a true triangulation between the optic and trocars because the two working ports used for instruments are located higher compared with the usual position. In fact, we prefer to place them on the umbilical line at the same level of the optic to create more distance between the ports and the internal inguinal ring [16, 18, 20].

In very small babies, under 3 kg of weight, where the working space is extremely limited, you can also place a balloon trocar in the umbilicus for the optic; in this way, during the intervention, the cameraman can lift up the trocar without dislodging it, thus creating more working space into the abdominal cavity; or, alternatively, you can put a transabdominal stitch, passed transparietally, and use it to lift up the abdominal wall.

In regard to trocar insertion, it is sometimes safer to insert the working ports through the cannula of the umbilical optic trocar ("trocar in trocar"), considering the limited working space in newborns (Fig. 26.8).

Another important point of the technique in infants is to adopt 3-mm screw trocars that remain stable during the entire procedure, in particular during the change of instruments. In case you have only smooth trocars, you can put a piece of Nelaton catheter around the cannula and then fix the piece of Nelaton catheter to the skin to stabilize the trocar (Fig. 26.4). As for the needle size, it is difficult to manage large needle in premature

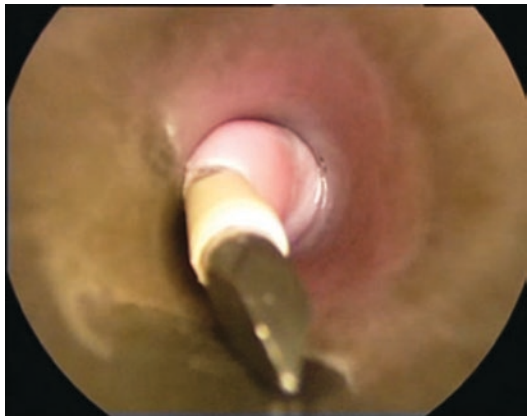

Fig. 26.8 In newborns, it is safer to perform insertion of working trocars through the cannula of the optic trocar ("trocar in trocar")

infants; probably the needle length has to be maximum of 17–20 mm, because larger needles are difficult to manage with a higher risk of complications.

In addition, it is important to use a CO_2 flow of 1 L/min and to maintain the intra-abdominal pressure (IAP) around values of 6–8 mmHg throughout the operation in order to avoid anesthesiologic problems during and after the intervention.

In regard to the operative technique, it is also important to close well the medial part of the internal inguinal ring, in particular the peritoneum between the inner spermatic vessels and the vas deferens, because this is the location of most of recurrences [16, 18, 20].

By adding these technical refinements, LH has become an easy approach in tough repairs such as neonatal inguinal hernias.

26.4 Management of Incarcerated Inguinal Hernias

The incidence of inguinal hernia incarceration has been reported in the general pediatric population to be between 6 and 18% [29]. However, the risk of incarceration is higher in infancy, with a reported incidence of approximately 30% [62]. A nonreducible hernia in children requires operative exploration.

These hernias, unless treated, are likely to progress to strangulation and infarction. The initial management of an incarcerated inguinal hernia without strangulation should be nonoperative [62]. Analgesia or sedation can also be used to aid the reduction of an incarcerated hernia. Reduction may spontaneously occur prior to a manual attempt, if the infant's buttocks are elevated slightly to assist in the reduction of hernia contents. The hernia is palpated distally, while the clinician's fingers are located to the proximal neck of the hernia. Compression of the hernia can then occur. The pressure is maintained slowly and consistently until the hernia is reduced. Gentle compression is usually successful in 70 to 85% of patients [63], and an elective repair can be performed in 24–48 h. This time allows some resolution of the edema, minimizing the difficulty of the dissection and the risk of complications. However, failure to reduce the hernia, even with sedation, is an indication for an immediate operation.

The operative management is determined by the viability of the intestine. If the incarcerated intestine is viable, the surgeon can simply reduce the hernia and perform a high ligation of the sac. If the intestine is no longer viable, it should be resected, either through the sac or through a separate abdominal incision. An incarcerated hernia in an infant is more technically difficult and has a higher complication rate since the hernia sac is typically edematous and fragile. The testicular vessels and the vas are particularly susceptible to injury because of the edema and often difficult dissection.

It has been reported that probably one of the main advantages of laparoscopy is in the cases of nonreducible hernias [64]. In fact thanks to laparoscopic traction and the manual pressure from the outside, it is easy to reduce hernia content, and in case of vascular damages of appendix or bowel loops, it is easy to exteriorize the specimen through the umbilicus and to perform a bowel resection (Fig. 26.9).

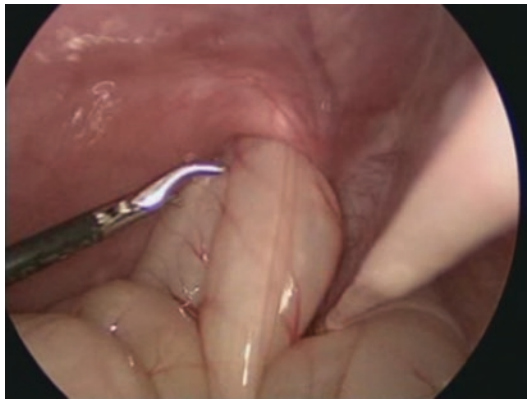

Fig. 26.9 Laparoscopic view of a left incarcerated inguinal hernia in a newborn

26.5 Outcome Analysis of Open and Laparoscopic Inguinal Hernia Repair in Neonates and Premature Infants

In the last decade, despite laparoscopic inguinal hernia repair (or herniorrhaphy) (LH) becoming popular in older children, there are few reports in newborns. Most recently published series have reported encouraging results [16, 18, 20, 21]. The use of LH in neonates is a technically demanding procedure because intracorporeal suturing requires to be done in a very limited working space. However, open herniotomy (OH) in newborns is also considered a technically demanding surgery with an increased overall rate of postoperative complications (recurrence, testicular hypotrophy/atrophy, high testis) compared to older children [11]. Serious intraoperative complications such as bladder injury or rupture can also occur in open surgery with excessive mobilization of the sac [20]. Miyano et al. reported the need for sigmoidocolocystoplasty for bladder augmentation after a bladder injury caused by open herniotomy [65].

Analyzing literature reports focused on open and laparoscopic inguinal hernia repairs in newborns and/or premature infants, outcome parameters reported included postoperative hydrocele, wound infection, iatrogenic cryptorchidism, testicular atrophy, incidence of metachronous hernia, and contralateral patent processus vaginalis (CPPV) (Table 26.1).

26.5.1 Recurrence

Recurrence rate was significantly higher after OH compared with LH (2.6 vs. 1.9%, $p = 0.001$).

It has been reported that low gestational age and specific comorbidities may be associated with a higher likelihood of recurrence. However, considering the operative technique, the medial aspect of the internal inguinal ring is the most crucial [16, 18, 20]. The great advantage of laparoscopic approach over open technique could be due to the better visualization of the medial aspect of the internal inguinal ring allowed by laparoscopy. On the upper part of the internal inguinal ring, slightly more tissue is usually included, not only in the peritoneum but also in some underlying musculature. On the lower part of the ring, however, less tissue is present because more crucial nerves and vessels are present. For this reason, it is important to put the most medial stitches as close as possible to the epigastric vessels and vas deferens. A tightened closure of the inguinal ring seems to reduce the recurrence rates [20, 21].

In addition, the key of the success is the use of nonabsorbable suture, together with the section of periorificial peritoneum, as long as the medial side of PPV is properly closed [6, 7].

26.5.2 Wound Infection

Studies focused on LH reported fewer wound infection rates (range 0–1.6%) compared with the studies focused on the inguinal open approach (range 1.1–2.3%). However, looking at the average values, the difference between the two groups is not statistically significant (LH = 0.8% vs. OH = 1.1%, $p = 0.66$).

In our opinion, the higher wound infection rate following OH may be due to the fact that the laparoscopic scars are located higher on the

Table 26.1 Outcome analysis of OH and LH series in neonates and premature infants

Reference	LH	OH	Recurrence	Acquired cryptorchidism requiring surgery	Testicular atrophy	Wound infections	Hydrocele	CPPV	MIH
Turial et al. [20]	147		4 (2%)	7 (4.1%)	0	1 (0.4%)	0	61 (57%)	1 (0.4%)
Pastore et al. [21]	30		0	3 (10%)	0	0	0	12 (63%)	0
Esposito et al. [16, 18]	67		3 (4.4%)	4 (5.9%)	0	0	0	NR	0
Pini Prato et al. [3]		184	8 (4.5%)	1 (0.5%)	5 (2.7%)	2 (1.1%)	4 (2.2%)	NR	13 (10.5%)
Chan et al. [15]	79		1 (1.3%)	0	0	0	0	52 (66%)	0
Choi et al. [66]	299		4 (1%)	1 (0.3%)	1 (0.3%)	5 (1.6%)	4 (1%)	136 (54%)	0
Hughes et al. [67]		408	8 (1.9%)	10 (2.4%)	2 (0.4%)	5 (1.2%)	1 (0.2%)	NR	26 (6.3%)
Nagraj et al. [11]		221	5 (2.3%)	6 (2.7%)	6 (2.7%)	5 (2.3%)	0	NR	NR
Marinkovic et al. [68]		144	3 (2%)	NR	1 (1%)	NR	NR	NR	7 (5%)
Krieger et al. [13]		24	1 (4.2%)	NR	2 (8.4%)	NR	NR	NR	NR
Saha et al. [69]	30		1 (3.3%)	0	0	NR	2 (6.6%)	18 (66%)	0
Saha et al. [69]		32	2 (6.0%)	0	0	NR	1 (3.0%)	NR	2 (7.4%)
Lin et al. [70]	24		0	NR	NR	NR	NR	13 (65%)	0
Lin et al. [70]		31	1 (3.2%)	NR	NR	NR	NR	NR	4 (18%)

LH laparoscopic herniorrhaphy, *OH* open herniotomy, *NR* not reported, *CPPV* contralateral patent processus vaginalis, *MIH* metachronous inguinal hernia

abdominal wall compared with inguinal scars, which are inside the diaper area; for this reason they are subject to urine or fecal contamination, which may lead to a higher infection rate.

26.5.3 Iatrogenic Cryptorchidism, Testicular Atrophy, and Hydrocele

Incidence of testicular atrophy following OH in infants and premature babies was significantly higher compared with LH approach (1.5 vs. 0.1%, $p = 0.001$).

Acquired cryptorchidism requiring surgery did not show any significant difference between LH series (average 2.2%; range 0.3–10%) and OH ones (average 1.6%; range 0.5–2.7%) ($p = 0.30$).

Also postoperative hydrocele rates did not show any significant difference between LH series (average 0.8%; range 1–6.6%) and OH ones (average 0.5%; range 0.2–3.0%) ($p = 0.30$).

The etiology of testicular atrophy and maldescending testes in infants following hernia repair is poorly understood. It has been reported that testicular atrophy has the highest incidence after incarceration [12]. It may be either due to prematurity and low weight at the time of surgery or associated with demanding surgery [3]. During laparoscopic repair, the risk of complications associated with dissection is minimized. Laparoscopic surgery approaches the internal ring without any dissection of the abdominal wall or spermatic cord structures. This advantage is important, especially in neonates, in whom the vas deferens and the vessels are very small and the hernia sac is very friable and fragile [16, 18, 20].

Laparoscopic purse-string closure of internal ring has been reported to cause holding up of the testis by entangling its vaso-vasal pedicle. It is not very clear if the high-lying testis is the result of arrested normal descend or the result of testicular ascend following purse-string suture [71]. In our experience, all patients who developed iatrogenic cryptorchidism following LH presented a testis located in high scrotal position at the moment of the operation, and we decided preoperatively together with the parents to correct this condition at 1 year of age according to the guidelines for management of undescended testis [16, 18].

Postoperative hydrocele is recognized as a common complication but it has been rarely discussed. Some authors reported a higher incidence of hydrocele following incarceration. The reason for this association remains unknown; probably severe inflammation and derangement of the tunica vaginalis surrounding the testicle may explain this issue [3].

26.5.4 Metachronous Inguinal Hernia (MIH) and Contralateral Patent Processus Vaginalis (CPPV)

Studies focused on OH reported an incidence of metachronous inguinal hernia (MIH) ranging from 5% [68] to 18% [70]. A paper focused on LH recorded one case of MIH (0.4%) [20].

Six studies reported the coexistence of a unilateral inguinal hernia with a contralateral patent processus vaginalis (CPPV), with an incidence of contralateral patency between 54% [66] and 66% [15, 69].

Considering the high incidence of CPPV in patients with unilateral inguinal hernia underwent LH, another clear advantage of laparoscopic repair is to treat bilateral inguinal hernia in the same operation or close a CPPV in order to prevent future metachronous hernia [26–28, 72]. This is particularly important for newborn and preterm babies, in whom the risk of MIH is higher, thus obviating the need for a second operation and thus anesthesia and reducing both economic impact and risk to the patient [21].

26.5.5 Other Advantages of Laparoscopic Inguinal Hernia Repair in Infants

It has been reported that laparoscopy presents several other advantages over open surgery in the treatment of inguinal hernia in infants. First of all, laparoscopy permits to identify and treat rare and uncommon types of hernia, such as direct

hernias, femoral hernias, double hernias, and the so-called hernia en pantalon [16, 18].

In case of direct hernia, a key point of the technique is to remove the lipoma always present in this pathology and to close the defect using a purse-string suture or separated stitches. In case of a huge hole, the lateral bladder ligament can be adopted in order to reinforce the closure [16, 18, 73].

In addition, laparoscopy is particularly helpful in patients who experience a hernia recurrence after initial repair, whether from previous open surgery or a laparoscopic approach. In fact, in those cases, the manipulation of the sac surrounded by a thigh scar can be dangerous and harmful for the cord, whereas the intra-abdominal laparoscopic closure of the internal ring can be less traumatic and even less technically demanding. In such cases laparoscopy permits to identify and treat the cause of recurrence [74].

Another advantage of laparoscopy may be in the management of incarcerated hernias, especially in infants. In fact, the reduction of the incarcerated loops can be facilitated using both laparoscopic reduction and with external manual reduction. The pneumoperitoneum may also help to widen the internal ring, allowing an easier reduction. Immediate inspection of the incarcerated bowel status is possible before closing the peritoneal vaginal duct (PVD), allowing resection if necessary. Furthermore, the hernia could be immediately repaired, perhaps avoiding the edematous tissues and decreasing the higher complication rate associated with incarcerated hernias [64, 75].

An improvement in the cosmetic outcome is another proposed advantage of laparoscopic technique (Fig. 26.10).

Despite LH having always been considered a time-consuming procedure, more reports showed that operative time of LH is not only comparable with operative time of OH [76] but also, especially in neonates and certainly in bilateral inguinal hernias, it could be shorter when the laparoscopic surgeons have gained enough experience [21, 26–28].

It is clear that there is no definitive evidence in the literature about which technique between laparoscopy and inguinal approach is preferable to repair an inguinal hernia in infants.

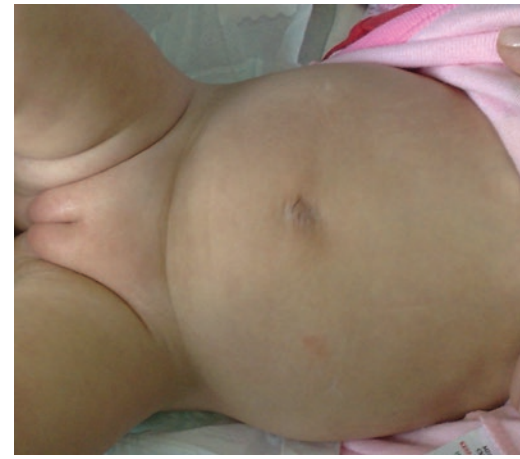

Fig. 26.10 Cosmetic outcome 6 months after laparoscopic inguinal hernia repair

Age, size, and weight of the child are not limiting factors for the laparoscopic approach in terms of surgical technique. Anesthetists tend to object to laparoscopy for small children considering the risk of opening right-to-left shunts due to the increased intra-abdominal pressure.

However, despite a steep learning curve for pediatric anesthesiologists, patient safety has increased generally as laparoscopy has become a routine procedure. Only patients with clear contraindications with laparoscopy, including respiratory distress syndrome, severe bronchodysplasia, or other medical conditions, should be offered open herniotomy.

On the basis of our 20-year experience [55], we believe that laparoscopic hernia repair is a safe and easy procedure to perform also in infants and small babies and a strict collaboration with anesthesiologist is fundamental for the good outcome of the procedure.

26.6 Current Management of Hydrocele

When examining a child with an inguinal hernia, a hydrocele must be considered in the differential diagnosis. This determination can typically be made by clinical examination. By palpation, one

can feel the narrowing of the hydrocele neck at the external inguinal ring without extension into the inguinal canal. Ultrasound can also be helpful in making this distinction. The patent processus vaginalis spontaneously closes over a period of 1–2 years in most instances. Therefore, most pediatric surgeons avoid operation within the first 1 to 2 years of life unless a hernia cannot be excluded. After the age of 2 years, the hydrocele is unlikely to resolve and an operation is required. If the hydrocele shows signs of communication (frequently changing in size), then there is a significant exchange of fluid between the peritoneal cavity and the hydrocele sac. Many pediatric surgeons choose to repair a communicating hydrocele earlier [29].

The surgical procedure is the same described for the open inguinal hernia repair. A high ligation of the patent processus vaginalis is performed through a groin incision, and in case of communicating hydrocele, the distal fluid collection should be emptied. This often requires an incision distally, down to the scrotal tunica vaginalis, to release any residual fluid. In case of communicant hydrocele, laparoscopic repair can be proposed. It is similar to laparoscopic treatment of inguinal hernia, the fluid is aspirated, and the PVD is closed with a purse-string suture at the level of internal inguinal ring. However, at the moment, the preferred technique to treat hydrocele remains the open inguinal approach [6, 7].

In our practice, we recommend a groin exploration for all patients with hydroceles who are over 2 years of age.

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Intestinal Malrotation and Volvulus

27

Luisa Ferrero, François Becmeur, and Olivier Reinberg

27.1 Introduction

Intestinal malrotation is a common name for a large variety of abnormalities of intestinal rotations and attachments that occur during fetal development.

27.2 History

The first cases of malrotation were reported in the literature in the mid-1700s [1, 2]. No progress was made until normal intestinal embryology was first described by Meckel in 1817 [3] and then later by Mall in 1897 who wrote the first description of the embryology of the midgut [4]. In 1923, Dott applied the embryology to the understanding of intestinal malrotations. Based only on five clinical observations, he correlated them with the sequences of embryological development describing theoretically many of the potential errors and their consequences without having seen them [5]. In 1931, William E. Ladd presented in a seminar five cases of obstruction of the duodenum and wrote a reference article on the treatment of malrotation, describing his surgical approach, the "Ladd's procedure," which still remains today the basic rules of good practice [1]. By the 1950s Snyder and Chaffin [6] in the United States and Grob [7, 8] in Switzerland have done much to clarify our understanding of these malformations. Most of the available drawings are reproductions of the initial drawings by Grob.

27.3 Epidemiology

The true incidence of malrotation remains unknown. According to literature it ranges from 1/6000 [9, 10] to 1/200 [11] of all live births. Autopsy studies estimate that it may be as high as 1% of the total population [9, 12]. Males are more frequently affected than females with a ratio of 2:1 [6, 13, 14].

Case reports have suggested a strong concordance of intestinal malrotation between identical twins and even between non-twin siblings. Genetic factors may thus play some role in its pathogenesis [15–18].

Most cases of malrotation are discovered in the first few months of life, and of those, most will present within the first week of life. Approximately 90% are discovered before 1 year of age. However a significant percentage of patients reach adulthood with an undiagnosed malrotation [19]. Unfortunately, for those patients delays in diagnosis are common.

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27.4 Embryology

The final anatomic arrangement of the midgut follows a complex series of events [6]. By the 4th week of fetal life, the embryo is about 5 mm, and the primitive intestine is an almost straight tube, the same length as the ectodermal and mesodermal germ layers, and lays on the midline. It consists, cephalad-caudally, in the foregut, midgut, and hindgut.

Rotation of the midgut happens during the 2nd month of the fetal life, to become the medial part of the gastrointestinal tract (GIT). At this stage the midgut is in continuity with the vitelline duct inside the umbilical duct and still connected to the yolk sac. The aorta gives blood supply to the GIT through three arteries, respectively, the coeliac artery for the foregut, the superior mesenteric artery (SMA) for the midgut, and the inferior mesenteric artery for the hindgut.

The GIT develops faster than the coelomic cavity resulting in a lack of space. Thus by 6 weeks, it forced to herniate inside the umbilical cord with the SMA forming the axe of a U-loop in the sagittal plane (Fig. 27.1a).

As it protrudes, the midgut makes a first rotation of 90° counterclockwise, so its distal part comes to the left, and its proximal part is to the right. The loop is now in a horizontal plane. The distal part of the loop develops a pouch that will become the cecum. The proximal part of the loop becomes tortuous. These loops still lie outside the abdominal cavity (Fig. 27.1b).

By 10 weeks, the body of the embryo is now large enough for the bowel to develop inside the abdomen, so the midgut reintegrates the abdomen. The proximal part of the loop returns first. It passes under the distal one and comes to the left making a second 90° counterclockwise rotation. Then the distal part follows it passing in front of the proximal part and rotates to the right. This is making the third 90° counterclockwise rotation. With this development, the proximal part of the midgut becomes placed posteriorly to the distal one that will become the transverse colon with the SMA between them (Fig. 27.1c).

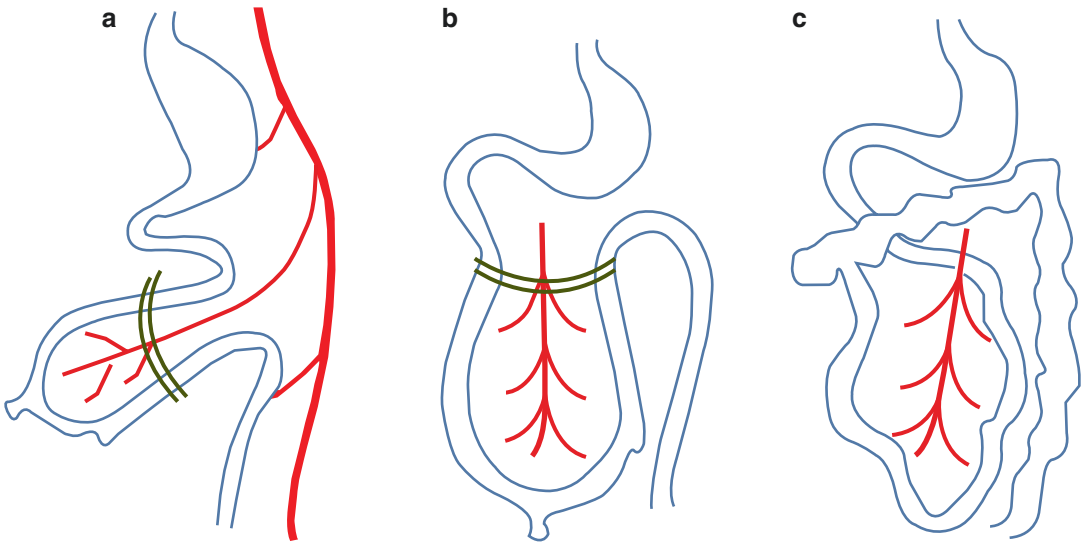

Fig. 27.1 Normal embryological development of the midgut [23]. (**a**) The midgut has not rotated yet and remains in a sagittal plane. The aorta gives blood supply to the GIT through three arteries, respectively, the coeliac artery for the foregut (up), the superior mesenteric artery (SMA) for the midgut (middle), and the inferior mesenteric artery for the hindgut (lower). It forms an U-loop around the SMA. (**b**) The midgut has made a first rotation of 90° counterclockwise, so its distal part comes to the left, and its proximal part is to the right. The loop is now in a horizontal plane. The distal part of the loop develops a pouch that will become the cecum. (**c**) The second 90° counterclockwise rotation. The proximal part of the loop returns first, passes under the distal one, and comes to the left. The distal part follows it passing in front of the proximal part and rotates to the right

At this time, both parts of the midgut have rotated 270° in a counterclockwise manner. Then the period of fixation lasts until after birth. The descending and ascending colon mesenteries fuse with the retroperitoneum, and the small bowel is fixed by a broad mesentery from the duodenojejunal junction in the left upper quadrant to the ileocecal valve in the right lower abdomen. The broad base of the small bowel mesentery stabilizes its position and prevents volvulus.

According to Kluth, this description of the processes of rotation is schematic. It has been done in order to better explain the background of the pathology of malrotation than to study the embryology of the midgut. Using his technique of scanning electron microscopy pictures of the developing midgut in a series of rat embryos, he demonstrated that the *primum movens* of the process was not the rotations but the lengthening of the bowel, mainly the small bowel, in a small cavity. Thus the bowel components enter into a position where space allows [20].

27.5 Classification

The term malrotation comprises a range of anatomical anomalies in the arrangement of GIT in the abdominal cavity, each reflecting the time at which errors occur during these organogenetic steps either by omission or by opposite rotation(s). Three main types are described, i.e., nonrotation, partial malrotation, and reversed malrotation [6, 9–11, 13, 21–23].

27.5.1 Complete Nonrotation

In nonrotation, only the initial 90° counterclockwise rotation occurs so that the duodenojejunal junction lies on the right side and the colon lies of the left side of the SMA. It is characterized by the small and large bowel coursing vertically and a common longitudinal mesentery [23]. This malrotation is often called "left-sided colon" (Fig. 27.2).

27.5.2 Partial (Incomplete) Malrotation

Partial (incomplete) malrotation implies a failure of the midgut loop to complete the final 90° counterclockwise rotation; thus, terminal ileum enters the abdominal cavity first. This term is used in all cases of anomalies in the arrangement of the midgut ranging from a nonrotation to a normal rotation. In the most common forms, the

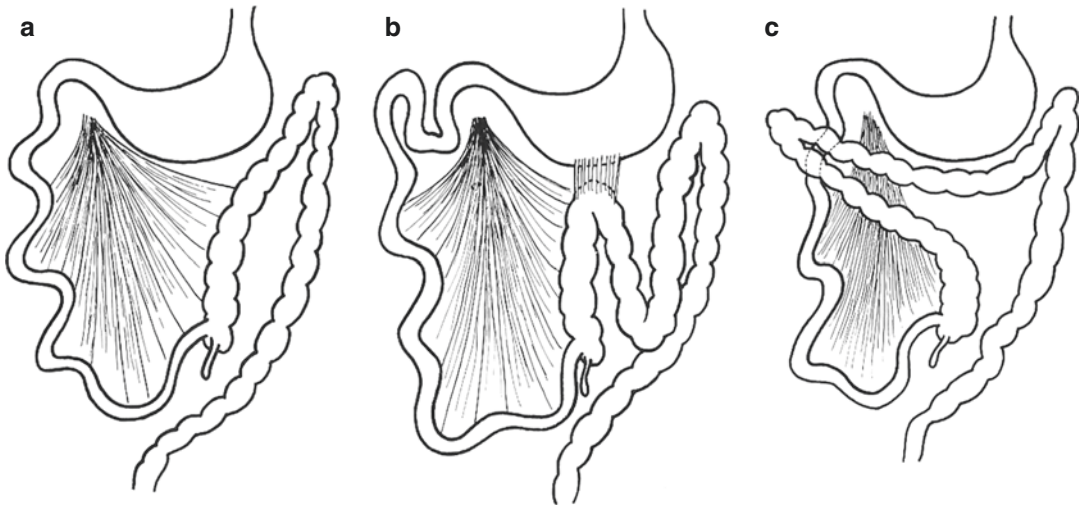

Fig. 27.2 Nonrotation. (**a**) Pure form; (**b**) with colonic adhesion to the stomach; (**c**) with a right position of the proximal colon compressing the second duodenum. Note: the ileocecal valve faces to the right (Drawings from Max Grob) [8]

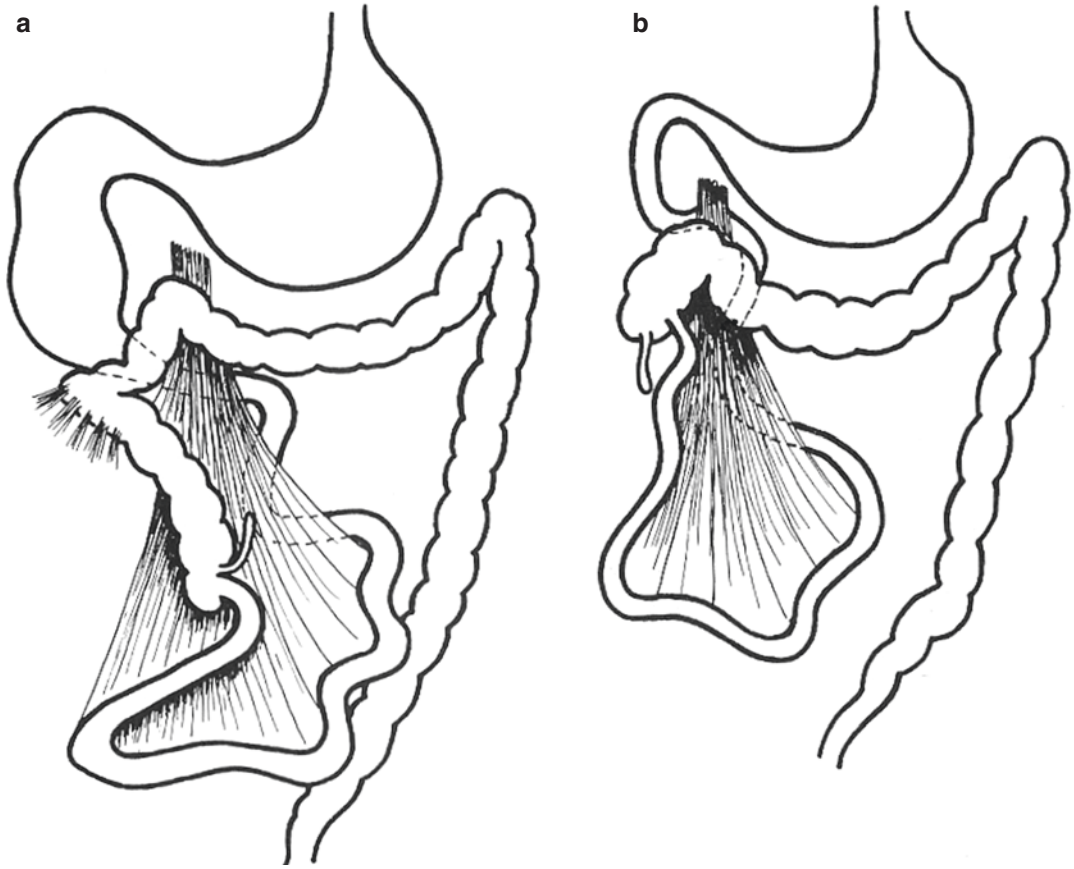

Fig. 27.3 Partial (incomplete) rotation: two forms (**a** and **b**). In form (**a**) the cecum lies below the pylorus and is fixed to the posterior abdominal wall by peritoneal bands ("Ladd's bands") that cross over the duodenum and cause extrinsic obstruction. (**b**) This is one of the commonest malrotations. Counterclockwise rotations have stopped at 180°. Note: the ileocecal valve faces to the left (Drawings from Max Grob) [8]

cecum lies below the pylorus and is fixed to the posterior abdominal wall by peritoneal bands ("Ladd's bands") that cross over the duodenum and cause extrinsic obstruction. The duodenum and small bowel are located on the right side of the SMA and the cecum and colon on the left (Fig. 27.3).

27.5.3 Malrotation

This term refers to anomalies occurring during the second rotation. Several types have been described according to the degree of rotation accomplished. In the commonest type, the rotation has stopped at some point just before the 180°, and the duodenojejunal loop has failed to cross the midline and lies to the right of the SMA. The caecocolic loop has rotated from almost 180° but no further and lies anterior to the duodenum and to the SMA. Congenital adhesive bands ("Ladd's bands") course from the cecum to the parietal peritoneum usually obstructing the second part of the duodenum [23] (Fig. 27.4).

27.5.4 Reversed Malrotation

When rotation is clockwise, the result is said reversed malrotation in which the duodenum lies anteriorly to the colon. Small intestine lies on the left and large intestine on the right. The cecum is

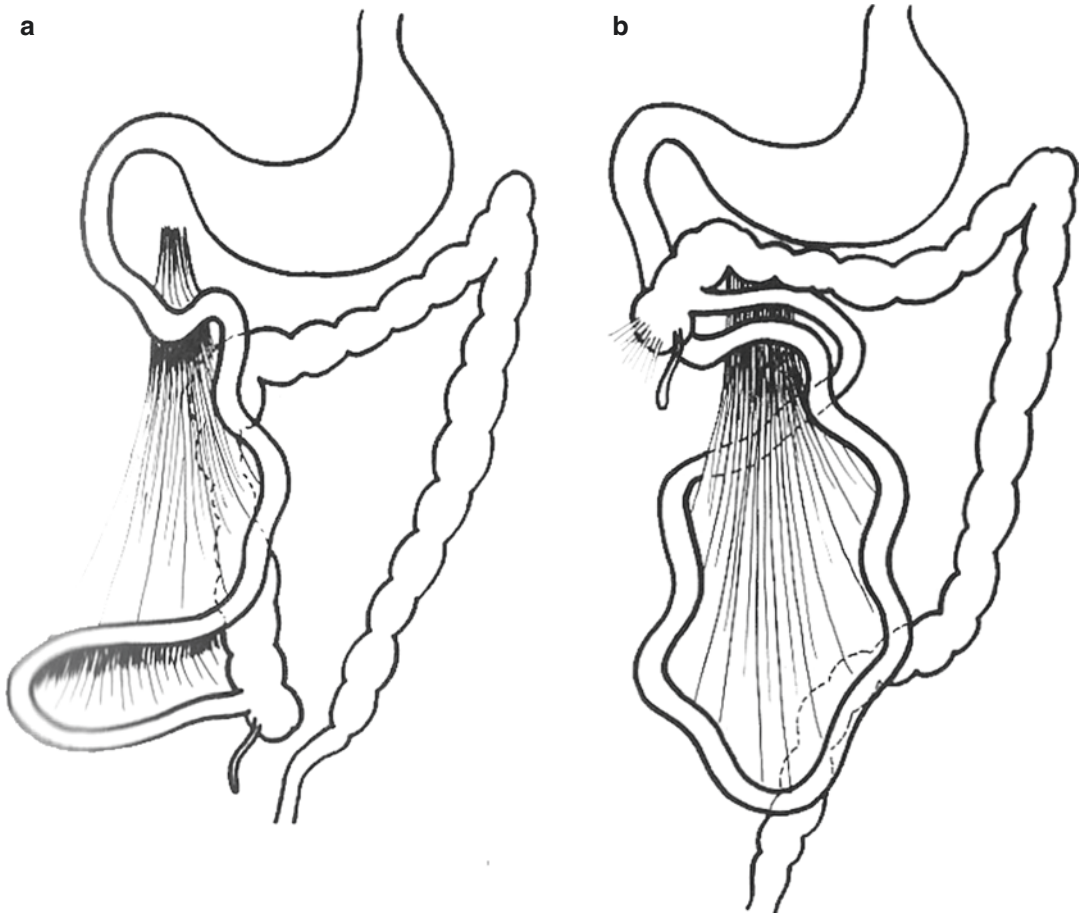

Fig. 27.4 Malrotations: (**a**) these are results from reverse second rotation following the initial counterclockwise rotation. (**b**) In this type of malrotation, the cecum came from behind the mesentery and has passed toward the right in front of the duodenum. A compressive Ladd's band compresses the second duodenum (Drawings from Max Grob) [8]

found in the midline. Duodenum lies in front of the SMA and transverse colon behind it, which may cause an extrinsic colonic obstruction. This is a rare malrotation (Fig. 27.5).

In addition to these terms, defining malrotations and abnormal fixation of the mesentery must be mentioned as it may cause intestinal internal herniation ("hernia mesocolica") [14, 24] (Fig. 27.6).

In individuals with malrotation, the mesenteric attachment of the midgut, particularly the portion from the duodenojejunal junction to the cecum, is abnormally short. The gut is therefore prone to twist counterclockwise around the SMA. This condition is known as midgut volvulus (Fig. 27.7).

27.6 Associated Anomalies

Malrotation may occur in association with other congenital abnormalities or syndromes with wide differences according to authors ranging from 17 to 60% of patients [14, 22, 25]. The most common associated ones are other gastrointestinal abnormalities, especially jejunal and duodenal stenosis or atresia, annular pancreas, and Hirschsprung's disease. Malrotation of the bowel is always present in children with congenital abdominal wall defects (omphalocele and gastroschisis) or congenital diaphragmatic hernia in whom the normal embryologic positioning of

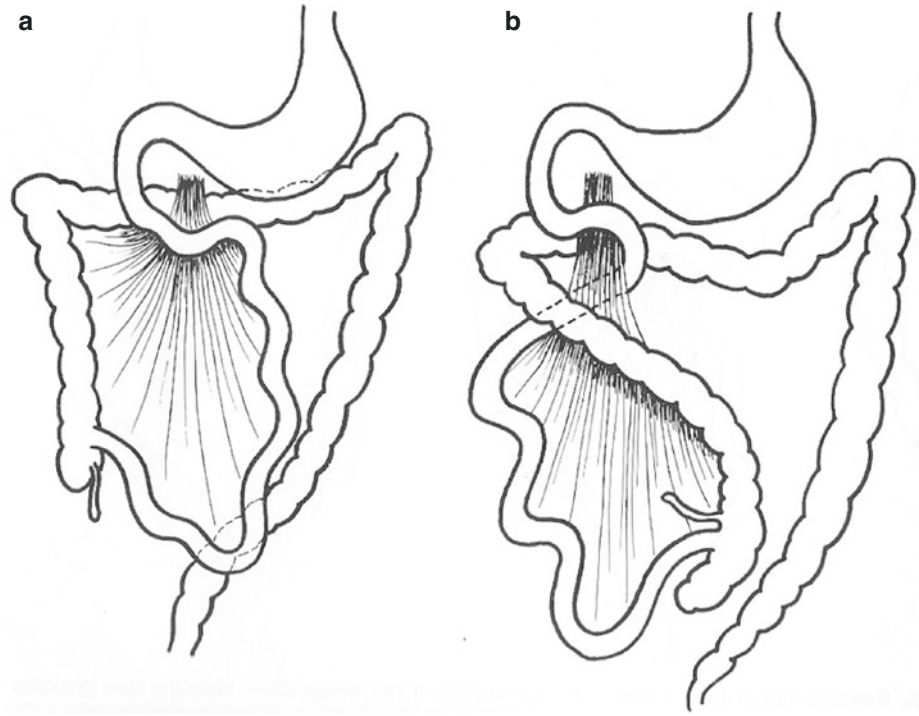

Fig. 27.5 Two types of reverse completed 180° clockwise rotation. (**a**) The transverse colon comes to lie behind the SMA, but the cecum and proximal colon are in the right side of the abdomen. (**b**) The colon can be compressed by the SMA (Drawings from Max Grob) [8]

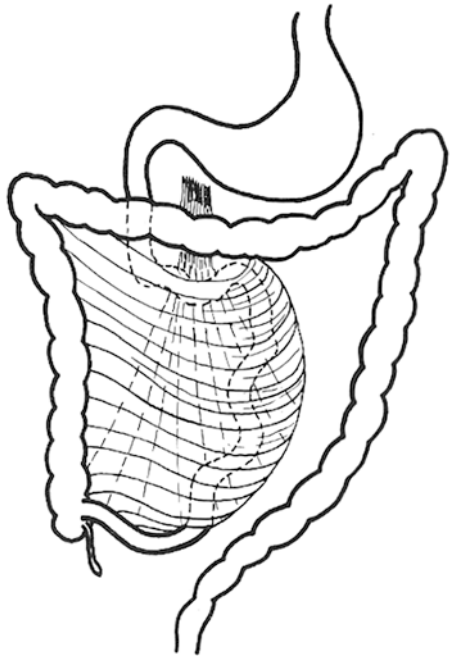

Fig. 27.6 "Hernia mesocolica": abnormal fixation of the mesentery may cause intestinal internal herniation

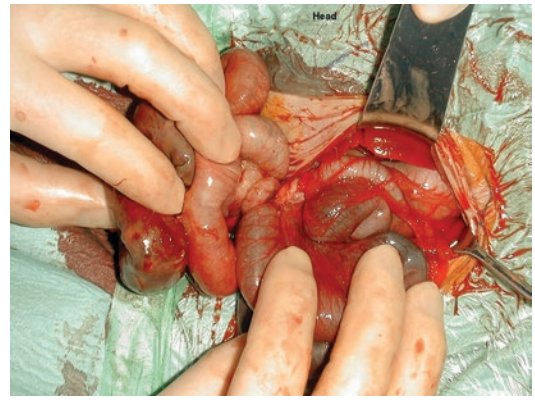

Fig. 27.7 Boy 3 weeks old. Urgent laparotomy for acute midgut volvulus in a partial rotation. Discoloration without necrosis. No resection

the developing gut was disrupted. But many other malformations have been occasionally described in association with malrotations such as absence of the kidney or ureter, esophageal atresia, biliary atresia, imperforate anus, and intestinal pseudo-obstruction. Several syndromes are associated with malrotations. It may be present in patients with heterotaxy syndrome (asplenia or right isomerism and polysplenia or left isomerism). Patients presenting with this syndrome should be investigated for the possibility of malrotation [26]. It has also been described in association with Cornelia de Lange, cat eye, Coffin-Siris, Marfan, Prune-Belly syndromes, and trisomy 21 [27].

27.7 Clinical Presentation

The prenatal diagnosis of malrotation can be suggested by identification of its complications, such as bowel dilatation, ascites, or meconium peritonitis, that can be evidenced on ultrasounds (US). With US it is possible to diagnose intestinal volvulus in utero. Combined with Doppler it gives information on the viability of the involved intestinal segment [28–30].

Various clinical presentations may result from failure of normal intestinal rotation and fixation, ranging from chronic abdominal pain to acute midgut volvulus. The most common features in newborns are bilious vomiting with or without abdominal distention associated with either duodenal obstructive bands or midgut volvulus [13, 25, 31]. Clinical diagnosis of malrotation with volvulus is based on a high index of suspicion.

The major complications of malrotation is a midgut volvulus and infarction of the bowel that can be life-threatening if total or without fatal issue can lead to a significant loss of bowel with a subsequent short bowel syndrome and dependence on total parenteral nutrition (TPN). The infant presents in a shocked and collapsed state with bilious vomiting (which often contains altered blood), abdominal tenderness with or (more commonly) without distension, and the passage of dark blood rectally. Edema and erythema of the abdominal wall develop as the volvulus becomes complicated by intestinal gangrene, perforation, and peritonitis. A high index of suspicion for midgut volvulus is based on the history, physical examination findings, and presence of metabolic acidosis. A delay in diagnosis and treatment may result in small bowel necrosis, short gut syndrome, and dependence on TPN. Mortality in affected newborns was approximately 30% by the 1950s and 1960s but today has markedly decreased down to 3–5% [32].

27.8 Diagnostic Imaging Investigations

Clinical diagnosis of malrotation must be confirmed by investigations.

Plain abdominal radiographs (Rx) are neither sensitive nor specific for intestinal malrotation [25, 33, 34]. They are usually performed to evidence an occlusion (Figs. 27.8a and 27.9a). A duodenal obstruction gives a typical image of the double bubble sign whatever the cause, i.e., duodenal atresia or high located volvulus [21, 25]. Plain abdominal Rx may yield hints of abnormally located bowel, e.g., small bowel markings predominantly on the right and large bowel on the left. Such findings should prompt further investigations. However a patient with midgut volvulus may have a normal radiograph.

The upper GI series (UGI) remains the imaging reference standard for the diagnosis of malrotation with or without volvulus [21, 22, 25, 35].

Normally the duodenum descends to the right of the midline, courses transversely to the left, and then ascends to the left of the midline at the level of the pylorus; thus the duodenojejunal junction is located to the left of the vertebral body at the level of the duodenal bulb on a standard AP view [25], and the loops of the proximal jejunum are seen on the left of the midline. On a lateral view, the duodenojejunal junction is located posteriorly [25]. However, variations of the normal location may appear, particularly on frontal views in the upper GI series, that mimic malrotation [25, 36]. A grossly distended stomach may displace the bulb. Then the stomach must be emptied and the position of the flexure reassessed.

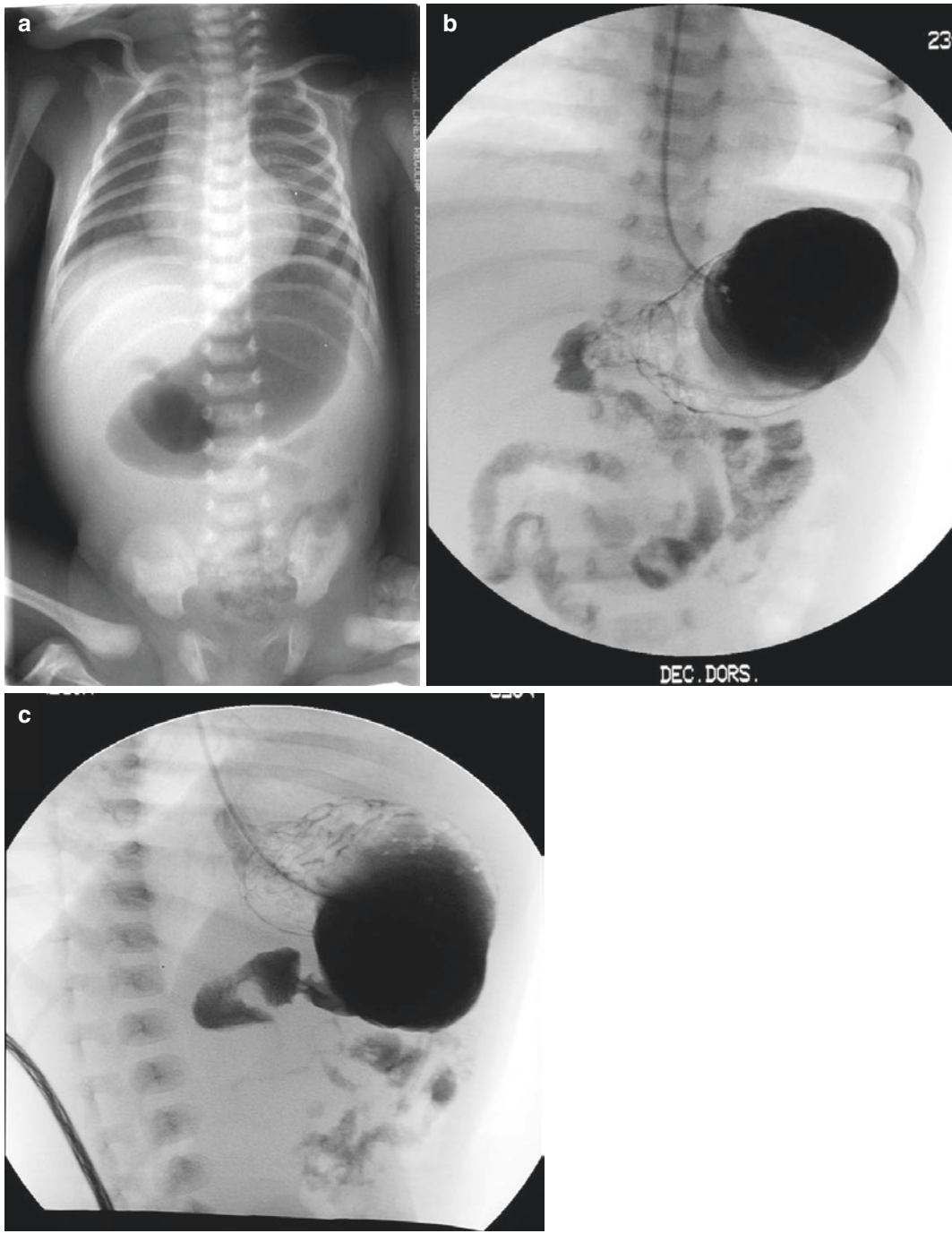

Fig. 27.8 Boy D5. Partial rotation with obstructive Ladd's bands. (**a**) Plain abdominal Rx performed to evidence an occlusion showing gastric distension. Note that some gas has passed below the duodenum. (**b**) UGI AP view; abnormal position of the duodenojejunal junction that fails to cross midline looking down below the level of the duodenal bulb. The proximal jejunal loops are in the right abdomen. (**c**) UGI lateral view; the duodenojejunal junction has an anterior location

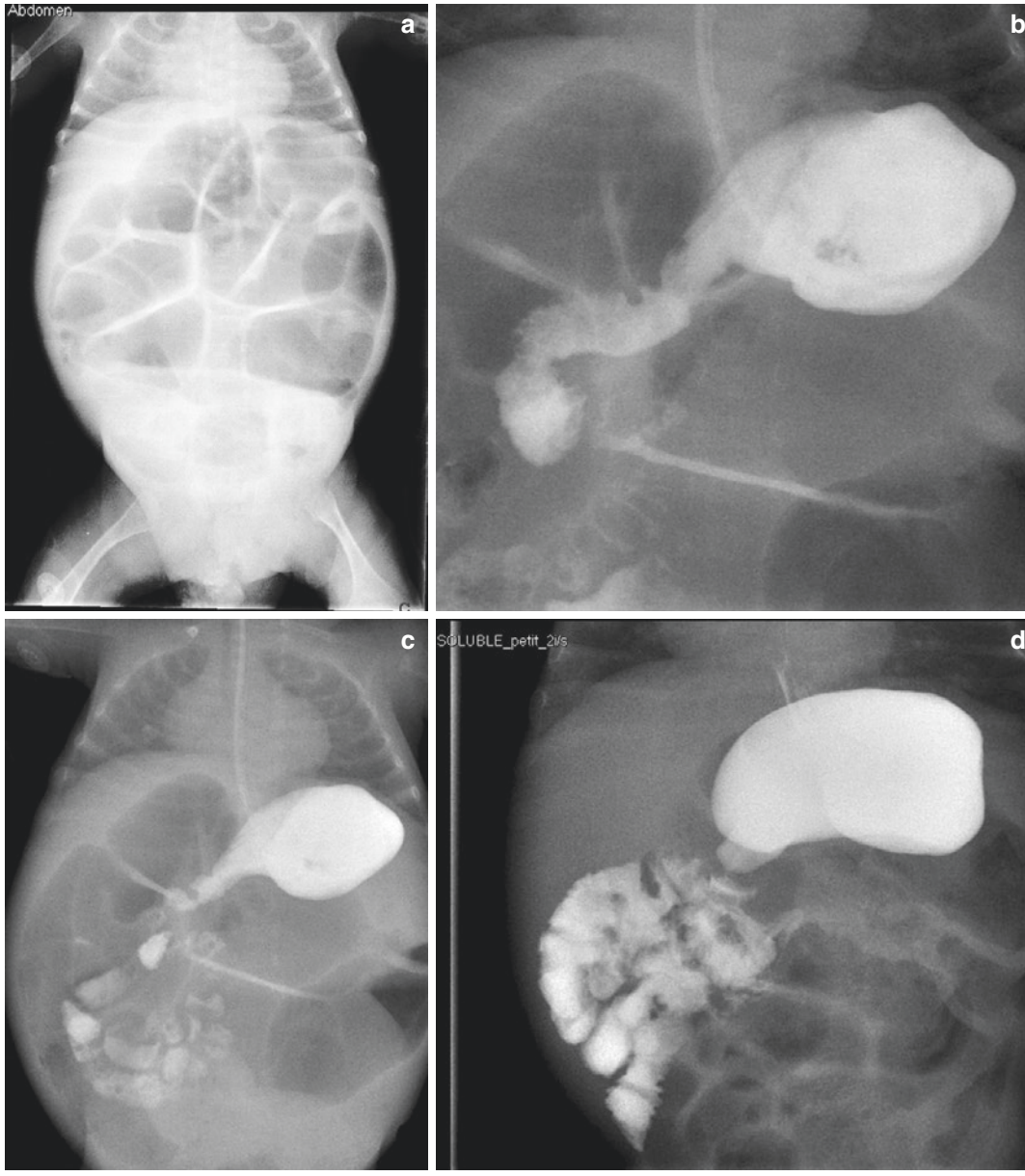

Fig. 27.9 Boy D15. Nonrotation type and volvulus. (**a**) Plain abdominal radiographs performed to evidence an occlusion showing bowel distension. (**b** and **c**) UGI AP view; abnormal position of the duodenojejunal junction that fails to cross midline looking down below the level of the duodenal bulb. (**d**) The proximal jejunal loops are in the right abdomen

In infants, an inferior displacement of a normal duodenojejunal junction is a common variation seen on AP views. This is even more common in prematures. It could be due to a relative mobile ligament of Treitz [36].

In malrotation, the distal duodenum has an abnormal course. On a strict AP view, this appears as an abnormal position of the duodenojejunal junction that fails to cross midline and is located to the right of the vertebral body and, in some

cases, below the level of the duodenal bulb (Figs. 27.8b and 27.9b, c). The duodenojejunal junction may have an anterior location that can be depicted on a lateral view (Fig. 27.8c). In addition, in some malrotations, the duodenojejunal flexure may disappear making its localization difficult. Without occlusion, the contrast media demonstrates the presence of the proximal jejunal loops in the right abdomen (Fig. 27.8d). The cecum is abnormally positioned in 80% of patients with malrotation [21, 25, 35]. A midgut volvulus produces an obstruction of the descending distal duodenum or the proximal jejunum with the appearance of extrinsic compression and torsion, described as "bird's beak," "corkscrew," "twisted ribbon," or "coiled" in appearance according to authors [21, 25, 37].

The sensitivity of the UGI series for the diagnosis of malrotation has been reported as 93–100%, but a sensitivity of only 54% was reported for the diagnosis of midgut volvulus [25, 37].

By 1987, ultrasounds (US) has been introduced as an alternative for the diagnosis of malrotation, with emphasis on the relationship of the superior mesenteric vessels and in the detection of the so-called "whirlpool sign" in cases of volvulus [38–42] (Fig. 27.10a, b). This is due to

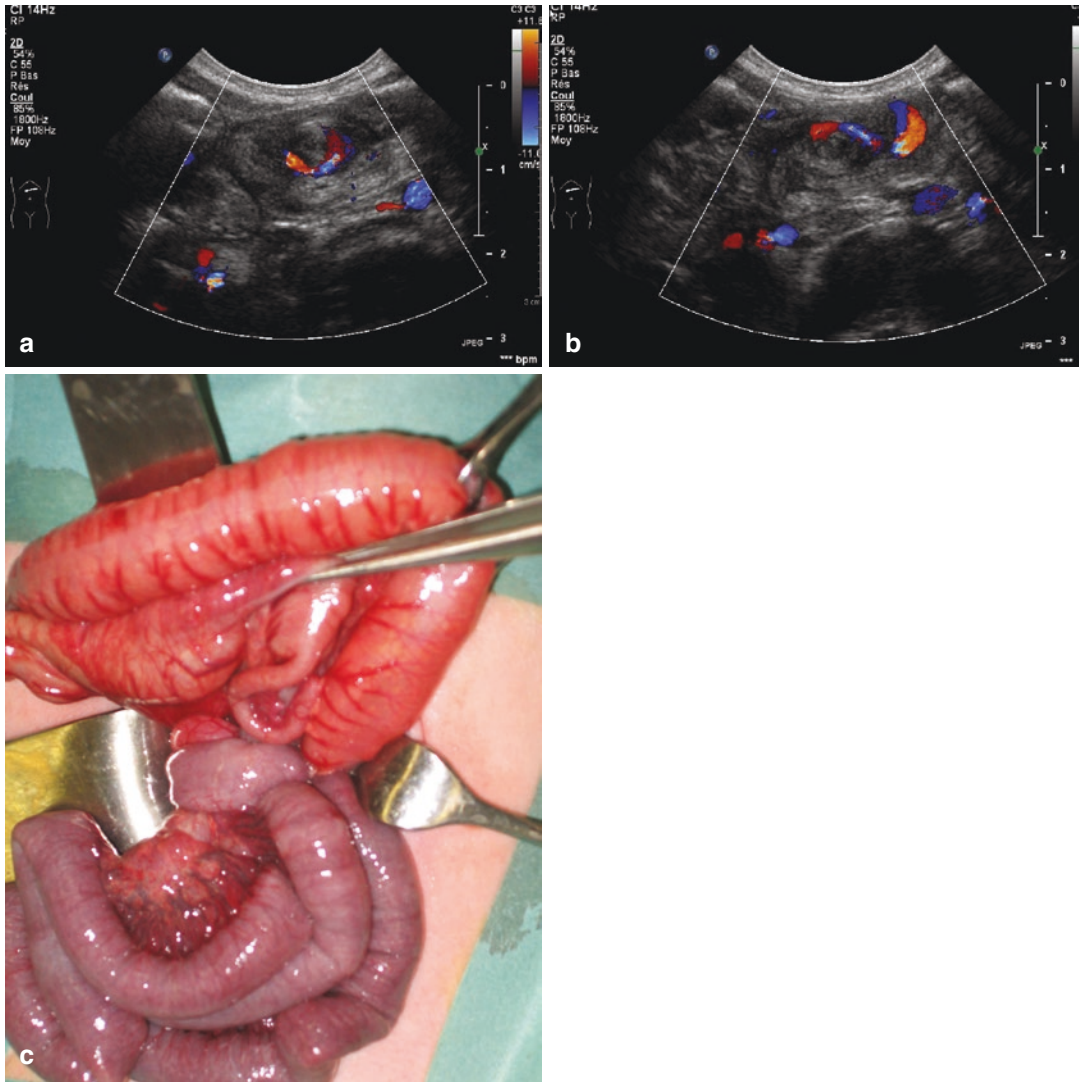

Fig. 27.10 Boy D12. Nonrotation type and volvulus. (**a**, **b**) US, whirlpool sign. (**c**) Peroperative view of the volvulus

the rotation of the superior mesenteric vessels associated with the twist of the bowel. Normally the superior mesenteric vein (SMV) lies to the right of the superior mesenteric artery (SMA). In malrotation the SMV is coiling around the artery coming left to the SMA and more anteriorly. The highest sensitivity is achieved when the "whirlpool sign" is shown, several studies suggesting it to be diagnostic in 100% of the cases [12, 21, 37, 43–45].

US has the potential benefits of portability and lack of radiation. Although US is an excellent imaging modality, the results are strongly operator dependent. Additionally, due to the superimposed intestinal air, both the SMV and the SMA are not always clearly detectable. Orzech et al. reported sensitivity of 86.5%, specificity of 75%, positive predictive value of 42%, and negative predictive value of 96% for US [31]. Several studies have suggested that inversion of the superior mesenteric vessels, (i.e., the SMV to the left of the SMA), is diagnostic of malrotation in 100% of the cases [12, 37, 43, 44]. Consequently, an abnormal US study requires further radiologic and clinical investigation.

However, it has been shown by other authors that inversion of the SMV/SMA relationship can also be seen in patients with normal midgut rotation [12, 21, 43] and in patients with abdominal masses and distal ileocolic intussusception [46]. Furthermore, not all cases of malrotation have abnormal SMV/SMA orientation on US [47]. Because of the lower sensitivity and specificity of US compared with UGI, and because of the fact that US cannot estimate the length of the mesenteric base (which determines the risk of midgut volvulus), UGI has remained the gold standard diagnostic modality [31, 48].

Contrast enema (CE) has been used to demonstrate the position of the cecum. However, CE is less reliable in identifying malrotation because the position of the cecum and colon is highly variable and may even be normal [33]. Reversely 20–30% of malrotations have a normally sited colon [42]. Today it is considered at suppress used in low diagnosis value used and is rarely used.

Both computed tomography (CT) and magnetic resonance imaging (MRI) can be used to display the relationship between SMV and SMA as well as signs of volvulus such as the "whirlpool" sign. CT and MRI can also depict the location of both small and large bowel. An additional advantage of these imaging techniques is that other abnormalities, in association with syndromes or anomalies, can be illustrated. However CT is not considered to be the first imaging modality of choice due to the related irradiation and should be restricted to some unusual cases.

27.9 Treatments

The surgical treatment of a malrotation includes:

- Careful inspection of the bowel and of the mesenteric root in order to recognize the type of malrotation. A precise description is better than the use of a classification type.
- Detorsion of the volvulus counterclockwise if present.
- Lysis of all abnormal bands and adhesions of peritoneum, the so-called Ladd's bands, between the cecum and the duodenum. This is known as the "Ladd's procedure" [1] (Fig. 27.11).
- Straightening and freeing of the duodenum such that it descends directly into the right lower quadrant.
- Broadening of the base of the small bowel mesentery by severing its serosal leaves as to create the longest distance between the duodenojejunal junction and the ileocecal one.
- Placement of the bowel in a nonrotation position in the abdomen with the duodenum and upper jejunum on the right of the abdomen and the cecocolic loop in the left upper quadrant.

The important steps are the broadening of the mesentery which prevents recurrent volvulus and the freeing of the duodenum to relieve the gastrointestinal symptoms these patients have (emesis, reflux, failure to thrive). Turbid fluid at surgery is almost always due to chylous ascites related to lymphatic congestion from partial volvulus and does not evidence a bowel perforation.

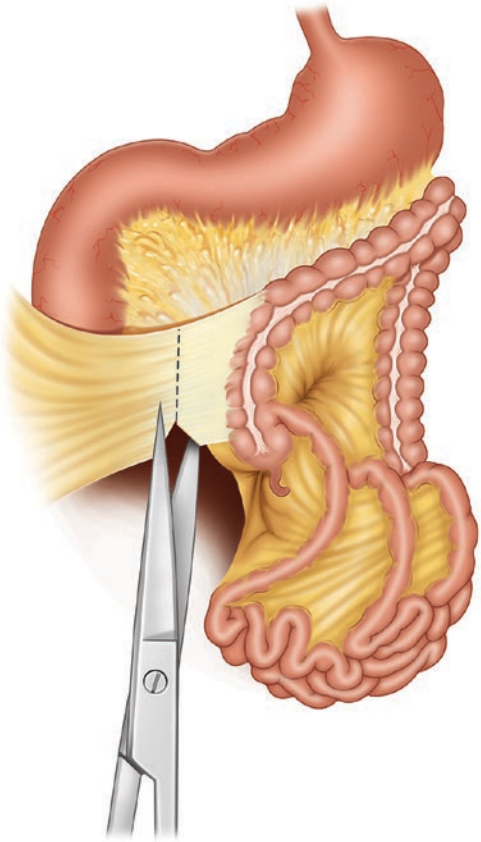

Fig. 27.11 Division of obstructive Ladd's bands

Performing an appendectomy is debatable. A few decades ago, it was the rule. The argument put forward was that the appendix could be in an unusual position, thus making the diagnosis of a future appendicitis more difficult or even unrecognized. Today pediatric surgeons are more respectful of the appendix and avoid removing it unnecessarily specially since the era of laparoscopy that makes its search easier. Much has been written about a pexy of the cecum to prevent future volvulus. There is no evidence that cecopexy improves outcomes or prevents from recurrences [49]. Reversely it creates sites around which a volvulus could occur.

Patients with an acute abdomen require appropriate resuscitation and prompt operative exploration. If a segment of volvulized bowel is identified as ischemic, resection is not mandatory. Only in case of certainly necrotic segment, resection has to be performed. It is wiser to wait before resecting as reperfusion is frequently observed after detorsion, warming, and observation. If viability is in question, it is better to plan a second look procedure within 1 or 2 days than to resect in haste.

In the absence of acute midgut volvulus, patients with symptomatic malrotation can be scheduled for an elective Ladd's procedure.

The Ladd's procedure can be performed open or laparoscopically, but the steps remain the same regardless of the approach.

If preferred, laparotomy is performed via an upper abdominal, transverse, muscle-cutting incision, extending mainly to the right side. Exteriorization of the entire bowel is necessary, avoiding traction to the mesentery, in order to understand the anatomy. The volvulus is usually untwisted by a counterclockwise rotation until the transverse colon and cecum are brought anteriorly to the superior mesenteric pedicle. The bowel is wrapped with warm moist pads until its perfusion is returned to normal.

The use of minimally invasive surgical techniques in the diagnosis and treatment of malrotation has been described in the literature since the beginning of the 1990s [50–52]. Bax reported nine cases of neonates being operated laparoscopically between 1994 and 1997 for volvulus [50].

For the laparoscopic procedure, the child is placed in a supine, anti-Trendelenburg, "frog" position. The surgeon stands at the bottom end of the table with the camera assistant to the left and the scrub nurse to the right. The principal monitor is placed over the child's head to face the surgeon if possible or to the right of the patient's head. Three trocars are used: the first trocar is inserted in an open fashion through the inferior umbilical fold (Hasson's technique) and will contain a ø 5 mm × 30° telescope, and two working trocars are positioned, one pararectally on the right at umbilical level and one in the left hypochondrium. An extra cannula can be inserted subcostally on the left to be used for retraction. Ladd's bands are divided, and the mesentery is widened laparoscopically using the same principles as with the open technique [50, 53–56].

They are major challenges in the laparoscopic procedure for malrotation. In case of occlusion, the bowel distension in an already limited field reduces the surgeon's vision as also does a chylous ascites or inflammatory mesentery resulting from bowel suffering. At the end of the procedure, the small operating field in a neonate makes the assessment of the proper position of the bowel difficult. The use of laparoscopy is safe and effective, and the number of reports in literature increases significantly. However a high rate of conversion is noted ranging from 12 to 33% [14, 54, 56, 57].

The debate between open and laparoscopic approaches on Ladd's procedure is still open. The comparative studies between open and laparoscopic approaches are limited by the small number of cases and subsequently by the lack of prospective randomized design [14, 53, 55]. In a series comparing 2 similar groups of 20 neonates, each suffering malrotations and being operated either open or by laparoscopy demonstrated that the laparoscopic group recovered full diet shortly and left the hospital earlier. Rehospitalization due to recurrence of occlusive symptoms occurred in 30% of patients in the laparoscopic group versus 40% in the open group [14]. Additionally, what is believed to be an advantage of laparoscopy (less postoperative adhesions) could not be either one if the bowel does not stay in the nonrotation position at the end of the Ladd's procedure. If malrotation cannot be excluded from imaging, laparoscopy is an ideal tool to look at the position of the bowel and the appearance and the width of the mesentery [56].

Malrotation that is discovered at the time of operation raises an interesting dilemma with respect to consent. Should the malrotation not be involved in the disease process, its treatment would be considered an additional procedure except if consent can be given by the parents during the course of operation.

Another dilemma is the asymptomatic malrotation discovered fortuitously. Asymptomatic midgut volvulus bears a risk of sudden dramatic event with vascular compromise. No mean can predict it. On the other hand, there are adult patients who remain asymptomatic for their entire lives. So the question raised is, should we perform preventive surgery? In 1993, Schey et al. retrospectively reviewed 53 cases of pediatric and adult malrotations and categorized them into 5 distinct patterns based on relative positions of the duodenojejunal junction and the cecum. They suggested that configurations involving an abnormal position of the duodenojejunal junction were at highest risk for acute midgut volvulus and should be surgically corrected, even if asymptomatic. Configurations involving malrotation of the cecum bear also a risk for volvulus but with less catastrophic consequences due to the smaller vascular distribution involved. According to Schey, these patients should not be operated unless symptomatic [58]. In 2002, Mehall et al. retrospectively reviewed 201 cases of pediatric malrotation. They classified them into three groups based on the location of the duodenojejunal junction. The junction was described as "typical" if it was located right to the midline, "low" if it was located left to the midline and below the vertebra T12, and "high" if it was located left to the midline and above T12. Operative findings of volvulus were more common in the "typical" cases as compared with the other groups, namely, "low" and "high" cases. Operative complications and persistent symptoms after surgery occurred more frequently in the "low" and "high" cases than in the "typical" cases. Given the lower risk of volvulus, higher operative morbidity, and lower success rate, they concluded that consideration should be given to nonoperative management of asymptomatic patients with duodenojejunal junctions classified as "low" or "high" [59].

27.10 Postoperative Course

The postoperative course depends upon the indications for surgery and the intraoperative findings. Dilatation of the duodenum and vascular compromise of the bowel might cause prolonged ileus. It should be managed with expectant policy, maintaining gastric decompression through a nasogastric aspiration and IV fluids. Patient having an extensive bowel injury with or without resection should benefit of a TPN.

During the postoperative course of malrotations, intussusception may occur. The incidence is higher (3.1%) than for other laparotomies (0.05%) [60]. The incidence of postoperative adhesive ileus is 4%. The incidence of recurrent volvulus ranges from 0.5 to 1.3% according to literature [23].

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Part V

Liver and Biliary Tract

Biliary Atresia: New Developments

28

Filippo Parolini and Mark Davenport

28.1 Introduction

Biliary atresia (BA) is an idiopathic neonatal hepatobiliary disease characterized by progressive fibrosing obstruction of the intra- and extrahepatic biliary tree [1]. Although there have been some changes in modern management, its principles have been largely unchanged since the 1980s involving an initial attempt at restoration of bile flow with the Kasai portoenterostomy (KPE), and if this is unsuccessful or complications ensue, then liver transplantation is offered [2–7]. Nowadays, long-term survival with a normal life is possible with either KPE or a functioning liver transplant, in most centres, for more than 90% of patients [1–3]. Here, we review the recent advances in basic research and clinical progress in these diseases, as well as the diagnostic assessment and therapeutic approach.

28.1.1 Epidemiology and Burden of Disease

The incidence of BA varies dramatically according to geography, with the highest rates being reported from Taiwan, Japan and China (1 in 5–10,000 live births) [2–5]. In the UK, Europe and North America, the incidence ranges from about 1 in 15–20,000 [2, 4]. Although rare, BA is the most common cause of severe chronic progressive liver disease in childhood and is still the leading indication for liver transplantation in childhood (about 50%) [5, 6]. This disproportion can be gauged by considering that in the United States, $77 million (2003 figures) is spent annually on paediatric liver transplantation-related costs, i.e. about 2% of total healthcare expenditures for only 0.0006% of the entire paediatric population [5].

28.1.2 Macroscopic Classification

The Japanese classification of BA describes the macroscopic appearance of the extrahepatic ducts and is based on the level of the most proximal obstruction of the extrahepatic biliary tree [1, 7] (Fig. 28.1):

- Type 1 (5%): level of common bile duct (CBD) and often associated with a cyst which therefore should contain bile.
- Type 2 (2%): level of common hepatic duct (CHD). Transection of the proximal porta hepatis should show both right and left ducts with bile present.
- Type 3 (>90%): Transection of the porta hepatis should not show any remnant bile ducts, as these if present are microscopic. Typically there is a solid dense fibro-inflammatory

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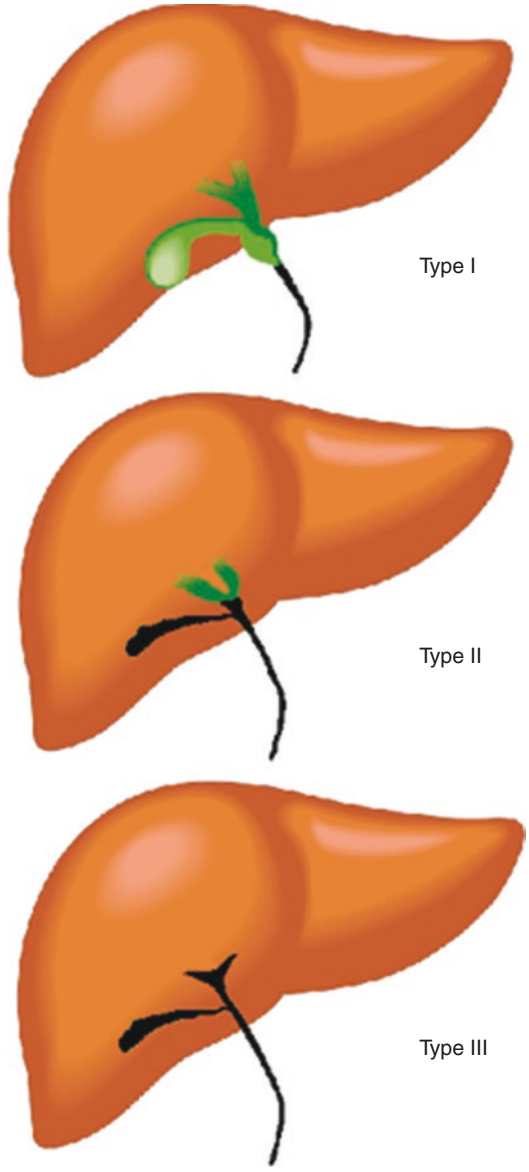

Fig. 28.1 The Japanese classification of biliary atresia

proximal remnant at the porta hepatis. The distal duct may be atrophic, absent or relatively well preserved, if so, usually in connection with a mucus-filled gallbladder.

Intrahepatic bile ducts are always non-dilated and if visualized (rarely) are grossly abnormal with perhaps a myriad of ductules coalescing at the porta hepatis.

28.1.3 Aetiopathogenesis and Phenotypic Classification

The true aetiology of BA is unknown, although developmental and infective hypotheses have been suggested and fashions change [1, 2, 8]. Certainly, BA is not a single uniform disease and at least four different variants with a different pathological background are identifiable from clinical observation alone (Fig. 28.2).

- Syndromic BA, typically the biliary atresia splenic malformation syndrome, but there are others such as the cat eye syndrome [9, 10]
- Cystic BA [11]
- Cytomegalovirus (CMV) IgM + ve BA [12]

The others, for which we use the term "isolated BA", lack any real clue to their aetiology and account for the majority of cases.

"Developmental" BA is a term used to include patients with BASM and cystic BA, where the onset is certainly during prenatal life and evident at the time of birth and usually where there is the clear female predominance.

28.1.4 Development of the Extrahepatic Bile Ducts

The extrahepatic bile duct begins as a diverticulum from the duodenum around 20 days' gestation. It is enveloped by the amorphous hepatic primordium and forms its own diverticulum—the gallbladder. Throughout this phase, ending about 45 days, it retains a lumen. It is lined by cholangiocytes expressing transcription factors common to the pancreas and duodenum (e.g. PDX-1, PROX-1, HNF-6) [1, 13]. This is occurring parallel with key changes in visceral rotation, cardiac and splenic development and evolution of the portal and inferior vena cava. Bile duct maldevelopment at this stage could explain the *biliary atresia splenic malformation (BASM) syndrome*, a subset noted in 10% of European BA cases and that encompasses splenic malformation (usually polysplenia), situs inversus, malrotation, absence of the inferior vena cava and a preduodenal portal

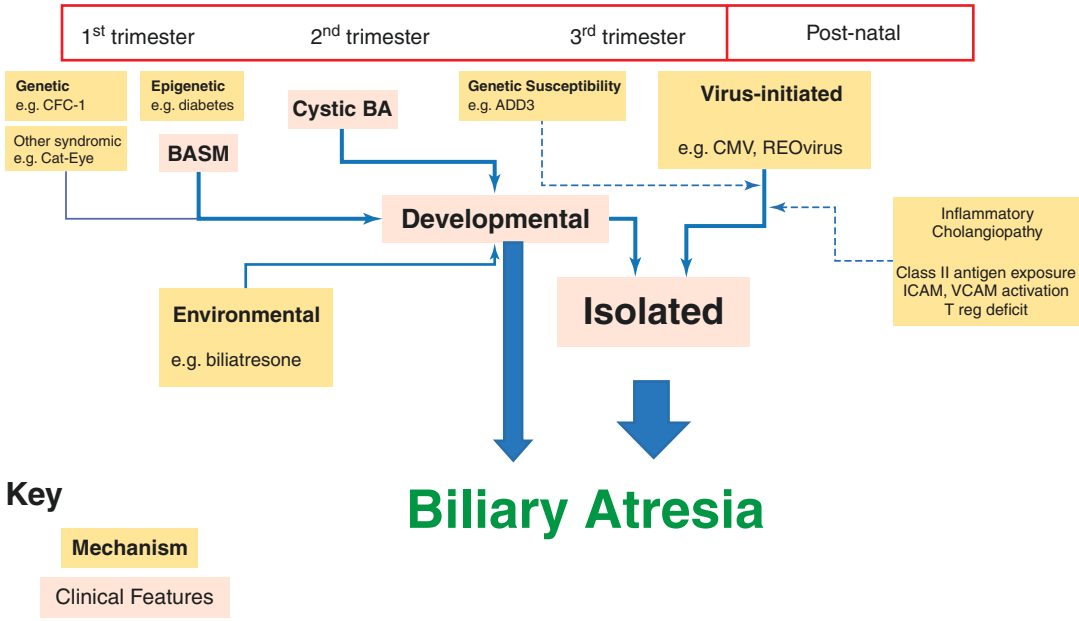

Fig. 28.2 Possible aetiological pathways in biliary atresia

vein [10]. Some of these infants seem to come from an abnormal intrauterine environment (e.g. maternal diabetes and thyrotoxicosis).

Postnatally, infants with BASM have absence of the CBD, an atrophic gallbladder and a normal appearing liver at the time of birth [10, 14]. Mutations in the CFC-1 gene, encoding for CRYPTIC protein which is also related to disorders of heterotaxy and cardiac anomalies, at least in mice, have been identified in 50% of a French series of infants with BASM [15].

28.1.5 Cystic BA

Cystic BA accounts for about 10% of cases and is caused by extrahepatic cyst formation in an otherwise obliterated biliary tract [11]. The cyst may be filled by mucus or bile and can be detected antenatally. Cystic BA may lead to diagnostic confusion with early obstructed cystic choledochal malformation though both need urgent exploration. We speculate that this variant occurs relatively late in gestation beyond the period of initial bile production at 12 weeks with at least in some luminal integrity between intrahepatic and extrahepatic systems. These infants also have a better outcome following surgery, probably because of this more mature intrahepatic bile system [6, 11].

28.1.6 Cytomegalovirus-Associated BA

In 1974, Benjamin Landing proposed that BA could be caused by the effects of a virus [16]. Since then DNA and RNA from a range of candidate viruses (e.g. reovirus, rotavirus and CMV) have been isolated from clinical cases although not consistently so [17, 18].

One of the candidates, CMV, is a double-stranded DNA virus from the *Herpesviridae* family that has the capability to infect and injure bile duct epithelia, and serological evidence of infection in the infant (CMV IgM + ve) has been shown in up to 50% of BA patients in some Chinese series [12, 17–19]. Nevertheless, whether the biliary damage is related to a direct cytopathic effect of the virus or to secondary autoimmune reaction triggered by viral exposure still remains unclear. Patients with CMV IgM + ve BA (about 10% of cases in our series) showed several

distinct clinical and histological features compared to CMV IgM-ve BA infants such as an older age at KPE, a greater degree of splenomegaly and a greater degree of inflammation and fibrosis in the liver even if age-matched [12]; further quantification of the T cell infiltrate also suggested a Th-1 predominance [19]. These patients have also a poor outcome in terms of response to KPE and a higher mortality compared to those who were CMV IgM-ve [12, 20, 21].

28.1.7 Isolated BA

Whatever remains, termed "isolated BA", lack any real clue to their aetiology, though its onset must be after those with BASM given the lack of other affected systems [3]. We also know that formation of the intrahepatic bile duct system only begins beyond about 7 weeks gestation and has to be essentially complete and linking with the extrahepatic bile ducts at the porta hepatis by 12 weeks [13]. One obvious speculation is that this linkage phase is incomplete—so-called "interface" BA.

Alternatively there is normal formation of a functional duct system but later obliteration as a secondary phenomenon.

28.2 Cellular Kinetics and Inflammation

In about 40% of cases of BA (possibly with the exception of BASM), there is a marked inflammatory process with mononuclear cell infiltrate and expression of a variety of adhesion molecules on intrahepatic biliary and vascular surfaces [1, 22]. The immunohistochemical appearance is characterized by abnormal expression of Class II antigens and cytokines such as intercellular adhesion molecule (ICAM), predominantly on the biliary epithelium, and vascular cell adhesion molecule (VCAM), predominantly on the sinusoidal endothelium [22]. There is also an infiltration of activated CD4 + ve lymphocytes and CD56 + ve natural killer (NK) cells. Most studies suggest polarization with a predominantly Th1 and Th17 effector profile [19]. This systemic response to hepatobiliary inflammation can be detected as increased levels of cellular adhesion molecules (ICAM and VCAM) and pro-inflammatory cytokines such as interleukin-2 (IL-2), IL-18 and tumour necrosis factor-α (TNF-α) [23].

28.2.1 Initiators of Cholangiopathy

A number of extrinsic factors have at one time been suggested as triggers to the inflammatory process whereby the end product is bile duct damage and obliteration. Viruses, particularly CMV, may play a role but other mechanisms have been suggested. Thus recently a toxin has been isolated and named biliatresone for its property of causing either damage or developmental arrest. Figure 28.3 illustrates the story behind this piece of biological detective work.

28.3 Clinical Features

Antenatal detection of those with cystic BA (<10%) is possible on the maternal ultrasound scan, usually between 18 and 22 weeks' gestation [11, 24]. For the remaining patients, the disease is usually suspected soon after birth with persistent conjugated jaundice, acholic stools and dark urine in an otherwise healthy neonate. Most infants eventually demonstrate a degree of failure to thrive due to reduced fat absorption, and certainly fat-soluble vitamin deficiency is common (A, D, E and K) [25]. Liver fibrosis and cirrhosis are secondary features which depend on the age of the child, whilst ascites and hepatosplenomegaly are not usually seen until after about 3 months [1].

28.3.1 Diagnostic Assessment

Liver biochemistry is non-specific and shows a conjugated hyperbilirubinemia, slightly raised transaminases (AST and ALT) and significantly raised γ-glutamyl transpeptidase (GGT). Protein and albumin levels are usually normal. The

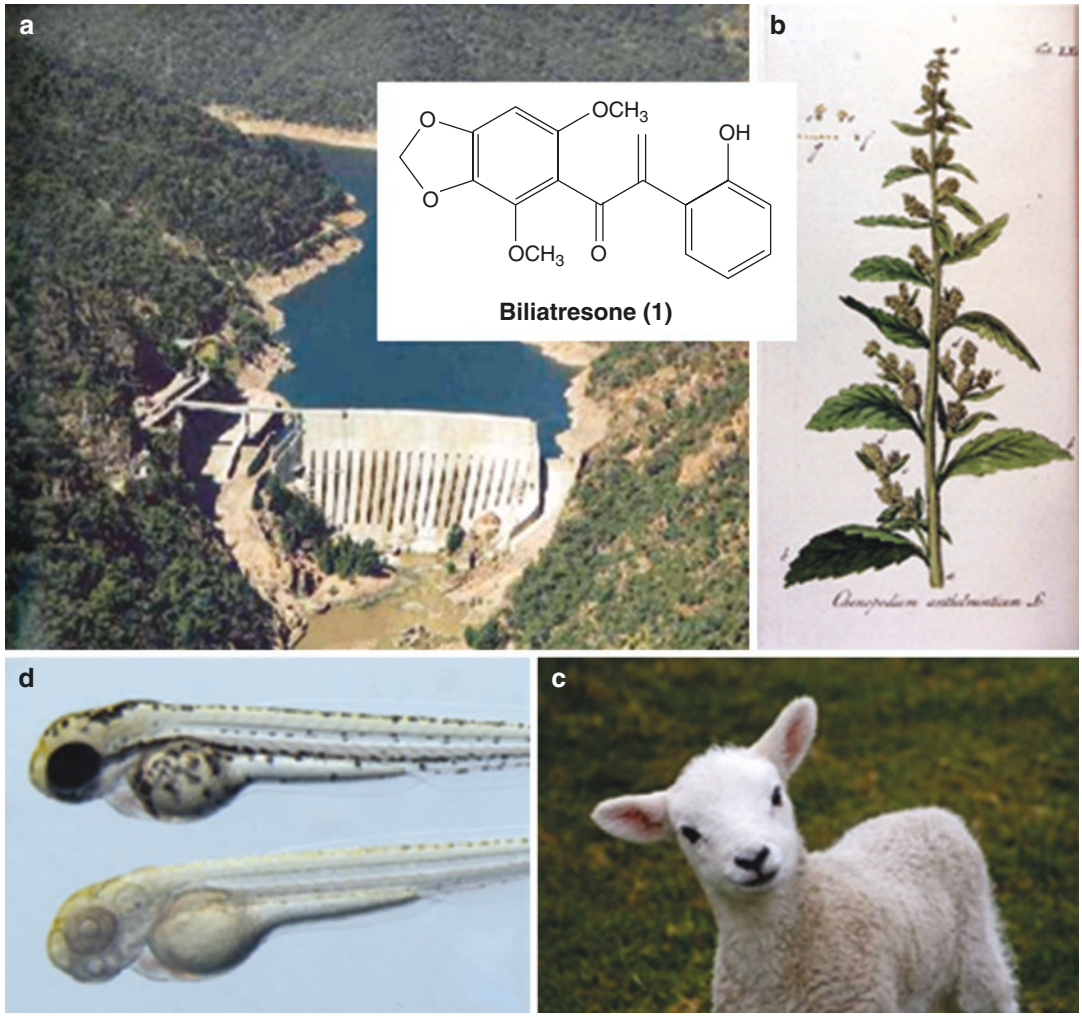

Fig. 28.3 The Biliatresone story: In 1964 in the area surrounding the Burrinjuck Dam in New South Wales, Australia (**a**), the silt foreshores of the dam became exposed by declining water levels causing abnormal colonization by a particular weed termed the red crumbweed (*Dysphania glomulifera* subsp. *glomulifera*) (**b**). This area was then used as grazing land by local farmers and lambs (**c**) subsequently born were affected by BA-like pathology. An isoflavonoid isolated in extracts of the Red Crumbweed, now known as Biliatresone, has been clearly demonstrated to cause biliary maldevelopment in Zebrafish larvae model (**d**). *Picture reproduced with permission from reference* 13

AST-to-platelet ratio index (APRi) can also be calculated and has been used as a surrogate marker of liver fibrosis in larger studies even predicting native liver survival [26, 27].

Abdominal ultrasound is a key investigation in other possible surgical diagnoses characterized by intrahepatic or common bile duct dilatation (e.g. choledocal malformation, inspissated bile syndrome). Actual positive signs of BA are less specific though may include evidence of an atrophic gallbladder or the so-called triangular cord sign, representing the appearance of the solid proximal biliary remnant in front of the bifurcation of the portal vein.

Radioisotope hepatobiliary imaging should show absence of biliary excretion in BA but is non-specific [28]. In the UK and North America, percutaneous liver biopsy is popular and has a

positive predictive value of >90% and typically shows the histological features of "large-duct obstruction", i.e. oedematous expansion of the portal areas, ductular proliferation, bile plugs and portal fibrosis [29]. There is in some a marked inflammatory aspect with infiltration of activated mononuclear cells, such as CD4+ T cells and NK cells. As the disease progresses, then monocytes/macrophages also appear with progressive bridging fibrosis between portal areas [1].

Sometimes, direct cholangiography has to be performed to prove (or disprove) the diagnosis. This can be performed using endoscopic retrograde cholangiopancreatography (ERCP) or at laparoscopy or indeed via a small incision directly over the gallbladder.

28.4 Screening for BA

Population screening programmes for BA are based on the provision of stool colour cards to parents of newborns in order to identify acholic stools and have been in use Japan [30], Taiwan [31], Switzerland [32] and Canada [33]. A large-scale prospective study which enrolled more than 6000 Canadian families demonstrated the practicality and cost-effectiveness of the stool colour card [33], even if this success may be more limited in countries without routine 30-day-old well-child visits for review of the stool colour card [34]. Recently, a pilot study on a mobile application that utilizes a smartphone's camera and colour recognition software to analyse an infant's stool in the perinatal period (PoopMD©) showed that it may have value as a tool to help parents identify acholic stools and provide guidance as to whether additional evaluation with their paediatrician is indicated [35].

28.5 Management

Following confirmation of the diagnosis, it is important to consider how far advanced the disease is. Primary liver transplant is uncommon in Western series (<2% in the UK) and could be an option in some countries, but it should probably only be a consideration in those presenting late (>100 days) or with obvious cirrhosis, ascites and portal hypertension and liver failure (increasing INR and decreasing albumin). For the remainder a KPE is indicated as attempt to retain the native liver.

28.5.1 "Maximally Invasive" Surgery

Conventional open portoenterostomy, first described by Japanese surgeon Morio Kasai in 1957, still represents the gold standard of treatment. The key part of the procedure is the dissection at the level of the portal plate. Our practice is to exteriorize the liver on the abdominal wall by division of the left triangular and falciform ligaments. The gallbladder is then mobilized from its bed and the distal CBD divided and then dissected back towards the porta hepatis (Fig. 28.4). Division of small veins from the back of the portal confluence to the porta plate facilitates downwards traction of the portal vein 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 the right vascular pedicle into anterior and posterior branches should be visualized. The "width" of the transected portal plate should extend from this bifurcation into Rouviere's fossa on the extreme right to the point where the left portal vein gives off its first branches to segment IV. A 40–45-cm retrocolic Roux-en-Y loop should be constructed. The jejunojejunostomy lies about 10 cms from the ligament of Treitz and can be stapled or sutured. The proximal anastomosis must be wide (~2 cms) and typically end-to-side.

28.5.2 "Minimally Invasive" Surgery

During the early years of the new century, there was a brief flirtation with the concept of the

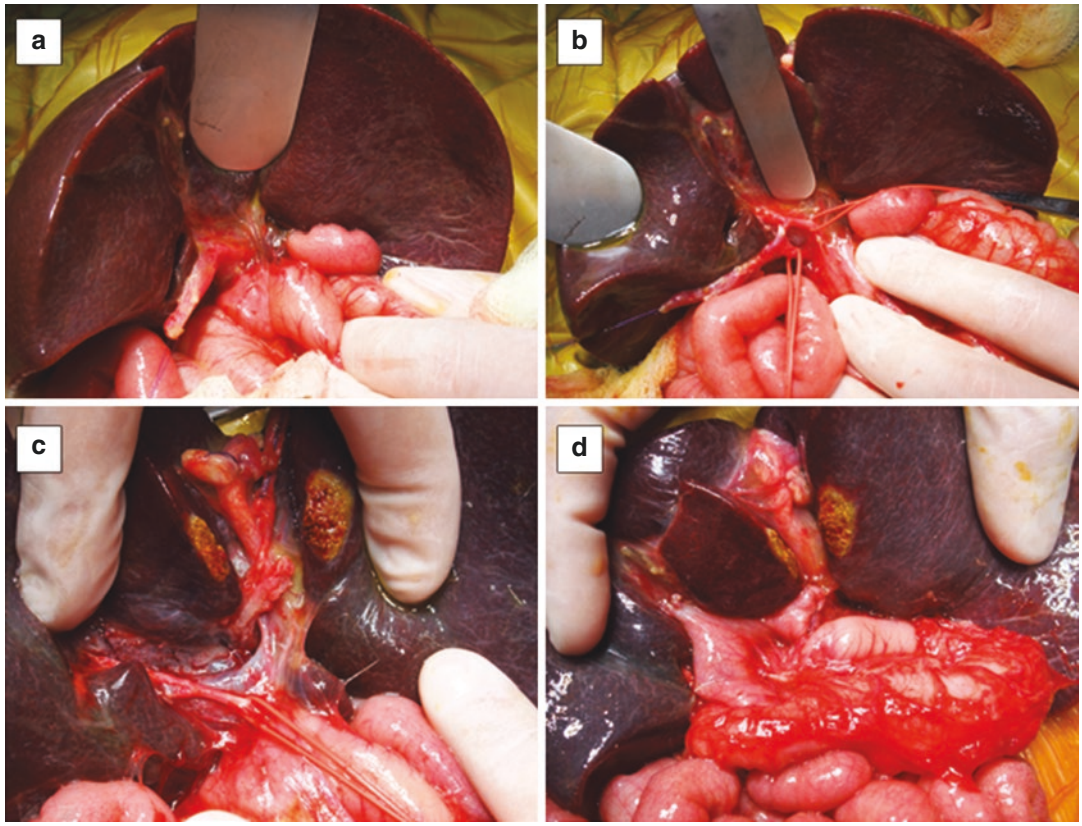

Fig. 28.4 Intraoperative picture of Kasai portoenterostomy. (**a**) Exteriorisation of the liver and exposure of the porta hepatis. (**b**) The gallbladder is then mobilized from its bed and the distal CBD divided and then dissected back towards the porta hepatis. (**c**) Exposure and transection of portal plate. (**d**) Reconstruction with Roux-en-Y loop

laparoscopic Kasai option. This procedure was reported first by a Brazilian team in 2002 [36] and there have been small case series since [37]. It has become apparent that laparoscopic KPE does not offer anything advantageous to the child beyond a better scar. Clinically meaningful results are certainly not better and rarely comparable to open surgery [38]. Two large centres have reverted from laparoscopic to the open operation with restoration of their previous results [38, 39]. A recent systematic review found no significant difference between the laparoscopic and open KPE groups in terms of operative time, early clearance of jaundice and cholangitis, but the rate of 2-year survival with native liver was significantly higher in the open group than in the laparoscopic [40]. This is likely to be because of the difficulties with portal plate dissection using laparoscopic instruments, as delicate dissection and radical resection of all extrahepatic biliary remnants are key features to maximize the results. Laparoscopic KPE is still being practised in a few centres in Japan, but one team at least has reverted to a less extensive dissection and more superficial transection [41, 42].

28.6 Adjuvant Therapy for Biliary Atresia

The success of the operation is gauged by clearance of jaundice (within 6 months), and each centre treating infants with BA will have its own

Table 28.1 Adjuvant postoperative therapy after KPE

Therapy	Rationale
Corticosteroids	Anti-inflammatory effect and choleretic effect
Antibiotics	Decreases risk of ascending cholangitis
UDCA	Establishes bile flow, possible anti-inflammatory action
Ganciclovir/ valganciclovir	Competitive inhibitor of deoxyguanosine triphosphate (dGTP) of CMV
Fat-soluble vitamin supplementation	Restores intrinsic deficiency due to impairment of bile flow
Phenobarbitone	Induces liver microsomal enzymes and thereby increases bile flow
MCT-based formula milk	Effective maintenance of calorie intake, as MCT does not require bile for its absorption in the gastrointestinal tract

Legend: *UDCA* ursodeoxycholic acid, *CMV* cytomegalovirus, *MCT* medium-chain triglyceride

postoperative regimen to try and maximize the restoration of bile flow. Most will include a prolonged period of oral antibiotics, ursodeoxycholic acid, fat-soluble vitamin supplementation, medium-chain triglyceride (MCT)-based formula milk and usually steroids (Table 28.1).

28.6.1 Corticosteroids

Steroids have been used for at least 30 years albeit delivered in an uncontrolled pragmatic fashion [43]. The rationale behind the use of steroids maybe twofold: firstly, there is a pronounced inflammatory element in a proportion of infants with BA, and steroids have many anti-inflammatory properties. Moreover, steroids have a positive choleretic effect which may improve bile flow and keep open the primitive bile ductule-Roux loop connection in the early postoperative phase [44]. There have been two prospective, double-blind, randomized, placebo-controlled trials. The first one used a low dose of prednisolone (2 mg/kg/day) in two English high-volume centres in 73 infants [45]. This showed a statistically significant improvement in early bilirubin levels (especially in the "younger" liver) in the steroid group but did not translate to a reduced need for transplant or improved overall survival. The other study is the START trial [46]; this randomized 140 infants from 14 North American centres to a steroid arm using initially IV methylprednisolone 4 mg/kg/day for the first 3 days followed by oral prednisolone (4 mg/kg/day till the second week, 2 mg/kg × 2 weeks, followed by a tapering protocol over the next 9-week period). Although there was a difference in the clearance of jaundice from 49% in the placebo group to 59% in the steroid group, this did not attain statistical significance. They also did a subgroup analysis of infants <70 days at KPE ($n = 76$) and showed that 72% (28/39) in the steroid group cleared their jaundice compared to 57% (21/37) in the placebo group, unfortunately still not statistically different ($P = 0.36$).

A follow-up study [47] to the original UK trial examined the use of a high-dose prednisolone cohort (starting at 5 mg/kg/day) and reported the same beneficial biochemical effects (now including a reduction in AST and APRi levels) with a statistically significant higher proportion of those who cleared their jaundice in the steroid groups. Later analysis showed that the key appeared to be the age of the infant at time of KPE [48]. In practice, all three of the English specialist centres (London, Leeds and Birmingham) use high-dose steroids albeit in a variety of regimens.

28.6.2 Ursodeoxycholic Acid (UDCA)

This is widely thought to be beneficial, but only if surgery has already restored bile flow to reasonable levels. 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. There is but a single study which looked at the effect of UDCA on liver function in 16 children >1 year post-KPE how who had resolved their jaundice. Its crossover design looked at UDCA (25 mg/kg/day in three divided doses) in an 18 month period followed by 6 months washout and then resumption. All but two had sustained significant worsening in their liver enzymes that on restarting UDCA reversed [49].

28.6.3 Antiviral Treatment for CMV IgM + ve

Antiviral treatment with intravenous ganciclovir and/or its oral prodrug valganciclovir has been trialled and shown to be well-tolerated and effective in prevention of long-term neurological damage (e.g. hearing loss) in newborns with symptomatic congenital CMV infection [50, 51]. The real potential for antiviral therapy in children with CMV IgM + ve BA (10% of cases) exists, even if no convincing studies have been published to date [20, 21]. In our own unpublished series of 37 consecutive IgM + ve BA patients, the group who received adjuvant antiviral postoperative therapy (9 patients) presented a statistically significant higher clearance of jaundice compared with those who did not receive such treatment (89 vs. 41%).

28.7 Postoperative Complications

The most common problem after KPE is that there is no or ineffective restoration of bile flow; jaundice therefore worsens and end-stage liver disease and cirrhosis beckon. The key in these infants is to prepare the way to a safe liver transplant by strict attention to nutrition, vitamin deficiencies and fluid management. There are some specific complications, which can occur independently of this process though.

28.7.1 Cholangitis

Ascending bacterial cholangitis are relatively common and at least one episode is seen in up to 50% of most large series. The CHiLDREN consortium reviewed 219 long-term survivors and reported an incidence of cholangitis of 17% in the preceding 12 months [52]. The risk is most apparent in the first 2 years post-surgery although the reason for the diminution in risk is obscure, though it could be related to some time-dependent change in local immunologic defence within cholangioles. The key clinical features are pyrexia, worsening jaundice and a change in liver biochemistry. Following blood culture, episodes should be treated aggressively with broad-spectrum intravenous antibiotics effective against Gram–ve organisms (e.g. gentamicin, meropenem, piperacillin/tazobactam) [53].

28.7.2 Portal Hypertension and Oesophageal Varices

Abnormally raised portal venous pressure is seen at the time of KPE in about 70% of BA infants. It is caused by liver fibrosis and correlates with the age at KPE, bilirubin level and ultrasound-measured spleen size [54]. However the initial measured pressure is a poor predictor of outcome either in terms of response to KPE or more surprisingly even in those who will go on to develop varices. About 60% of children who have survived with their native liver beyond 2 years will have definite varices visible at endoscopy, and of these about 20–30% will bleed. Upper gastrointestinal varices take time to develop, and bleeding is unusual before 9 months of age and more usually occurring from 2 to 3 years. Emergency treatment of bleeding varices specifically includes the use of vasopressin or somatostatin analogues and sometimes even a Sengstaken-Blakemore tube. Most can be treated endoscopically with banding or in the very young, injection sclerotherapy [55].

Recently we proposed a new prediction score associated with good specificity and sensibility in the selection of children with clinically significant varices eligible for a screening endoscopy [56]. Some children also develop haemorrhoids and anorectal varices later during childhood [57].

28.8 Miscellaneous

Ascites is related to and caused by portal hypertension in part, but there are other contributory factors which include hypoalbuminaemia and hyponatraemia. Conventional treatment includes a low-salt diet, fluid restriction and the use of diuretics particularly spironolactone. Often seen in settings of malnutrition, consideration should be given to nasogastric feeding to try and increase calorie and protein intake.

Hepatopulmonary syndrome (HPS) may develop even in anicteric children, especially in those with BASM. The exact mechanism of HPS is still unknown, even though it may be a manifestation of preexisting congenital vascular anomaly. HPS can be diagnosed using arterial blood gas estimation with and without inspired oxygen, and typically hypoxia is worse in the standing position (platypnea). This complication is usually resistant to conventional therapy, and liver transplantation appears to be the only specific treatment.

Malignant change involving both cholangiocarcinoma and hepatocellular carcinoma (HCC) has been reported in children post-KPE [58]. It is related to the underlying cirrhosis of most of the long-term survivors. Surveillance using regular serum alpha-fetoprotein levels and ultrasound are helpful but not absolute markers of the malignant change, and suspicious nodules should be thoroughly investigated with magnetic resonance imaging (MRI) or computed tomography (CT) and biopsy.

28.9 Outcome and Results

In order to allow meaningful comparison between series, it is important to use reproducible outcome measures which accurately reflect performance and effective management of BA.

These are:

- *Clearance of jaundice* to a preset level (typically ≤20 μmol/L in Europe and < 1.5 mg/dl in North America). This is influenced by type of BA, age at surgery, the experience of the surgeon and the nature of the surgery performed. A clearance rate higher than 50% should be expected in experienced surgeons operating on infants <70 days of age.
- *Actuarial native liver survival* (end-points of death and liver transplant). This is influenced mostly by clearance of jaundice rate but also by postoperative complications and quality of medical follow-up. Obviously, increased access to transplantation and softening of the indications will reduce the native liver survival over time.
- *Actuarial true survival* (end-point death). This reflects on not only the success of the original operation but also access and safety of the transplant procedure and minimization of postoperative risk. The burden of associated anomalies, mainly cardiac, should be also considered.

Centralization of the resources has been the single most important public health measure and has changed the outcome of BA. Since 1999, the treatment of BA has been centralized to three centres in England and Wales (London, Birmingham and Leeds), and the benchmark study of outcome following this centralization has allowed publication of key national statistics. In this cohort of 424 patients who underwent KPE from 1999 to 2010, clearance of jaundice was achieved in 55%, with a 5- and 10-year native liver survival estimated in 47% and 43%, respectively [6]. Following this English experience, encouraging results were achieved in smaller countries such as Finland [59] and Denmark [60] and Switzerland [61]. The only constraint is geography such as in the relatively low population density countries such as Canada [62] and Australia [63]. Published national outcomes are given in Table 28.2. Essentially if your country is not listed, then its outcomes will be worse. The recently launched online registry "bard-online" (www.bard-online.com) might aid

Table 28.2 National outcomes in Biliary Atresia

	Period	*N*	Age at KPE, days (mean/median)	Clearance of Jaundice[a]	4- to 5-year native liver survival	4- to 5-year true survival
Centralized national series						
England and Wales [6]	1999–2009	443	54	56%	46%	90%
Finland [59]	1987–2010	72	64	75%	75%[b]	92%[b]
Decentralized national series						
France [64]	2003–2009	329	59	33–39%	33–39%	85–92%
Swiss [61]	1994–2004	48	59	39.5%	37%	91%
Netherlands [65]	1987–2008	214	59	38%	46%	73%
Canada [62]	1992–2002	230	64	n/a	39%	83%
Germany [66]	2001–2005	183	57	18%	20%	83%
Multicentre, not National						
USA [67]	1997–2000	104	54	55%	46%	89%
Italy[c]	2001–2005	59	78	51%	38%	87%
National Asia						
Japan [68]	1989–1998	1381	65	57–62%	52–62%	70–78%

[a]Clearance of jaundice variably defined
[b]Outcome at 2 years after KPE
[c]Unpublished data from Italian Survey on BA including patients from five centres (Brescia, Bergamo, Modena, Naples and Rome) (Alberti D, personal communication)
n/a: not available

in the collection of multinational data, including from countries without registries [69].

28.10 Conclusions

Origins of BA are mysterious, its diagnosis contentious, and its outcome uncertain. The future will see improvements in understanding the basis for this enigmatic disease, but it is noteworthy that all currently successful treatments have been surgical. Nowadays, long-term survival with a normal life is possible with KPE or a functioning liver transplantation for more than 90% of patients which is *incroyable* compared to the equivalent statistic of around 10% widely held as the norm in the 1970s.

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Congenital Hepatic Cysts

29

Morven Allan and Mark Davenport

29.1 Introduction

The incidence of congenital hepatic cysts is not known. A 10-year retrospective study of antenatally diagnosed abdominal cysts, carried out at a single Australian centre, showed that three hepatic cysts were detected in 22,000 live births during the period January 1991–January 2002 [1]. However, with the increasing prevalence of antenatal ultrasonography, it is inevitable that this incidence will increase. Whilst the diagnosis can certainly be suspected antenatally, a precise diagnosis may be difficult due to lack of specific features. Of course, this is true of any intra-abdominal cystic lesion in a newborn infant where the differential diagnosis includes mesenteric cyst, duplication cyst, haemangioma, teratoma, lymphangioma, cystic choledochal malformation, renal cysts, ovarian cysts, etc.

Those antenatal cysts that can be seen to arise from within the liver parenchyma can be divided into four possible categories: simple hepatic cysts, mesenchymal hamartomas, ciliated foregut cysts, and intrahepatic choledochal malformations (typically Type V) [2, 3]. Only the first three on this list will be discussed in any detail.

29.2 Simple Hepatic Cysts

The majority of antenatally detected liver cysts are simple in origin. The first one proving to be a simple liver cyst was described by Michel et al. in 1986 [4].

Their adult counterparts are regarded as a common but usually incidental finding. So, one study identified a simple cyst in about 2.5% of an adult population, occurring most frequently in the fourth and fifth decade of life [5], with an increased incidence in females (M:F 1: 4) [6]. However, antenatal diagnosis is infrequent with fewer than 30 cases of simple liver cysts being reported in the literature [4, 5, 7–19]. The largest single-centre series ($n = 11$) was reported by ourselves in 2007 [18].

Histologically they can be defined as a fluid-filled space lined by cuboidal or columnar epithelium with a distinct lack of mesenchymal stroma and with an outer layer of fibrous tissue [12]. The majority (90%) are unilocular, ranging in size from mm to cm, the largest reported being >150 cm on postnatal imaging [16] (Fig. 29.1).

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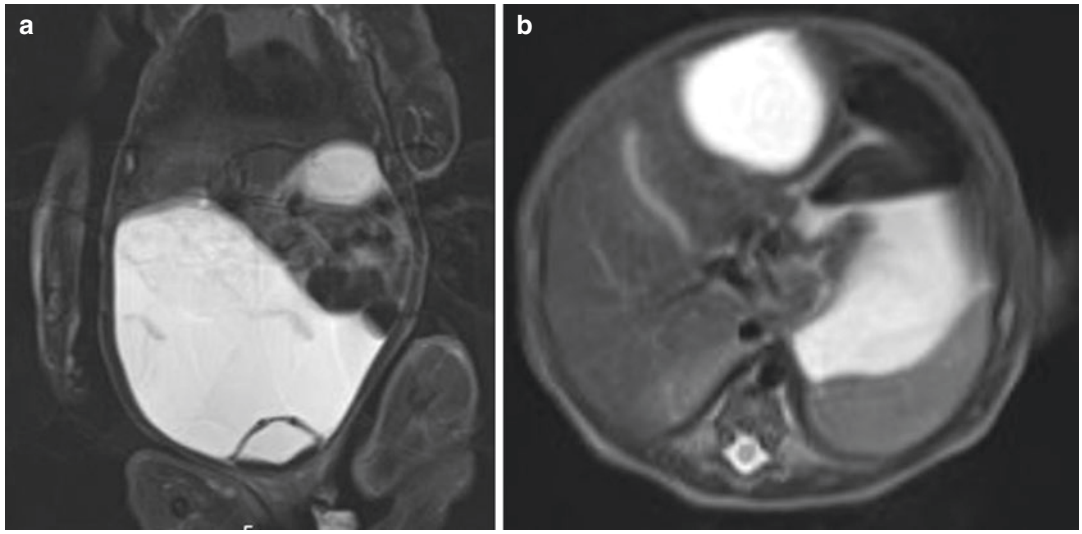

Fig. 29.1 Simple liver cyst antenatal detection on routine maternal USS from 24-week gestation. Confirmed on postnatal USS. MR scan shows giant cyst occupying entire right-side of abdominal cavity (T2 weighting)—(**a**). At operation, confirmed to be thin-walled rising from region of umbilical fissure (**b**). Contained 600 mls of bile-tinged (cyst bilirubin = 100 μmol/L, probably reflecting serum bilirubin as no bile connection) and was completely resected without incident

29.2.1 Aetiology

Their aetiology has been suggested to be an aberrant development of intrahepatic bile ducts due to the cuboidal appearance of the epithelial lining and location within the portal triad [11]. Hypoplasia of the ducts is perhaps secondary to inflammation or obstruction, with the subsequent retention of fluid perhaps leading to cyst formation.

29.2.2 Presentation

A successful antenatal diagnosis is challenging, particularly in differentiating from a choledochal malformation. On US, a simple liver cyst appears as an anechoic, unilocular fluid-filled space, most frequently originating within the right hepatic lobe [6]. The cysts are most frequently picked up in the third trimester although diagnosis has been made as early as the 17th week of gestation [17]. Prenatal MRI can be performed and typically will show a high-intensity signal if T2-weighted [17].

29.2.3 Management

These cysts seldom require intervention before birth. Percutaneous transuterine aspiration has been performed (up to five times in one case [13]) but only in the few cases [8, 13, 14, 18] where hydrops was present or where there was obvious displacement of abdominal and thoracic organs due to size. This of course is only a holding measure as the cyst will reaccumulate shortly after.

It is our view that most simple cysts do not require any intervention postnatally as the majority stay asymptomatic and usually either remain unchanged or undergo a diminution in size as detected by postnatal USS (Fig. 29.2). Larger cysts may obstruct adjacent structures and can lead to bowel or biliary obstruction and in one case IVC obstruction [17]. Infrequently they can cause infection or haemorrhage [17]. Ito et al. [13] reported one case where there had been five repeated aspirations antenatally with a further successful postnatal aspiration on day 14. No further intervention was required with resolution until at least the time of the report at 21 months.

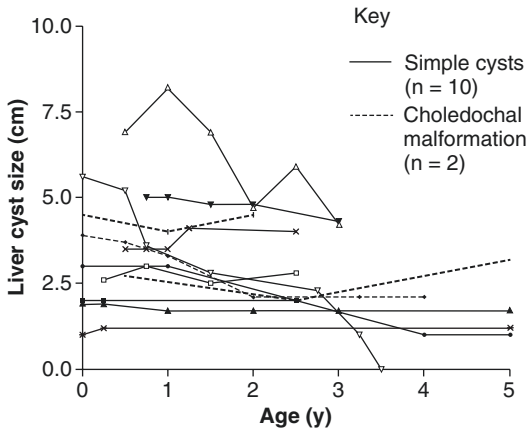

Fig. 29.2 Postnatal course of the antenatally detected liver cysts of 12 infants that did not require surgery [Reproduced with permission from Ref. 18]

Surgical excision should be reserved for those with large lesions causing symptoms or mass effect. Laparoscopic resection has been performed on simple liver cysts and shown to be safe [19]. Ideally, complete resection should be attempted to avoid recurrence. However, this depends on anatomical location as marsupialization or subtotal excision has also been shown to be effective in our hands [15, 18].

29.2.4 Prognosis

The prognosis is good, with only a handful of cases being reported in the literature associated with squamous cell metaplasia arising from simple cysts. All of these cases were diagnosed in adults (>30 years), and it is believed that such histological transformation is only likely to result from chronic inflammation [20, 21].

In the adult population, the risk of recurrence is reported to be high (>60%) in those treated with aspiration or partial excision, and therefore total excision with the lowest recurrence rate, is favoured [22]. However, of the aforementioned neonatal cases treated with surgical management (partial or complete resection), no recurrences were reported, and of those which underwent antenatal aspiration, two of the three reaccumulated in the antenatal period but resolved postnatally.

29.3 Mesenchymal Hamartoma

Mesenchymal hamartoma (MH), although the second most common benign hepatic tumour in children, remains rare. It usually presents as a large, rapidly growing mass, occurring almost exclusively within infancy and childhood (<2 years). Antenatal diagnosis is infrequent, with fewer than 30 cases reported in the literature to date [18, 23–44]. The first antenatal case to be reported was by Foucar in 1983, when a woman was referred at 33 weeks of gestation with an inappropriately small uterus and maternal hypertension [23]. On sonography several large hypoechoic masses replacing the liver parenchyma were seen. Labour was induced the following week, resulting in a stillborn female. Diagnosis of mesenchymal hamartoma was confirmed at post-mortem.

MH can be defined as a benign overgrowth of mature normal cells and stroma native to the liver. The majority are multicystic (75%) in nature, with the remaining being solid (echogenic) or mixed. On histological appearance, the cystic component is composed of tortuous or cystic bile ducts and the degeneration of myxoid stroma, with a lack of epithelial lining and instead lined by loose connective tissue. The solid component is predominantly hepatocytes but with proliferation of vessels [45].

Placental pathology has also been reported in association with MH, typically a honeycombed multicystic enlargement which can be visualized by maternal USS. Several terms have been used to describe this condition such as mesenchymal stem villous hyperplasia and placental mesenchymal dysplasia. Histologically the placenta shows enlarged dysplastic villi, thrombosis of the chorionic vessels, and a multifocal cyst transformation of the villi [18, 43].

29.3.1 Aetiology

It has been hypothesized that there is an inadequate blood supply to the placenta which causes aneurysmal dilatation of the chorionic vessels and hyperplasia of stem villi. Ischaemic lesions

of the fetal liver occurs in response, although the mechanism is unclear, but this results in large cystic masses seen by the second and third trimester [43].

29.3.2 Clinical Features

The most common presentation has been of an abdominal mass detected by antenatal USS at varying gestations (range 15–38 weeks). The larger lesions have been associated with polyhydramnios and foetal hydrops. Lesions have been reported to be in range of 5–14 cm, with the most common site again being the right lobe of the liver (50–75%) [46, 47]. Maternal α-fetoprotein and β-human chorionic gonadotrophin (HCG) levels may also be seen to rise.

A definitive diagnosis can be challenging in the antenatal period and probably is not necessary, but if the characteristic features can be demonstrated of a rapidly growing multiloculated cystic lesion, then MH is probable. There are only six cases reported of an antenatal diagnosis of MH [27, 32, 35, 39, 40, 43], whilst the rest are content with "intra-abdominal cystic lesions" and postnatal confirmation.

MRI can also be useful to identify liver tissue and thus origin of the mass, since it is the only foetal organ to produce a hyperintense signal on T1 imaging [44, 45]. Whilst it has been used frequently in the postnatal period, there are only two reports of its use antenatally [35, 39].

29.3.3 Management

There have been a total of 24 cases of antenatally detected MHs reported in the literature to date.

Four cases developed fetal hydrops during the second trimester [28, 29, 32, 36], and this has a very poor prognosis with two being stillborn and a third dying shortly after birth. This is an indication for expedited delivery to try and save such infants. The one survivor was born at 30-week gestation following intrauterine drainage of a cyst and survived [29].

There have been three cases reported where antenatal aspiration of the cyst occurred. Bejvan et al. [29] undertook prenatal aspiration and insertion of a pigtail drain at 27-week gestation; however, in this case premature rupture of membranes occurred and preterm labour at 30/40. The infant then underwent a resection on day 21 of life with survival. In the second case, percutaneous drainage of 110mls occurred just prior to an emergency Caesarean section for maternal hypertension. However, the infant needed an urgent laparotomy on day 1 of life due to haemorrhage from the puncture site [35]. The third case was more successful with three percutaneous aspirations occurring prior to a spontaneous vaginal delivery at 35 weeks gestation and a subsequent laparoscopic excision on day 1 of life [36].

Definitive surgical resection is usually recommended, particularly in those who develop respiratory distress secondary to diaphragmatic splinting with the aim being to reduce volume. This occurred in 17 of the 24 infants in the literature with survival in all. One infant underwent repeated cyst aspiration leading to regression [43]. There have been six deaths. Of these, surgery was performed in one case despite a poor preoperative prognosis, with non-immune hydrops present in a neonate born at 34-week gestation [36].

A laparotomy with partial or complete cyst resection, with or without an associated segmentectomy or lobectomy, is performed. There seems to be no consensus on when surgery should occur (range 1 day–5 months). However, those who underwent laparotomy early in life were often due to neonatal respiratory distress, whilst in those undergoing a delayed laparotomy, the indication was failure of cyst regression or increasing abdominal size.

There have been two infants reported where more conservative approaches have resulted in spontaneous regression of the cyst. In one case, repeated postnatal percutaneous cyst aspiration was performed to relieve abdominal pressures

and improve pulmonary function. This led to subsequent cyst regression despite formation of intrahepatic calcification being noted [43]. Postsurgical cyst recurrence has been reported in two cases [35, 42]. However, both of these were only of moderate size and were seen to regress on subsequent imaging.

As spontaneous regression is possible and the likelihood is that these are histologically benign, then an initially conservative approach is reasonable in otherwise asymptomatic infants.

29.3.4 Prognosis

Antenatally diagnosed MH has a mortality rate of up to 20% and is higher than those presenting later. Poor prognostic factors include the development of non-immune hydrops and a rapidly increasing cyst size with compression of thoracic and abdominal organs.

29.4 Congenital Hepatic Foregut Cysts

Congenital hepatic foregut cysts (CFHC) are rare lesions arising from embryonic foregut. Wheeler and Edmonson first coined the term in 1984 and defined their characteristics [48]. To date there have been only five cases of antenatally detected CFHC reported in the literature (Table 29.1) [49–52].

It has been hypothesized that these represent an abnormal foregut bud, arising from the thorax, which becomes entrapped in the liver through two patent pleuroperitoneal canals [50]. They have a histological relationship in this respect with oesophageal and bronchogenic cysts.

29.4.1 Histology

The classic histological feature of CFHC is a cyst composed of four layers: a pseudostratified

Table 29.1 Summary of the literature on antenatally diagnosed ciliated hepatic foregut cysts

Source	Gender	Gestational age at diagnosis	Location (segment)	Size (cm)	Type	Postnatal	Surgery	Squamous metaplasia
Stringer [49]	M	30	V, IV, VIII	7	Unilocular	Aspiration Day 5.	Extended right hepatectomy	Y
Betalli [50]	F	20	IV	3	Unilocular	Biliary obstruction and progressive increase in size	Resection, 16 months	N
Guerin [51]	M	22	IV, V, VII	3	Multilocular	Progressive increase in size	Central hepatectomy and Roux-en-Y, 11 months	N
Guerin [51]	F	22	V	2	Multilocular		Central hepatectomy and Roux-en-Y, 14 months	Y
Khoddami [52]	M	36	IV	2	Unilocular	Re-presented at 3 years—abdominal pain	Resection, 3.5 years	N

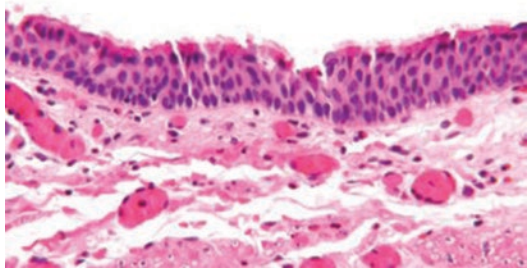

Fig. 29.3 Ciliated hepatic foregut cyst. Classic histological appearance of ciliated, pseudostratified, epithelial cyst lining (haematoxylin-eosin) [By permission from Ref. 54]

columnar epithelium composed of ciliated cells with numerous goblet cells, a sub-epithelial connective tissue layer, a smooth muscle layer, and a fibrous capsule [48] (Fig. 29.3). The presence of a liver lesion containing ciliated columnar cells is pathognomonic for CHFC. These cysts do have a malignant potential, but this is always deferred to adult life. Squamous metaplasia ($n = 6$) and squamous cell carcinoma arising from the innermost lining ($n = 5$) have been reported in adults with the youngest being reported in a 21-year-old male who had a diagnosis of liver cyst made in infancy but never followed up [53, 54].

29.4.2 Presentation

Imaging, both USS and cross-sectional, suggest that these are predominantly unilocular with the cyst fluid containing sediment (reflecting the mucinous content). Mural calcification can be present, and they tend to be subcapsular and located in the central liver segments, typically Couinaud segment IV. It had been suggested that this predominance of segment IV is because it makes up most of the liver substance in the 4th–8th week of development [50]. Aspiration cytology may show the presence of ciliated columnar epithelial cells suspended in a mucinoid background and again is pathognomonic.

Interestingly, one third of childhood and adult cases have also raised tumour markers (e.g. CA19–9, CEA and α-FP). However, none of these cases were associated with metaplasia, and those cases which did have associated metaplasia had normal tumour markers [54]. This observation can thus be misleading and should be interpreted with care.

29.4.3 Treatment

Whilst some have suggested treatment with sclerotherapy [54], surgical resection again is the preferred method given the possibility for later malignant transformation. Some indications for surgery have included increasing size, diameter > 4 cm, clinical symptoms, unexplained abnormal liver function tests, or cyst wall abnormalities on imaging.

Like many central cysts, the intrahepatic bile ducts are at risk during resection. Damage mandates some form of biliary reconstruction [50], and this may be a reason to defer surgery until 1 year of age as this can be quite complex.

29.4.4 Prognosis

Overall prognosis is good with no reports of recurrence post-surgery. Cysts have been seen to enlarge following biopsy and may also recur after sclerotherapy [54].

29.5 Conclusion

Most of the liver cysts that are diagnosed antenatally are incidental, innocuous with a relatively benign natural history. Nonetheless all deserve a full postnatal investigation work-up including cross-sectional imaging (CT or MR as tolerated) to make a diagnosis. Discrimination from type V choledochal malformations is usually straightforward but may need radioisotope imaging (Fig. 29.4). Virtually all the aforementioned lesions have no isotope uptake and are “cold”, whilst isotope concentration should define a “warm” or “hot” intrahepatic choledochal cyst.

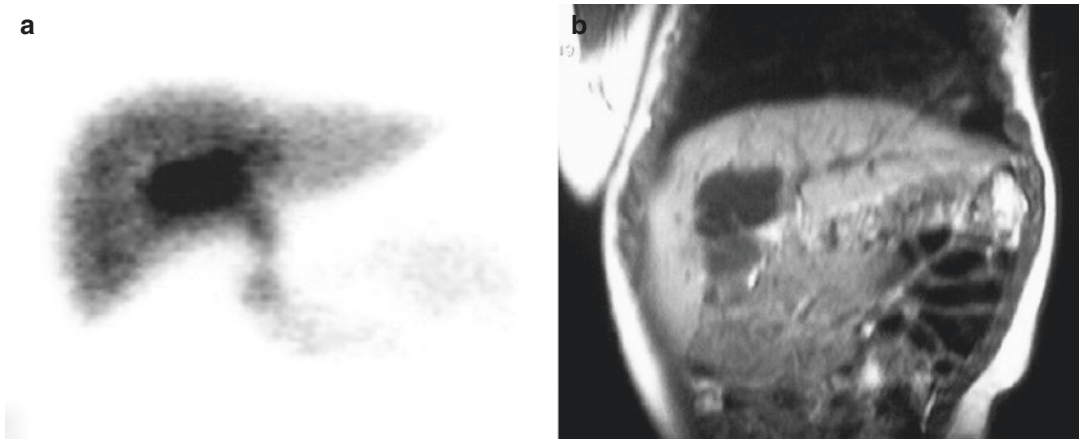

Fig. 29.4 (**a**) Antenatal detection with imaging at 1 year showing early radioisotope uptake. (**b**) Corresponding MR image showing type V choledochal malformation [Reproduced with permission from Ref. 18]

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Choledochal Cyst and Congenital Biliary Dilatation

30

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30.1 Introduction

Benign biliary diseases include a wide spectrum of conditions, which may have similar clinical and laboratory findings, but they can differ significantly with regard to etiopathogenesis, treatment, and prognosis [1]. Imaging plays an important role in diagnosis, differential diagnosis, treatment decision and planning, and follow-up. They can be incidentally discovered in clinically asymptomatic patients during either routine laboratory tests or work-up for other diseases or alternatively during the diagnostic work-up in cholestatic patients [2]. Patient history may address the diagnosis. We focus our attention in particular on two of these pathological conditions: congenital biliary dilatation and choledochal cyst.

30.2 Congenital Biliary Dilatation

Congenital biliary dilatation, or Caroli's disease, is a rare autosomal recessive congenital disorder characterized by multifocal, nonobstructive, saccular, or fusiform dilatation of the large-sized intrahepatic bile ducts, which communicate with the biliary tree [3]. It can be diffused or confined to a lobe (predominantly the left one) or to a segment. Two types have been described, which may represent different stages of the same disease: Caroli's disease, the "pure form," with no liver involvement, and Caroli's syndrome when congenital hepatic fibrosis coexists secondary to defective remodeling involving the entire intrahepatic bile duct tree [2].

Well-defined anechoic intrahepatic cystic lesions are demonstrated at ultrasound, which may also present with intra-cystic sludge or calculi [4]. Contrast-enhanced CT and MRI studies can demonstrate the presence of the pathognomonic "central dot sign," which corresponds to the fibrovascular bundle within the dilated cystic intrahepatic bile duct, appearing as a hyper-enhancing focus. Complications are related to bile stasis predisposing to stone formation, recurrent cholangitis, secondary biliary cirrhosis, and, rarely, cholangiocarcinoma. Magnetic resonance cholangiopancreatography (MRCPO) may be helpful in the differential diagnosis with polycystic liver disease or other conditions presenting with intrahepatic bile duct dilatation by demonstrating the characteristic features of saccular dilatation of the intrahepatic bile ducts communicating with the biliary tree. Moreover, MRI can be performed with hepato-specific contrast agent, which confirms the biliary communication. Management depends on clinical presentation, localization, and stage of the disease. Conservative treatment consists of antibi-

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otics to treat cholangitis and hepatic abscess and ursodeoxycholic acid to prevent stone formation. Radiological or endoscopic drainage procedures are indicated in the case of biliary obstruction, although related to high morbidity and mortality due to infectious complications. Partial hepatectomy is rarely recommended for localized disease, whereas liver transplantation may be a treatment option when there is diffuse liver involvement [5].

30.3 Choledochal Cyst

A choledochal cyst is the congenital cystic dilatation of the extrahepatic and/or intrahepatic biliary tree. It is a congenital anomaly usually found in the pediatric population (Fig. 30.1), and is estimated to occur in 1 in 5000 live births, with a higher frequency in Asians. Common symptoms include abdominal pain and vomiting, but these are nonspecific, and therefore the condition is usually difficult to diagnose during infancy. On the other hand, jaundice is a more specific symptom, and the diagnosis is usually made early if the jaundice is prolonged during the neonatal period or related to the abnormal liver function test because of cholestasis or cholangitis [6].

The presence of the triad of symptoms is the classic description of a choledochal cyst, but it is rare. The diagnosis is usually made in the first few years of life; in particular more and more patients have been diagnosed antenatally in recent years (Fig. 30.2) [7]. As there is an increased risk for developing cholangiocarcinoma, the recognition and proper management of choledochal cyst disease are important. Choledochal cysts are generally classified using the Todani modification of the Alonso-Lej classification (Fig. 30.3) [8]. As the underlying etiology of various subtypes of cysts remains unknown, the current classification may potentially be describing overlapping subtypes. We, as other authors, have attempted to ask if type IV choledochal cysts could be part of the disease progression of type I cysts. As for the surgical management of this pathological condition, laparoscopic surgery is safe and feasible in selected patients, but it technically highly demanding. The short-term complications of patients are generally good, with an early complication rate of less than 5%. Recurrent strictures and intrahepatic stone formations are well-known and well-described long-term complications, with the risks being forever present. The long-term complication rate is about 15%. There has been no malignancy documented so far in any of our patients. As antenatal ultrasound becomes more popular and easily available in this era, more and more of

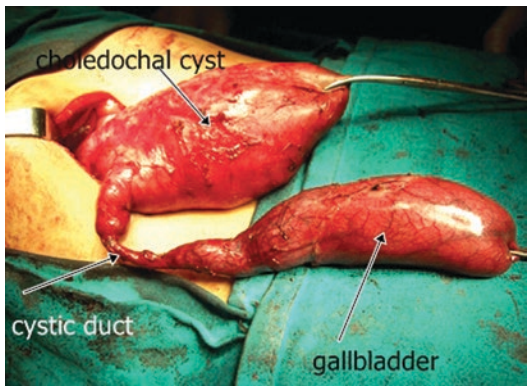

Fig. 30.1 A surgical aspect of a giant choledochal cyst

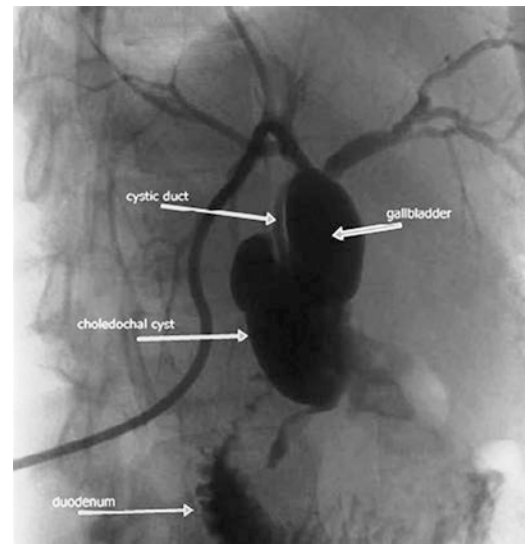

Fig. 30.2 Ultrasound-guided, contrast-enhanced transhepatic cholangiographic images. The right and left main hepatic ducts were dilated. Cystic dilatation of the proximal choledochal duct and transition of contrast media to the intestine were observed

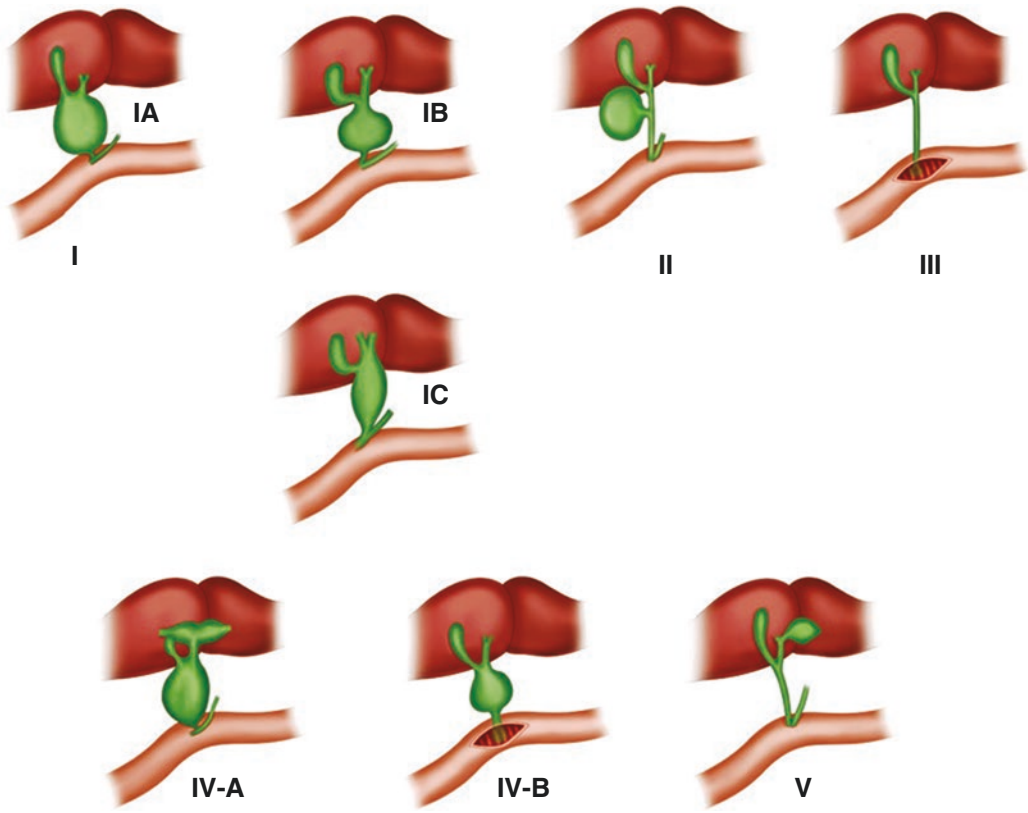

Fig. 30.3 Todani classification

the diagnoses are made antenatally [9]. This allows us to have better communication with the parents. The parents are likely to have better acceptance and be more prepared to agree to early surgical intervention for the patients. The common bile duct pathological condition can be detected antenatally as early as 15 weeks' gestation. All the patients diagnosed antenatally had been asymptomatic before the operation. Early surgery greatly decreases the occurrence of disease-related complications, for example, acute cholangitis, acute pancreatitis, early formation of biliary stone disease, biliary cirrhosis, liver cirrhosis, and malignancy [10]. Although the postoperative complication rates in the antenatal and postnatal group did not show any statistical significance, possibly because of the small number, we have experienced easier dissection during the surgical procedure in antenatally diagnosed patients as a result of decreased periductal inflammation [11]. Type I and type IV choledochal cysts are two distinct entities according to the Todani classification [8]. Type I cyst has no intrahepatic component, and the common hepatic duct proximal to the cyst is usually normal, whereas type IV disease contains multiple cysts, with involvement of the intrahepatic bile ducts. In our experience, type I cysts occur more frequently in those patients diagnosed earlier in their lives, whereas type IV cysts are usually found in older children [12]. The usual presenting symptoms for older children are the complications of choledochal cysts, that is, stone formation and acute cholangitis. Because of repeated cholangitis, there could be bile duct stricture formation. It would be possible to deduce that dilatation of the proximal segment takes time to develop and is a gradual process. Hence, the diagnosis of a type IV choledochal cyst could well be a result of the chronic complications of a type I choledochal

cyst. The chronic inflammation may result in further stone and stricture formation. The final result would be the dilatation of the more proximal segments and therefore the presence of multiple cysts, that is, "type IV" choledochal cysts. In conclusion, choledochal cyst is a rare disease and is commonly present in childhood. Antenatal diagnosis by means of routine ultrasound screening is possible and allows earlier surgical intervention, which may prevent later complications [13]. Laparoscopic surgery is feasible but is technically demanding. Long-term follow-up is necessary to identify those who are at risk for complications.

30.4 Discussion

Reported cases of dilated biliary tracts have a higher prevalence in Asia than in Western countries. In a nationwide survey of Korean children, acquired biliary diseases and congenital hepatobiliary diseases were 7.6 and 12.6% of total hepatobiliary diseases respectively [1]. Therefore, it is important to define abnormal bile duct dilatation because of its possible association with congenital malformation and pathological conditions, such as infection, calculi, biliary dysfunction, and malignancy. Various kinds of pathological conditions, such as flow disturbances of bile and pancreatic juice, reciprocal reflux between bile and pancreatic juice, and malignancy of biliary systems, can occur in the hepatobiliary system and pancreas secondary to bile duct dilatation and pancreaticobiliary maljunction.

Ultrasound is a useful method of evaluating the biliary tract system in children. It is rapid and noninvasive and does not involve radiation exposure. As for congenital bile duct dilatation, complications are related to bile stasis predisposing to stone formation, recurrent cholangitis, secondary biliary cirrhosis, and rarely, cholangiocarcinoma. Conservative treatment consists in the use of antibiotics to treat cholangitis and hepatic abscess and ursodeoxycholic acid to prevent stone formation. Radiological or endoscopic drainage procedures are indicated in the case of biliary obstruction, though related to high morbidity and mortality due to infectious complications. Partial hepatectomy is rarely recommended for localized disease, whereas liver transplantation is a treatment option when there is diffuse liver involvement.

As for choledochal cysts, as they have been widely known to be extremely highly associated with pancreaticobiliary maljunction, Todani made his classification to include a concept of pancreaticobiliary maljunction in 1995. According to the accumulation of case reports on congenital biliary dilatation from around the world, it has been understood that most cases are classified as either type I with local dilatation of the common bile duct or as type IV-A, which is associated with involvement of the intrahepatic bile duct. In addition, it has been clarified that pancreaticobiliary maljunction is extremely highly associated with types Ia, Ic, and IV-A; however, it is almost never associated with types Ib, II, III, IV-B, and V [8].

The presence of the triad of symptoms is the classic indication of a choledochal cyst, but it is rare. The diagnosis is usually made in the first few years of life; in particular, more and more patients have been diagnosed antenatally in recent years [9]. Laparoscopic surgery is safe and feasible in selected patients, but it is technically highly demanding [14]. The short-term complications of patients are generally good, with an early complication rate of less than 5% [15]. Recurrent strictures and intrahepatic stone formations are well-known and well-described long-term complications, with the risks being forever present. In conclusion, biliary congenital pathological conditions are a rare disease, and patients with these conditions, according to international guidelines, have to be sent to a national referral center where there is a high level of expertise in their treatment, to obtain excellent results, also using in some cases a minimally invasive surgical treatment.

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Part VI

Anterior Abdominal Wall Defects

Gastroschisis and Omphalocele

31

Mikko P. Pakarinen, Antti Koivusalo, and Janne Suominen

31.1 Introduction

Gastroschisis and omphalocele are the most common congenital abdominal wall defects with an unclear etiology. The incidence of gastroschisis approximates 3–4.5/10000 live births and that of omphalocele 2–3/1000 live births omphalocele 2-3/10000 live births [1]. The incidence of gastroschisis continues to increase in the Western world. For example, in Finland, the birth prevalence of gastroschisis has increased by 40% during the last 20 years.

Gastroschisis refers to a small developmental abdominal defect almost always right to the umbilicus through which uncovered small intestine and colon and occasionally stomach and gonads eviscerate. The abdominal wall and muscles around the defect are normally developed. In omphalocele, the intestine and other abdominal organs, including the liver, the spleen, and gonads covered by the amniotic membrane, eviscerate through a large umbilical defect. The rectus muscles are separated to a variable degree above the abdominal defect, and omphalocele may present as a part of more extensive cephalo-caudal fold defects such as pentalogy of Cantrell and cloacal exstrophy, which fall outside the scope of this review.

The main goals of the management are prompt protective coverage of eviscerated organs and abdominal wall closure while avoiding iatrogenic injuries. This is usually relatively straightforward in gastroschisis, and abdominal closure is accomplished in most patients during the first week of life, whereas in patients with large omphaloceles, the final fascial closure of the abdominal wall may be achieved only after several years following skin grafting and multiple surgeries. In the management of gastroschisis, one of the most significant challenges is caused by associated intestinal dysmotility, which may require prolonged parenteral nutrition, predisposing to complications of intestinal failure, including septic episodes and liver disease [2]. The risk of irreversible intestinal failure is further increased when complications require significant bowel resections in patients with associated atresia and perforation of necrosis of the intestine or when there is congenital loss of the midgut in patients with vanishing or closed gastroschisis [3–7]. Comprehensive treatment of omphalocele is often complicated by significant associated disorders, which need to be managed in carefully planned coordination with the abdominal wall defect for optimal outcomes [8].

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31.2 Embryology and Pathophysiology

Even though the incidence of gastroschisis has increased during past decades, the etiology and exact pathogenesis have remained unclear. Normally, during the third week of gestation, the midgut becomes distinct from the yolk sac, and at sixth week the midgut elongates resulting in physiologic development of an umbilical hernia. The lateral body wall folds form early in gestation as a combination of the parietal layer of lateral plate mesoderm and overlying ectoderm and move ventrally into the midline [9]. At 10 weeks, the midgut returns rapidly to the embryonic abdominal cavity, and the defect in the abdominal wall closes. In gastroschisis, the fusion of lateral body folds fails to occur leading to an opening in the abdominal wall. Several hypotheses leading to the formation of gastroschisis have been introduced [10, 11]. Young maternal age has been linked to the incidence of gastroschisis in several studies as well as maternal smoking and drug usage implying a role for teratogens in the development of gastroschisis [12]. Ethnic background and body mass index may have a role as well. Although compelling epidemiologic risk factors have been identified, the underlying pathogenesis of gastroschisis remains controversial, and most likely the origin of this defect is multifactorial.

The exact pathogenesis behind omphalocele is also still unsolved. Omphalocele results from the failure of bowel to return to the abdominal cavity following the physiological herniation of the umbilical cord between the 6th and 11th week of development. Omphalocele is more often seen in conjunction with syndromes that have genetic background like Beckwith-Wiedemann suggesting different etiologies for the two congenital anomalies.

31.3 Antenatal Screening and Follow-up

Gastroschisis and omphalocele are detected in developed countries in over 90% of cases within the second trimester of pregnancy, and delivery methods can usually be considered in time before labor [13]. Prenatal ultrasound (US) is the primary imaging modality during pregnancy because it is noninvasive and rapid and it allows real-time fetal examination. Maternal serum alpha-fetoprotein (AFP) is usually elevated with abdominal wall defects, although there is variation between gastroschisis and omphalocele. In gastroschisis, maternal serum AFP is usually markedly abnormal, whereas in omphalocele AFP is usually elevated more moderately with a much wider range. Current practice for antenatal surveillance in gastroschisis is variable, but regular US monitoring aims to determine possible bowel dilatation and thickening, amount of amniotic fluid, and fetal growth and to detect any other associated malformations. Prenatal definition of simple and complex (atresia, necrosis, perforation, or volvulus) gastroschisis is used in prenatal counseling and planning postnatal medical and surgical treatment. In antenatal US, intra-abdominal bowel dilatation and polyhydramnios are associated with an increased risk of bowel atresia, and gastric dilatation has been linked to the occurrence of death in the neonatal period [14]. Doppler US has been used to determine the mesenteric circulation during late pregnancy, but this data is scarce to provide guidelines for the timing of delivery. Usually antenatal magnetic resonance imaging (MRI) is not necessary in fetuses with gastroschisis but should be used as an adjunct to provide better understanding on anatomy if US reveals untypical findings. Fetal karyotyping is not necessarily indicated in gastroschisis, as neither single genes have been identified as responsible for the occurrence of gastroschisis nor recognized syndromes [15]. The risk of familial recurrence approximates 2.5% [16].

As associated anomalies are more common with omphalocele than with gastroschisis, MRI should be done after US has revealed omphalocele with special emphasis on evaluation of cardiac and central nervous system. Fetal echocardiography and karyotyping should also be performed. Complex cardiac defects, nervous system anomalies, and chromosomal alterations define the prognosis and mortality more strongly than the

size and nature of omphalocele itself. Even if imaging modalities have evolved during the past decades, there is still remarkable proportion of fetuses that appear to be isolated omphaloceles in antenatal scans but are found to have multiple anomalies postnatally, an important issue to be discussed with parents during pregnancy.

31.4 Delivery

The most discussed issues concerning the delivery of a fetus with an abdominal wall defect are the facilities that manage the delivery, the timing of the delivery, and the mode of delivery. Contemporary evidence suggests that the delivery of a fetus with an abdominal wall defect should occur in a tertiary perinatal center. The high risk of preterm labor in pregnancies with gastroschisis and postnatal management of gastroschisis closure and associated complications such as intestinal atresia or perforation, as well as the risk of respiratory compromise and associated cardiac defects in fetuses with omphalocele, requires immediate access to expert neonatal intensive care and pediatric surgical service [17, 18]. In fetuses without prenatally diagnosed lesions, successful deliveries may, however, occur in lower-grade perinatal units, and with appropriate postnatal care and timely transfer to a specialist center, good outcomes can be achieved. Contemporary studies have failed to show any significant difference in the outcome of fetuses with gastroschisis after planned late preterm delivery (35–37 weeks) or delivery at a later date (≥38 weeks). Because of the high risk of preterm labor and associated neonatal death, pregnant women with a fetus with gastroschisis should be alerted for the signs of preterm labor and be admitted to an appropriate maternity unit without delay. There is no evidence that US findings of bowel distension should guide the timing of the delivery. In fetuses with gastroschisis, induced or spontaneous vaginal delivery is safe and can be attempted unless there are obstetric indications for cesarean section [19–21].

Most infants with omphalocele are born at term. There is no difference in the outcome of a fetus with omphalocele whether the chosen mode of delivery is cesarean section or vaginal delivery. Cesarean section is, however, favored in fetuses with large defects containing an extra-abdominal liver [21].

31.5 Clinical Features and Associated Malformations

31.5.1 Omphalocele

In omphalocele, there is variable-sized defect in abdominal wall at the site of umbilical cord leading to protrusion of intestines and sometimes the liver, spleen, and gonads through the defect. Eviscerated organs are covered by a sac formed of peritoneum, Wharton's jelly, and amnion, and this sac is normally intact. Abdominal wall muscles are usually intact but hypoplastic and displaced laterally. Variability in the size of the omphalocele is remarkable ranging from a small loop of the intestine to giant omphaloceles where most of the intestines and abdominal organs occur within the amniotic membrane outside the poorly developed abdominal cavity. The size of omphalocele together with associated malformations determines largely both the early treatment strategies and long-term outcomes. Associated malformations among patients with omphalocele are common as over 75% of the patients have been reported to have either chromosomal anomaly or defect in other organ systems than abdominal wall [22, 23]. If the sac covering omphalocele is ruptured, this needs to be repaired in prompt fashion, but otherwise other malformations define the treatment more than omphalocele itself. Babies born with large omphalocele may have hypoplastic thoracic cavity associated with pulmonary hypoplasia leading to severely compromised respiratory function soon after birth. Up to one third of omphalocele patients may have congenital heart defects [23]. Interestingly, associated anomalies may occur more commonly in minor rather than in large omphaloceles [24]. Chromosomal anomalies are significantly more common in offspring of

women 35 years and older [22]. Live-born infants with trisomy 13 and trisomy 18 have omphalocele in up to 7.5% of cases, and these chromosomal anomalies are more common; the earlier omphaloceles are detected during pregnancy, whereas the association between trisomy 21 and omphalocele is controversial [25]. When the diagnosis is made in early pregnancy, the proportion of aneuploidy can increase up to two thirds. If molecular karyotype has not been assessed during pregnancy, it should be verified after the birth. Survival among neonates with isolated omphalocele ought to be over 90%, but associated anomalies have impact on survival rates as especially chromosomal abnormalities worsen the prognosis.

31.5.2 Gastroschisis

As the bowel remains eviscerated, it is not rotated normally, and also intestinal atresias among these patients can be regarded as a consequence rather than a true associated anomaly. Cryptorchidism presumably develops secondary to bowel evisceration and lack of intra-abdominal pressure. However, there is increasing evidence implying that up to one third of gastroschisis cases are associated with a variety of anomalies [13, 23]. Cardiac anomalies have traditionally been linked to omphalocele but seem to be present in gastroschisis as well. Furthermore, it appears that fetuses with gastroschisis that die in utero or are terminated during pregnancy have more often associated anomalies than surviving babies with gastroschisis [26]. Taken together, recent data supports careful evaluation of possible associated anomalies also in patients with gastroschisis.

The bowel that has floated freely on amniotic fluid is never quite the same as in healthy newborns. The bowel can be thickened and edematous, is often covered with fibrinous peel, and in 15–20% of cases intestinal atresia is noted [23]. Even without atresia, the bowel length among gastroschisis patients is shortened compared with healthy babies, and intestinal dysmotility to variable degree is always accompanied with gastroschisis.

31.6 Management and Complications

31.6.1 Omphalocele

After delivery infants with large omphaloceles with hypoplastic rib cage and pulmonary hypoplasia may require intubation and ventilation. Nasogastric tube is inserted for gastric decompression. Intravenous access is inserted and adequate fluid resuscitation started. Coexisting diaphragmatic defects can be seen in chest X-ray.

If the omphalocele is ruptured, the eviscerated organs are protected with cling film as in gastroschisis, and intravenous antibiotics are started. If a primary skin closure is not feasible, the ruptured sac should be repaired by suturing, or cadaver skin grafting should be done without undue delay [27, 28].

A detailed evaluation for associated anomalies including echocardiography, abdominal US for renal anomalies, assessment of molecular karyotype, and external examination for other visible anomalies should be made in all infants with omphalocele regardless of the size of the defect. Postnatal hypoglycemia may indicate Beckwith-Wiedemann syndrome. In majority of infants with omphalocele, enteral feeding can be started within days the period with parenteral nutrition and the need of central venous catheter is short; in many patients, insertion of central venous catheter is unnecessary.

Surgical management of the omphalocele aims for complete fascial and skin closure of the defect. In infants with small omphaloceles, direct closure of all layers can be accomplished during the first days of life. In larger defects, the obstacles in the completion of the final repair include small abdominal cavity and lateral migration of the margins of the abdominal musculature. In infants with cardiac defects, lung hypoplasia, or prematurity-elevated intra-abdominal pressure after even minor attempts of reduction, the contents of the sac may cause cardiopulmonary compromise. In large defects with extracorporeal liver, early reduction of the contents causes abdominal compartment syndrome and is generally not possible, and staged closure is advisable.

Closure of a defect located high in the epigastrium may also be challenging because of proximity of the costal arcs of the narrow belt of abdominal musculature around the defect.

If staged closure is chosen, the surgeon has several options. There is no hurry to perform complete closure. Covering the defect by widely mobilizing the abdominal skin and suturing the mobilized skin over the sac is possible in medium-sized omphaloceles, but overt tension in the closure may result in dehiscence, rupture, or large central scar. The epithelization of the sac can be achieved by dressing with nontoxic topical agents (e.g., silver sulfadiazine) or by covering the sac with cadaveric skin grafts. A recent small series described the use of vacuum suction device [29]. Omphalocele may be supported with a tethered dressing for the first weeks of life. Complete maturation and epithelization of the scar may take several months, during which time the relative size of omphalocele usually grows smaller. Despite a large remaining ventral hernia, infants are able to develop motor skills appropriate for age such as walking and climbing.

Timing of the final closure of a large defect depends on the infant's general condition, and treatment of associated anomalies and final closure may occur anywhere between 1 and 7 years of age. It may be possible to close the defect with prosthetic mesh followed by serial excision of the mesh until apposition of the fascia margins is achieved. Use of subcutaneously located prosthetic material can be complicated with dehiscence and infections and can be unsuitable for long-term solution. If possible, it is better to perform one well-planned operation instead of several incomplete attempts. In the planning of the final closure, the size of the contents of the sac in relation with the volume of the abdominal cavity is assessed. In this assessment, whole-body MRI imaging may be helpful, and the location of the margins of the abdominal musculature can be verified. Small abdominal domain can be gradually widened with the help of intra-abdominal tissue expander inserted through a Pfannenstiel incision (Figs. 31.1, 31.2, and 31.3).

Closure of the abdominal musculature can be achieved with component separation technique in which the abdominal wall surface is enlarged by translation of the muscular layers without compromising the innervation and blood supply of the muscles [30]. Cooperation with a plastic surgeon familiar with compartment separation technique is advisable. If the need arises, the patient can be prepared for a pedicled latissimus dorsi myocutaneous flap.

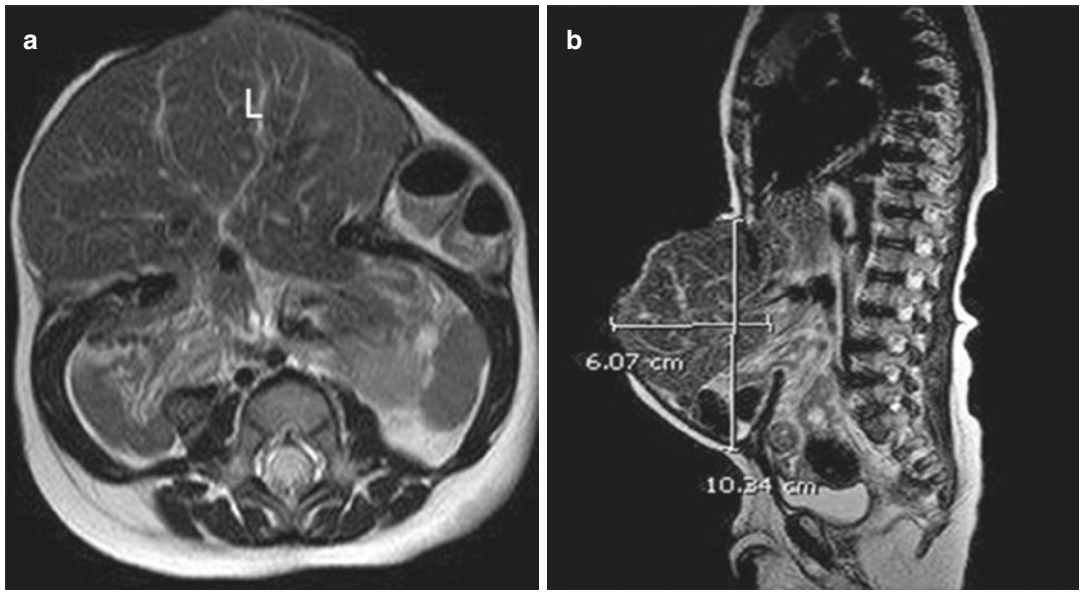

Fig. 31.1 Axial (**a**) and sagittal (**b**) preoperative MRI images of a 1-year-old infant with omphalocele. Omphalocele sac is epithelialized and contains the liver (L); defect diameter is 10 cm

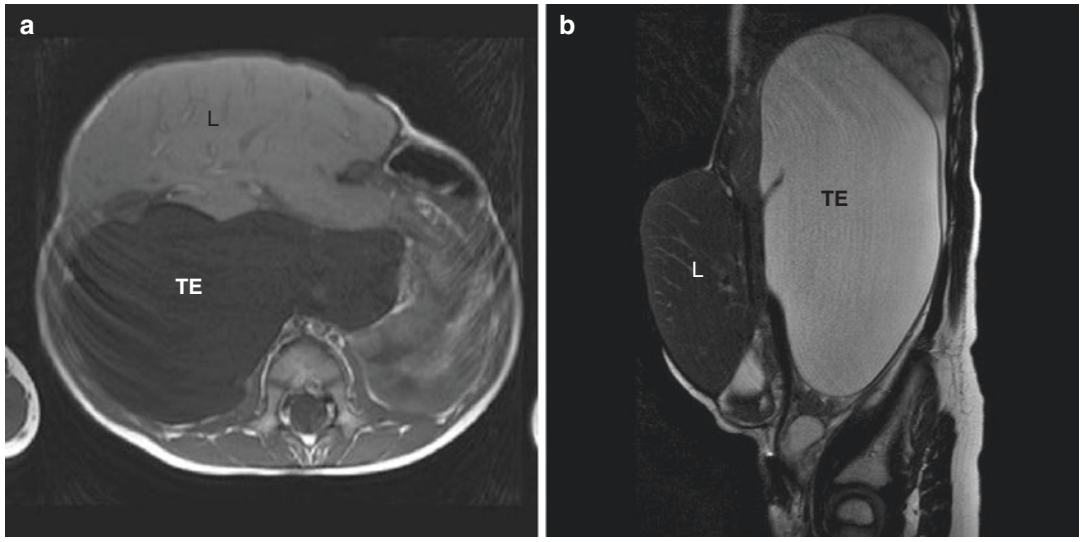

Fig. 31.2 Same patient as in Fig. 31.1. Widening of the abdominal domain with intra-abdominal tissue expander (TE) in axial (**a**) and sagittal (**b**) MRI projections. (L) denotes the liver

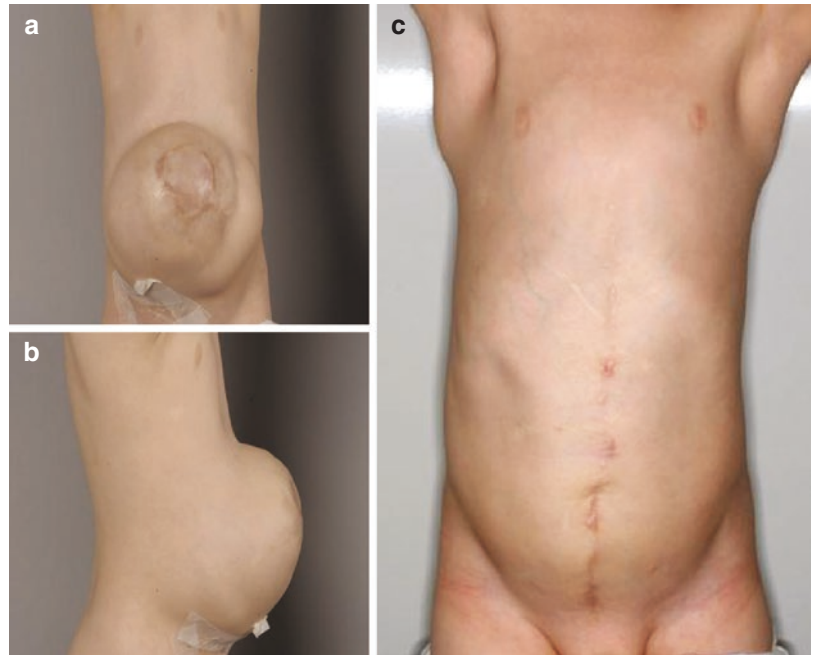

Fig. 31.3 Same patient as in Figs. 31.1 and 31.2. Widening of abdominal domain is under way with intra-abdominal tissue expander in situ (**a** and **b**) and the result after removal of tissue expander and final closure of anterior abdominal wall with compartment separation technique (**c**)

Postoperative monitoring includes monitoring of intra-abdominal pressure, central venous pressure and diuresis, and serial measurement of blood lactic acid. In a well-planned repair without undue tension, abdominal compartment syndrome and prolonged mechanical ventilation are avoidable.

31.6.2 Gastroschisis

After delivery, a baby with gastroschisis is transferred to neonatal intensive care unit with lower body wrapped in transparent cling film or plastic bag so that eviscerated intestines remain pro-

tected, supported, and visible for inspection. In addition to bowel protection, the initial care consists of maintenance of body temperature and fluid and electrolyte balance as well as respiratory support when required. Bowel viability is ascertained and checked for any mesenteric twisting or restrictive compression against a small fascial defect. Intravenous fluid replacement is guided by clinical signs of hypovolemia to avoid excessive rehydration and undesirable tissue edema. Venous access, preferentially using percutaneous jugular catheter, is established to allow several weeks of parenteral nutrition before recovery of bowel function, and nasogastric tube is inserted to facilitate intestinal decompression. The presence of associated malformations is routinely screened with US examination of the heart, head, and abdomen.

The surgical care of gastroschisis aims for bowel reduction and abdominal wall closure without harmful increases in the intra-abdominal pressure (Fig. 31.4). In some patients, this can be achieved right after birth with primary abdominal closure, while others require gradual bowel reduction with silo and staged abdominal closure. Before final selection of the closure method, the intestine should be carefully examined for atresia, perforation, or necrotic areas, which significantly affect surgical treatment.

Primary abdominal closure is not usually safe in the presence of thickened, edematous bowel coated with fibrinous peel and a small abdominal domain. These cases are best treated by placing eviscerated bowel into a transparent spring-loaded preformed silo under adequate analgesia and sedation at bedside. Bowel is gradually reduced into the abdominal cavity by daily reductions in silo usually within a week followed by abdominal closure, which can be performed by suturing or by simply stretching the umbilical remnant over defect without fascial closure (Fig. 31.5). The umbilical cord covered defect contracts spontaneously in a few weeks and preserves aesthetically normal umbilicus [1].

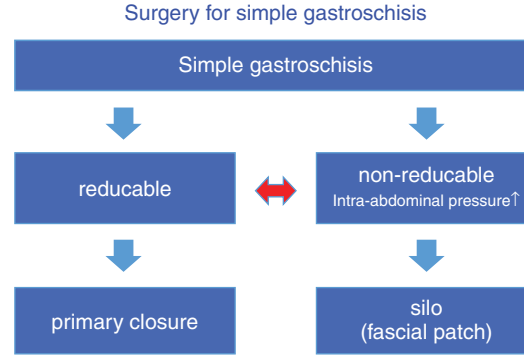

Fig. 31.4 Outline of surgical management principles of isolated gastroschisis

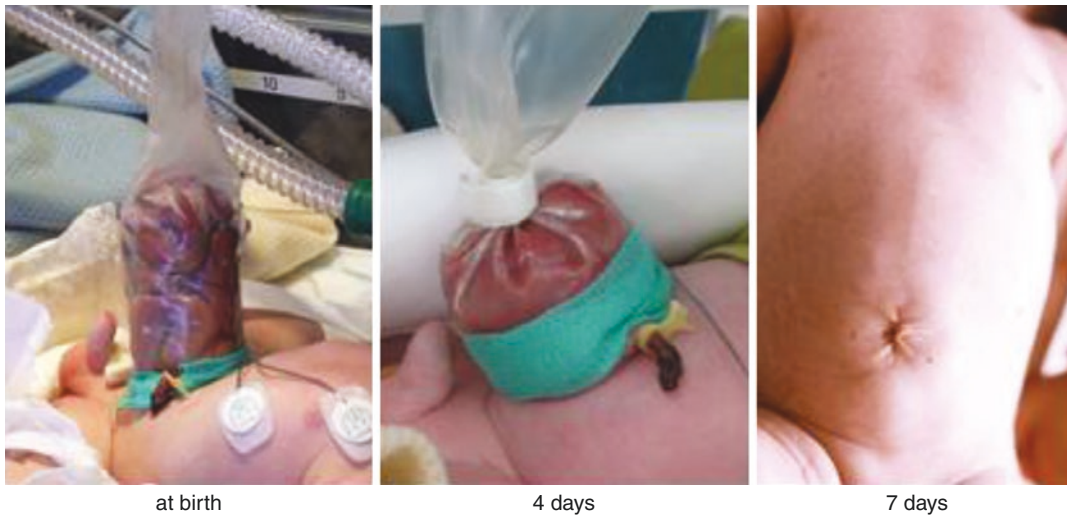

Fig. 31.5 Gradual bowel reduction with preformed silo and staged abdominal closure

The most feared and devastating, although a rare complication of primary abdominal closure, is abdominal compartment syndrome, which may lead to a massive intestinal resection and short bowel syndrome. Forceful reduction of the intestine may result in an intolerable increase in intra-abdominal pressure. Resulting abdominal compartment syndrome is a life-threating complication characterized by decreased venous return, low cardiac output, ventilatory compromise, mesenteric ischemia, and renal hypoperfusion that necessitates immediate decompressive laparotomy to avoid intestinal necrosis. Removal of fascial sutures and placement of a circumferential fascial patch or silo reduce intra-abdominal pressure efficiently. Measurement of bladder pressure through a Foley catheter or renal perfusion with infrared spectroscopy is useful in monitoring intra-abdominal pressure after primary closure and each repeated reduction during silo treatment. Abdominal compartment syndrome is efficiently avoided by using staged abdominal closure with silo whenever any concern of ventilatory or hemodynamic compromise arises during attempted primary closure.

There are several surgical options to manage gastroschisis complicated by intestinal atresia, perforation, or necrosis (Fig. 31.6). The safest option is to remove the diseased part of the intestine and exteriorize both bowel ends as ostomies. If the patient's general condition is good, and there is no significant abdominal contamination, a primary anastomosis may be performed.

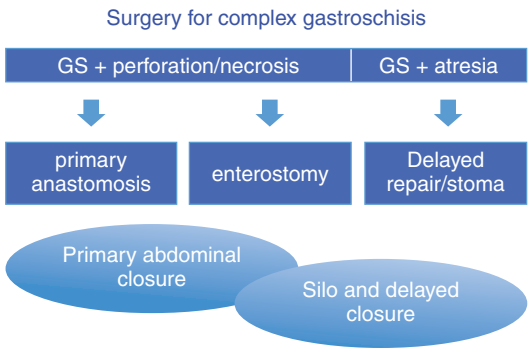

Fig. 31.6 Outline of surgical management principles of complicated gastroschisis

Intestinal diversion and primary anastomosis are combined either with primary abdominal wall closure or staged silo closure depending on operative findings. Another surgical option with associated intestinal atresia is to leave the atresia initially untouched, continue parenteral nutrition and intestinal decompression with nasogastric tube, and perform delayed atresia repair once the reduction has been completed. Delayed repair of intestinal atresia is most commonly performed in a separate laparotomy only several weeks after abdominal wall closure has healed, and abdominal inflammation has settled facilitating adhesiolysis and identification of the dilated and dysmotile small intestinal segment above the atresia. In vanishing gastroschisis, all the remaining bowel should be preserved, and the dilated small bowel proximal to the atresia is dealt with a suitable tailoring/lengthening procedure at the time of atresia repair.

Once abdominal closure has been achieved, babies are weaned from ventilatory support, and enteral nutrition is instituted through nasogastric tube. Oral feeds, preferentially fresh breast milk, are advanced according to individual tolerance. Intermittent feeding intolerance is common especially during the early postoperative period. The possibility of missed intestinal atresia should be ruled out with small intestinal contrast study if bowel function has not recovered in 2–3 weeks.

The risk of intestinal failure is 12 times higher in patients with complicated gastroschisis when compared to isolated gastroschisis [3]. Because of the increased risk for developing intestinal failure, management of complicated gastroschisis in this respect should start from the very beginning. Among other things, this includes the use of percutaneous tunneled single-lumen central venous catheters with antimicrobial locks to prevent septic episodes and novel parenteral lipid emulsions to prevent intestinal failure-associated liver disease. When intestinal diversion is applied, routine refeeding of the distal mucous fistula promotes bowel function and minimizes the requirement of parenteral support while supporting physiological liver function.

31.7 Early Outcomes

31.7.1 Omphalocele

In live-born fetuses with omphalocele, infant mortality of 25% can be expected (Table 31.1). Associated congenital heart defects, central nervous system defects, prematurity, and chromosomal defects increase the risk of infant death 2.4–7.7-fold [22]. Important predictors of mortality include also respiratory insufficiency at birth and development of pulmonary hypertension. Pulmonary hypertension is characterized by increased oxygen requirement and right ventricular pressures (>40 mmHg) in early echocardiogram and often observed in patients with giant omphaloceles [32]. Isolated omphaloceles which comprise about 20–25% of all live-birth cases have the best prognosis with 7.8% infant death rate [22].

Neurodevelopmental dysfunctions have been reported in half of survivors with giant omphaloceles in whom the primary hospitalization is prolonged and includes mechanical ventilation, oxygen supplementation, delayed enteral feeding, and delayed closure of the abdominal wall. Autism, hypotonicity, neurodevelopmental delays, and poor motor function are the most often reported dysfunctions [33].

Long-term complications include failure to thrive, gastroesophageal reflux, and intermittent abdominal pain. Cosmetic issues including the missing umbilicus and extensive abdominal scar are common in all omphalocele patients regardless of the size of the defect. At young adult age, most omphalocele survivors have similar quality of life as their healthy peers [21].

Table 31.1 Infant mortality among live-born fetuses with omphalocele

Author (year)	Period	Live births	Infant mortality (%)
Marshall et al. [24] 2015, USA	1995–2005	1729	28.7
Corey et al. [31] 2014, USA	1997–2012	1448	20.0
Finnish Register of Congenital Malformations 2011, Finland	1993–2011	245	21.6
Summary		4001	25 (average)

31.7.2 Gastroschisis

Infants with complicated gastroschisis are prone to face much more complicated clinical course than their counterparts with isolated disease. In isolated gastroschisis, average duration of mechanical ventilation is 4–6 days, which is nearly doubled in complicated gastroschisis [3, 4]. Gastroschisis is associated with different degrees of intestinal dysmotility, which delays return of propulsive peristalsis and prolongs the need for parenteral support (Table 31.2). The gastroschisis-associated dysmotility is resistant to medical therapy, and according a Cochrane review, there is no benefit of erythromycin on feeding tolerance in patients with gastroschisis. In patients with isolated gastroschisis, mean duration of parenteral nutrition and length of hospital stay is just over 1 month, while a small percentage of patients develop intestinal failure-associated liver disease, and around 4% still die. The respective figures are markedly higher for patients with gastroschisis complicated by intestinal atresia, perforation, or necrosis (Table 31.2). In these patients, length of stay, duration of parenteral nutrition, and incidence of intestinal failure-associated liver disease are twice higher and mortality about four times higher than in patients with isolated gastroschisis [3, 4].

Table 31.2 Comparative outcomes of isolated and complicated gastroschisis

	Isolated gastroschisis	Complicated gastroschisis
Length of stay (days)	36 (28–32)	76 (67–84)
Duration of parenteral nutrition (days)	34 (25–41)	72 (63–81)
Intestinal failure-associated liver disease (%)	12 (4–20)	28 (23–33)
Mortality (%)	4 (1–8)	15 (4–30)

Data are combined means (range) of four studies (Arnold et al. [5], Bradnock et al. [6], Gover et al. [7], Lap et al. [4]) including 5161 patients

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32 Omphalomesenteric Duct and Urachal Remnants

Daniele Alberti and Giovanni Boroni

32.1 Introduction

Omphalomesenteric duct and urachus are two transitory structures, normally encountered during the embryonic development. The first usually disappears by the fifth to seventh week of gestation, while the urachus progressively narrows and is obliterated by fibrous proliferation during the fetal life. Remnants of these embryonic structures account for a wide variety of abnormalities that may require surgical correction.

32.2 Normal Embryology

In the early stages of development, the disk-shaped trilaminar embryo presents the amnion located in a dorsal direction, whereas the yolk sac occupies a ventral position. From the fourth week of gestation, the different growth of embryonic tissues produces a cephalocaudal and lateral folding of the embryo. As a result the dorsal portion of the yolk sac cavity is incorporated into the embryo to form the primitive gut, which maintains a connection with the extracoelomic portion of the yolk sac through the omphalomesenteric or vitelline duct. With the growth, the placenta becomes the primary source of nourishment for the fetus, and the extraembryonic yolk sac regresses; the omphalomesenteric duct normally obliterates between the fifth and the seventh week of gestation [1, 2] (Fig. 32.1).

Meantime, on about day 16 of gestation, a fingerlike outpouching, the allantois, forms from the caudal wall of the yolk sac. In some lower vertebrates, this structure serves as a reservoir for excretion products of the developing renal system, but in humans, it remains rudimentary and has no known role. The cranial end of the bladder, that develops from the ventral portion of the distal hindgut, the cloaca, initially opens into the allantois at the level of the umbilicus. By the fourth to fifth months, the bladder descends into the pelvis, and its apical portion narrows to form the urachus, a fibromuscular band that connects the bladder with the allantois. The urachus is finally obliterated by fibrous proliferation by the latter half of fetal life, giving rise to a fibrous cord running from the inferior aspect of the umbilicus to the dome of the bladder, the median umbilical ligament [2, 3].

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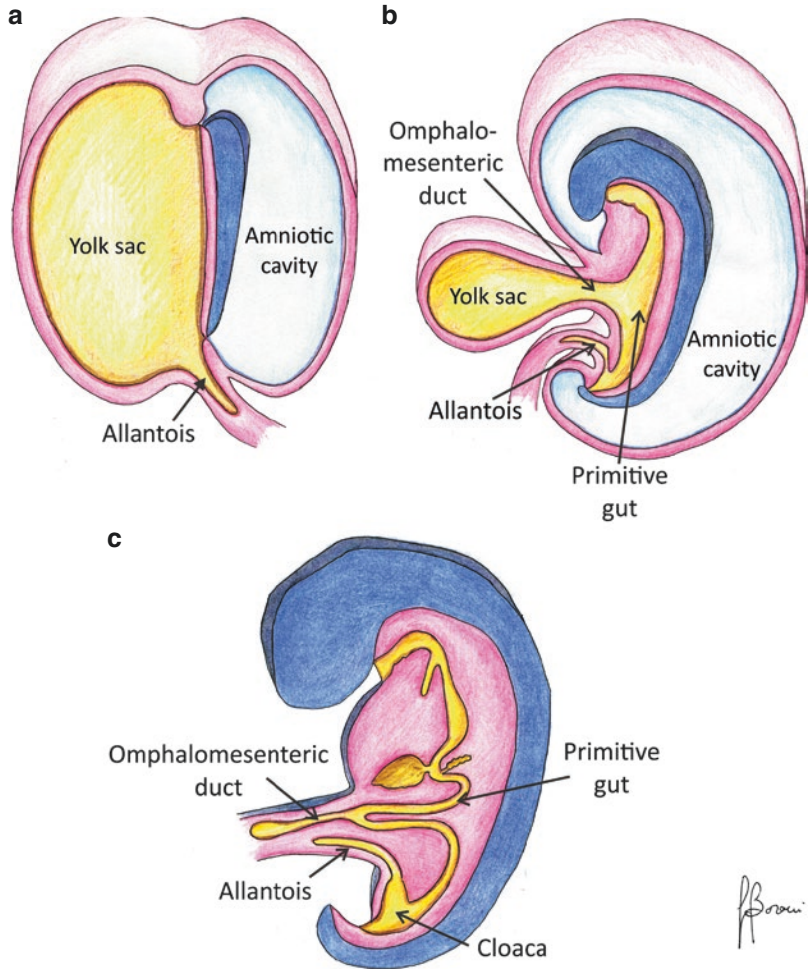

Fig. 32.1 Normal embryology of the omphalomesenteric duct. (**a**) A 3-week embryo; (**b**) a 4-week embryo; (**c**) a 5-week embryo. Explanation in the text

32.3 Omphalomesenteric Duct Remnants

Failure of complete involution of the omphalomesenteric duct results in a heterogeneous variety of anomalies, sometimes evident since birth, which may require surgical correction.

The commonest omphalomesenteric duct remnant is the Meckel diverticulum, accounting for 67% of all defects [4]; other pathologic varieties include umbilical fistulas, sinus, cysts, mucosal remnants, congenital bands, and combinations of these entities (i.e., a fibrous band containing a cyst or a Meckel diverticulum attached to the umbilicus).

An omphalomesenteric fistula (Fig. 32.2a) occurs when there is a complete patency of the vitelline duct from the ileum to the umbilicus and is one of the least common variants (about 5%) [5]. Usually it presents by fecal umbilical drainage in the neonatal period, although a small fistula can occur with granulation tissue or umbilical polyp and little or no secretion. Occasionally, the ileum can prolapse exteriorly through the patent duct, leading to obstructive symptoms and ischemic damage of the incarcerated ileum. Even in case of obvious diagnosis (fecal umbilical drainage), imaging workup should include ultrasonography and a fistulogram to identify the communication with the bowel [4]. The management of omphalomesenteric fistula requires surgical excision from the umbilicus up to the ileum and should be done promptly after the diagnosis (Fig. 32.3a, b).

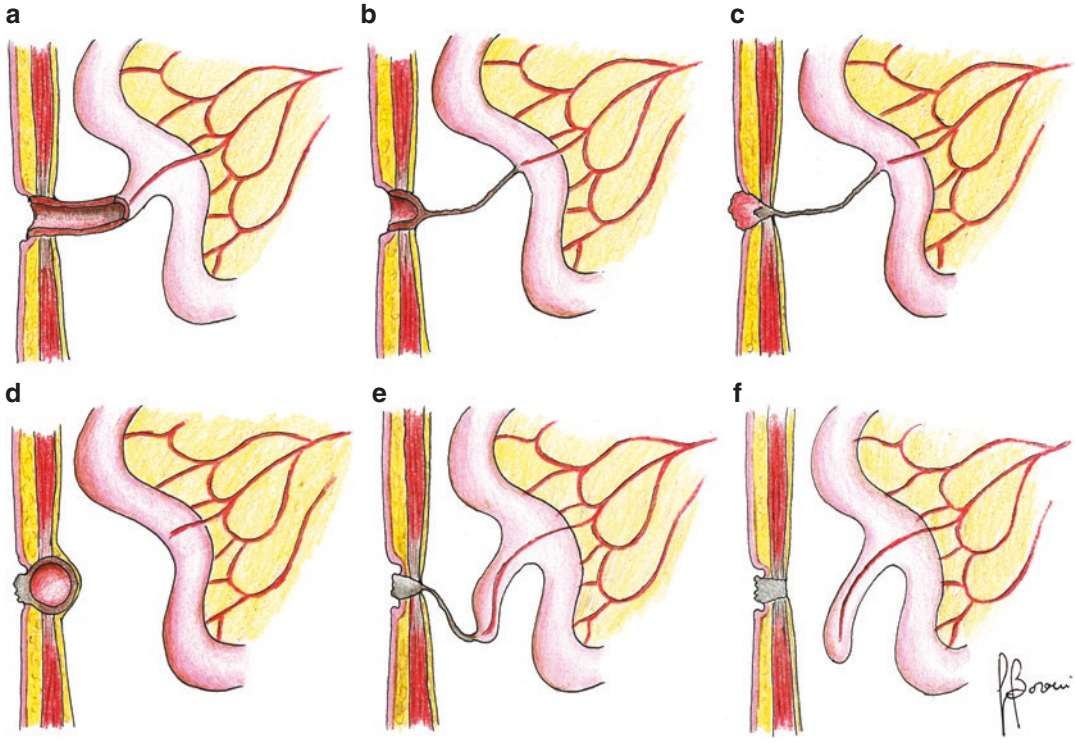

Fig. 32.2 Various omphalomesenteric duct remnants. (**a**) Omphalomesenteric fistula; (**b**) omphalomesenteric sinus with a fibrous band; (**c**) umbilical polyp with a band; (**d**) omphalomesenteric (umbilical) cyst; (**e**, **f**) Meckel diverticulum with and without fibrous band

Omphalomesenteric sinus (Fig. 32.2b) is caused by the failure of obliteration of the outer portion of the vitelline duct; the ileal attachment may persist as a fibrous cord or be lost. Clinically, this condition may lead to the discharge of mucus; injection of contrast medium may be helpful in defining the diagnosis. During surgical removal, a full exploration is mandatory to identify and remove any attachment to the small bowel [2, 4].

An umbilical polyp (Fig. 32.2c) represents exposed gastrointestinal mucosa at the umbilicus. The most common ectopic mucosa encountered in this situation is of gastric or pancreatic origin; acid secretion by the gastric mucosa can lead to chemical dermatitis of the periumbilical skin. Sometimes the polyp is misdiagnosed as umbilical granuloma and treated by cauterization with silver nitrate, without resolution. Surgical resection is required, with careful identification of any remnant under the umbilicus [4, 6].

An omphalomesenteric cyst (Fig. 32.2d) is caused by failed obliteration of an intermediate portion of the vitelline duct. The cyst may be located under the umbilicus (umbilical cyst) or in the context of the fibrous remnant. The cyst usually has columnar epithelium: gastric mucosa is the most common, but small intestinal, colonic, or pancreatic tissue can be present [4]. This condition is typically asymptomatic, but the cyst can become infected, leading to erythematous swelling at the umbilicus and sometimes spontaneous external drainage with discharge of pus. Like for the umbilical polyp, during the surgical removal of umbilical cyst, any associated remnant must be looked for and removed.

The persistence of a fibrous band between the umbilicus and ileum, representing an obliterated omphalomesenteric duct, possibly associated with other remnants (Fig. 32.2b, c, e), may cause angulation, volvulus, herniation, or strangulation of intestinal loops, resulting in mechanical intestinal obstruction [2].

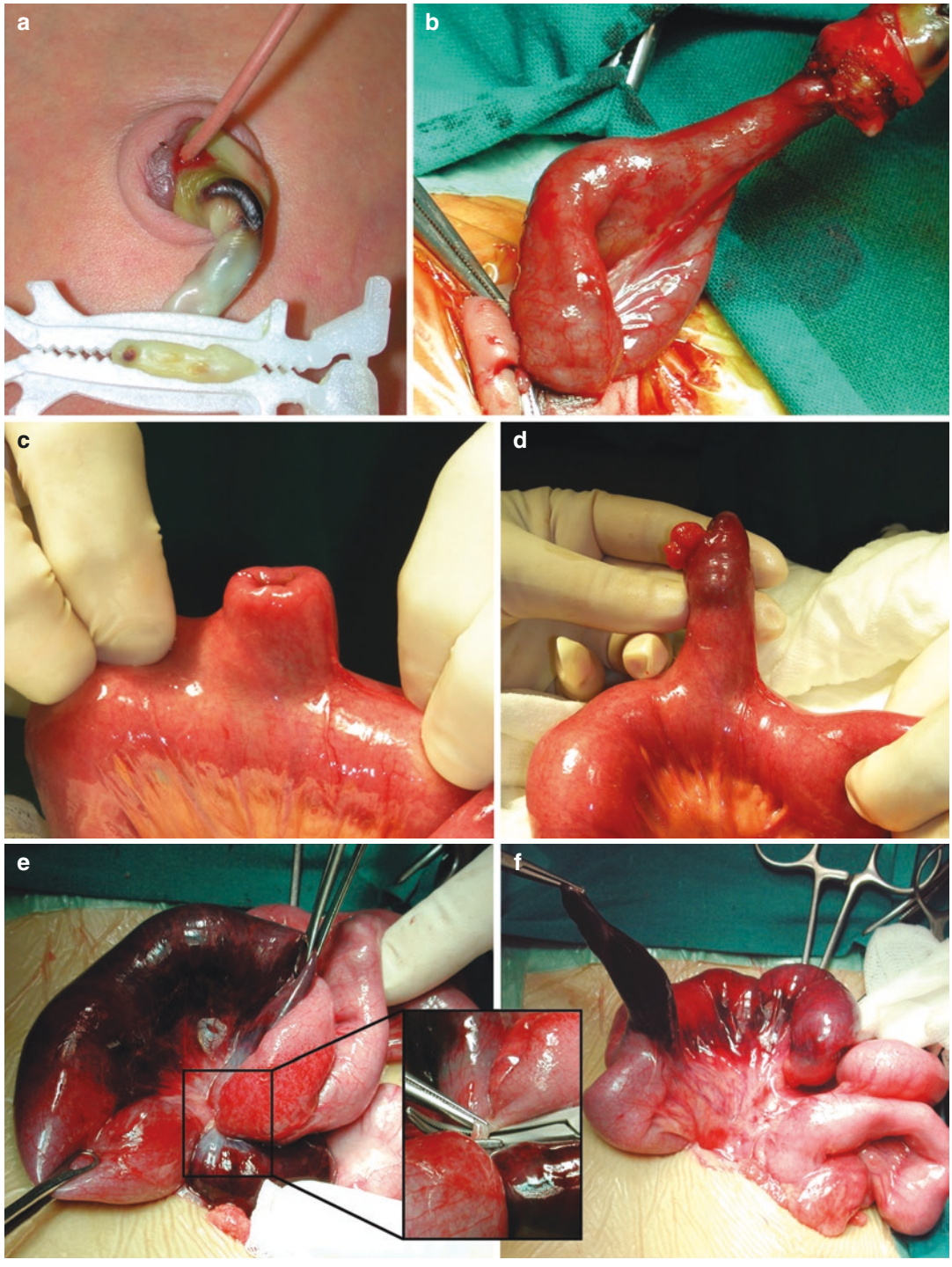

Fig. 32.3 Various clinical presentations and complications of omphalomesenteric remnants. (**a**, **b**) Omphalomesenteric fistula cannulated at the beginning of the intervention and during the dissection; (**c, d**) inverted Meckel diverticulum leading to intestinal obstruction; (**e**, **f**) internal hernia due to a mesodiverticular band, leading to ischemic damage of the diverticulum and the adjacent ileum; (**g**) perforation of a giant Meckel diverticulum secondary to peptic ulceration; (**h**) torsion of Meckel diverticulum

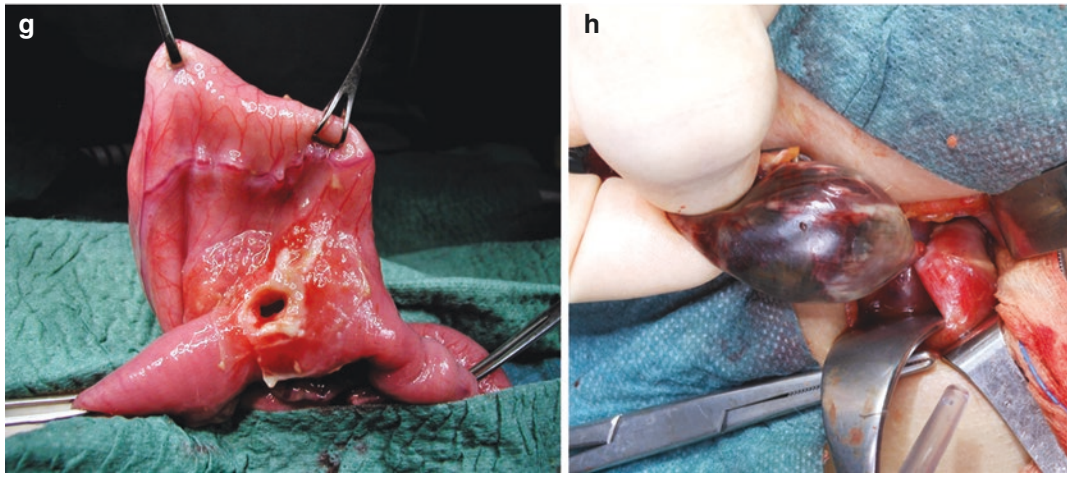

Fig. 32.3 (Continued)

32.4 Meckel Diverticulum

Meckel diverticulum (MD) results from the incomplete obliteration of the inner (intestinal) portion of the omphalomesenteric duct. The German surgeon Wilhelm Fabricius Hildanus first described this "unusual" diverticulum of the small bowel in 1598, but this entity was no named until 1908, when Johann Friedrich Meckel the Younger published his research describing its anatomy, embryology, and clinical presentation [7]. MD is the most common congenital malformation of the gastrointestinal tract and is found in 1.2–3% of the population. In autopsy series, MD was discovered in 386 of 31,499 autopsies, resulting in a prevalence of 1.23% [8]. The male-to-female ratio is almost equal in asymptomatic patients, whereas the symptomatic cases are more frequently males, with a male-to-female ratio of 2–3:1 [9, 10]. Most cases of MD are isolated, without other associated abnormalities. Simms et al. showed an increased incidence of Meckel diverticulum in children born with major malformation of the umbilicus, alimentary tract, nervous system, or cardiovascular system. They found MD in 24.5% of patients with small omphalocele, in 12% of patients with esophageal atresia, in 11% of those with imperforate anus, and, respectively, in 6, 4.6 and 4.2% of patients with neurologic abnormality, congenital cardiovascular abnormality, and duodenal atresia [11].

In some textbooks, a mnemonic trick, known as "the rule of two", is cited: MD is found in 2% of the population and becomes symptomatic before 2 years of age, two times as common in males, 2 ft. from the ileocecal valve, 2 inch. long, and 2 cm in diameter, containing two types of heterotopic tissue (gastric and pancreatic) [12].

32.4.1 Pathology

MD is a true diverticulum, containing all three layers of the intestinal wall, and receives its blood flow from the vitelline artery, a terminal branch of the superior mesenteric artery. It is usually located on the antimesenteric border of the ileum, but sometimes it can be found on the lateral aspect or on the mesenteric border. These locations are explained by the presence of a short vitelline artery that fixes the tip of the diverticulum to the mesentery, determining the diversion away from the mesenteric border during the growth of the intestine [4]. Three-fourths of MD are unattached to the abdominal wall and free-floating within the peritoneal cavity (Fig. 32.2e, f). Most of the MD are located within 100 cm of the ileocecal valve and have a length of 2–3 cm. In a review of 100 cases of symptomatic MD in pediatric age, the mean distance to the ileocecal valve was 47.58 ± 14.50 cm, the diverticular length was 3.72 ± 1.95 cm, and the mean diverticular diameter was 1.65 ± 0.66 cm

[9]. In one study on adult patients, more than one-fourth of MD were located between 91 and 161 cm from the ileocecal valve.

The presence of heterotopic mucosa is reported with an overall incidence of 15–50%, with a great variability between symptomatic and incidental cases. The most common type of heterotopia is gastric, followed by pancreatic mucosa, whereas other types are rare. Park, on 1476 patients with Meckel diverticulum, reported an overall incidence of heterotopic tissue of 21.5%. In asymptomatic patients, the incidence was 11% in pediatric age and 14% in adults, whereas in symptomatic cases, it was, respectively, 59 and 43% in children and adults. In bleeding diverticula, gastric heterotopia was present in 63% of adults and in 78% of pediatric cases [10]. Huang reported the presence of ectopic tissue in 73% of symptomatic children (61% gastric, 2% pancreatic, 10% coexistence of gastric and pancreatic mucosa); ectopic gastric tissues was found in 97.7% of patients with gastrointestinal bleeding, whereas the presence of ectopic pancreatic tissue was more frequent in patients with intussusception [9].

32.4.2 Clinical Presentation

Most MD are clinicaly silent and often detected incidentally during surgery for some other indications. They usually become symptomatic when a complication occurs. According to the original papers of Johann Friedrich Meckel, the risk of complication of MD was 25%, but in the recent literature, the estimated lifetime risk of symptoms ranges between 4 and 6% [5]. In children gastrointestinal bleeding is the most common presentation, especially in those younger than 2 years, followed by obstruction and inflammation. In adults the most frequent complications are obstruction, ulceration, diverticulitis, and perforation [7]. Neoplasia becomes a more frequent complication in the elderly.

Gastrointestinal bleeding from MD is usually described as brick red, maroon, or less commonly tarry; in neonatal population, bright red blood may be present, owing to the rapid intestinal transit. Usually patients present episodic painless or minimal painful gastrointestinal bleeding; up to 70% of patients presents with massive bleeding and requires blood transfusion [9]. Chronic bleeding with isolated iron-deficiency anemia is the presentation symptom in a small number of patients and is seen more in adults than in children.

The main mechanism of bleeding is the acid secretion from ectopic mucosa, which leads to ulceration of adjacent ileal mucosa; gastric heterotopia is described in at least 60% of bleeding diverticula and in some series up to almost 100% [9].

Intestinal obstruction is the second most common complication of MD in pediatric age, primarily observed in older children, with several possible mechanisms. MD can act as a pathological lead point for an ileoileal or ileocolic intussusception. Most of these intussusceptions are not reducible with pneumatic or contrast enema, and rarely preoperative imaging identifies the underlying cause, which can only be suspected. However, only 5–10% of patients with intussusception after 2 years of life have a MD [5]. Fibrous cord from the tip of the diverticulum to the umbilicus can cause volvulus, providing a point of fixation for the bowel to twist around. Fibrous remnants can also cause intestinal obstruction favoring compression and kinking of intestinal loops.

The presence of a mesodiverticular band, a remnant of vitelline vessels, that arises from the mesentery and implants on the diverticulum, can create a loop which predisposes to internal hernia [13] (Fig. 32.3e, f). Adhesions due to inflammatory process may also result in obstruction. Rarer causes of obstruction are the inversion of the diverticulum (Fig. 32.3c, d), enteroliths, foreign bodies, or tumors within the diverticulum.

MD may also be found within a hernia (Littre hernia) which may get incarcerated and obstructed [14]. During adulthood Littre hernia occurs typically in the inguinal region, whereas in pediatric population, umbilical type is more common.

Meckel diverticulitis usually occurs in older children and is commonly misdiagnosed as appendicitis because of the overlapping clinical features. Inflammation of MD is secondary to acid secretion from ectopic mucosa or, similar to

appendicitis, can result in owing to obstruction of the lumen by an enterolith or foreign body leading to stasis and bacterial proliferation [4].

Intestinal perforation (Fig. 32.3g) is a very rare clinical manifestation and is secondary to diverticulitis, ischemia due to torsion of the diverticulum (Fig. 32.3h), or peptic ulceration due to ectopic gastric mucosa [14].

Malignancies in MD are reported to account for only 0.5–3.2% of the complications. Several types of tumor of the MD have been described, and malignant tumors predominate, with carcinoids being the most common. Other pathological types include adenocarcinoma, pancreatic carcinoma, intraductal papillary mucinous neoplasm, gastrointestinal stromal tumor (GIST), leiomyosarcoma, lymphoma, lipoma, adenomyoma, and villous adenoma [15, 16]. Mean annual incidence rate of MD cancer is 1.8 per 10 million person-years; incidence increases progressively with age, reaching a peak in the eighth decade. Carcinoid is the most common pathologic type, representing 76.5% of all MD cancer [15]. The average age of appearance of a carcinoid on a MD is 55 years, with an incidence 2.5 times in men than women. The classic carcinoid syndrome, supported by serotonin secretion, usually in patients with liver metastasis, is present in 10–20% of patients. Carcinoid tumors smaller than 1 cm have an incidence of 2% of metastasis; lesions between 1 and 2 cm metastasize in 50% of cases and those bigger than 2 cm in 80% of cases. The liver is the most common metastatic site, with a 5-year survival of 30% in patients with hepatic metastases [16]. In more than 70% of cases, carcinoids originate at the distal extremity of MD. In MD tumors, resection of the ileal tract containing the diverticulum and the corresponding mesentery is generally recommended.

32.4.3 Diagnosis

Most of the uncomplicated MD are asymptomatic and discovered as incidental finding, usually during laparotomic or laparoscopic procedures. Rarely, owing to increase in the use of more sensitive radiological tests, a MD can be suspected with imaging studies. On upper gastrointestinal contrast studies, the classic finding is a single diverticulum arising from the antimesenteric border of the distal ileum. On ultrasound and on CT scan, uncomplicated MD can be seldom identified as a round or tubular blind ending structure originating from the ileum [17].

In case of gastrointestinal bleeding, the technetium-99 m pertechnetate radionuclide study ("Meckel scan") is widely used. Harper introduced this study in 1962, but Jewett was the first to apply it clinically in 1970 [18]. ^{99M}Tc pertechnetate is taken up and secreted by the tubular glands of the gastric mucosa in the stomach, but also in ectopic gastric mucosa, which is present in 70–100% of bleeding MD in children (Fig. 32.4). In children the "Meckel scan" has a sensitivity of 80–90%, a specificity of 95%, and an accuracy of 90% [4, 7]. The accuracy of the study is improved by the administration of pentagastrin (which increases gastric mucosal uptake and stimulates acid secretion), H-2 blockers like cimetidine or ranitidine (which reduce the excretion of the isotope and increase cellular retention enhancing visualization), and glucagon (which, by its antiperistaltic effect, allows the isotope to persist longer in the diverticulum) [17]. Causes of false-positive results include intestinal duplication containing ectopic gastric mucosa, intussusception, bowel inflammation, retention of tracer in the urinary system, vascular lesion such hemangiomas, arteriovenous malformations, and gastrointestinal bleeding unrelated to MD. False-negative scintigraphy may result from absence or small size of gastric ectopic mucosa in the diverticulum: at least a 1 cm [2] of ectopic tissue is required. Other factors include tracer in the urinary bladder that may obscure a MD located in the pelvis, residual contrast in bowel from previous barium study that attenuates gamma radiation, and rapid dilution of the radiotracer from high bleeding rate or poor blood supply to the diverticulum [18]. Single photon emission computed tomography (SPECT) has been successful in identifying cases that are not visible using conventional planar imaging [17]. Mesenteric angiography can be used to investigate gastrointestinal hemorrhage associated with a MD, although a bleeding rate greater than 0.5 mL/min is required. In comparison a techne-

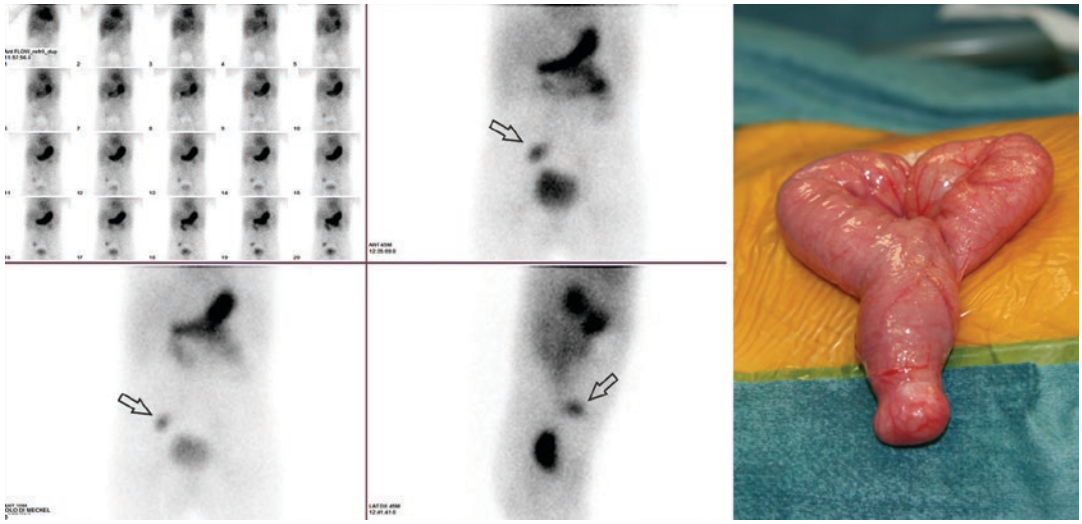

Fig. 32.4 Technetium-99 m pertechnetate radionuclide study, demonstrating a focus of uptake in the lower right abdomen in a case of bleeding Meckel diverticulum; on the right, intraoperative findings, with palpable ectopic mucosa at the tip of the diverticulum

tium-99 m-labeled red blood cell scan is a more sensitive test and can identify hemorrhage at rates as low as 0.1 mL/min, but it is not specific [17]. In presence of bleeding with typical characteristics and a repeat negative scintigraphy, some authors suggest exploratory laparoscopy.

Wireless capsule endoscopy is widely used in patients with obscure gastrointestinal bleeding, with an incidence of positive findings between 40 and 75% and diagnosis of MD in 3–15% of patients [19]. Retrograde double balloon enteroscopy was also successfully used for diagnosis of MD in children with negative scintigraphy [20].

Inflamed MD appears on ultrasound as a thick-walled, tubular, noncompressible lesion, with wall hyperemia on color Doppler; however these features often simulate those of acute appendicitis, leading to misdiagnosis. At CT scan, acute Meckel diverticulitis appears as a blind-ending, tubular or cystic, thick-walled structure, with wall enhancement and inflammatory changes of surrounding mesenteric fat [13, 17]. In intussusception cases, rarely enema permits to demonstrate a MD as a lead point, and usually the diagnosis is made intraoperatively. Itagaki described an ultrasound sign, which he named "double-target sign," with one target formed by the inverted Meckel diverticulum acting as a lead point and the second target by the intussuscepting ileum [4, 14].

In patients with intestinal obstruction or diverticular perforation, the radiologic findings are usually aspecific: dilated bowel loops, air-fluid levels, and free intraperitoneal gas.

32.4.4 Treatment

The treatment of choice for symptomatic MD is the surgical resection, which can be done with open or laparoscopic techniques. Laparoscopy is increasingly used both for diagnosis and treatment of MD: in most cases the diverticulum is identified, grasped, and exteriorized and then removed extracorporeally. This can be achieved either by simple diverticulectomy and transverse closure of the ileum or by segmental bowel resection and reanastomosis. Diverticulectomy alone can result in either retained mucosa or, in case of bleeding, a retained ulcer on the mesenteric aspect of the bowel or in the neck of the diverticulum. In patients with bleeding or inflammatory symptoms, resection of the ileal segment including the diverticulum may be the safest option [5, 12].

The management of incidentally detected MD remains controversial. The classic approach is in favor of resection, with the rationale to remove a potential cause of complications throughout life. In 1976, Soltero first argued that asymptomatic MD should not be removed, demonstrating that there was only a small asymptomatic diverticulum causing disease in later life [8]. Other authors recommended a "selective" approach, advising resection of incidentally detected Meckel in selected cases. For example, Park recommended removing all diverticula with any of the four features most commonly associated with symptomatic Meckel: age less than 50 years, male sex, diverticulum length greater than 2 cm, ectopic tissue, or abnormal features within the diverticulum [10]. Nevertheless, about the last point, the same author reported that a palpable mass was identified during surgery only in 38% of the diverticula with histopathologic diagnosis of ectopic tissue [10]. A recent meta-analysis by Zani concluded that resection of incidentally detected MD has a significantly higher early complication rate than leaving it in situ (5.3% in the resected compared with 1.3% in the nonresected MD); the estimated lifetime chance of complications requiring an operation is 2.9%, and 758 resections of asymptomatic diverticula are required to prevent 1 death from MD [8].

32.5 Urachal Remnants

Failure or delay in complete fibrous obliteration of the urachus may lead to a variety of urachal remnants, including patent urachus, urachal sinus, urachal cyst, and vesicourachal diverticulum.

32.5.1 Epidemiology and Classification

Bartholomaeus Cabrolius first described the persistence of the urachus in 1550 [21]. Urachal anomalies have been historically considered rare; even if their incidence at birth was formerly estimated to be 1 in 5000–8000 live births [22, 23], the true prevalence is probably higher. Schubert found, at autopsy, tubular urachal remnants in 38% of 122 specimens in adults [24]. Urachal remnants are diagnosed quite frequently since abdominal ultrasonography is often used as a screening test, but the clinical significance of these incidentally diagnosed remnants is unclear. In 2003, Ueno reviewed the ultrasound reports of 3400 patients and found 56 children with urachal remnants, with an incidence of 1.6%; 36 of these 56 cases were asymptomatic [25]. Recently Gleason reviewed abdominal imaging study of 64,803 patients younger than 18 years, during a 13-year period. Of those patients, 721 were radiographically diagnosed with an urachal anomaly (1.1%); only 54 of these urachal anomalies (7.5%) were symptomatic [26]. The incidence is slightly higher in males, with a male-to-female ratio of 1.36:1 [23]. The most common type of urachal anomaly is the urachal cyst (36–61%) (Fig. 32.5d), which develops if the urachus closes at both the umbilicus and bladder site but remains patent between these two points. Umbilical urachal sinus (Fig. 32.5c), a blind-ending remnant that opens at the umbilicus, represents 16–49% of the anomalies; the patent urachus (Fig. 32.5a), in which a persistent communication exists between the bladder lumen and the umbilicus, accounts for 10–23% of remnants [27, 28]. Urachal diverticulum (Fig. 32.5b), consisting of outpouching of the bladder at the insertion of the urachus, is very rare, representing only 1–3% of urachal anomalies [3, 27].

32.5.2 Clinical Presentation

With the widespread diffusion of abdominal ultrasonography, the number of incidentally diagnosed urachal remnants, without any symptom, is increasing. In the symptomatic cases, drainage from the umbilicus is the most frequent modality of presentation. Pain, erythema and other signs of infection, palpable cyst or mass, and dysuria or urinary tract infection are other presenting clinical symptoms [27, 28]. Umbilical retraction with voiding can be a sign of urachal anomalies [5].

A patent urachus is usually associated with urine leakage during the neonatal period. In

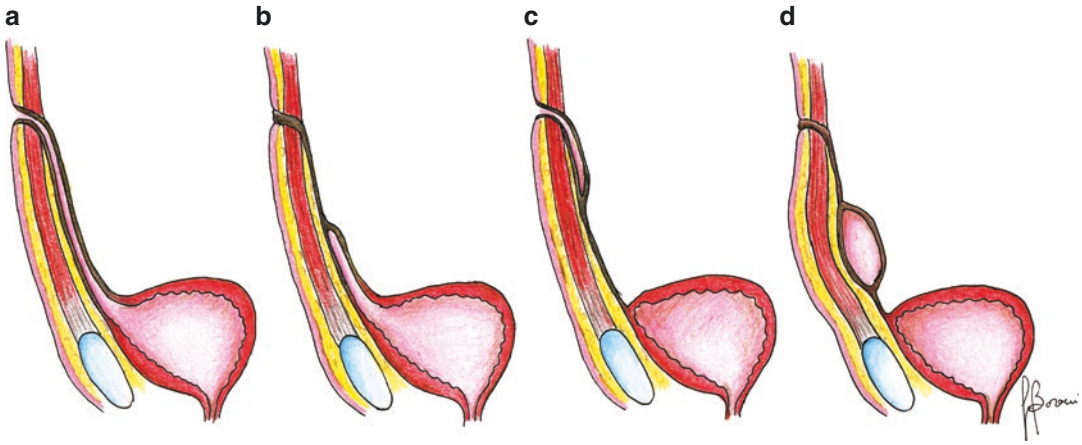

Fig. 32.5 Various urachal remnants. (**a**) Patent urachus; (**b**) vesicourachal diverticulum; (**c**) urachal sinus; (**d**) urachal cyst

addition it may be one of the causes of giant umbilical cord in the newborn [2, 3]. Umbilical urachal sinus may be asymptomatic or may present with periodic discharge, usually associated with an infection. Urachal cyst are sometimes found as incidental masses during routine examination; they become symptomatic when they enlarge or when an infection occurs, with symptoms such as acute abdominal pain, fever, urinary tract infection, and abdominal mass [29, 30]. Most of the vesicourachal diverticula are asymptomatic but may be complicated by urinary tract infection and intraurachal stone formation, particularly if they retain urine [3, 5]. Urachal anomalies are thought to be associated with an increased risk of urachal cancer. Malignant urachal neoplasms are rare, accounting for 0.1–0.5% of all bladder malignancies; adenocarcinoma, that represents the majority of cases (88–97% of all urachal cancer), has an estimated incidence of 0.18/100,000 individuals yearly. The peak median age at diagnosis is mostly in the fifth and sixth decade, and the gender distribution shows a tendency toward the male sex [26, 31]. Urachal tumors are typically silent, and a large proportion of patients presents with disease at stage pT3 or higher. The most frequent symptom is hematuria, owing to the origin of 90% of carcinomas in the juxtavesical portion of the urachus. Five-year cancer-specific survival ranges between 43 and 61% [31]; local invasion and systemic metastases result in a 5-year survival rate of 6.5–15% [3].

32.5.3 Diagnosis

Any child suspected to have an urachal abnormality should undergo ultrasound evaluation as initial screening test. Ultrasound is diagnostic in most of urachal cysts (82–100%) and in a variable percentage of urachal sinus and patent urachus, ranging, among the studies, between 33 and 100%. In presence of drainage from the umbilicus, a sinogram/fistulogram is useful to delineate the anatomy of the defect and to exclude an omphalomesenteric remnant [27]. Most authors have suggested that voiding cystourethrography is rarely informative and then not necessary in patients with suspected urachal anomalies. Nevertheless a voiding cystourethrography (VCUG) may be useful in the rare vesicourachal diverticulum to delineate the anatomy of the diverticulum and in patent urachus to exclude posterior urethral valves or other bladder obstruction. Currently this association seems very rare, but, in the past, posterior urethral valves have been reported in about one-third of patients with patent urachus [3, 32]. In selected cases, when the ultrasound is not diagnostic, a CT scan or an MRI can be proposed [27].

32.5.4 Treatment

Traditionally urachal anomalies in children have been removed, in order to avoid infection, as well to prevent malignant degeneration later in life. In the recent literature, several authors propose conservative management for the incidentally detected urachal remnants and even in cases of infected anomalies, especially in younger patients [21, 23, 32]. This new trend in management of urachal remnant is justified by some evidences: the increasing number of incidentally detected urachal remnants and the rate of spontaneous resolution that can reach 80% in patients younger than 6 months [28, 32]. Moreover, the exact role of urachal remnant resection in order to prevent urachal cancer is unknown. Gleason calculated that the number needed to treat to prevent a single case of urachal adenocarcinoma is 5.721 urachal remnants and concluded that prophylactic surgical excision is neither reasonable nor recommended [26].

In patients with persistent symptoms despite appropriate conservative management, particularly if older than 1 year, resection of urachal remnant remains the most accepted treatment. In patients with infected urachal cyst, some authors suggest a two-stage approach, first with drainage and antibiotics, followed by excision [21].

The recommended surgical management includes the radical excision of the urachal remnants from the umbilicus to the bladder dome, with a cuff of the bladder wall: most urachal cancers, in fact, occur at the distal part of the urachus [29]. The traditional open approach, via the umbilicus, may need a lateral expanded incision, a midline vertical incision, or a hypogastric transverse incision to achieve total excision, mostly in older children [30]. In 1993 Trondsen described the first laparoscopic excision of urachal remnants, and in 1995, Fahlenkamp extended the procedure to pediatric patients [29, 30]. Currently laparoscopic approach is widely used; most reports describe a three-port approach, with one port for a 30° telescope and two working ports. The camera port is placed infraumbilical or supraumbilical and the working ports, respectively, in right and left mid-abdominal wall position [29]. Other placement techniques involve placement of all the ports at the right or at the left of the midline: the first port in the upper abdomen; the second at the level of the umbilicus, laterally to the midclavicular line; and the third in the lower abdomen, on the midclavicular line [30]. A Foley catheter must be placed to initially empty the bladder, during the port placement and the dissection of the urachal remnant. The bladder should then be inflated with saline solution or with vital dye diluted, allowing better visualization of the borderline between the bladder and urachus and prompt recognition of any leakage after the removal of the urachus. After opening of the anterior parietal peritoneum, the urachal remnant is dissected off the transversalis fascia, with hook, scissors, or harmonic scalpel, and then divided at its superior end, near the umbilicus. The dissection is carried down until the bladder, and the urachal remnant is then ligated by an endoloop just above the dome of the bladder and sectioned with a small pad of detrusor. One or two additional stitches may be placed to ensure complete closure of the bladder. The urinary catheter should be left for 2–3 days in order to prevent urinary leakage [29, 30].

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The Bladder Exstrophy-Epispadias Complex (BEEC)

33

Geoffroy de Sallmard, Omar Alhadeedi, Delphine Demède, and Pierre Mouriquand

The BEEC complex is the result of a failed cavitation and separation of the pelvic organs and a failed closure of the pelvic ring. During the first 2 months of gestation, the embryo (germinal disc) is subjected to a complex process (delimitation) [1] of cranio-caudal tubularization resulting in the cavitation and connection of the pelvic organs to the pelvic floor. This leads to the creation of separated urinary, genital and intestinal cavities independently connected to the perineal surface by distinct conduits and their corresponding sphincter. If the delimitation process is interrupted early, the distal bowels, the bladder and the urethra are not individualized and appear as contiguous and often duplicated plates. This is a cloacal exstrophy and is often associated with other abnormalities. If the process halts later in the gestation, the bowels are properly formed and connected, but the bladder and urethra are both widely open, presenting as a classical bladder exstrophy. Finally, when the process stops late, only the urethra and the urethral sphincter are open and incompetent, presenting as an epispadias. Depending on the timing of the cavitation failure, one should distinguish posterior epispadias where the sphincteric mechanisms are involved and the child incontinent at various degrees and anterior epispadias where the continence mechanisms are completely or partially respected but the genital tubercle remains abnormal. Epispadias exists both in males and females.

Complex embryonic hypotheses have been described to explain these abnormalities. They involve the formation and positioning of the cloacal membrane which is situated at the caudal end of the germinal disc and occupies the infra-umbilical abdominal wall. Between the two layers (ectoderm and endoderm) initially forming the cloacal membrane comes a mesenchymal ingrowth [2] which will result in the formation of the lower abdominal muscles and the pelvic bones [3]. The surrounding mesoderm will be at the origin of the genital tubercle. The 3D development of the embryo progresses from the cephalic to the caudal extremity and from the dorsum to the ventrum of the embryo. When the caudal delimitation is aborted, the mesenchymal ingrowth between the ectodermal and endodermal layers fails to progress, and the overstretched cloacal membrane becomes fragile and subject to a premature rupture leading to exstrophy (or non-cavitation) of the pelvic organs [4]. This "zip down" process [5] explains the progressive closure of the pelvis and the cavitation of the pelvic organs from the back to the front and from the top to the bottom of the embryo. It is possible that the middle period of the cloacal delimitation is more

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vulnerable than the early and late stages. This would explain why bladder exstrophy is more frequent than cloacal exstrophy and epispadias [6]. Other embryonic hypotheses have been reported [7–10].

Epidemiological data confirms that the incidence of bladder exstrophy is between 2.15 and 3.3 per 100,000 births [11, 12]. The incidence of epispadias is 1 per 101,000 [13] with a sex ratio from almost equal to a marked male predominance of 5:1 [14]. The sex ratio of bladder exstrophy ranges from 1:1 to 6:1 with a male predominance [15]. White children, in vitro fertilization [16] and socioeconomic status appear to be interacting factors. Significant genetic predisposition remains uncertain considering the small reported cohorts [17–19]. The recurrence risk varies from 0.3% [20] to 2.3% [17–19].

33.1 Anatomy of BEEC (Fig. 33.1a, b; Fig. 33.2a, b; Fig. 33.3; Fig. 33.4a, b; Fig. 33.5a, b; Fig. 33.6)

1. Bony anomalies include a rotation and separation of the two hemi-pelvises creating a gap between the two hemi-pubis, a flattening of the pelvic cavity, an ascent of the perineum with an anteriorly positioned anus and vagina in girls and a disorganization of the abdominal muscles with frequent inguinal hernias [21]. The pelvic floor and the pubo-rectal sling are subsequently stretched apart explaining frequent genital prolapses in girls and occasional rectal prolapses [22].
2. In the classical bladder exstrophy, the lower urinary tract is exposed with an opened bladder reservoir and urethra. The sphincteric mechanisms are deficient leading to a total urinary incontinence. The uretero-vesical junctions are abnormal with short ureteric submucosal tunnels leading to vesicoureteric reflux once the reservoir is closed.
3. Variants exist with partial exstrophies ("split symphysis variants"), duplicated pelvic organs [23], myelomeningocele, spinal anomalies, omphalocele, short guts or anorectal malformation.
4. In boys, the epispadiac penis is short and broad with an abnormal distribution of the penile skin. There is a dorsal curvature of the penis due to an abnormal rotation of the corpora cavernosa. Erection mechanisms are respected. The urethral plate is wide open on the dorsum of the penis. The glans is dorsally open and split in two. The neurovascular bundles are divided in two wide strips leading to each hemi-glans and positioned on the lateral aspects of each corpus.

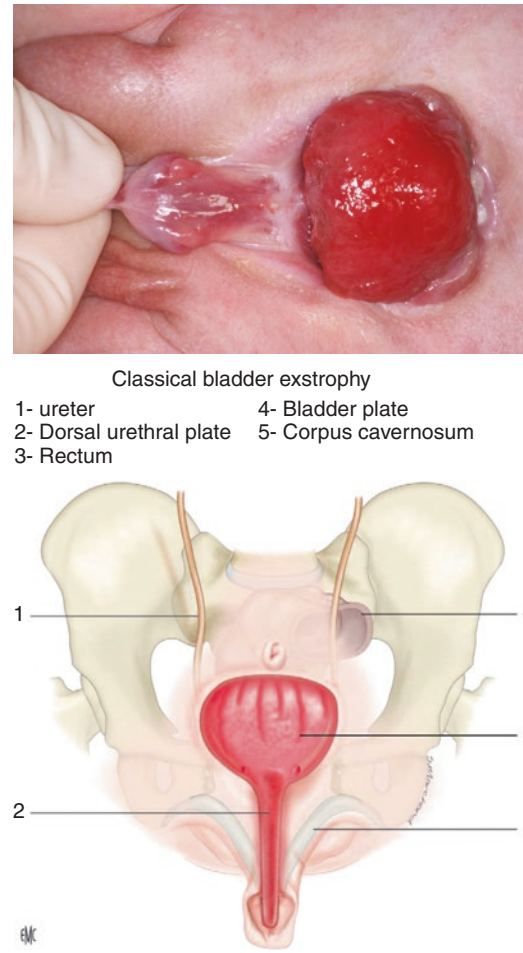


Fig. 33.1 Classical bladder exstrophy in a boy. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

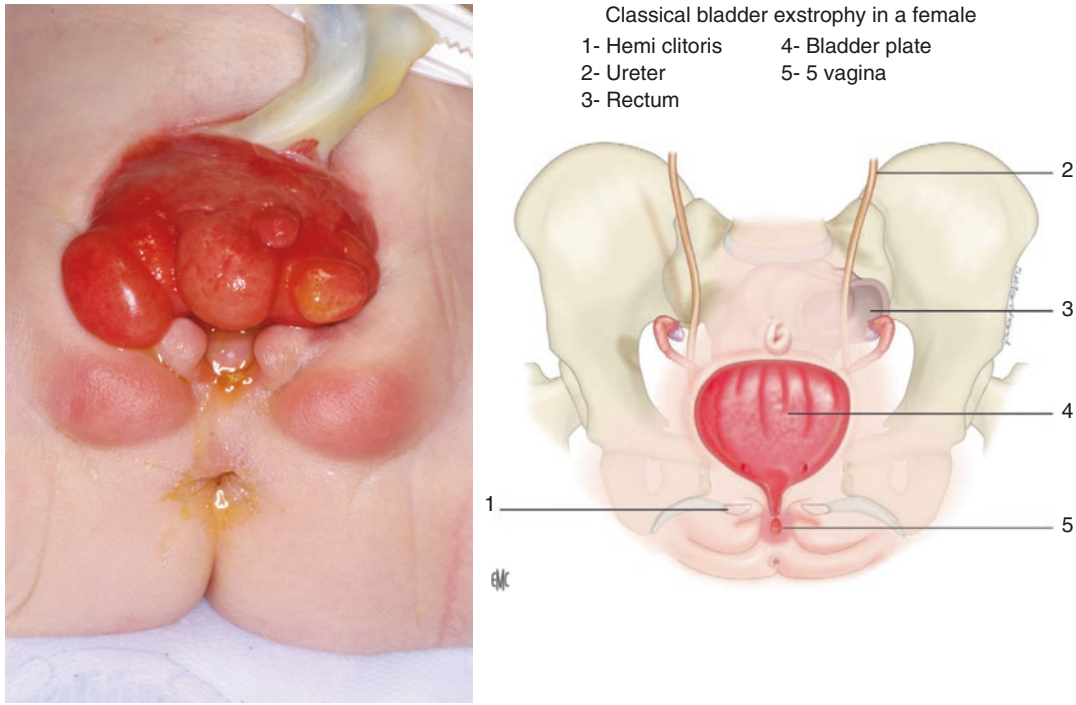


Fig. 33.2 Classical bladder exstrophy in a girl. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

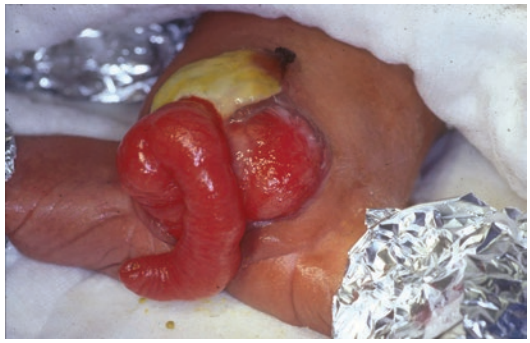


Fig. 33.3 Cloacal exstrophy

5. In rare cases, the epispadiac urethra is concealed by a tight complete foreskin. The penis is buried due to a congenital defect of the penile skin shaft [24].
6. In girls, the urethra is also wide open exposing the bladder neck or the bladder reservoir itself. The continence mechanisms are therefore deficient as well [25]. The two hemi-clitorises are split on each side of the urethral plate. The vaginal orifice is anteriorly positioned and often narrow. The separation of the two hemi-pubes creates a triangular hairless area between the two hemi-mons [25].
7. In cloacal exstrophies, abdominal defects are more severe with a possible omphalocele. The bowels are also exstrophied separating two hemi-bladders. The small bowel is short and the large bowel poorly developed ("hindgut"). The genital tubercle in boys is very poor. The child is incontinent of urine and faeces.

33.2 Diagnosis of BEEC

Prenatal ultrasound scan can alert on the diagnosis of exstrophy from the 16th week of gestation when a low implantation of the umbilical cord, a non-visualized bladder, an inter-pubic gap and a

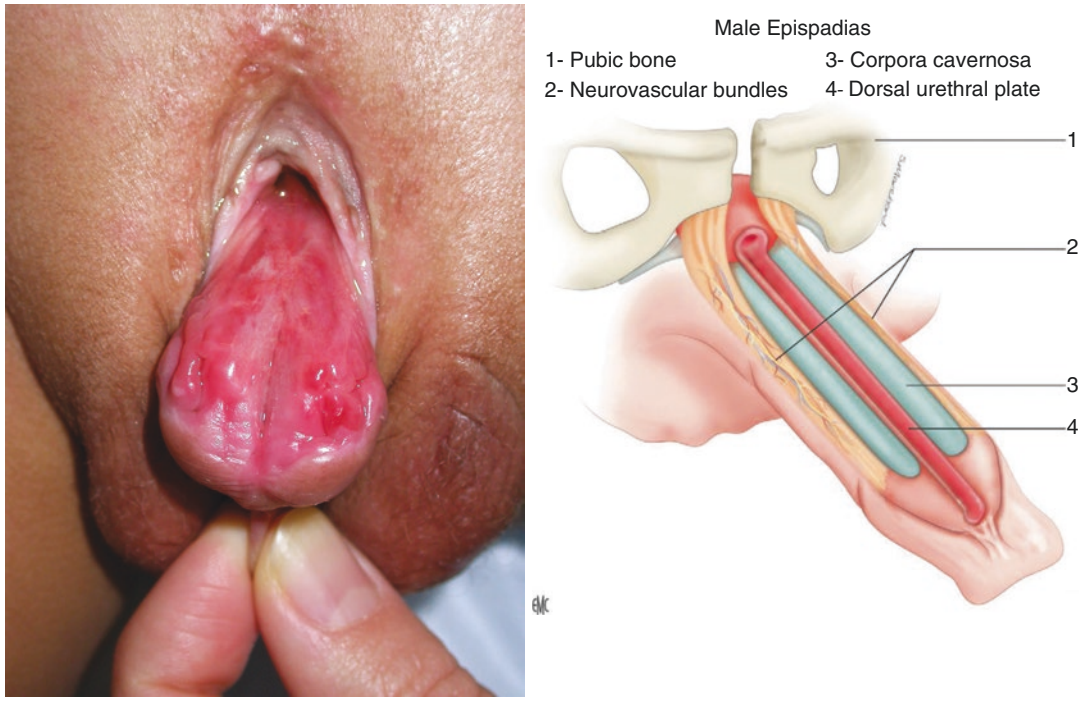


Fig. 33.4 Incontinent (posterior) male epispadias. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

protrusion of the infra-umbilical wall are demonstrated. In cloacal exstrophy, an omphalocele can be seen as well. The diagnosis is still often made at birth [26].

33.3 Management of BEEC

The objectives of the management of BEEC are to preserve renal functions, to achieve "social dryness", to refashion the genital area, to help future sexual life and future fertility and to provide an ongoing psychological support all along childhood and adolescence.

33.3.1 At Birth

The umbilical clamp should be removed and the cord sutured to avoid damage to the bladder surface. The bladder should be covered with paraffin- or saline-soaked gauze or a protective silicone mesh, and the child should be transferred to a dedicated department of paediatric urology.

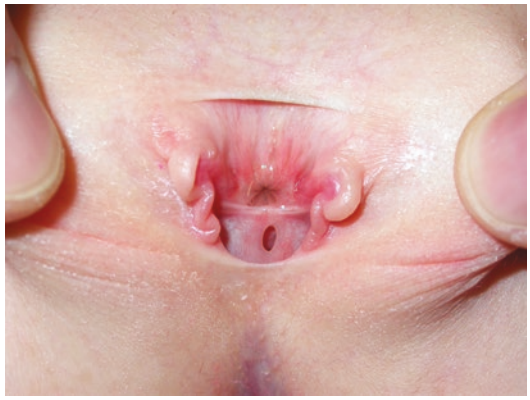
33.4 Two Major Treatment Approaches Exist

33.4.1 The Classic Stepwise Approach

Described by Robert Jeffs in Baltimore [27], the three-step approach includes (1) a closure of the bladder plaque in the neonatal period with or without osteotomy; (2) a reconstruction of the genital tubercle between 6 and 18 months of age with or without androgen stimulation, with or without osteotomy; and (3) bladder neck surgery between after 4 years of age with or without bladder augmentation, with or without a Mitrofanoff diversion.

33.4.2 Closure of the Bladder Plate (Fig. 33.7a, b; Fig. 33.8; Fig. 33.9)

Once the ureters have been catheterized, the bladder plate is carefully dissected off the adjacent structures, following several important landmarks:



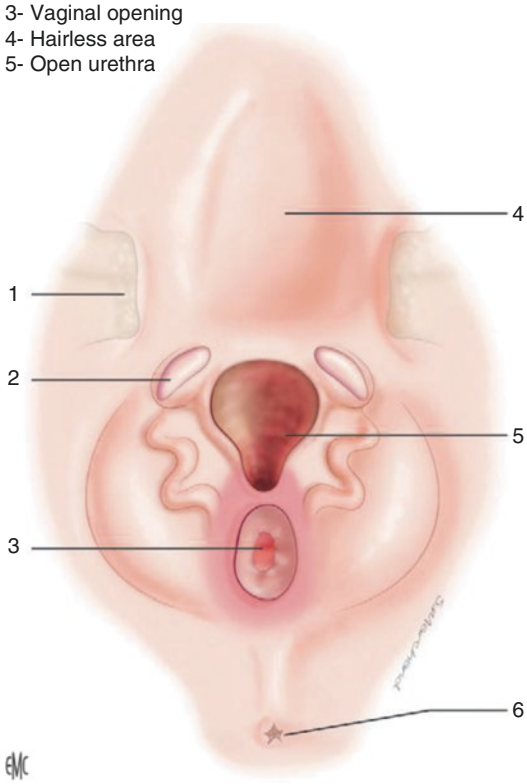


Fig. 33.5 Female epispadias. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

the medial edges of the straight muscles, the medial edges of each hemi-pubis until the pelvic floor is well exposed, the umbilicus and the peritoneum. The bladder cavity is then closed with a double layer of interrupted stitches down to the

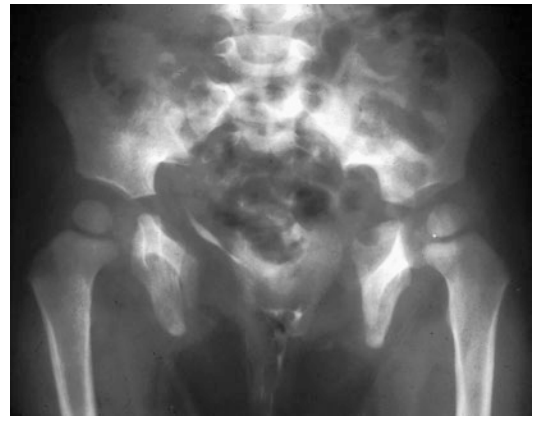


Fig. 33.6 Pelvic ring in an exstrophy with a significant gap between the two hemi-pubis

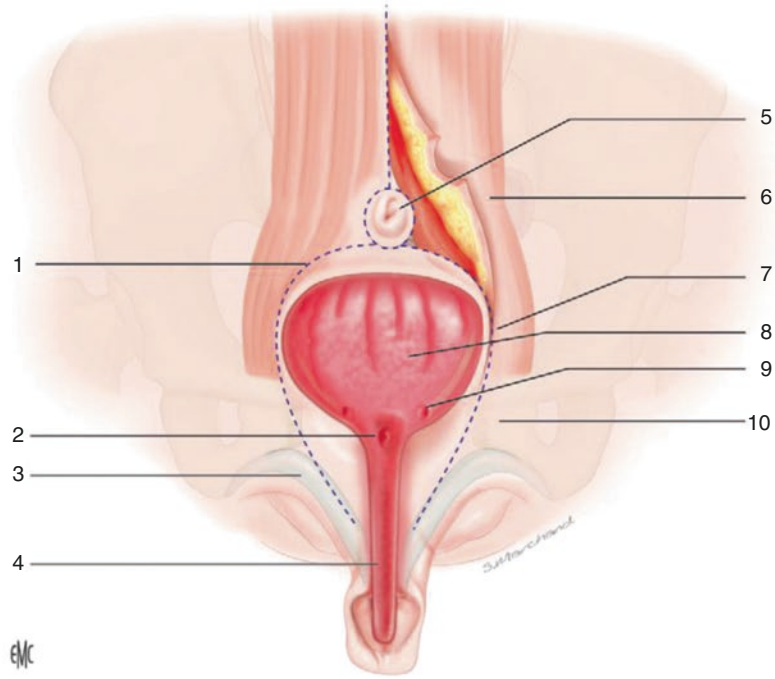
level of the bladder neck. The anterior muscular abdominal wall is closed and the two hemi-pubis sutured together with a strong stitch. This manoeuvre allows the relocation of the bladder and posterior urethra inside the pelvic ring. The pelvic bones are usually flexible enough soon after birth to allow the closure of the pelvic ring. Some still prefer to perform a pelvic osteotomy to facilitate the joining of the two hemi-pelvises without osteotomy. In the first days of life, posterior pelvic osteotomies allow the insertion of pins and external fixation as the bones are thicker posteriorly. Anterior oblique osteotomies are feasible although insertion of pins from the front is more difficult in the newborn. The Bryant traction is then preferred. The pros of neonatal osteotomy are the facilitation of the abdominal and pelvic ring closure by reducing the tensions on the wound. It also helps the relocation of the bladder and posterior urethra inside the pelvis. Furthermore, it makes post-operative nursing care much easier. It increases, however, the magnitude of the procedure and the morbidity in a period of life when the child loses weight and may be unfit for major surgery.

33.4.3 Surgery of the Epispadiac Genital Tubercle and Urethra (Figs. 33.10, 33.11, 33.12, 33.13, 33.14)

Surgical repair of these genital anomalies is usually performed during the first 2 years of life.

Surgical landmarks in the male exstrophy

1- Incision line around the bladder plate
2- Veru montanum
3- Corpus cavernosa
4- Dorsal urethral plate
5- Umbilicus
6- Rectus muscle
7- Medial edge of the rectus muscle
8- Bladder plate
9- Ureteric orifice
10- Pubic bone



Surgical landmarks in a female

1- Ureteric orifice
2- Incision lines
3- Midline incision
4- Umbilicus
5- Rectus muscle
6- Pubic bone
7- Hemi clitoris
8- Vaginal opening
9- Anus

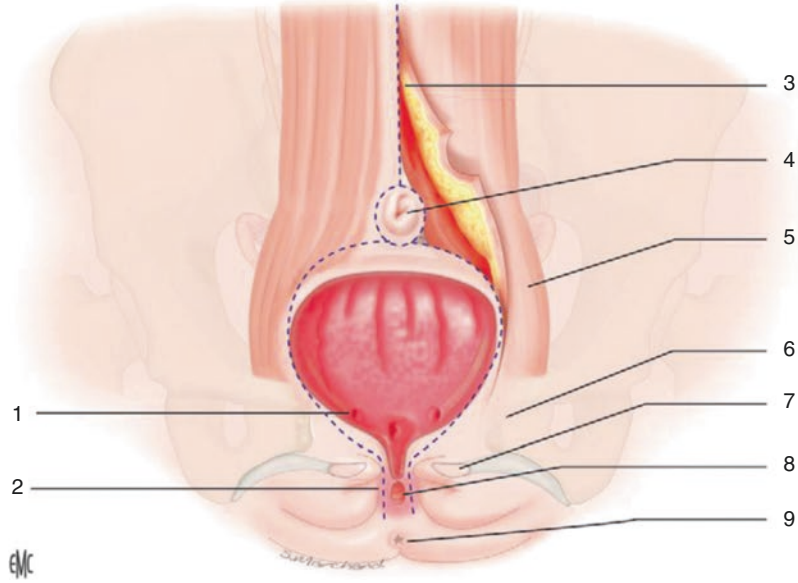


Fig. 33.7 Anatomical landmarks for bladder plate dissection in male and female exstrophies. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

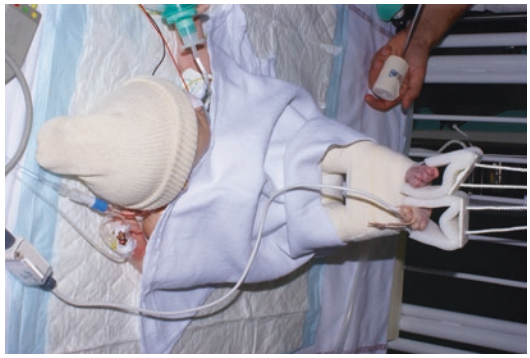


Fig. 33.8 Bryant traction

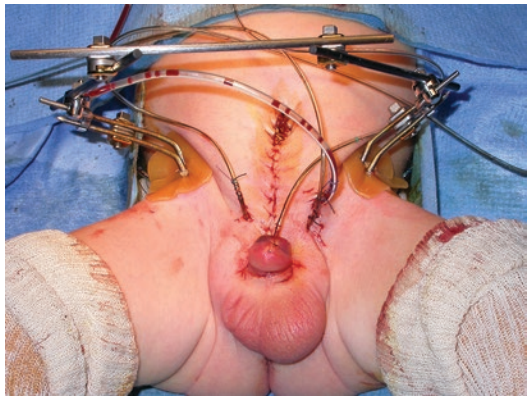


Fig. 33.9 External fixation after neonatal bladder closure

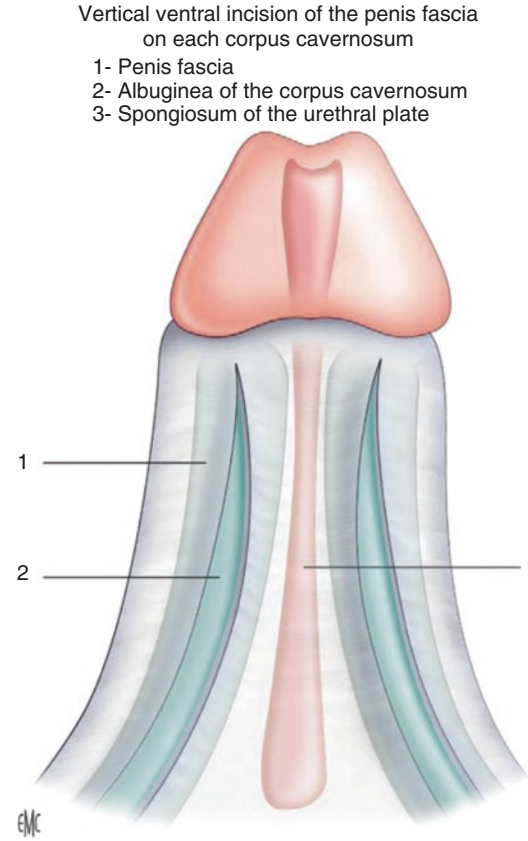


Fig. 33.10 Ventral approach of the corpora cavernosa. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

(a) In boys, the aims of this surgery are (1) to correct the dorsal curvature of the penis by de-rotating the corpora cavernosa to obtain a dangling penis, (2) to relocate the reconstructed urethra on the ventral side of the penis and (3) to redistribute the skin around the penis to compensate the dorsal skin defect. Although many procedures have been described over the years, the techniques of Ransley, Mitchell and Kelly are probably the most commonly used today. Preoperative androgen stimulation of the genital tubercle makes surgery easier.

- In Ransley's technique [28], the incision begins in the midline above the urethral opening and continues down on each side of the urethral plate (backed by the corpus spongiosum) and sweeps ventrally around the coronal sulcus separating the prepuce and ventral skin from the corpora. Once the ventral aspects of the corpora are fully exposed, the fascia covering each corpus is vertically opened along the entire ventral aspect of each corpus. This manoeuvre permits the exposure of the albuginea of each corpus. Dissection continues under the fascia around the albuginea of each corpus medially to separate the vascular tissues (spongiosum) leading to the urethral plate and externally to separate the wide strip of neurological fibres innervating the glans. Each neurovascular bundle and the urethral plate with its spongiosal tissue are then separated from adjacent structures. The urethral plate is tubularized, and a plasty (IPGAM = reverse MAGPI) of its distal end allows the ventralization of the future urethral meatus. The corpora are then de-rotated medially by approximately 90° and maintained in this new configuration by a proximal

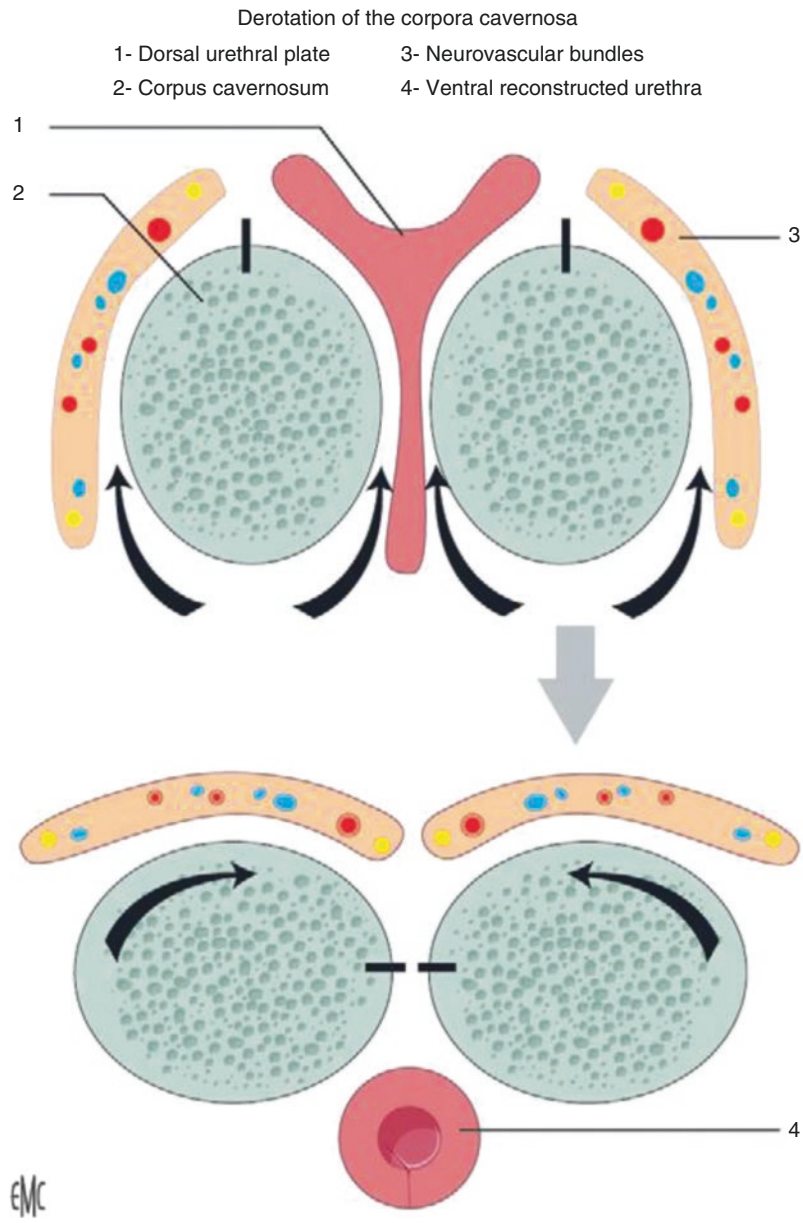


Fig. 33.11 Derotation of the corpora cavernosa. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

caverno-cavernostomy. This new anastomosis between the corpora keeps the urethra in its ventral position and gives the penis a dangling position when flaccid. The skin shaft is covered with a transverse flap of ventral skin dissected with its pedicle and transferred to the dorsal side of the penis (reverse Duckett).

- Mitchell's technique [29, 30] is based on a complete disassembly of the penile structures, which allows a tubularization and ventralization of the entire urethra, and a more complete release of the corporal rotation. The corpora cavernosa are completely separated from each other with their corresponding hemi-glans. The urethral plate is dissected off of the corporeal bodies respecting its blood supply coming from underneath. It is then tubularized and transferred ventrally. The corpora

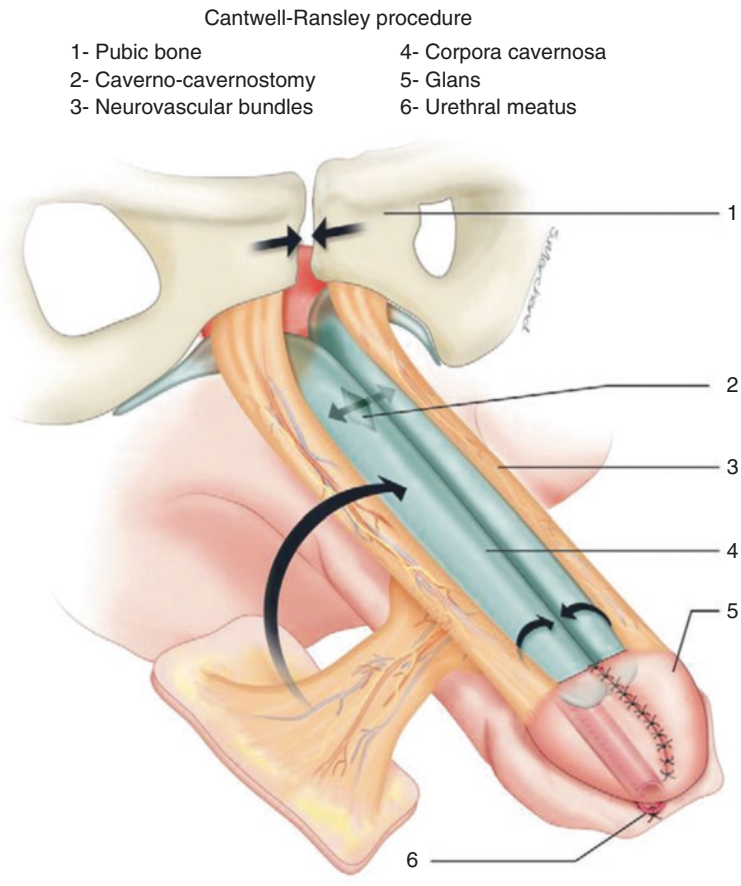


Fig. 33.12 Dérotation of the corpora and skin cover of the dorsum of the genital tubercle. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

entirely separated and independent are rotated to correct the dorsal chordee and sutured together. The glans halves are subsequently brought together.

- The Kelly procedure, or radical soft tissue mobilization, is used by some [31, 32]. The technique is described elsewhere [33] and may be a valuable alternative for primary or secondary penile reconstruction in EEC patients. The periosteum on the inner side of the ischium and pubis with the attachment of the sphincter muscles, the pudendal vessels and nerves are mobilized on both sides so that the outstretched muscles can help to reconstitute the membranous urethra without osteotomy. Others [34] have suggested a mobilization of the crura from the pubic rami to get more penile length without the complete Kelly mobilization.

(b) In girls, the open urethral plate extending from the bladder neck to the medial aspect of both hemi-clitoris anteriorly and to the anterior vaginal edge posteriorly is separated from the adjacent structures to the perineal muscles and subsequently tubularized. The triangular hairless area separating both hemi-pubes is excised. The perineal muscles located in front of and between the neo-urethral conduit and the vaginal orifice are both sutured together which significantly increases the bladder outlet resistance and provides social continence in most cases. A secondary plasty of the mons venus may be needed at puberty if the cosmetic appearance of this area remains unsatisfactory. It is recommended not to dissect and suture together both medial aspects of the two hemi-clitoris to avoid any damage of the clitoral sensitivity [35].

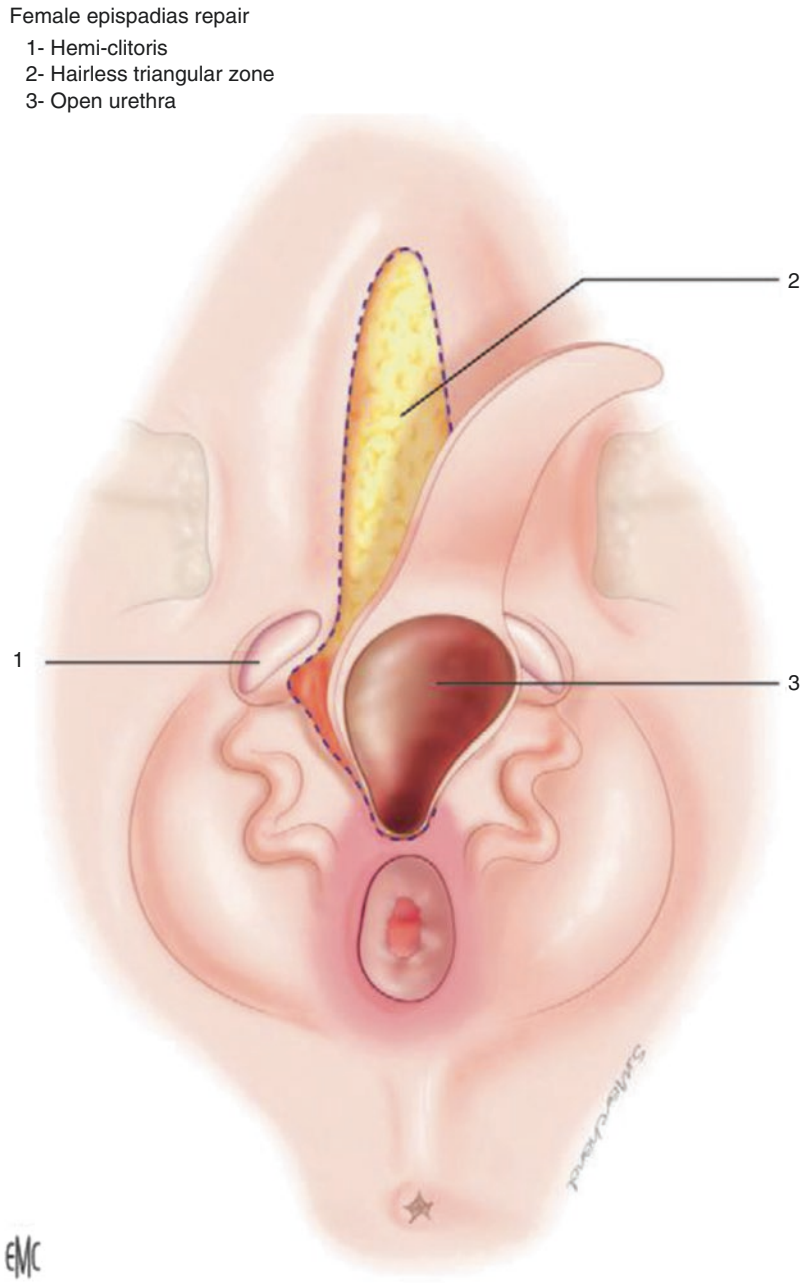


Fig. 33.13 Surgical landmarks in a female epispadias. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

33.4.4 Incontinence Surgery (Fig. 33.15a–c)

All procedures aim at increasing the bladder outlet resistance to achieve social dryness (>3 h) and allowing bladder emptying either via the reconstructed urethra or via a continent conduit (Mitrofanoff) [36]. Continence, which implies complex, coordinated active neuromuscular mechanisms, cannot be achieved by conventional surgery. Surgery can only create a sufficient static obstacle which, in the best cases, allows the child to hold urine for at least 3 h without significant leakage. This is dryness which implies passive mechanisms not always easily controllable.

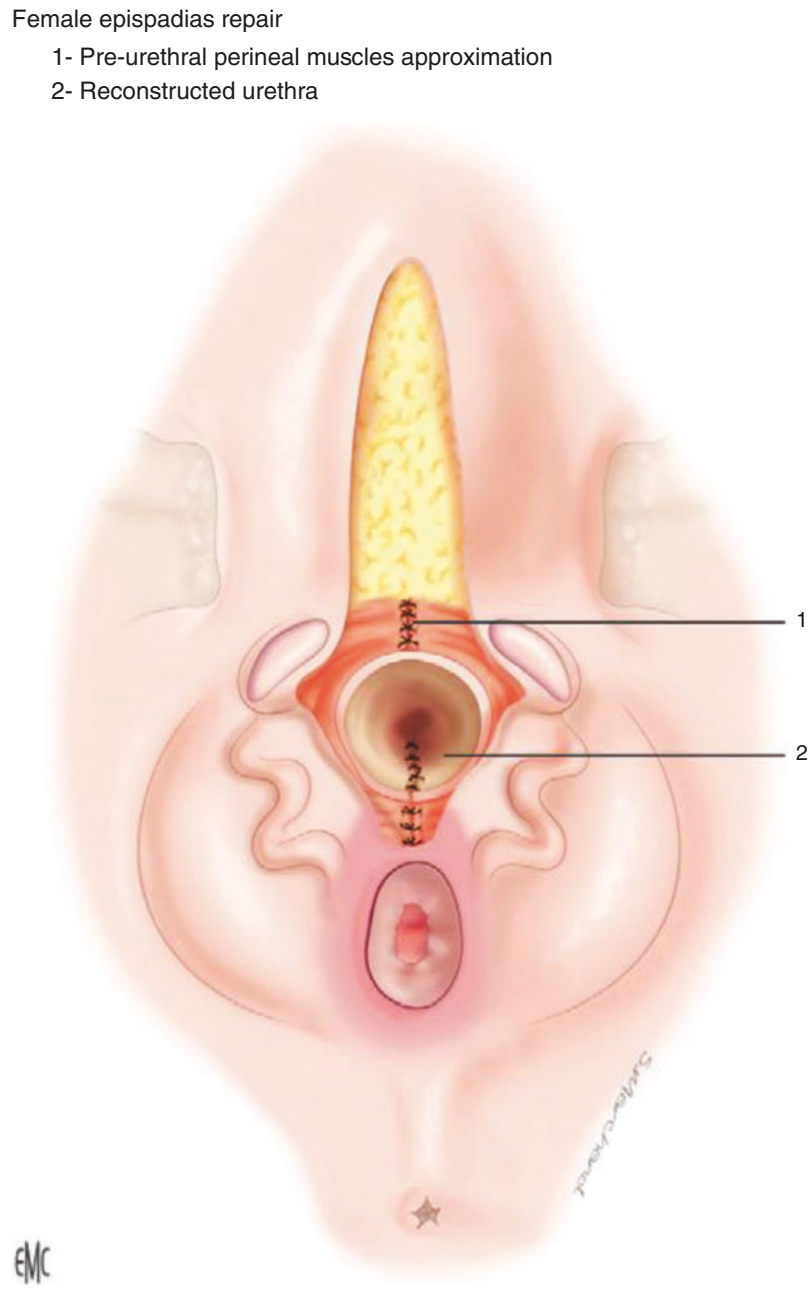
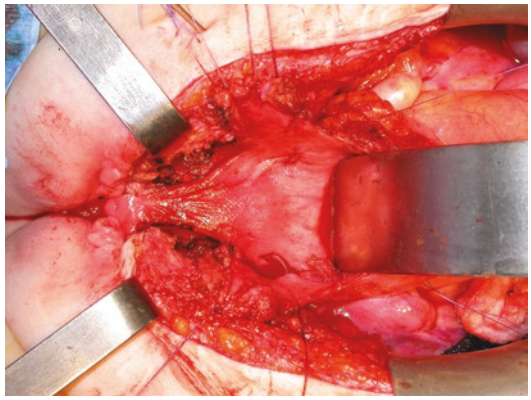


Fig. 33.14 Urethroplasty in a female epispadias. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

(a) The peri-cervical injection of biocompatible substance: It is the simplest option to increase the outlet resistance by injecting a bulking agent in the bladder neck region. Although not very invasive, this procedure provides disappointing results on a medium- and long-term basis. The most optimistic results [37] report 30–40% of dryness with several years of follow-up. Although immediate results can be encouraging, continuous deterioration with increased leakage is common. It has been demonstrated that the efficacy of bulking agents is much increased whilst used as a post-operative adjunct to bladder neck surgery than as an isolated treatment [38]. It does not seem that the type of bulking agents used makes much difference [39].



Bladder neck reconstruction
1- Triangular bladder flaps
2- Ureter
3- Reimplanted ureters (Jeffs technique)
4- Bladder reservoir

Bladder reconstruction 2
1- Mitrofanoff conduit
2- Lengthening of the urethra
3- Integration of the 2 triangular flaps into the bladder reservoir

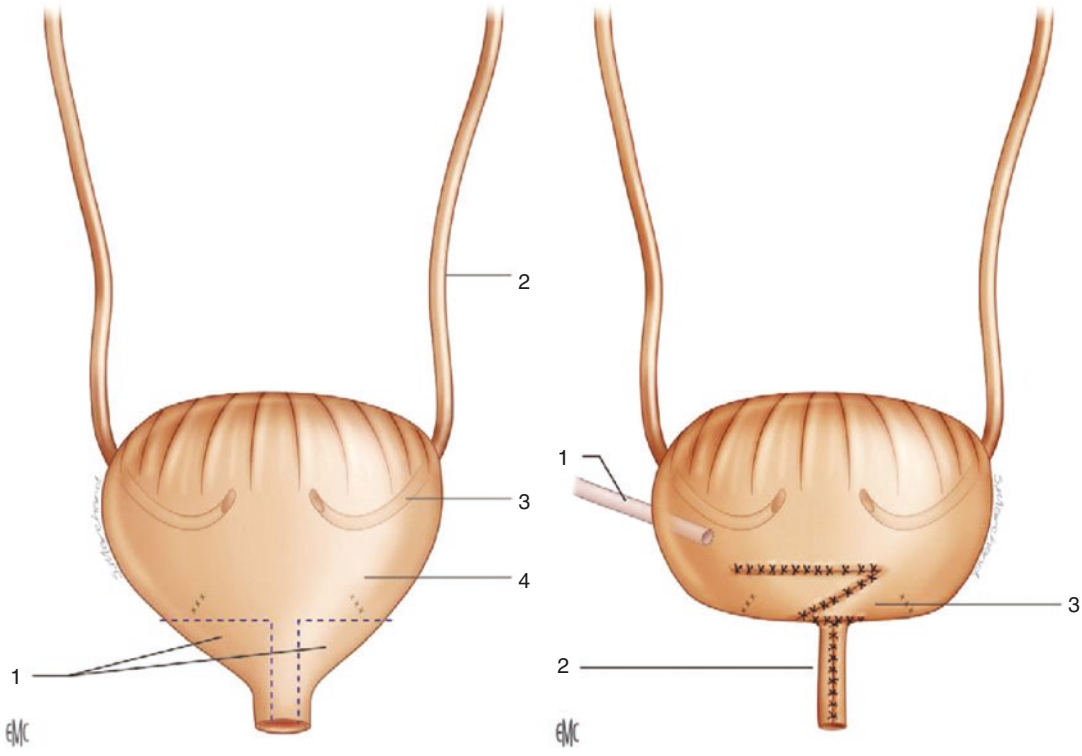


Fig. 33.15 Cervico-cystoplasty to increase bladder outlet resistance. Courtesy of: Mouriquand P., Vidal I. Complexe Exstrophie Epispade. Encyclopédie Médico-Chirurgicale—Urologie. Volume 18-208-A-10 2012. pp 1–18

(b) The cervicocystoplasty: This surgery is usually performed in incontinent epispadias after the age of 3 or 4 years when some collaboration between the child and the medical team can be established and when the bladder capacity is big enough (>80 mL). It is the most hazardous part of this reconstruction as it aims at increasing the bladder outlet resistance to achieve intervals of dryness of at least 3 h without compromising complete

bladder emptying and upper tract drainage. Experience shows that this challenge is rarely achieved in the exstrophy group although results are better in the epispadiac group as the bladder behaviour is probably more normal. The principle of bladder neck plasty is to narrow the bladder outlet and reintegrate the verumontanum inside the urethral lumen. Bladder neck tightness is achieved by creating a muscular muff which itself creates a static outlet resistance. Ureteric reimplantation is needed to prevent reflux which is almost constant once the bladder is closed and to create enough trigonal space to tighten the outlet. Bladder neck wrapping is based on the Young-Dees-Leadbetter procedure and its multiple variants. This technique often leads to "obstructive" micturition, i.e. high-pressure emptying which represents a threat for the bladder and the whole upper tracts. Trigonal dissection can also damage the genital tracts. These patients often have poor or retrograde ejaculations related to the deficient sphincteric area.

(c) The artificial urinary sphincter: Insertion of an artificial sphincter cuff around the EEC bladder neck has poor records although individual experience is always limited. There is a much higher risk of erosion in a reconstructed bladder neck and urethra [40, 41]. The artificial sphincter is therefore not a frontline solution in the EEC group although silicone sheath placement has been reported to facilitate the insertion of the cuff in selected patients [42, 43].

(d) The bladder neck closure: It is the ultimate solution when all others have failed. It is a difficult operation as all cervical tissues have been previously dissected and the separation of the trigone from the bladder neck region can be tricky. This procedure although quite successful in terms of dryness is irreversible and obviously implies a concomitant Mitrofanoff diversion [44].

(e) Complementary procedures: The unpredictable results of cervicocystoplasty often lead to a combined Mitrofanoff continent diversion which allows complete, regular and low-pressure bladder emptying [36]. If the bladder capacity does not increase after urethroplasty, it is sometime necessary to augment the bladder capacity with a bowel segment. Finally, most EEC bladders are associated with reflux, which is usually corrected at the time of the cervicocystoplasty. Urinary diversions towards the distal colon [45] and their variants (Mainz Pouch II) have the advantage of reducing the number of operations and achieving a reasonable level of continence although they expose patients to a high risk of severe retrograde urinary infection and bowel cancer [46]. Non-continent diversions (Bricker) are another ultimate option.

(f) Late procedures: Refashioning external genitalia and umbilicoplasty are often requested in the adolescent group of BEEC. The hairless triangle and the midline pubic depression are often the source of concerns. Rotation of hairy pubic flaps is then needed. Various techniques of umbilicoplasty have been published. We favour Ransley's technique which needs to be seen to be understood. Introitoplasty and treatment of uterine prolapse are also common and challenging procedures in female adolescents. Anchoring the uterus to the sacrum often fails, and radical surgery is sometimes needed after pregnancies. Finally, phalloplasty is the ultimate option in case of complete penile failure. This complex procedure should be performed in identified centres.

(g) In cloacal exstrophy, procedures are similar although most patients require an intestinal diversion from birth to separate the urinary and intestinal compartments.

33.5 Complete Primary Repair of Exstrophy (CPRE)

Begun in 1989 by the Seattle group [47–49], a complete primary repair is based on early, one-step treatment with or without pelvic osteotomy with a primary goal of achieving early bladder outlet resistance and bladder growth, thus

avoiding the need for bladder neck reconstruction. The surgery is performed either within the first 3 days of life or between 6 and 8 weeks of life and combines primary abdominal wall and bladder closure with epispadias repair and partial tightening of the bladder neck. The most common indication for delayed surgery is to allow for the growth of the small bladder plate, followed by delayed referral [50]. This technique may decrease the morbidity associated with multiple operations and stimulate early bladder growth. Many children however require surgery for resulting hypospadias, persistent vesicoureteral reflux, incontinence or failed primary closure [51–54]. Wound dehiscence, bladder prolapse, vesicocutaneous fistula and loss of penile tissue are associated with CPRE [55, 56]. Ultimately 74% of patients in the Seattle group achieved social dryness; however, a disappointing 80% of boys and 57% of girls required subsequent bladder neck repair [53]. More promising results from Gargollo et al. report the need for bladder neck repair after primary closure in only 43% of boys and 27% of girls [54]. However, long-term urinary continence with CPRE may be similar to staged repair of bladder exstrophy [53]. The need for neonatal osteotomy is independent of the surgical approach, although a single-institution experience demonstrated a feasibility of primary closure without osteotomy with successfully closure in 95% of cases [57].

33.6 Results

33.6.1 Cosmetic

Reported results are usually better in the epispadiac group compared to the exstrophy group and better in girls than in boys. Cosmetically, the outcome is satisfactory in girls although complementary surgery of the mons venus may be requested at puberty. The repaired epispadiac penis is often short and broad with better result in isolated epispadias compared to the exstrophy group. Undoubtedly the Cantwell-Ransley penile repair has been a major step forward not only in the surgical outcome but also in the understanding of this condition [58–62]. The Mitchell penile disassembly [29, 30, 47, 63, 64] provides equivalent results with possibly a higher risk of glans or hemi-glans necrosis. The Kelly procedure has strong supporters who have a solid experience of this difficult dissection associated with a significant risk of penile loss [32, 65]. Skin coverage of the reconstructed epispadiac penis aims at transferring the ventral skin to the dorsum. The postoperative cosmetic appearance may often be disappointing with a penis which often looks small and buried. Attempts to improve this have been reported [66].

33.6.2 Dryness

Functionally the primary reconstruction of the urethra in both sexes is an essential first step which allows the bladder to grow. Social dryness is defined variably in the literature, although a gap of 3 h of dryness is a generally accepted standard [67]. In the Baltimore group [68], social dryness was achieved in approximately 75% of their exstrophy females compared to 87.5% of dry patients 15 years earlier. Our long-term results [69], those from the Indianapolis group [70] and others [71] clearly showed a long-term deterioration of dryness as well as serious complications related to “obstructive” micturition (infections, stones, bladder perforation, upper tract dilatation) mostly in the exstrophy group. In our own series of 25 incontinent epispadias, dryness was achieved day and night in 28%, day only >3 h in 24%, between 1 and 3 h 16% and less than 1 h in 8%. These results were better in this group than in the exstrophy group (80 patients) where only 45% presented with a dry interval of >3 h with transurethral voiding. Complications related to “obstructive micturition” and other complications were also significant with 48% of recurrent urinary tract infections (vs. 65% in the exstrophy group), 8% of stone (vs. 24%), 20% of upper urinary tract dilatation (vs. 26%), 4% of bladder perforation (vs. 16%) and one patient with adenocarcinoma in both groups [69]. Simplification of the technique of bladder neck plasty has been reported [72]. The key issue is the

growth of the bladder after increasing the outlet resistance. The epispadiac bladder has a much safer behaviour and therefore a better dryness outcome than the exstrophy bladder, which is essentially abnormal [73]. The role of endoscopic injection remains uncertain as published series are short, retrospective and often mix neurological bladder and EEC. It might be helpful to treat partial urinary incontinence and to help bladder growth. Small group studies show promising results after the use of bHCG stimulation test preoperatively as a prognostic indicator with significantly improved continence scores after a 4-year follow-up [74]. Redo bladder neck is an even greater challenge with little success in our series [58, 69] leading to other technical adjustments [75] using bladder neck wraparound.

33.6.3 Psychosexual

Sexual and psychological dysfunctions are significantly high in the BEEC patients with a lesser degree in the pure epispadiac group. Female patients probably have a better adjustment to this handicap than males whose repaired penis is often short and broad with preserved erections but poor ejaculations [76–80].

33.7 Conclusion

BEEC is a complex and rare malformation requiring a very challenging surgical reconstruction to achieve acceptable cosmetic and functional results. Its rarity implies that these patients should be referred to a limited number of expert centres for management. Current management of epispadias usually starts with a urethral reconstruction to increase the outlet resistance and to let the bladder grow. In some cases (mainly in girls), this sole procedure may be sufficient to achieve social dryness. If not, an attempt to use injections of bulking agents around the bladder neck might be temporarily helpful. On a long-term basis, cervicocystoplasty associated with anti-reflux surgery is the classical approach knowing that the outcome of this surgery is unpredictable with a significant morbidity. Bladder neck closure is the ultimate solution especially in boys despite long-term complications. Outcomes in adolescents and adults and large series are lacking which should encourage prospective multicentric studies.

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Prune-Belly Syndrome

34

Mario Messina, Francesco Molinaro, and Rossella Angotti

34.1 Definition

The term *prune-belly syndrome* (PBS) was coined in 1901 by William Osier because of the wrinkled appearance of the abdominal wall in affected patients. Prune-belly syndrome also is known as the triad syndrome, because it has three major manifestations and Eagle-Barrett syndrome. It is a rare congenital disorder characterized by three major features: deficient abdominal wall musculature, urinary tract anomalies, and bilateral cryptorchidism in males [1].

34.2 Epidemiology

PBS occurs mostly in boys (>95%) and its annual incidence is estimated between 1/30,000 and 1/50,000 live births. Females constitute about 3–5% of known cases [2].

34.3 Pathophysiology

The exact pathogenesis of PBS is not clearly known as yet. Many theories have been proposed, but none of them have universal acceptance because none completely explains the whole constellation of findings in the syndrome. The impossibility to test these theories, furthermore, due to the absence of experimental model contributes to consider them only conjectures [3–10].

Three major theories are known:

1. Fetal outlet obstruction: This theory has been proposed by Strumme in 1903. Urinary dilatation and atrophy of abdominal wall are considered as final result of early in utero posterior urethral obstruction that produces a significant back pressure at a critical time during development.
2. Theory of mesodermal arrest: This theory suggests that the etiology of prune-belly syndrome is a primary defect of lateral plate mesoderm. This is the precursor of the ureters, bladder, prostate, urethra, and gubernaculum [13, 14]. Nevertheless, the mesodermal arrest theory does not explain the male predominance of the syndrome. It also fails to explain the myriad associated anomalies and the presence of the abdominal wall abnormalities with a normal urinary tract.
3. A yolk sac defect: This has been proposed by Stephens. It is based on an error in embryogenesis of the yolk sac and allantois. This theory postulates that the yolk sac does not resorb. The abdomen closes around it, leaving the abdominal musculature highly redundant.

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34.4 Genetic [11–13]

No specific gene defect has been identified for PBS to date, even if the high male-to-female ratio, the occasional occurrence in male siblings and cousins, and the increased occurrence in twins suggest a genetic basis. Most cases are sporadic and have a normal karyotype. Some patients have chromosomal abnormalities, including Turner's syndrome and trisomies 13 and 18. The consensus, however, remains that an associated chromosomal abnormality is the exception rather than the rule [3].

34.5 Clinical Features [1, 3]

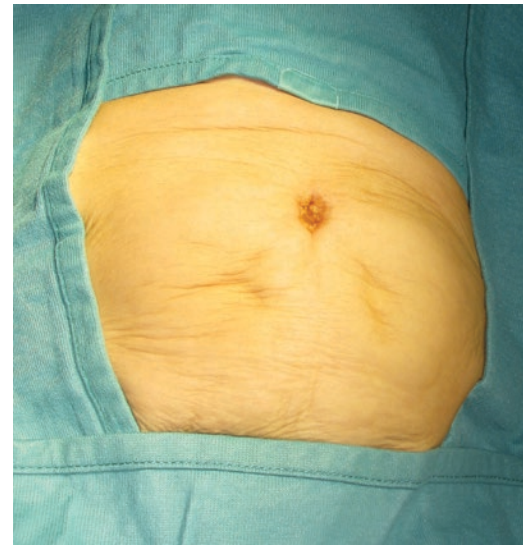

Fig. 34.1 Abdominal wall in prune-belly syndrome

- *Abdominal Wall*
- The deficiency of abdominal wall muscles can be partial or complete. The abdominal wall is lax, thin, and protuberant (Fig. 34.1). It may be associated with flaring rib margins, depressed lower sternum, and kyphoscoliosis in severe cases. The skin is wrinkly until older age when it can often become smoother. Absence and muscular hypoplasia especially in the lower and central areas are the main histological features of the abdominal wall. Which is the clinical effect of all these characteristics of the abdominal wall? Firstly, cough mechanism in many of these children is ineffective, exposing them to recurrent respiratory infections and worsening their pulmonary condition; secondly, the absence of Valsalva maneuver contributes to the ineffective function of the bladder and the small intestine.
- *Urinary Tract*
  Urinary tract, in terms of upper and lower urinary tract, is all involved in many ways.
  – *Renal:* Renal dysplasia and hydronephrosis are common characteristics.
    The involvement of kidneys varies widely from normality and dysplasia. Prognosis is directly related to renal function and the degree of renal dysplasia. The renal dysplasia is found in more than half of patients and it is a major determinant of patients' prognosis. The degree of dysplasia may also vary greatly from side to side in the same patient.
  – *Ureter*s: The ureters are typically dilated, elongated, and tortuous. The lower third of the ureter is more affected than the proximal portion. Their radiographic aspect is hallmark of the syndrome. Hydroureteronephrosis, usually nonobstructive, is not correlated with the degree of renal dysplasia. Their architecture of walls is dysmorphic and their peristalsis is poor and ineffective. Vesicoureteral reflux involves up to 85% of patients with PBS. Its degree can be difficult to establish by the conventional system of grading due to dysmorphism of the ureter, renal pelvis, and calices. Histologic examination of the ureter shows a profound subverted architecture at level of the ureteral wall that contributes to the poor ureteral peristalsis. The dilatation and reduced peristalsis of the ureters interfere with the output of the bladder, cause a urinary stasis, and increase the risk of urinary infection that represents the greatest threat to the renal parenchyma.
  – *Bladder*: Megacystis is typical of patients with PBS. The bladder is usually enlarged, with a thick and smooth wall, not

trabeculated; the dome is elongated similar to a large diverticulum consisting of the urachal remnant and giving the bladder an hourglass configuration. A patent urachus can be present, especially in association with urethral anomalies (atresia or microurethra). The ureteral orifices are often lateral, dilated, and out of the trigone explaining the presence of massive reflux. Histologic examination of the bladder demonstrates an alteration in the ratio of connective tissue to smooth muscle causing a poor contractility even if the involvement of the bladder is less than the ureter following in a good compliance.

– *Urethra*: The known anomalies of the anterior urethra range from urethral atresia to megalourethra. Urethral atresia, stenosis, or microurethra is present in cases with poor prognosis, and survival of these patients is related to the presence of a patent urachus.

Megalourethra may be scaphoid or fusiform. The fusiform megalourethra, accompanied by deficient corpora cavernosa, is a more severe defect frequently associated with renal dysplasia and lethal anomalies. Scaphoid megalourethra is characterized as a deficiency of the corpus spongiosum with normal glans and fossa navicularis. The aspect of VCUG like heart is typical. Urethral obstructions at the level of verumontanum are present up to 50% of patients (posterior urethral valves in 10% of cases).

- *Testis, Epididymis, Seminal Vesicles, Prostate, and Vas Deferens*

Undescended testis is a needful feature in PBS. As other mesenchyme-derived genitourinary organs, also epididymis, seminal vesicles, and vas deferens can be involved in terms of anomalies in PBS. All of these findings contribute to the known infertility associated with prune belly syndrome. Testicles are usually intra-abdominal, sited at the level of internal inguinal ring, with increased risk of malignant degeneration. Gonads are small with short vessels. The gubernaculum is usually attached proximally to the tail of the epididymis, travels via the inguinal canal, and attaches distally at the pubic tubercle. Discontinuity between the ductuli efferentes and rete testis and between the body of the epididymis and testis is common. The vas deferens is thickened and may drain ectopically. The seminal vesicles may be dilated, atretic, or absent. Verumontanum is small or absent and reflux into the vas deferens can be present. Prostate is hypoplastic and it is one of the etiologies of infertility in this syndrome.

34.6 Associated Anomalies [1, 3, 14]

Patients with prune belly syndrome are often affected from many associated conditions that influence their prognosis determining a long-term morbidity in 75% of them and mortality. Multidisciplinary approach is often mandatory to care of these patients. Many associated anomalies are known in patients with PBS as it is reported in Table 34.1.

Table 34.1 Associated anomalies with percentage of incidence [1]

Cardiac	10%	Patent ductus arteriosus, atrial septal defect, ventricular septal defect, tetralogy of Fallot
Gastrointestinal	30%	Malrotation, intestinal atresia, intestinal stenosis, volvulus, anorectal agenesis, imperforate anus, omphalocele, gastroschisis, hepatobiliary anomalies, acquired megacolon
Orthopedic	45–60%	Congenital dislocation of hips, chest wall deformity: pectus excavatum Pectus carinatum, scoliosis, genu valgum, talipes equinovarus, severe leg maldevelopment: arthrogryposis
Pulmonary	50%	Pulmonary hypoplasia, pneumothorax, pneumomediastinum, lobar atelectasis, pneumonia, chronic bronchitis

34.7 Spectrum of Disease [1, 15, 16]

Based on the many anomalies present in PBS, it is understandable that there is a wide spectrum of clinical presentations. Classification systems based on this clinical spectrum have been formulated by numerous authors, and all take into consideration initial and subsequent renal function. Three major categories of presentation in the neonatal period were described by Woodard as it is reported in Table 34.2.

Category I includes patients with the most severe form of the prune belly syndrome. Oligohydramnios, pulmonary hypoplasia or pneumothorax, and several renal dysplasia are present. Urethral obstruction or atresia, which represents the lethal form of PBS, may be present. Patients of this category usually die in the few days after birth due to pulmonary complications.

Category II includes babies without pulmonary hypoplasia but with renal dysplasia of different grades. They usually have no immediate problems with survival.

Category III patients, who are the majority of patients with PBS, have the typical external abdominal features and undescended testes, but pulmonary and renal functions are preserved despite the markedly dilated urinary tracts.

Table 34.2 Categories of presentation in the neonatal period described by Woodard

Category classification	Clinical features
I	Oligohydramnios, pulmonary hypoplasia, or pneumothorax. May have urethral obstruction or patent urachus and clubfoot
II	Typical external features. Uropathy of the full-blown syndrome but no immediate problem with survival. May have mild or unilateral renal dysplasia. May or may not develop urosepsis or gradual azotemia
III	External features may be mild or incomplete. Uropathy less severe. Stable renal function

Each of them includes specific clinical features and different postnatal management and prognosis [1]

34.8 Pseudoprune Syndrome

The term "pseudoprune" has been suggested to define females and males, who do not have all features of prune belly syndrome (incomplete syndrome).

Incomplete Syndrome

Abdominal wall features usually lack in the incomplete syndrome, but the common uropathy and cryptorchidism are present. Many of these patients risk to develop a renal failure probably because of the delay of diagnosis. Some of them may present as late as adulthood with symptoms of renal failure and hypertension. For these reasons, they require close observation, careful monitoring, and specific interventions [17].

Female Syndrome

Three to five percent of PBS patients are female; most of them have the abdominal wall deficiency and the abnormal urinary tract, but it is known also the association between typical abdominal wall deficit and a normal urinary tract. They are often affected by omphalocele and bladder outlet obstructive lesions [18].

34.9 Investigations

34.9.1 Prenatal

Prenatal diagnosis of prune belly syndrome can be made from 11 weeks of gestation on ultrasound. Ultrasonic diagnostic accuracy varies from 30% to 85%. The importance of prenatal diagnosis is related to the possibility to make an in utero treatment known as the vesicoamniotic shunt procedure. Sonographic findings include oligohydramnios or anhydramnios, hydroureter, a distended bladder, and a thin, attenuated abdominal wall. Megacystis megaureter syndrome, megacystis-microcolon-intestinal hypoperistalsis syndrome, vesicoureteral reflux, or posterior urethral valves may have similar findings in fetal ultrasonogram. Although modern ultrasonic capabilities and visualization have improved, it can still be difficult to establish a definite prenatal diagnosis.

Vesicoamniotic shunt: A double pigtail catheter is inserted percutaneously via trochar and

positioned to drain urine from the obstructed fetal bladder into the amniotic fluid.

It is clear that this intervention can be made only in specific cases (normal karyotype, severe oligohydramnios, and predicted good renal function) [19–26].

34.9.2 Postnatal

The phenotype of patients with PBS is typical, and physical examination at birth doesn't leave little doubt regardless of prenatal suspicion. A multidisciplinary team must take care of the patient. The major initial concern is the management of cardiac and respiratory issues. An immediate chest X-ray needs to exclude common associated pulmonary abnormalities such as pneumothorax, pneumomediastinum, and pulmonary hypoplasia, which often occur as a result of oligohydramnios. A renal ultrasound must be done to have informations on the state of kidneys in terms of cortical thickness, the presence of cystic changes, the renal size, and the degree of urinary tract dilation.

Serial urinalysis and urine cultures are extremely important.

A voiding cystourethrogram (VCUG) must be performed to show the presence of vesicoureteral reflux (85% of patients with PBS) and to assess the bladder emptying (Fig. 34.2). After initial evaluation, a technetium 99m (99mTc) diethylenetriaminepentaacetic acid (DTPA) renal scan and a mercaptoacetyltriglycine (MAG3) renal scan can be made to give functional and anatomic informations. It is performed at 4–6 weeks of age to prevent difficulties in interpretation due to transitional neonatal physiology.

Urethrocystoscopy for evaluation of the urethral pathoanatomy may be performed. Serial creatinine measurements are mandatory.

Although an initial creatinine determination is important in establishing a baseline, it is known that its level at birth reflects maternal renal function. The trend in creatinine levels over the course of the early postnatal days or weeks is much more predictive of long-term renal function. A progressive increase of serum creatinine over the first few weeks of life is related to a poor prognosis. If after 48–72 h the serum creatinine is >1.0 mg/dL in the term infant or 1.5 mg/dL in the preterm infant, a degree of renal insufficiency can be diagnosed. If initial creatinine's value is <0.7 mg/dL, a subsequent renal failure is improbable. The serum and

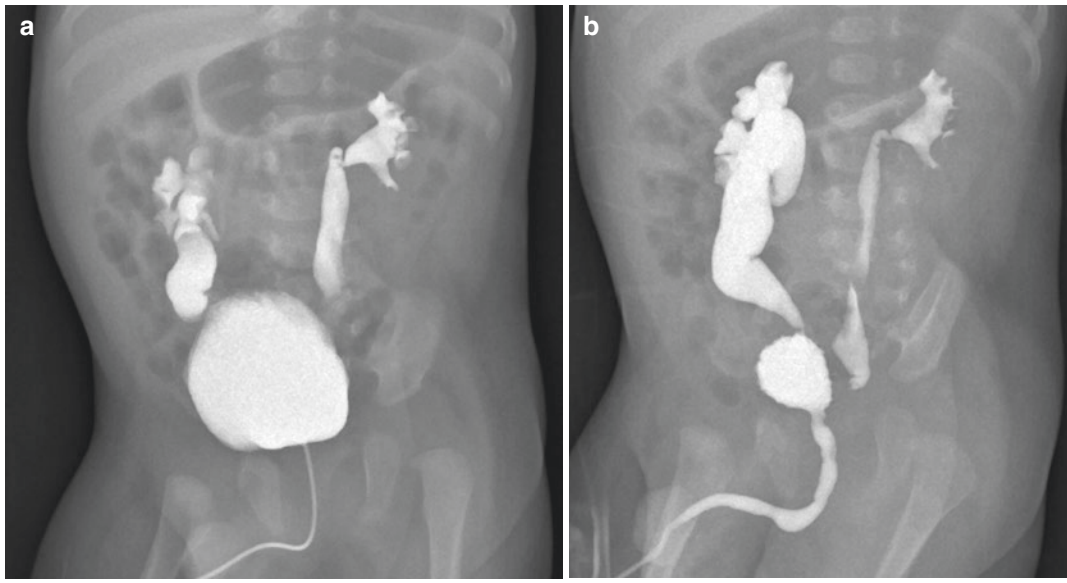

Fig. 34.2 VCUG showing bilateral high-grade reflux in both passive (**a**) and active (**b**) phases

urinary electrolyte levels and analysis of serum blood urea nitrogen (BUN) are useful to assess for the potential systemic acidosis and electrolyte imbalances that may be seen in renal insufficiency. Finally, the glomerular filtration rate (GFR) is initially low in the premature and full-term infant and then rapidly increases. This is an important consideration before performing exam with administration of intravenous contrast agents, which can cause elevated plasma osmolality, causing intraventricular hemorrhage as well as further impairment of renal function. Specific exams based on associated malformations of patients are useful in the initial diagnosis of patients. Finally, ultrasound of the heart and abdominal and chest radiographs should be obtained [1, 3].

34.10 Management

The main goal of treatment of patients with PBS is to preserve renal function. The prognosis and the postnatal management of these patients, indeed, are closely related to it. The spectrum of therapeutic possibilities range from a "wait and see" approach to immediate or delayed urologic surgery. It should be emphasized that surgery in these infants should not be undertaken unless expert anesthesiology and medical support are available and the surgeon has extensive experience doing such surgery. Furthermore, aggressive approach must be considered with caution because the surgery is difficult and the patients are vulnerable to pulmonary complications.

The neonates requiring an early surgical intervention are few. They are patients with bladder outlet obstruction, who usually die in the immediate postnatal period due to pulmonary complications (category I). The vesicostomy or cutaneous pyelostomy is needed in these cases to provide an immediate urinary drainage. Surgical approach, nevertheless, doesn't modify their poor long-term survival due to severe underlying renal dysplasia. Patients with different renal dysplasia grades but without pulmonary hypoplasia (category II) are managed with antibiotic prophylaxis at birth, urinary diversion if necessary to ensure a valid urinary drainage, and delayed surgical reconstruction, at 3 months of age or more, according to pulmonary maturation. Patients with preserved renal function (category III) are usually managed by conservative approach. Antibiotic prophylaxis is usually recommended to avoid urinary infections. Regular monitoring of urinary tract dilation (ultrasonography) and renal function (serum creatinine measurements) must be planned. Urologic surgery is not usually necessary and it should be reserved for those patients who have repeated urinary infections. These patients benefit from early orchidopexy and abdominoplasty [3, 16].

34.11 Surgical Management [1, 3]

Surgical management of children with PBS includes three different possibilities: urological surgery, abdominal wall reconstruction, and orchidopexy.

1. *Urological surgery* consists in two different options: temporary urinary diversion and urinary tract reconstruction
   (a) *Temporary urinary diversion* usually is not indicated. It can be necessary, as a temporary measure to decompress the entire urinary tract for children with a documented site of obstruction. Cutaneous vesicostomy usually is the procedure of choice and it can be performed in intensive care. The Blocksom technique as modified by Duckett [27] is most commonly method used to create a generous stoma and prevent stomal stenosis. A short transverse incision, halfway between the umbilicus and symphysis pubis, is made. After dissection of the peritoneum from the dome of the bladder, a small circular hole in the bladder dome posteriorly is performed. This is important to minimize the risk of prolapse of the posterior bladder wall through the stoma, resulting in obstruction. Quadrant sutures are placed between the anterior rectus sheath of the anterior abdominal wall and the bladder

adjacent to the vesicostomy. The lateral edges of the rectus sheath are closed with interrupted absorbable sutures. An 18- to 24-Fr Foley catheter is introduced into the bladder via the vesicostomy and should remain in situ for a few days postoperatively to minimize the risk of prolapse or stenosis. Thereafter the vesicostomy should be left to drain freely into the child's nappy/diaper. If a large urachal diverticulum is encountered during creation of the vesicostomy, it can be excised. Rarely it is indicated a more proximal diversion like as cutaneous pyeloplasty that it is chosen. The proximal ureterostomy is usually avoided because it provides to worst upper tract drainage and sacrifices a normal proximal ureter that might be useful in later reconstruction.

(b) *Urinary tract reconstruction* is generally performed in cases of progressive or severe hydronephrosis, recurrent upper tract infections, and worsening renal function. Timing is quite controversial. Some experts advocate immediate reconstruction, believing that it reduces the risk of infection and progressive renal failure. Other experts recommend nonoperative management because urinary tract function often improves with age. However, extensive reconstructive surgery is not recommended before the age of 3–6 months [1, 3].

- *Ureteral remodeling*: Ureteral tailoring and reimplantation are usually undertaken. The goal of ureteral remodeling is to preserve the upper few centimeters of proximal ureter for reconstruction. Meticulous ureteral dissection is needed. The distal, redundant, and ectatic ureter is excised, and common ureteral tailoring techniques are used to decrease the size of the ureter. Ureteral reimplantation into the abnormal and floppy bladder can be difficult because the creation of a submucosal tunnel is challenging [28].
- *Internal urethrotomy* should be considered in the older patient with a true anatomic obstruction of the urethra. However, it is known that it is the second choice after considering intermittent catheterization if the urodynamic criteria of outlet obstruction are not present [29, 30]. Endoscopic urethrotomy by hot or cold knife is usually performed with careful avoidance of the urinary sphincter.
- *Anterior urethral reconstruction*: Prune belly syndrome is associated with microurethra and megalourethra. Progressive dilatation of the urethra can be used. If the anterior urethra is not usable, urethroplasty techniques combining skin flaps and grafts are necessary to bridge the anterior urethral defect. Megalourethra can be repaired by application of hypospadias operative techniques [3, 31, 32].
- *Reduction cystoplasty*: Poor contractibility and inefficient voiding are typical aspects of the bladder in PBS. Reduction cystoplasty is performed to reduce volume and improve emptying. A variety of techniques have been proposed, from simple excision of the urachal diverticulum to the excision of redundant mucosa with the creation of overlapping flaps to improve contractibility. Reduction cystoplasty should be done only to remove the larger urachal diverticulum or as part of a more extensive internal reconstruction. Intermittent catheterization through the urethra or through an appendicovesicostomy channel is likely to afford better long-term bladder emptying and reduction of residual urinary volumes [33–35].

2. *Abdominal wall reconstruction*

Despite the mild degrees of abdominal wall laxity which can mature, the potential psychological crippling justifies the abdominal wall reconstruction.

In addition to the cosmetic benefit, however, it is known also its role in improvement of bladder, bowel, and pulmonary function.

The timing of abdominal wall reconstruction should be dictated by the need for other surgical interventions. If upper tract remodeling is not anticipated, then the abdominal wall can be addressed at any time. Between many described techniques of abdominoplasty in patients with PBS, Monfort technique collects to date general consensus because it recognizes the best functional and cosmetic results [35–40].

After estimation of the amount of redundant abdominal wall, an elliptical incision that extends from the tip of the xiphoid to the pubis is done. A second incision is made around the umbilicus to preserve it in situ.

The skin and subcutaneous tissue are separated from the attenuated fascia and muscle, extending the dissection laterally to the anterior axillary line. Vertical fascial incisions are made lateral to the superior epigastric arteries, leaving a central fascial bridge. With this approach the exposure of the urinary tract or abdominal testes is perfect, and intra-abdominal surgery can be done.

The lateral fascia is then advanced over the central fascial bridge from both sides, alleviating the redundancy and increasing the thickness of the abdominal wall. A recent modification of the Monfort technique uses laparoscopy approach.

3. *Orchidopexy* [41–48]

The early orchidopexy is mandatory in patients with PBS to permit a regular examination of testes in relation to potential risk of testicular carcinoma and to ensure normal hormonal function at puberty. These reasons justify early surgery although the fertility potential of the PBS patient is known to be compromised. Transabdominal bilateral orchidopexy at about 6 months of age is currently considered the approach of choice. This approach is often used in conjunction with other abdominal surgeries, such as vesicostomy, urinary tract reconstruction, or abdominal wall reconstruction. In the absence of need for other abdominal surgeries, this procedure can be accomplished laparoscopically.

Orchidopexy in older children frequently requires division of the spermatic vessels that can be obtained with many techniques as Fowler-Stephens orchidopexy, staged Fowler-Stephens orchidopexy, and microvascular autotransplantation.

34.12 Long-Term Outcomes [49, 50]

Prognosis of a child with prune belly syndrome is directly related to renal function and the degree of renal dysplasia. Despite known management of renal dysplasia, approximately 30% of patients presenting with impaired renal function at initial evaluation will develop chronic renal failure during childhood or in their adolescent years. When the deterioration of kidneys develops in young age, peritoneal dialysis often can be used temporarily until the child is of adequate size to accept a transplant.

A normal growth and a normal pattern of secondary sexual development can be expected in most of the patients. Infertility of these patients is known. Many factors contribute to its etiology as anatomical elements (prostatic hypoplasia; lack of continuity between the ductuli efferentes and rete testis; abnormally thickened vas deferens and ectopic drainage; atretic, absent, or dilated seminal vesicles; intra-abdominal location of the testes) and retrograde ejaculation related to an open bladder neck and hypoplastic prostate. However, fertility with assisted reproductive techniques may be feasible in those who have had successful early orchidopexy. The overall outlook for the PBS patient, both for survival and for quality of life, has improved considerably, largely in the last years. The key to management is individualization of timing of care. Long-term follow-up about the urinary tract is essential, because it can change over time.

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Part VII

Tumors

Neuroblastoma in Neonates

35

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In neonatal period, tumours, although very rare, represent an important cause of morbidity and mortality. The prevalence of neoplasms, within the first month after birth, occurs once in every 12,500–27,500 live births, and malignant tumours develop in approximately 40–50% of them. Diagnosis often occur during prenatal screening or during follow-up for a known cancer predisposition syndrome; in fact the presence of congenital anomalies, multifocal or bilateral diseases and cancer in close relatives is suggestive for an underlying cancer predisposition syndrome, and genetic counselling and testing should be considered to investigate these possibilities.

Neonatal tumours differ from cancer in older children because they arise generally from embryonic and immature tissue due to intrinsic dysfunction of cellular growth and proliferation; for these reasons incidence, genetic, histological features, clinical behaviour and treatment are different in neonates. In newborn, benign tumours and masses could have malignant potential if untreated; nevertheless different tumours, with malignant histological features, have a benign clinical behaviour, or on the contrary certain malignant tumours could regress in neonates without treatment.

Management of malignancy in newborn combines the expertise of paediatric surgeons to paediatric medical oncologists because it represents a difficult challenge due to vulnerability of this period which is characterized by rapid growth of cells and tissues and a haematopoietic and immune system not fully developed.

In neonatal solid tumours, surgery plays a central role in diagnosis and treatment. Chemotherapy is administered balancing the treatment most indicated with the risk of irreversible damage to the rapidly growing organs; drug doses should be calculated according to body weight than surface area and started at reduced levels and increased as well tolerated. The radiation instead is avoided due to risk of irreversible damage of growth organs and tissues and the risk of secondary malignancies [1–3].

35.1 Introduction and Epidemiology

Neuroblastoma occurs frequently in newborn and represents the most common tumour diagnosed in neonatal period, accounting for 7–8 cases per million per year, with an incidence rate

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almost double that of leukaemia, the next most prevalent malignancy occurring during the first year of life [4].

This neoplasm originates from neural crest cells that will give rise to the development of the peripheral sympathetic nervous system. The adrenal gland was the most common primary tumour site, occurring in almost 50% of neuroblastoma cases, followed by connective tissue, the retroperitoneum and the mediastinum [4]. Different cases have been detected during prenatal screening, and some of these patients, together with those diagnosed in the first years of life, have been observed to undergo spontaneous regression even if metastatic [5].

35.2 Genetic and Risk Factors

Neuroblastoma arising in neonatal period suggests a need to investigate exposure events before conception and during gestation. Different studies correlate neuroblastoma with maternal alcohol and tobacco use during pregnancy [6], preconception parental occupation and prenatal exposure to drugs (e.g. codeine, oral contraceptives, anticonvulsant drugs) [7], ambient air toxics [8] or maternal folate deficiency [9].

Most neuroblastoma occurs sporadically but inheritance should be considered in newborn. Germ line mutations in ALK and PHOX2B are the most frequent genes involved in hereditary neuroblastoma which is occurring in neonates [10].

ALK, the anaplastic lymphoma kinase gene, has been recently identified as the first neuroblastoma-predisposing gene. ALK is a transmembrane receptor tyrosine kinase frequently expressed in the central and peripheral nervous system [11]. We can find ALK mutation in up to 10% of sporadic neuroblastomas and in many other neoplasm-like small-cell lung cancers and anaplastic large-cell lymphomas, and for these reasons, it represents an attractive therapeutic target [12].

PHOX2B is a gene involved in normal sympathetic neuronal development and catecholamine synthesis. Germ line mutations were identified first in patients with congenital central hypoventilation syndrome (CCHS). In many cases Hirschsprung's disease is associated with CCHS because of migration failure of neural crest cell in the gut wall. PHOX2B mutations were found also in families with neuroblastoma in which were identified these other conditions [13].

Neuroblastoma is also present in other cancer predisposition syndromes like NF-1 (*von* Recklinghausen disease) because both disorders result from defective development of the neural crest cells [14].

If we consider the pathogenesis of tumour disease in the context of the embryonic development of the neural crest, we can understand how the clinical and pathological heterogeneity of neuroblastoma derives from alterations of molecular drivers which guide these cells during the different maturation stages. Many genetic features of neuroblastomas have now been identified, which configure different subtypes of these tumours with distinct genetic abnormalities and clinical behaviour [14].

MYCN amplification: Amplification of the *MYCN* oncogene at 2p24 occurs in about 20% of all neuroblastomas, and of these, 90% are associated with poor clinical outcomes [15]. In neonatal period *MYCN* amplification represents an adverse prognostic factor, and treatment should be intensified [5].

Allelic loss of 1p: Loss of heterozygosity of 1p occurs in up to 35% of neuroblastoma and correlates with *MYCN* amplification and advanced disease stage independently of age and stage [16, 17].

Unbalanced 17q gain: This is the most frequent genetic abnormality in neuroblastoma, occurring in up to 70% tumours [18].

Allelic loss/imbalance of 11q: Those genetic abnormalities are reported in 40% of neuroblastomas, and they are prognostic factors associated with poor outcomes in patients affected by neuroblastoma and without *MYCN* amplification.

DNA index/ploidy: Hyperdiploid and near-triploid neuroblastomas showed a better outcome compared to diploid neuroblastomas, this latter being associated to rapid tumour progression and a poor prognosis even in

infants and patients with lower stages of disease [5, 14].

35.3 Pathology

Neuroblastoma generally is defined as lobulated masses intimately related to the adrenal gland or sympathetic chain delimited by delicate, membranous capsule covering soft, fleshy, grey, partially haemorrhagic tumour. Two main cell populations are frequently recognized at microscopic exam: neuroblastic/ganglion cells and Schwannian stroma cells which different percentage defines four groups of neuroblastic tumours which are characterized by favourable or unfavourable prognosis:

- Neuroblastoma (Schwannian stroma-poor)
- Ganglioneuroblastoma, intermixed (Schwannian stroma-rich)
- Ganglioneuroma (Schwannian stroma-dominant)
- Ganglioneuroblastoma, nodular (composite Schwannian stroma-rich/stroma-dominant and stroma-poor [19]

Neuroblastic tumours such as ganglioneuroblastomas and ganglioneuromas are rare entity in newborn because maturation process needs month to years to occur [5].

35.4 Clinical Features

Foetal neuroblastoma can be detected during screening in the third trimester, when an adrenal mass with solid or cystic characteristics and foci of calcification could be seen at ultrasound. The differential diagnosis includes adrenal haemorrhages, enteric duplication cysts, subdiaphragmatic extralobar pulmonary sequestration, adrenal cytomegaly, adrenocortical tumours, adrenal abscess and neuroblastoma.

Clinical features of neuroblastoma in children can be due to tumour primary localization along the sympathetic chain. Frequently neuroblastoma could be detected in the adrenal glands, paravertebral retroperitoneum, posterior mediastinum, pelvic and neck. Neonatal neuroblastoma occurs more frequently along thoracic and cervical tracts than the older children; abdominal mass is often the more frequent clinical features; pelvic tumours could alter bowel and bladder habit. Flaccid leg paralysis, associated or not with the bladder and bowel dysfunction, and Horner's syndrome occur due to compression of the spinal cord and neck sympathetic chain, respectively [5].

In 42% of neonates, neuroblastoma could occur as a localized primary tumour associated with multiple metastases which are limited to the skin, liver and/or bone marrow. Subcutaneous nodules (bluish and blanching with a 'blueberry muffin' appearance) and a rapidly enlarging and diffusely involved liver, which may cause respiratory compromise, renal impairment, bowel dysfunction and coagulopathy, represent the clinical features of neuroblastoma stage 4s/Ms [5, 20].

Paraneoplastic syndromes can occur also in neonates; opsoclonus-myoclonus syndrome known as dancing eyes syndrome accounts for 2–3% of all neuroblastoma with a median age of presentation of 18–22 months [21]. Vasoactive intestinal peptide syndrome (VIP) known as 'Kerner-Morrison' syndrome is characterized nevertheless by intractable secretary diarrhoea [22].

35.5 Diagnosis

Ultrasound scanning is the first approach in a neonate with an abdominal mass. MRI is the gold standard to evaluate paravertebral and pelvic tumours, and it is preferred than CT to avoid the risk association with radiation exposure. Urinary catecholamines like homovanillic acid (HVA) and vanillylmandelic acid (VMA) are raised generally in >90% of children affected by neuroblastomas, but only 33% of neonates have shown that increasing. Full blood count, biochemistry and lactate dehydrogenase levels (LDH) in serum could be administered, but the evaluations of LDH, ferritin and NSE are only markers of tumour bulk but not specific to neuroblastoma [5].

^{123}I-meta-iodo benzyl guanidine (^{123}I-mIBG) scintigraphy is highly sensitive and specific to neuroblastoma; it is important not only to resolve differential diagnosis but also to evaluate metastases and then treatment response [23]. Frequently perinatal neuroblastomas are mIBG avid [5].

According to the International Neuroblastoma Staging System (INSS) guidelines, a diagnosis of neuroblastoma is established if either of the following sets of criteria are met:

- Unequivocal pathological diagnosis made from tumour tissue and immunohistology and raised urine catecholamines. If histology is equivocal, genetics may help.
- Bone marrow aspirate or trephine biopsy contains unequivocal tumour cells, e.g. syncytia or immunocytological clumps of cells, *and* increased levels of urine catecholamines [24].

35.6 Prognostic Factors and Risk Stratification

The new International Neuroblastoma Risk Group stratification is based on prognosis, but clinical behaviour, histological features and genetic abnormalities play also an important role to define the different three risk groups. The clinical features include the degree of resectability of

Image-defined risk factors in neuroblastic tumours [25]	
Ipsilateral tumour extension within two body compartments	• Neck-chest • Chest-abdomen • Abdomen-pelvis
Neck	• Tumour encasing the carotid and/or vertebral artery and/or internal jugular vein • Tumour extending to base of the skull • Tumour compressing the trachea
Cervico-thoracic junction	• Tumour encasing brachial plexus roots • Tumour encasing subclavian vessels and/or the vertebral and/or carotid artery • Tumour compressing the trachea
Thorax	• Tumour encasing the aorta and/or major branches • Tumour compressing the trachea and/or principal bronchi • Lower mediastinal tumour, infiltrating the costovertebral junction between T9 and T12
Thoraco-abdominal	• Tumour encasing the aorta and/or vena cava
Abdomen/pelvis	• Tumour infiltrating the porta hepatis and/or the hepatoduodenal ligament • Tumour encasing branches of the superior mesenteric artery at the mesenteric root • Tumour encasing the origin of the coeliac axis and/or of the superior mesenteric artery • Tumour invading one or both renal pedicles • Tumour encasing the aorta and/or vena cava • Tumour encasing the iliac vessels • Pelvic tumour crossing the sciatic notch
Intraspinal tumour extension whatever the location provided that:	• More than one third of the spinal canal in the axial plane are invaded, and/or the perimedullary leptomeningeal spaces are not visible, and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/ structures	• Pericardium • Diaphragm • Kidney • Liver • Duodeno-pancreatic block and mesentery
Conditions to be recorded but not considered IDRFs	• Multifocal primary tumours • Pleural effusion, with or without malignant cells • Ascites, with or without malignant cells

the tumour as determined by its radiological appearance on MRI or CT.

This replaced the old international neuroblastoma staging system with L1 (stages 1 and 2) which includes localized tumours that do not involve vital structures as defined by the list of IDRF, L2 (stage 3) which includes locoregional tumours with one or more IDRFs, M (stage 4) which includes tumours with distant metastatic disease and Ms (stage 4s) metastatic disease in patients younger than 18 months with metastases confined to the skin, liver and/or bone marrow [25].

International Neuroblastoma Risk Group (INRG) Staging System [22]

Stage	Description
L1	Localized tumour noninvolving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Local regional tumour with the presence of one or more image-defined risk factors
M2	Distant metastatic disease
MS	Metastatic disease in children <18 month with metastases confirmed to the skin, liver and/or bone marrow

35.7 Therapeutic Management

35.7.1 Low Risk

Low-risk category includes approximately 70% of neonatal neuroblastomas which have an excellent 5-year survival accounting for 95–100%. Surgery alone is indicated for all localized, resectable (L1) tumours. In tumours which are not resectable or biopsy is not feasible is indicated a follow-up with MRI because some of these have a good chance to regress. Chemotherapy based on carboplatin administration is indicated in case of unresectable tumour (L2), stage 4s (Ms) or M (without bone, lung or CNS metastases) associated with clinical behaviour, e.g. due to spinal cord compression. In asymptomatic Ms patients without SCAs in fact, there is a high percentage of patient with spontaneous regression and a low risk of recurrence, and no treatment is needed.

35.7.2 Intermediate Risk

This risk group accounted for 20% of patients affected by neuroblastoma and includes M infants <12 months (with bone/lung/CNS metastases without *MYCN* amplification) who have a 2-year overall survival of 95% with modest treatment in confront of older children with a poor outcome who needed a more intensive treatment. Chemotherapy in these patients based on carboplatin associated with doxorubicin administration.

Surgical role in intermediate-risk patients is to obtain the most complete tumour resection when feasible taking in count the preservation of full organ and neurologic function. This may lead frequently to leave residual disease adherent to critical anatomic structures.

Radiation was administered in selected cases with infants with 4s disease and respiratory insufficiency or patients with epidural disease and symptoms of spinal cord compression.

35.7.3 High Risk

High-risk groups account for approximately 50% of all neuroblastoma but only around 5% in neonates who obtained only 30% 2-year overall survival despite intensive multimodal therapy.

SIOPEN HR-NBL-1 is a European trial which included infants <12 months with *MYCN*-amplified disease, and this shall comprise:

- Induction chemotherapy – multi-agent cisplatin-based dose-intensified chemotherapy
- Surgical resection of primary tumour
- Myeloablative therapy and autologous stem cell rescue
- Radiotherapy to site of primary tumour
- 13-*cis*-retinoic acid + anti-GD_2 immunotherapy (± IL-2)

Despite the uncertainty of the role of surgery, the COG high-risk protocol currently recommends attempting gross total resection of the primary tumour and locoregional disease in patients with high-risk neuroblastoma [2, 23].

35.8 Surgery of Neonatal Neuroblastoma

Surgical approach will depend upon the location of the primary tumour. The majority of primary tumours occur in adrenal glands (90%) followed by the sympathetic chains of the posterior mediastinum.

35.8.1 Primary Tumour from Adrenal Gland

The access is a long transverse supraumbilical incision; the peritoneum is entered (Fig. 35.1). The colon is mobilized medially incising the attachments to the lateral abdominal wall.

35.8.2 Right Adrenal Gland (Fig. 35.2)

The duodenum and the head of the pancreas are mobilized and retracted medially; the arterial blood supply usually comes from vessels from the right renal artery, aorta and diaphragmatic vessels; venous drainage is directed to the inferior vena cava. So the blood supply and venous drainage are severed (Fig. 35.3), and the dissection of the tumour is completed.

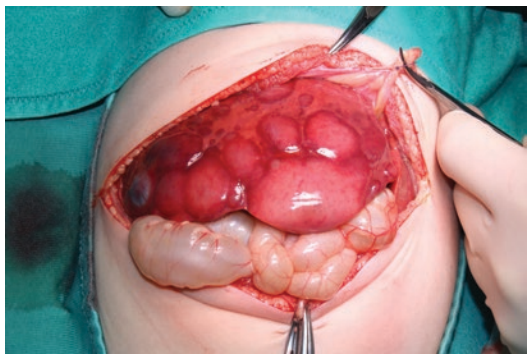

Fig. 35.1 Once the peritoneum is opened, tumour dissemination to the liver is clear in a 4s stage neuroblastoma

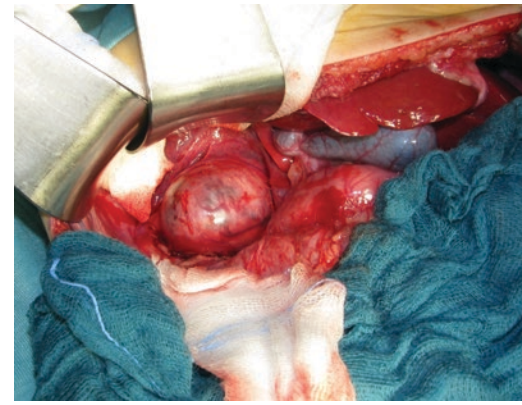

Fig. 35.2 Neuroblastoma arising from right adrenal gland

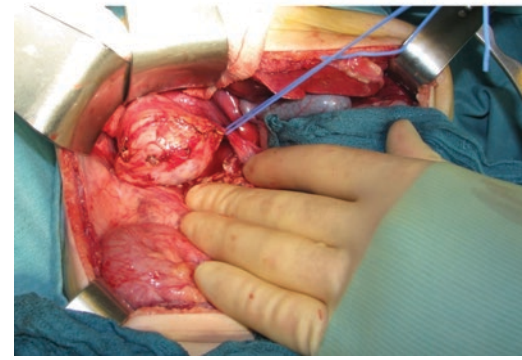

Fig. 35.3 The blood supply of the tumour is controlled

35.8.3 Left Adrenal Gland

The spleen, pancreas and stomach should be reflected to expose a left-side tumour; the arterial blood supply usually comes from vessels from descending aorta; the venous drainage is directed into the left renal vein and subdiaphragmatic vessels. So the blood supply and venous drainage are controlled (Fig. 35.4), and the dissection of the tumour is completed.

35.8.4 Mediastinal Neuroblastoma (Fig. 35.5)

The access is a posterolateral thoracotomy incision; the parietal pleura that covers the tumour is

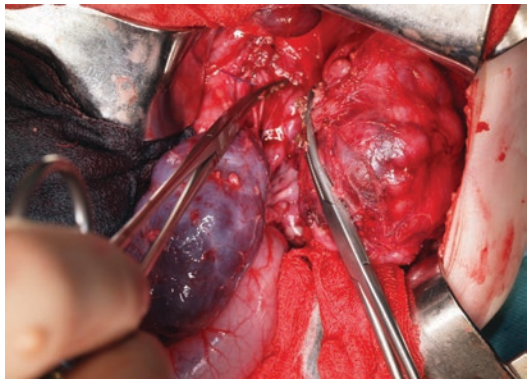

Fig. 35.4 Neuroblastoma arising from a left adrenal gland and the vascular control of the mass

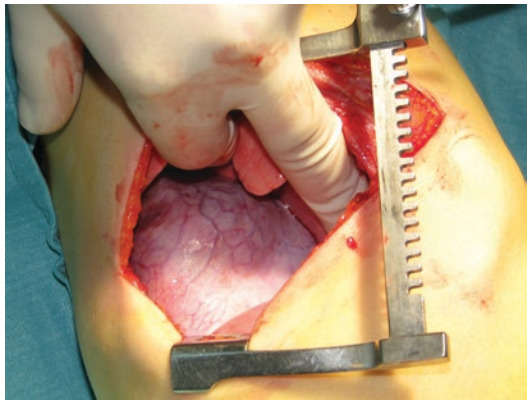

Fig. 35.5 Mediastinal neuroblastoma

incised, and the tumour is mobilized from the ribs. Vascular supply and drainage come from intercostal vessels that are identified and ligated. The tumour is then mobilized and retracted anteriorly exposing the intervertebral extension. Mediastinal neuroblastoma often extends into the intervertebral foramina. Leaving small remnants of residual tumour in the intervertebral foramina does not influence the outcome [5, 26].

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Hepatic Tumours

36

Matteo Carella, Riccardo Masetti, Claudio Antonellini, Beatrice Randi, and Andrea Pession

Liver tumours account for only 5% of all tumours in prenatal and neonatal period [1]. They include a variety of benign and malignant neoplasms with a different distribution than in older children (Table 36.1). The most common are vascular neoplasm, of which infantile haemangioendothelioma and cavernous haemangioma are the most frequently types, and embryonal hepatic cell tumours such as hepatoblastoma. Mesenchymal hamartomas and germ cell tumours can occur very rarely, and the differential diagnosis of these tumours could be very difficult.

Many of these are diagnosed during prenatal screening or in the first few weeks of life. Ultrasound is the first exam which may be administered because it can often give information on the type of neoplasm encountered. Staging and other important considerations need a computed tomography (CT) scan or a magnetic resonance imaging (MRI), which is preferred in neonatal period. Scintigraphy and vascular contrast imaging may be necessary to diagnosis or planning therapy in specific cases. Blood count, liver functionality parameters, infectious serology and the tumour markers such as alpha-fetoprotein (AFP), beta-human chorionic gonadotrophin (beta-HCG), lactate dehydrogenase and markers for neuroblastoma (catecholamine metabolites, neuron-specific enolase) may be essential to differential diagnosis. Neonates with hepatic neoplasm often have a clinical behaviour, and laboratory tests which are not conclusive and imaging results can be misleading, and for these reasons biopsy and histological exam may be necessary to correct diagnosis [2].

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36.1 Vascular Neoplasm

The most common hepatic tumours during neonatal period are vascular neoplasm such as hemangioendothelioma which occur more frequently in the newborn. These tumours are often diagnosed during prenatal US scan, or commonest are incidental findings in the first weeks of life. The pathogenesis of these vascular lesions is currently unclear. In 50% of cases, multiple haemangiomas on the skin and in other organs have been reported, and in a few cases, it could occur in associations with omphalocele and other congenital malformations.

Infantile haemangioendothelioma could present abdominal distension and hepatomegaly which could be complicated by severe arteriovenous

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Table 36.1 Malignant/benign tumours and tumour-like lesions in newborn

Malignant	Benign
Hepatoblastoma	Infantile haemangioendothelioma/cavernous
Hepatocellular carcinoma	Mesenchymal hamartoma
Rhabdoid tumour	Teratoma
Yolk-sac tumour	Adenoma
Choriocarcinoma	Focal nodular hyperplasia
Undifferentiated sarcoma	Hepatic cysts
Rhabdomyosarcoma	Liver abscess
	Inflammatory pseudotumour

shunting with congestive heart failure, haemodynamic anaemia, thrombocytopenia, coagulopathy, rupture with intraperitoneal haemorrhage and respiratory distress. Rapid growth or multiple lesions could deter a life-threatening status which develops in the first life weeks or sometimes even during the foetal period with a clinical behaviour characterized by hydrops fetalis and intrauterine heart failure.

Management of haemangioendotheliomas and haemangiomas is based on their clinical feature. Follow-up is recommended for asymptomatic lesions; if patient shows a gradual onset of controllable symptoms, medical treatment should be considered; digitalis and diuretics are administered for congestive heart failure, whereas administration of blood products may be considered to correct anaemia and coagulopathy. Steroid therapy is also recommended (PDN 2–5 mg/kg/day) but often is not succesful [3]. Treatment with alpha-2A-interferon can be more effective, but this is associated with potentially severe side effects [4]. In case of rapid onset of severe symptoms, resection should be considered when technically feasible, but in case of a large diffusion of haemangioendotheliomas in the hepatic tissue, hepatic arterial ligation or radiological embolization should be preferred. Surgery in 80% of patients is successful; however, in a few cases, the development of new vessels could be seen within days from first surgery [5].

36.2 Hepatoblastoma

Hepatoblastoma is the most common liver tumour of early childhood and in 10% of cases occurs during the neonatal period [2]. This neoplasm is often sporadic, and the most frequent genetic abnormalities associated to hepatoblastoma were founded in genes involved in the Wnt signalling pathway. Sometimes hepatoblastoma is associated with genetic anomalies like trisomy 18/Edward's syndrome and cancer predisposition syndromes like Beckwith–Wiedemann syndrome, familial adenomatous polyposis coli and foetal alcohol syndrome [6]. Extremely premature neonates have an increased risk to develop hepatoblastoma [7, 8].

Hepatoblastoma is characterized by malignant epithelial cells with variable differentiation, most often with embryonal or foetal characteristics. Mixed hepatoblastomas are a variant which is characterized by the presence of malignant mesenchymal tissue with immature fibrous areas, spindle cells and cartilage-like osteoid. In neonates, the relatively differentiated, pure foetal histology seems to predominate compared with older children [9].

Hepatoblastomas can be detected prenatally by US screening and may cause polyhydramnios and stillbirth. Clinical behaviour may also differ: metastases, which are often systemic, arise earlier and bypass lung because of differences in the foetal circulation [9]. Tumour rupture with massive haemorrhage is a possible life-threatening event in neonates. High values should be compared to normal ones for the age because AFP is still high in this period of life compared to older children [5].

Tumour biopsy may be performed, but different studies confirm that it may not be necessary for children aged less than 3 years with a very high AFP level.

SIOPEL (Société Internationale d'oncologie Pédiatrique) configures a pretreatment staging system, called PRETEXT, based on the anatomy of the liver and the radiological findings at diag-

nosis; therefore, staging of the tumour should include chest and brain CT.

In the PRETEXT system, the liver is divided into four sectors: an anterior and a posterior sector on the right and a medial and lateral sector on the left. In this way, four PRETEXT categories are identified (I–IV). The development of the disease beyond the liver is indicated using the following letters: "V" if the tumour extends into the vena cava and/or all three hepatic veins, "P" if the main and/or both left and right branches of the portal vein are involved by the tumour, "C" if there is involvement of the caudate lobe, "E" if there is evidence of extrahepatic intraabdominal disease and "M" if there are distant metastases [10, 11].

The risk stratification system proposed by the Children's Hepatic tumors International Collaboration includes PRETEXT staging system, patients age and AFP level serum.

Clinically relevant histologic subtypes are also being incorporated into risk stratification; in fact the Children's Oncology Group (COG) reported that complete tumour resection (stage I) associated with pure foetal histology configures excellent outcome; different studies confirm therefore that HBL patients presenting with low AFP levels (<100 ng/mL) and/or with undifferentiated histology have a poor outcome [12–14].

Surgery plays a central role in the treatment; standard−/low-risk patients in fact can safely undergo complete surgical resection associated or not to neoadjuvant chemotherapy. Cisplatin and doxorubicin are used in different regimens, which may reduce some extensive hepatoblastoma to an operable size. Liver transplant could be considered in absence of metastases that configure patients with very high-risk hepatoblastoma if present. These patients with unresectable liver tumours can undergo mastectomy associated to chemotherapy. The Japanese Study Group for Paediatric Liver Tumour showed that TACE (Transarterial chemoembolization) with cisplatin or anthracyclines could represent an important option of treatment in patient with PRETEXT IV non-metastatic tumour because of its equivalence and less toxicity in comparison with systemic chemotherapy [14, 15].

Generally in children affected by hepatoblastoma, the 3-year EFS and OS (event-free survival and oculus sinister) are similar between standard, intermediate and low-risk patients, estimated at 80–90% in all groups of patients. Patients with poor prognosis (high-risk tumours) were treated by COG and SIOPEL with increased dosages of platinum-based therapy which reported an improvement of their survival [8]. The SIOPEL 4 study, using a weekly administration of cisplatin as intravenous infusion in 24 h associated with monthly doxorubicin, reported an overall and event-free survival at 3 years for patients with PRETEXT IV tumours by approximately 83% and 76%, respectively. Patients with lung metastases nevertheless have an EFS and OS at 3 years by approximately 79% and 77% [16]. A retrospective review reported that the outcome in neonates affected by congenital hepatoblastoma is much better than those which were diagnosed at an older age [17].

36.3 Surgery of Hepatic Neonatal Tumours

Surgical treatment of a neonatal **haemangioendothelioma** is required if the newborn is still symptomatic (significant haemodynamic shunting) despite the medical therapy (corticosteroids, digoxin, diuretics, beta-blockade).

The surgical treatment includes the following:

- The hepatic artery ligation (the haemangioendothelioma becomes ischaemic because it is usually supplied by a hypertrophied hepatic artery rather than by the portal vein); it could be performed also by embolization, if specialist interventional radiologists are available.
- The surgical resection: only if the tumour is unilobar and, however, if possible, the surgical resection is to defer after the neonatal period.
- The liver transplantation is a therapeutic option reserved to lesions that are not resectable and are not suitable for ligation/embolization. An immediate preoperative radiological embolization is an alternative to decrease the blood flow through the tumor and minimize the risk of sharp bleeding during resection.

The treatment of a neonatal **mesenchymal hamartoma** is the complete excision because this tumour has an uncertain natural history.

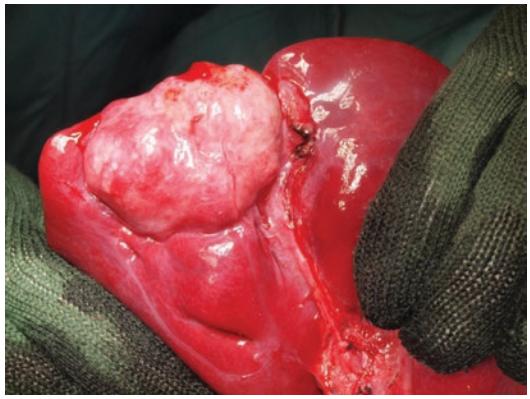

Fig. 36.1 Hepatoblastoma

For the treatment of **hepatoblastoma** (Fig. 36.1), surgical treatment is indicated at diagnosis in patients with PRETEXT I and any unifocal PRETEXT 2 tumours. All other patients will receive a diagnostic biopsy if necessary (open or preferably percutaneously), the placement of a vascular access and preoperative chemotherapy. Chemotherapy is used to reduce tumour size in tumours that are unresectable at presentation. In those cases in which the tumour remains inoperable, because of diffuse liver involvement, liver transplantation is considered.

The surgical treatment includes the following:

36.3.1 Atypical Resections (Nonanatomic Resection)

Atypical or wedge resections are not recommended because of the high risk of incomplete resection; the atypical resection could be applied only in rare form of pedunculated tumours or small peripheral lesions.

36.3.2 Partial Liver Resection (Anatomic Hepatectomy)

Partial hepatectomies are based on the anatomic classification of Couinaud that allows to remove each segment without damaging any of the others.

The liver is divided into the right and left lobe by the main portal fissure containing the middle hepatic vein. Each lobe is again divided into a paramedian and a lateral portion by the right and left hepatic veins. The four sectors are subdivided into anterior and posterior segments.

Each of the eight segments is supplied by a portal triad and drains into a hepatic vein. The portal triad is composed of a branch of the portal vein and hepatic artery and drained by a tributary of the right or left main hepatic ducts.

The major hepatic resections include the following:

- Left lateral lobectomy: removal of segments II–III.
- Left hepatic lobectomy (II, III, IV).
- Extended left hepatectomy (II, III, IV, V, VIII).
- Right hepatic lobectomy (V, VI, VII, VIII).
- Extended right hepatectomy (IV, V, VI, VII, VIII).
- Central hepatic resection (IV, V, VIII).

Segment I receives inflow from both the right and left branches of the hepatic artery and portal vein and drains directly into the inferior vena cava. So, if necessary, the caudate lobe could be resected during extended right or left hepatectomy.

A major hepatic resection is often performed through a trans-abdominal approach with total liver mobilization to provide possible vascular control (see below) (rapid access to the suprahepatic inferior vena cava). For right hepatic lesions, surgeon performs an upper abdominal transverse incision, extending the incision across the costal margin into the seventh intercostal space, a left upper abdominal transvers incision with a vertical midline extension into the chest for left hepatic lesions.

Mobilization of the liver is performed by the division of the falciform ligament, right ligament, coronary ligament and left triangular one.

The hepato-duodenal ligament is isolated and surrounded with a vascular loop to control the vascular inflow, if necessary (Pringle manoeuvre).

Then, in each type of major hepatic resection, the first step is the control of vascular inflow (branches of the hepatic artery and the portal vein) and biliary structures (hepatic duct branches).

The vascular inflow and biliary control can be performed through an extrahepatic vascular con-

trol or intraparenchymal. The advantage of the vascular control performed intraparenchymally is the protection of the other vascular pedicle, but for tumours close to the hilum, the extrahepatic technique is necessary.

Once the inflow and biliary control is achieved, the surgeon moves to the outflow control (right, middle and left hepatic veins). The last step is the parenchymal resection.

36.3.3 Liver Transplantation

Complete eradication of metastatic lesions by chemotherapy or surgical resection is a prerequisite for transplantation.

When tumour resection by partial hepatectomy is incomplete or when intrahepatic relapse is observed after a previous partial hepatectomy, performing a liver transplantation may be a relative contraindication because of the disappointing results observed.

Early indications for liver transplantation are the following:

- Multifocal PRETEXT IV hepatoblastoma is a clear indication for liver transplantation whatever the result of chemotherapy because of the high probability of microscopic neoplastic cells despite the apparent clearance of one liver lobe.
- Large, unifocal PRETEXT IV hepatoblastoma involving all four sections of the liver is an indication of liver transplantation only if the tumour does not downstage after chemotherapy.
- Unifocal, centrally located PRETEXT II and PRETEXT III involving main hilar structures or hepatic vein should be considered for liver transplantation because these structures presumably will not become free of tumour after chemotherapy [1, 18].

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Wilms Tumor in Neonates

37

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37.1 Introduction and Epidemiology

Wilms tumor (WT) or nephroblastoma is the second commonest neonatal renal tumor accounting for 20% of cases and represents the most important renal malignancy during childhood. This neoplasm develops from the primitive metanephric blastema, the primitive tissue of normal kidney, but it may be formed also by cell of nonrenal tissues. In neonates affected by nephroblastoma, only 16% of these are being diagnosed antenatally, and the rest are identified during investigation for maternal polyhydramnios, hydrops fetalis, or other congenital anomalies. Wilms tumor occurs in males and females equally, and in 1% of cases, there is a family history, and it is associated with various congenital syndromes [1, 2]. A recent Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) study reports that infants have a good prognosis than older children affected by WT because of a biological diversity and an earlier diagnosis occurring during screening test administered for the study of genitourinary abnormalities or genetic syndromes associated to early infancy [3].

37.2 Genetic and Risk Factors

The Wilms tumor 1 (*WT1*) gene is located at 11p13, and its defects are associated with combinations of Wilms tumor, genitourinary abnormalities, and renal dysfunction. In these patients Wilms tumor arises earlier (median age 1 year) than the other cases (median age 4 year).

WAGR syndrome is characterized by the association of Wilms, aniridia, genitourinary abnormalities, and mental retardation. It accounts for 7–8/1000 cases of Wilms tumor. Heterozygous constitutional microdeletions of WT1 (responsible of Wilms tumor and abnormalities of genitourinary tract) and PAX8 (responsible of aniridia) at 11p13 caused WAGR.

Denys-Drash syndrome is more strictly associated with Wilms tumor than WAGR syndrome, and, like these, it is caused by germline abnormalities on WT1. This syndrome is characterized by the association of Wilms tumor, nephropathy, and genitourinary abnormalities in males in which phenotype differs for severity in the different cases, ranging from mild hypospadia to pseudohermaphroditism. Nephropathy is characterized by mesangial sclerosis which lead to renal failure before the age of 10 years.

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Children affect by Beckwith-Wiedemann syndrome have an increased risk to develop Wilms tumor. This syndrome is caused by altered expressions of cluster of gene regulated by two imprinting control genes localized at 11p15. Defects in methylation of paternal and maternal alleles are involved in the development of this syndrome. Wilms tumor occurs in 10% of Beckwith-Wiedemann syndrome patients [4].

A moderately increased risk of Wilms' tumor (5–20%) has also been demonstrated in children affected by other overgrowth syndromes:

- Sotos syndrome, characterized by cerebral gigantism.
- Simpson-Golabi-Behmel syndrome, characterized by macroglossia, macrosomia, and renal and skeletal abnormalities associated to an increased risk of embryonal cancer.
- Perlman syndrome, characterized by fetal gigantism, renal dysplasia, Wilms tumor, islet cell hypertrophy, multiple congenital anomalies, and mental retardation.
- Isolated hemihypertrophy, characterized by abnormal growth of the bone, soft tissue, or both.

Loss of heterozygosity of chromosome 11p, 16q, and 1p has been identified in Wilms tumor and correlates with an increased risk of relapse and unfavorable outcome [5].

37.3 Clinical Features

Wilms tumor often arises asymptomatically; in neonates the majority of renal tumor patients (79%) presents with an asymptomatic abdominal mass, often found by relatives noticing during the bath an abdominal enlargement, followed by microscopic or gross hematuria in 10% of cases [6]. Rarely a newborn presenting with fetal hydrops could be associated with congenital Wilms tumor [7, 8]. In older children affected by Wilms tumor, malaise, pain, and hematuria are found in approximately 20–30% of cases. Hypertension is present in 25% of children because of increasing of renin activity. A rapid enlarging of abdominal mass associated to anemia, hypertension, pain, and fever may be caused by subcapsular hemorrhage within the tumor [9]. Wilms tumor must be suspected in children presenting clinical features known to be associated with predisposing syndromes.

37.4 Pathology

Wilms tumor histologically is characterized by a pattern of epithelial, stromal, and blastema components. The proportions of these components configure different histological groups with favorable prognosis in the current SIOP classification of pediatric renal tumors [10]. The presence of anaplastic elements is found in a particular histological group associated with adverse outcome, especially in the cases with diffused anaplasia and advanced tumor stage; thus, its recognition is essential for the prognosis and treatment [11].

Nephrogenic rests are an abnormal cluster of embryonic renal cell which are found in 35% of unilateral Wilms tumor and in 100% of kidneys with bilateral Wilms tumor [12, 13]. Nephroblastomatosis is the diffuse presence of these cluster of embryonal cells which are classified based on the category of rest (intralobar or perilobar nephrogenic rests) and their growth phase (incipient or dormant nephrogenic rests, hyperplastic nephrogenic rests, and regressing or sclerosing nephrogenic rests). Diffuse hyperplastic perilobar nephroblastomatosis represents a preneoplastic condition, and for this reason it is generally treated, when it presents bilateral lesions, with chemotherapy, to reduce the risk of developing Wilms tumor [14]. Rarely extrarenal nephrogenic rests may develop into extrarenal Wilms tumor [15].

37.5 Diagnosis

Ultrasonography is the technique used first to evaluate an abdominal mass. This exam can also evaluate tumor extension and involvement of

contralateral kidney; genitourinary abnormalities, the involvement of the inferior cava and liver metastases, must be considered during abdominal US exam. CT or preferably MRI scan of the abdomen must be performed in children with suspected renal tumor; particularly MRI should be preferred if bilateral renal lesions are suspected to avoid radiation exposition in early age children [16].

37.6 Prognostic Factors and Risk Stratification

COG (Cluster of Orthologous) group divides patients in different groups, to assign every group to different treatment, based on stage, histology, patient age, tumor weight, lung nodule response, and loss of heterozygosity (LOH) at chromosomes 1p and 16q. SIOP (Société Internationale d'Oncologie Pédiatrique) risk stratification system based on stage, histology, response to preoperative chemotherapy, and tumor volume [17].

AIEOP Wilms Tumor Working Group study configured a more sensitive risk stratification system where patients were stratified into six classes based on age, criteria for stage III (separating cases with LN or caval involvement from the others), and completeness of lung nodule response at 6 weeks in addition to stage and anaplasia histology, which represented the most powerful adverse prognostic factor for WT. In this study children aged less than 24 months and with stage II tumor are assigned in the very low-risk group. This because 1p, 16q loss and 1q gain are uncommon in the first 2 years of life and Wilms tumor developed in this age is considered therefore a biologically/histologically favorable tumor [18].

37.7 Therapeutic Management

Management of WT in children includes a combination of nephrectomy, chemotherapy, and radiotherapy. Treatment strategies differ in the two major study groups of Wilms tumor. NWTSG suggests nephrectomy, followed by chemotherapy basing on tumor staging; this approach nevertheless could cause a higher incidence of surgical adverse events such as tumor rupture and intraoperative spillage. SIOP however promotes the administration of neoadjuvant chemotherapy followed by surgical resection to reduce complications related to nephrectomy and consensually to evaluate treatment response; on the other hand, this strategy could deter an overtreatment of benign tumors and an undertreatment of high-risk renal tumors. Chemotherapy includes a combination of vincristine, dactinomycin, and doxorubicin in patient at any stage with favorable histology of disease; in addition anaplastic Wilms tumor or high-risk patients requires administration of cyclophosphamide, etoposide, and carboplatin [19, 20].

Recent studies suggest that, basing on tumor stage, children affected by WT and classified as very low risk (VLRWT) may be treated with nephrectomy alone. Although there is no difference in overall survival in VLRWT patients who receive surgery alone and patient who received neoadjuvant chemotherapy, these patients have a 10–15% chance of relapse, which required salvage chemotherapy.

Stage II and above are treated with chemotherapy regimen depending on the extent of the lesion and genetic risk factors. Chemotherapy is recommended in tumors associated with syndromes, unilateral kidney tumors, or bilateral tumors in which partial nephrectomy could be associated with neoadjuvant chemotherapy. In conclusion, neonatal Wilms tumor can be successfully treated with a combination of surgery and neoadjuvant chemotherapy, which is administered, where indicated, with 50% dose reduction due to increased incidence of toxicity. Radiotherapy is performed in high-risk patients and avoided when it is possible because of long-term adverse events [6, 21]. Nevertheless in infants less than 1 year of age, 50% dose reduction is recommended due to increased incidence of toxicity, and radiation is avoided because of long-term adverse events.

37.8 Surgery of Wilms Tumor

Neonatal Wilms tumors are usually low stage (stage I or II) at diagnosis, so the treatment is surgery, typically transabdominal nephrectomy.

Renal tumor must be resected through a generous transverse upper abdominal incision, from the flank of the tumor side to the flank of the opposite side (Fig. 37.1). A limited incision is associated with a high risk of tumor rupture.

The peritoneum is opened and the small bowel is delivered out of the peritoneal cavity. Then the abdomen is explored for hepatic metastasis, and the renal vein and the inferior vena cava should be palpated to assess for intravascular extension of the tumor. Also contralateral kidney should be controlled for synchronous lesions.

The retroperitoneal space is opened by an incision made lateral to the reflection of the peritoneum of the ascending colon for a right-sided tumor or lateral to the descending colon for a left-sided tumor. The colon is mobilized off the tumor and reflected medially (Fig. 37.2).

It's recommended the initial control of the renal hilum, but this is not always feasible for large tumors. For large tumors is necessary, first of all, the mobilization of the mass to expose the hilum.

The renal vein is isolated, and a vascular sling is passed around the vein to prevent the risk of tumor embolization during surgery. Then the renal artery and the ureter are mobilized (Fig. 37.3).

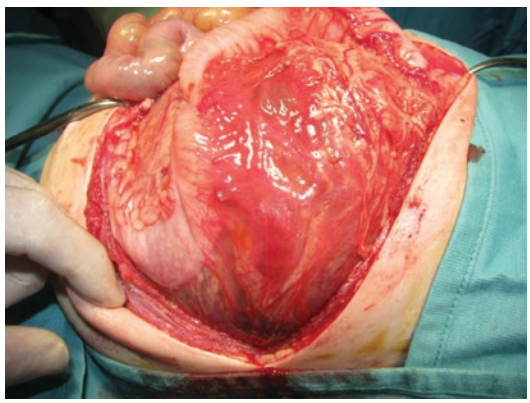

Fig. 37.1 A large neonatal left Wilms tumor approached throughout a generous transverse upper abdominal incision

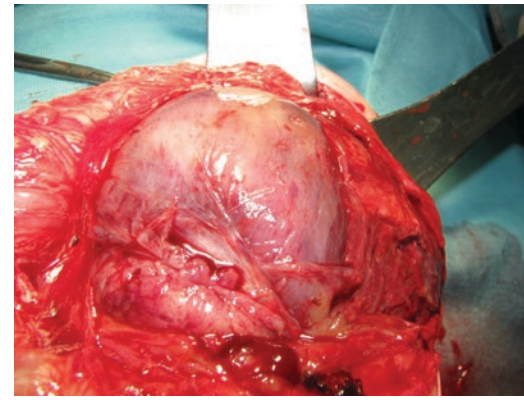

Fig. 37.2 The retroperitoneal space is opened by an incision made lateral to the reflection of the peritoneum of the descending colon, and the colon is reflected medially to expose the tumor

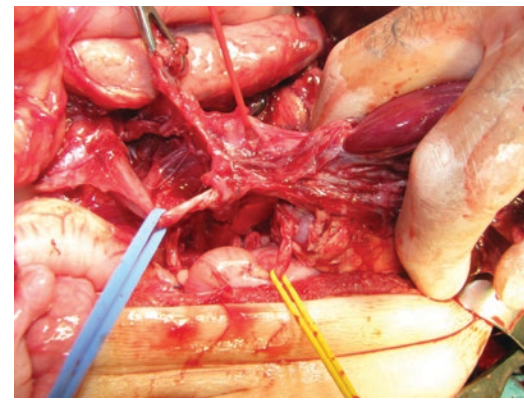

Fig. 37.3 Control of the renal hilum: the renal vein (blue vascular sling), the renal artery (red vascular sling), and the ureter (yellow vascular sling) are isolated

The renal artery is ligated and divided before the renal vein to avoid congestion of the tumor.

In cases with intravascular extension of the tumor (renal vein or vena cava), the vessel is opened by transverse incision between vascular slings and clamps, and the thrombus is removed with a suction cannula.

The para-aortic lymph nodes are sampled on the tumor side and on the opposite side.

The ureter is divided as low down as possible to avoid diverticulum.

Then the tumor is mobilized from the retroperitoneal space. Any lymph nodes should be included in the mobilization and removed with

the perinephric fat. Also lymph nodes of the renal hilum are included.

If the tumor involves the upper pole, the adrenal gland is resected to achieve adequate margins around the tumor. In lower pole lesions, the adrenal gland may be preserved.

Once removed, the tumor is sent fresh to pathology. The abdomen is closed in layers.

The most frequent complication of Wilms' surgery is intestinal obstruction (6–7%) followed by intraoperative hemorrhage (5–6%) and injuries to other visceral organs (1–2%) [2, 20, 22, 23].

Recently some 16 selected cases of WT have been proven to be resected safely and totally by laparoscopy. The choice is based on strict imaging preoperative criteria [24].

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Neonatal Ovarian Cysts

38

Gloria Pelizzo

38.1 Introduction

Ovarian cysts are the most common intra-abdominal masses found in female fetuses and neonates. The estimated incidence of clinically significant ovarian cysts is 1/2500 live births. The first neonatal ovarian cyst (NOC) was reported in 1889 upon an autopsy in a preterm stillborn infant [1, 2]. Nowadays, with advances in radiographic techniques, and especially following the extensive use of ultrasonography, NOCs are easily documented in fetuses, toward the end of the second trimester of gestation.

The fetal and neonatal ovary is usually dormant, but follicular cyst development may occur before and after birth. Fetal ovarian cysts generally manifest in the third trimester, and the most widely accepted theory is that exposure to fetal pituitary gonadotropins, placental human chorionic gonadotropins, and maternal estrogens stimulates the fetal ovary and causes follicle production and maturation [2–6]. Hormonal stimulation in fetal hypothyroidism, congenital adrenal hyperplasia, mutation of the G-protein α-subunit, preterm ovarian hyperstimulation syndrome (a rare and self-limiting disease), maternal diabetes, Rh iso-immune hemolytic disease, preeclampsia, and toxemia are generally recognized as causes of NOCs (Table 38.1) [6–13].

A decrease in maternal-placental estrogens and β-hCG after birth and the baby's neurologic maturation itself lead to spontaneous regression of the cysts. After birth, since the infant's FSH-LH levels continue to increase until the maturation of the gonadostat mechanism, cysts may continue to enlarge for about 3 months [5, 6, 14, 15]. To date, the prenatal detection rate for NOCs is more than 30%. Although spontaneous regression occurs in more than half of NOC cases prenatally detected [2–6, 16], complications of fetal ovarian cysts include compression of other viscera, cyst rupture, hemorrhage, and, most frequently, ovarian torsion with consequent loss of the ovary.

Table 38.1 Etiology of fetal ovarian cysts

Fetal hormonal stimulation
Fetal hypothyroidism
Congenital adrenal hyperplasia
Mutation of the G-protein α-subunit
Preterm ovarian hyperstimulation syndrome
Maternal and placental hormonal stimulation
Maternal diabetes
Rh iso-immune hemolytic disease
Preeclampsia
Toxemia

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Management includes watchful expectancy during the pregnancy and postnatally and antenatal aspiration of large simple cysts, to prevent torsion and ovarian loss. Prenatal monitoring of recurrent complex cysts and postnatal follow-up in the case of simple cyst recurrence are mandatory. Surgical intervention should be considered only in symptomatic or complex cases [2–4, 17–19]. When a surgical intervention is pursued, an ovary preserving approach should be emphasized for all types of cysts, regardless of size and complexity.

38.2 Imaging Appearance

Neonatal ovarian cysts are unilateral in 95% of cases. Cysts are classified with regard to their ultrasonographic features as "simple" or "complex" and with regard to their size as "small" (2.5–5 cm in diameter) or "large" (over 5 cm in diameter) cysts [17, 20, 21] (Fig. 38.1). Simple cysts are completely anechoic or may occasionally contain a single septation. The complex cyst may contain internal echoes, fluid levels, septations, or echogenic foci (Table 38.2, Figs. 38.2 and 38.3) [17, 22].

Cysts are usually unilateral and more often intra-abdominal versus intrapelvic. An ovarian cystic structure less than 20 mm in diameter is considered physiologic rather than a pathological maturing follicle. A cyst larger than 20 mm in diameter is considered abnormal and should be watched carefully [23–27].

Table 38.2 Pre- and postnatal sonographic appearance of ovarian cysts

Simple cysts	• Anechoic • Single septation
Complex cysts (torsion)	• Thick walled • Double-wall sign • Fluid-fluid level • Heterogeneous echogenicity • Calcification and solid component
Complex cysts (hemorrhage)	• Fluid-debris level • Retracting clot • Septation with or without internal echoes

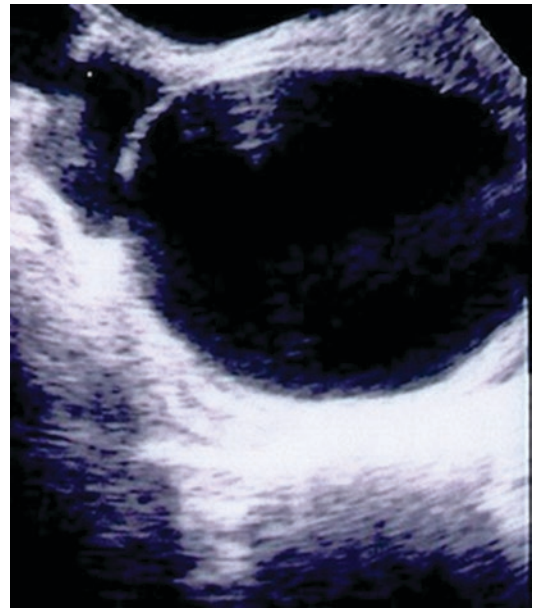

Fig. 38.1 Simple anechoic ovarian cyst (5 cm)

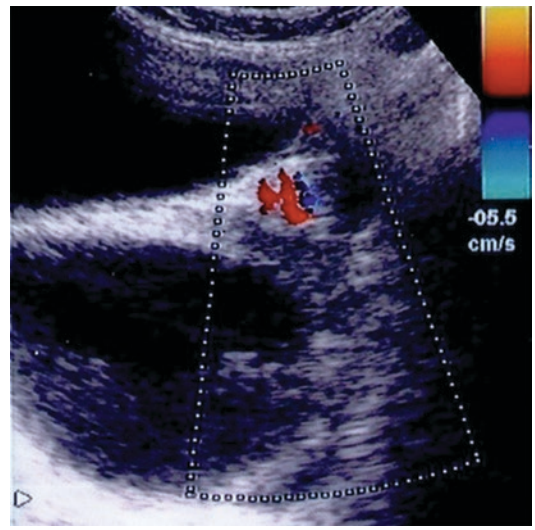

Fig. 38.2 Large ovarian cyst (8.5 cm), with internal echoes and normal ovarian vascularity and flow

Most simple cysts measuring less than 4 cm do not develop complications and resolve within the first 6 months as hormonal stimulation decreases. Rarely, are they complicated; this depends on their size and pedicle length [5, 6, 8, 24].

A complex heterogeneous ovarian cyst is defined by the presence of a fluid-debris level, a

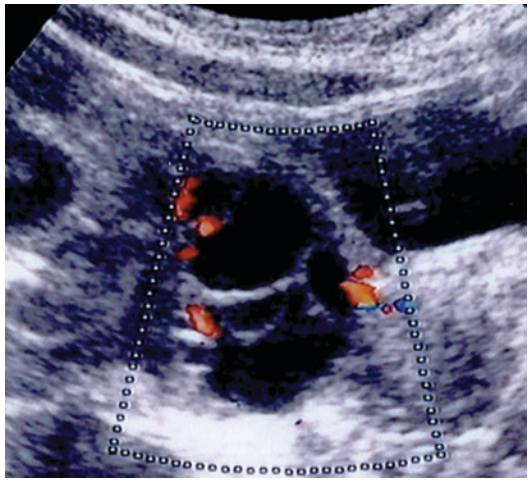

Fig. 38.3 Complex neonatal ovarian cyst with multiple septations

retracting clot, and multiple septation with or without internal echoes, indicating hemorrhage within the cyst. The most frequent and frightening complication of simple cysts is torsion of the ovary [28, 29]. Cystic torsion occurs more often in the fetus than in the neonate, and fetal sonographic appearance of a calcified abdominal mass and a solid component with or without wandering can be considered an autoamputated ovary [28, 29]. Complicated or complex ovarian cysts evaluated by ultrasound (US) present with thick wall and heterogeneous echogenicity. Complex cysts are thought to be the result of rupture, dystocia during birth, and pressure on nearby structures such as blood vessels, uterus, intestines, and urinary system [22, 30]. If a cyst presents with complex US features from the beginning, there is a probability of ovarian-vascular dysgenesis or a neoplasm [5, 8, 15, 28].

38.3 Clinical Manifestations and Complications

When small cysts, prenatally or postnatally detected, start to grow rapidly and their US features change, ovarian torsion should be considered. Ovarian torsion, rare in the postnatal period, is relatively more frequent in the intrauterine period (20–32%) and during delivery. At birth, in almost all cases, the neonate is asymptomatic and does not present signs related to ovarian torsion [4, 5, 10, 15, 21, 23].

Various complications are associated with ovarian cysts; torsion is the most commonly reported complication bearing an incidence of 50–78% for all neonatal ovarian cysts, followed by compression of other viscera, rupture of the cyst, and hemorrhage. Torsion is more common in cysts larger than 4–5 cm in size and may result in adhesion of the necrotic ovary to the bowel or other organs with possible intestinal obstruction or perforation, urinary obstruction, and even sudden infant death [5, 6, 8, 24]. Large NOCs may cause pain, irritability, vomiting, fever, and abdominal distension in neonates and infants. Serial monitoring of a fetal ovarian cyst, by evaluating its resolution or changes in appearance, is mandatory for making an early diagnosis of torsion [23]. US is usually sufficient to determine ovarian torsion, but sometimes an MRI is also necessary to determine the age of the hemorrhage [22].

38.4 Differential Diagnosis

Once a cyst is detected, close US follow-up is necessary in order to make a differential diagnosis (Table 38.3). The differential diagnosis includes choledochal, mesenteric, urachal, and

Table 38.3 NOCs sonographic characteristics used to distinguish cysts from other cystic masses [22]

Ovarian cyst	Female fetus only; "daughter cyst" sign (smaller cyst within a larger ovarian cyst)
Choledochal cyst	Unilocular cyst that communicates with the bile ducts; located in the right upper quadrant of the abdomen
Enteric duplication cyst	"Gut signature" sign (cyst wall is thick and layered)
Urachal cyst	Fluid-filled cyst restricted to the anterior midline between the bladder and umbilicus
Hydrocolpos	Fluid-filled midline pelvic mass posterior to the bladder; may be associated with uterine dilatation (hydrometrocolpos)
Lymphangioma	Thin-walled multilocular cystic mass with multiple septations; infiltrative; may involve the body wall

enteric duplication cysts and hydrometrocolpos [22]. Malignant tumors are rare in the neonatal period, but benign cystic teratomas are common ovarian tumors [22, 30, 31]. Lymphangiomas also are counted among the hamartomatous lesions of the fetal-neonatal ovary [22, 30].

38.5 Treatment

Treatment options include close follow-up with observation, cyst aspiration, laparoscopic interventions, or laparotomy. Prenatally detected simple cysts require watchful expectancy when the size is less than 4 cm in diameter; antenatal aspiration to prevent torsion loss is recommended when the size is greater than 4 cm; in the neonatal period, resection of all symptomatic, complex cysts is necessary to avoid ovarian loss [2, 3, 17, 19, 20]. Surgical treatment is essential in torsioned cysts [2, 3, 6, 32]. The major goal of both surgical and noninvasive treatment by US monitoring is optimal ovarian preservation even though long-term outcomes and risks to future fertility are unknown [19, 30].

38.5.1 Expectant Management

As long as the prenatal simple cyst is small, does not show a trend for rapid growth, and remains asymptomatic, it should be monitored by serial US and expectant management [2, 3, 17, 19, 20, 33]. Fetal cysts that are less than 5 cm in diameter are unlikely to cause problems and can be observed for spontaneous resolution. In the newborn there is no consensus regarding the modality and timing of NOC monitoring. Postpartum serial US examination should continue every 4–6 weeks until the cyst resolves, enlarges, becomes symptomatic, or persists for more than 6 months, and if a cyst is large (>5 cm), does not regress, or increases in size, it should be punctured or removed surgically [2, 3, 17, 19, 20, 33].

38.5.2 Ultrasound-Guided Cyst Aspiration

US-guided cyst aspiration in newborns is only recommended for simple cysts that are larger than 40 mm, in order to reduce the risk of ovarian torsion and other complications [34]. US-guided aspiration offers several advantages: it is a minimally invasive procedure, does not require general anesthesia, and enables preservation of the ovarian tissues [34]. The procedure is simple and safe, can be performed at the bedside, and may be repeated as required if the cyst refills.

Even though US-guided aspiration has many advantages, the condition of the ovary may not be ascertained accurately, the adjacent organs may interfere with the approach to the target, and US-guided aspiration may be rather limited in septated or complex cysts. Moreover the risk of recurrence is high and careful ultrasonographic follow-up and repeated aspirations may be necessary, which increases the risk of bleeding and infection in the cyst [22, 34–38].

38.5.3 Laparoscopic Interventions

Laparoscopy, with its minimally invasive nature, offers the advantages of prompt and good recovery in newborns and smooth postoperative recovery. The laparoscopic approach is preferred since it affords a diagnostic opportunity, allowing the surgeon to visualize both ovaries. Aspiration of the cyst, cystectomy, stripping of cysts, and, if necessary, oophorectomy are all possible with laparoscopy [39–43].

Laparoscopic aspiration also overcomes all of the US-guided aspiration disadvantages. This approach allows surgery without damaging the adjacent organs, which is the greatest concern during US-guided aspiration. Almost all fluid can be repeatedly aspirated from septated cysts via an approach from other directions. In addition, the ovary with torsion and the normal contralateral ovary may be visualized.

The operation time for an aspiration-only procedure takes less than 30 min and leaves minimal scarring, since only a 3-mm trocar/camera port is created. Surgeons may perform detorsion or cystectomy at the same time if an ovarian torsion is discovered. The magnitude of the cyst size is not a contraindication, since laparoscopic cyst puncture and aspiration allows sufficient reduction in size [39–42].

Surgical excision is generally indicated for cysts that are complex and symptomatic or increase in size and persist for more than 6 months. Early surgical intervention to exclude malignancy is also possible. Although US is inadequate to distinguish between a complicated cyst and an ovarian teratoma or other tumor, the presence of neonatal ovarian tumors is anecdotal [30, 31].

When surgical treatment is indicated, every attempt should be made to rescue as much of the gonadal tissue as possible. Indeed, even if no ovary is macroscopically visible, ovarian tissue may still be present, and surgery should be limited to removal or unroofing of the cyst.

The stripping technique for enucleation of large benign cysts is also feasible in infants and appears to be an organ-preserving procedure when the ovarian tissue is not inadvertently excided with the cyst wall [26].

In preparation for all laparoscopic procedures, preoperative assessment is crucial in all children. This can be a formal assessment in a dedicated preoperative assessment clinic held by experienced pediatric surgeons.

Positioning of the patient must allow adequate exposure and safe access to the operating field. The recommended alignment is to have the monitor, operating surgeon, and the patient or target organ in a straight line. During laparoscopic neonatal gynecological surgery, the patient is placed in a supine transverse position, across the operating table, so that the surgeon and assistant can work from the head of the patient, on the right side of the table [43, 44] (Fig. 38.4).

As illustrated in Fig. 38.5, three ports are usually used: a 3- or 5-mm umbilical port (camera) and two 3-mm ports in the right and left flank, respectively (working ports).

The peritoneal cavity is insufflated with CO_2 at a pressure of 5–8 mmH. The flow rate for insufflation of CO_2 ranges from 1 to 5 L/min.

The laparoscopic approach can be technically challenging in small children with large intra-abdominal cysts. First, it is often difficult to gain access to the peritoneal cavity for port placement and to dissect and manipulate the cyst because of the limited space in smaller children and the need for multiple instruments. Secondly, chemical peritonitis may result from leakage of benign cyst fluid into the peritoneal cavity [45–48].

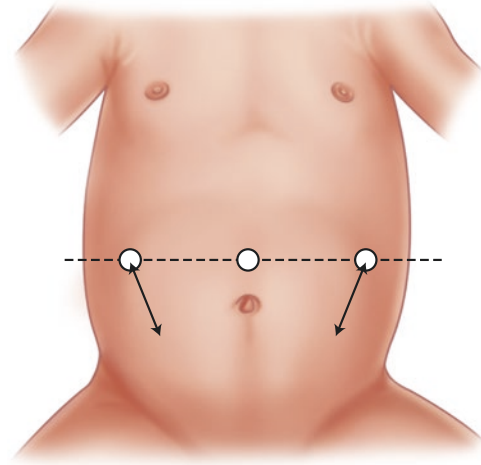

Fig. 38.5 Trocar positioning

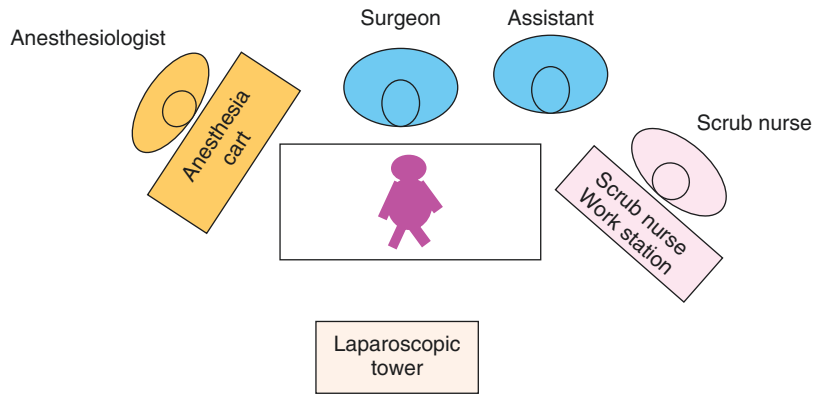

Fig. 38.4 The room setup for gynecological procedures in neonates

In order to address these issues, several laparoscopic approaches and modifications have been adopted. These include either drainage of the cyst by US-guided paracentesis or drainage during laparoscopy followed by excision or manipulation of the cyst or extracorporeal cystectomy. For drainage and manipulation of the cyst, different techniques have been described using a planned trocar placement through the cyst, percutaneous gastrostomy introduction set, soft cup aspirator set, suprapubic catheter, extracorporeal drainage via a minilaparotomy, and aspiration and traction through the port to facilitate dissection [45, 46]. These techniques provide controlled means of aspirating the cyst and allow traction to the cyst wall to facilitate intracorporeal manipulation and dissection of the cyst. The needle hitch technique minimizes the need for additional instrumentation and ports for traction and facilitates better ergonomics for intracorporeal manipulation and dissection of large cysts.

In contrast with open surgical procedures, laparoscopic treatment of ovarian cysts ends in only three punctiform scars, which give a satisfactory cosmetic appearance for the entire life of the patient. Shorter hospital stays and time to feedings, reduced pain, and quick return to normal activity (or parents to work) are additional advantages of the laparoscopic approach.

38.5.4 Lower Abdominal Laparotomy

Traditional surgery via an open lower abdominal laparotomy in patients with ovarian cysts remains a common surgical indication for the treatment of large ovarian cysts. Moreover, neonatal laparoscopy is a safe option; it offers better cosmetic results and should always be recommended whenever possible [40, 49, 50].

38.5.5 Robotic Surgery Approach

A robotic approach to cystectomy in the pediatric population is also a safe and feasible procedure with a low rate of complications and conversion to laparotomy [44]. To date, there is no evidence of better clinical outcomes with regard to traditional laparoscopic surgery. Due to limited data regarding neonatal cysts and the effective cost analysis, the robotic surgery approach is not promoted in infants and neonate.

38.6 Other Considerations

The NOCs need to be managed by a multidisciplinary team involving pediatric surgeons, pediatric radiologists, gynecologists, anesthesiologists, neonatologists, and pediatricians. Adequate perioperative and operative facilities instrumentation for minimally invasive surgery in infants are mandatory [51]. Counseling prior to surgery is essential and should involve both parents. During this discussion the risks, benefits, and alternatives to surgery should be conveyed and documented. Finally, sufficient pain management during the postoperative recovery is recommended.

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Teratoma: Sacrococcygeal and Cervical

39

Olivier Reinberg

39.1 General Considerations

Extragonadal teratoma is generally located all along the midline. They are found in decreasing incidence in the sacrococcygeal region (40%), pineal region (13.3%), cervical (13.1%), palatine and nasopharyngeal region (8%), heart (7.5%), stomach (2.6%), mediastinum (2.6%), orbits (2.4%), face (1.5%), placenta (1.5%), and other very rare locations (3%) [1]. Today with the improvement of ultrasounds (US), the diagnosis is done prenatally. Sacrococcygeal teratoma (SCT) although the commonest germ-cell tumor in children is a rare fetal anomaly. The majority present at birth as an external sacral mass; however, some intrapelvic SCT may be unapparent. A final paragraph will treat of the 10% cervical teratoma concerning the neck, the nasopharynx and/or the oropharynx.

39.2 History

Many cases have been reported, depicted, and drawn, but most of them are related to conjoined twins as they impressed the observers and are difficult to distinguish from mature SCT.

According to JW Ballantyne, a Scottish erudite in ancient medical literature dedicate to fetal diseases and abnormalities, the first reported case was on a Chaldean cuneiform tablet dated approximately 2000 BC [2].

Circa 600 AD, the Archbishop Isidore of Seville compiled the universal knowledge of that time in the "*Etymologiae*" in which he gave the first pseudoscientific descriptions of congenital anomalies. This book was the most popular compendium in medieval libraries. By the fifteenth century, more than ten editions were published showing his continued popularity during the Renaissance [Isidore of Seville, *Etymologiae*, Liber XI: *De hominibus et portentis (Of men and monsters)*].

From mid-sixteenth to mid-seventeenth century, monstrous births with SCT and/or conjoined twins have been described and depicted in several books by Jacob Rueff from Zurich in *De conceptu et generatione hominis* (1554); by Ambroise Paré from France in *Des monstres et prodiges* (1573); by Fortunio Liceti from Rapallo, who worked in Bologna in *De monstrorum natura, caussis et differentiis libri duo* (1616); and by Ulisse Aldrovandi from Bologna in *Monstrorum historia* (1642).

The term "teratoma," from the Greek (τερατώδης = monstruous; τερας = monster), was coined by the German pathologist Rudolf Virchow in 1869 to describe lesions which contained a foreign tissue to the part in which they arise [3].

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In the modern era, the first large series of 40 infants and children with SCT was reported by Gross in 1951 [4].

39.3 Epidemiology

Most authors report SCT incidences of 1:30,000–1:40,000 [5–9]. However these rates were based on data obtained before the 1970s, and more recent studies have shown incidences up to 1:23,300 [10–13]. It seems that the number is increasing [14, 15]. SCT is possibly more frequent in Northern Europe as reported in Sweden (1/13,000 [14]) and in Finland (1:10,000 [13]). But higher incidence of SCT in Scandinavian countries might be explained by the region's use of nationwide birth registries [14]. Most studies show a female to male preponderance of about 4:1 (from 1.9:1 to 8.3:1) [9, 12, 16–19]. SCT seem to be sporadic. However familial forms exist with different characteristics: they have an autosomal dominant inheritance, show no sex difference, and are presacral and usually benign with a low risk of malignancy [20–22]. Mature teratoma is the most common [14, 15, 23, 24]. Demography and ethnic origins could play a role in the risk of malignancy [25].

39.4 Etiologies

The etiology remains unknown. SCT arise from multipotential embryonic cells situated in Hensen's node. It could be the failure of a twining attempt or result from an abnormally placed set of stem or germ cells.

In the hypothesis of a twinning failure, the question raised is what is the difference between a mature SCT with all organized tissue components, conjoined ischiopagus or pygopagus twins, or a fetus in fetu. A definition of fetus in fetu was proposed by Gonzalez-Crussi [26] as "high organotypic development and presence of a vertebral axis with arrangement of tissue around this axis." Some authors raise the question whether highly differentiated teratoma and fetus in fetu could be the same pathology [16, 27, 28]. De Lagausie has described a case showing that fetus in fetu can be a remarkably complex, well-differentiated, highly organized teratoma. Mature SCT are derived from remnants of the three embryonic developmental tissues (ectoderm, mesoderm, endoderm) and demonstrate a lack of organ specificity whether conjoined twins have a more advanced structural organization.

SCT occur near the coccyx where the greatest concentration of germ cells is present for the longest period of time. Using immunohistochemistry, Buchs showed that SCT come from remnants of the epiblast-like tail bud blastema. He demonstrated that they contain cells positive for embryonic stem cell markers and may represent a novel source for human embryonic stem cells [29]. With the hypothesis of an abnormally placed set of stem or germ cells, they could migrate from the yolk sac to the gonad pathway, persist, differentiate, and mature resting anterior to the coccyx at the Hensen's node. The growth of the pluripotential cells could escape to the control of the embryonic inductors and organizers, resulting in a teratoma. Rearrangements into the proto-oncogene or in an abnormal regulatory sequence could result in molecular transformations of cells foreign to that anatomical site [29, 30].

39.5 Types and Classifications

All SCT are attached to the coccyx. They develop outside the pelvis, into the presacral area, or both. Altman described a four-stage classification of SCT according to the relative amounts of intrapelvic and external tumor [5] (Fig. 39.1). Altman also subclassified SCT into small (2–5 cm diameter), moderate (5–10 cm), and large types (more than 10 cm). This classification has been adopted by the Surgical Section of the American Academy of Pediatrics and then worldwide. Type I are primarily external and have only a small presacral component (Fig. 39.1a and Fig. 39.2). Type II are predominantly external but have a significant intrapelvic portion (Fig. 39.1b). Type III are partially external and predominantly intrapelvic with abdominal extension (Fig. 39.1c and Fig. 39.3). Type IV are

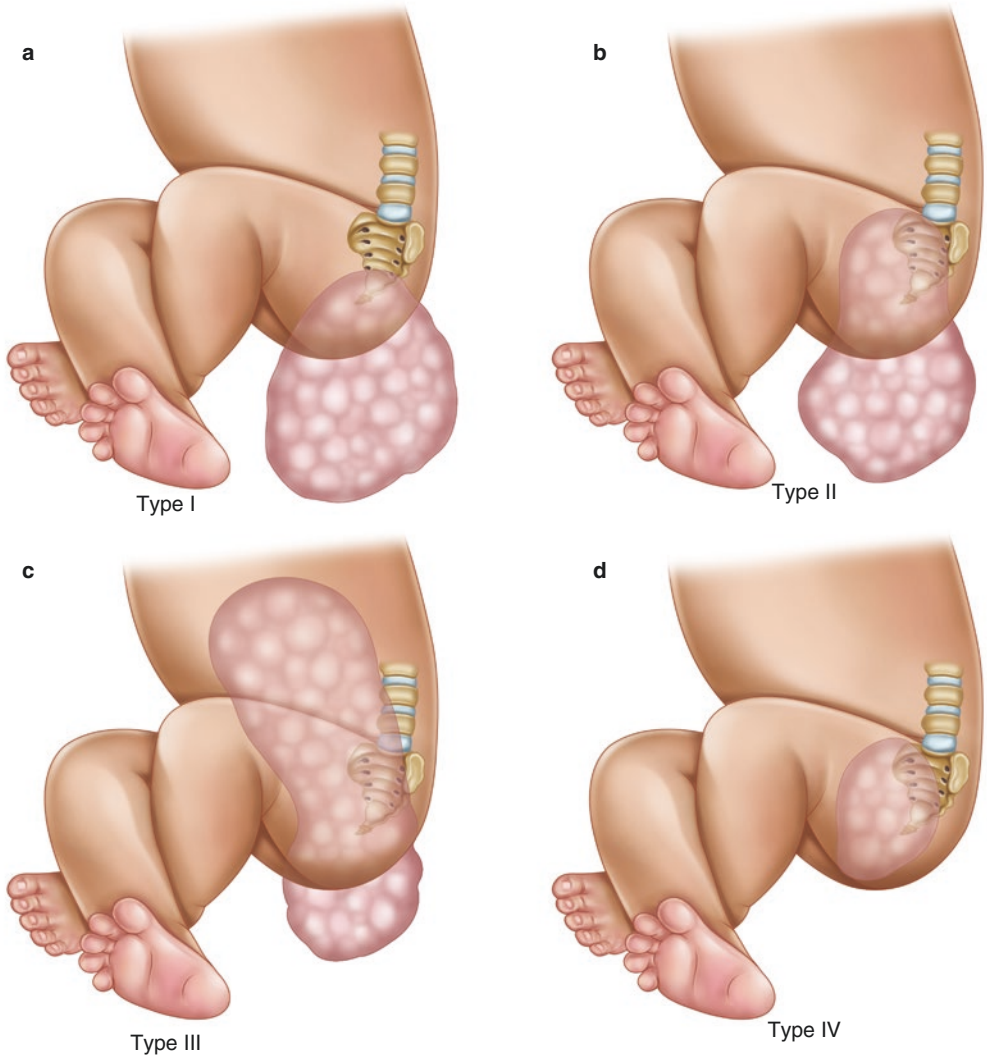

Fig. 39.1 Altman classification of SCT [5]

located entirely within the pelvis and abdomen (Fig. 39.1d). This classification is related to the ease of surgical resection and prenatal detection as well as the likelihood of malignancy. Type I are easy to detect and to resect with a very low incidence of malignancy. Reversely, SCT type IV are difficult to diagnose with prolonged delay of recognition, are not amenable to fetal resection, and are frequently malignant. Fortunately, the majority of SCT are type I or II.

Mature teratoma is multi-tissular with elements coming from the remnants of the three embryonic developmental tissues (ectoderm, mesoderm, endoderm) and thus reveal inhomogeneity with solid, cystic, and osseous parts. In mature SCT, any well-differentiated tissue can be present such as skin, bone, cartilage, and neural tissue but also nails, teeth, and hair (Fig. 39.4). SCT is said immature when undifferentiated cells, especially from neuroepithelial tissues, are dominant. Malignant SCT are mostly solid, while immature are frequently cystic. Mature and immature teratomas represent 87–93% of cases, while malignant tumors represent the other 7–13% [15, 31–33]. Malignant changes are more common in males [5, 34].

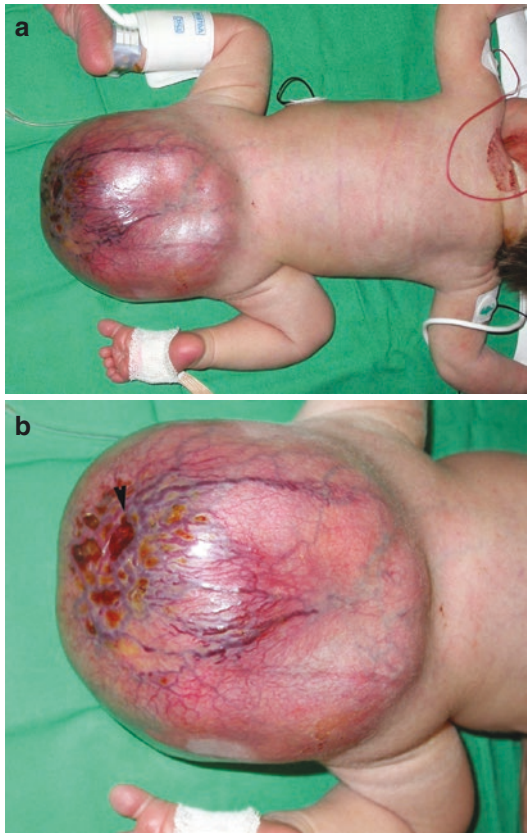

Fig. 39.2 (**a**, **b**) SCT Altman I in a female newborn on Day 1. On close view (**b**) note the large superficial vessels that may bleed and a superficial wound not correlated with delivery (Cesarean section) (*arrow head*)

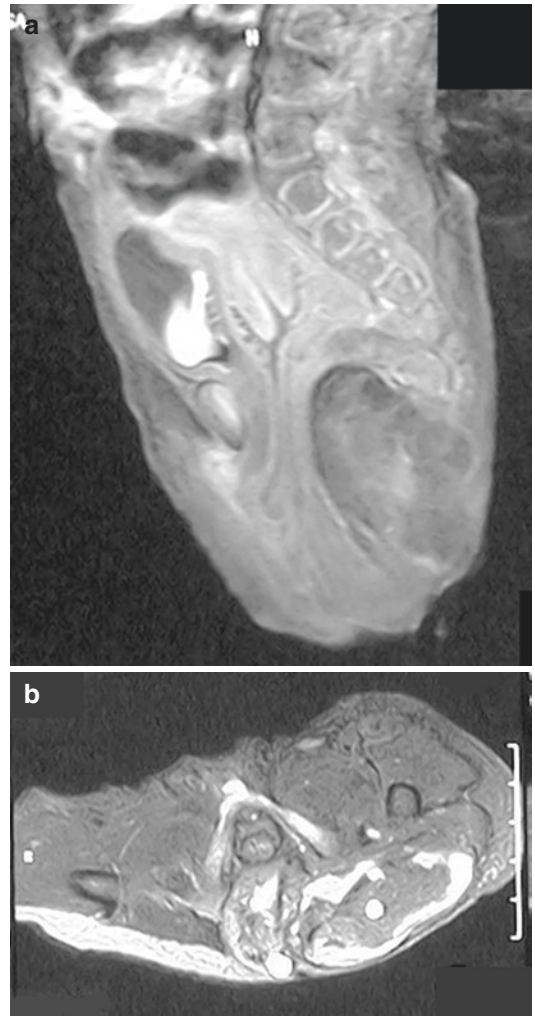

Fig. 39.3 (**a**, **b**) SCT Altman III in a female newborn. MRI performed on Day 2

The Gonzalez-Crussi's grading system for SCT (1978) is based on histology [31]. Grade 0 is totally mature and benign. Grade 1 is mainly mature with rare foci of immature tissue and has to be considered as benign. Grade 2 has significant parts of immature tissues, thus bearing a potential for malignancy. In Grade 3 multiples, places of immature tissue are found with or without yolk sac tumor and are considered to be malignant; thus additional cancer staging must be added.

Most SCT are benign (55–94%). Histological grading of SCT does not seem to correlate directly with prognosis unlike that of ovarian teratoma. Histology for malignancy increases from 10% at birth to 50–70% at 2 months.

Unusual forms of SCT have been described, such as SCT with intradural extension [35, 36]. Usually the SCT is well delimitated, but communication with the urethra or with the rectum may occur [37]. Proteus syndrome can be associated with a SCT [38].

39.6 Prenatal Diagnosis and Treatments

SCT are usually evidenced on a routine US. They appear as caudal or intrapelvic mass and require for more investigations. Following the diagnosis of a SCT, the parents need to be referred to a tertiary center where a multidisci-

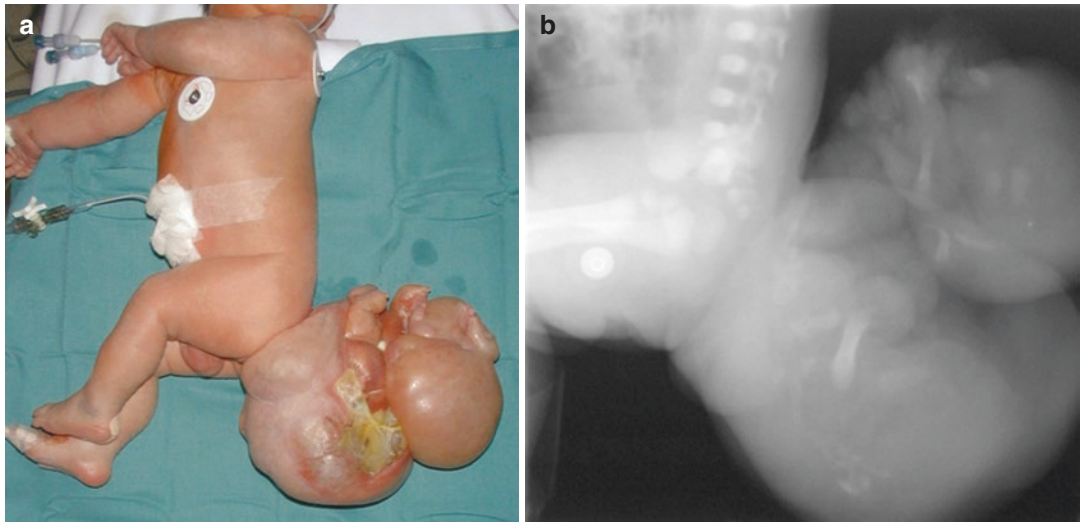

Fig. 39.4 (**a**, **b**) Mature SCT Altman I on a male newborn (**a**) and conventional plain Rx showing multiple limb-like osseous components (**b**) on Day 1

plinary team has experience with this condition. Parents should be reassured that the majority of tumors are benign with a good prognosis and a low recurrence risk if total resection is performed in the neonatal period. However they should be informed that a closed surveillance is mandatory and that death may occur during pregnancy or at birth.

Evaluation of SCT is best performed by MRI to document its content and its extension (Fig. 39.5). But 3D US with power Doppler is an alternative [39, 40]. It should be complemented by an echocardiography (EKG) with US Doppler measurements. Once the diagnosis of SCT is made, frequent evaluation (weekly ?) by US and EKG is mandatory as cardiac failure may occur.

The prenatal workup looks for anomalies associated to SCT that range between 5 and 26% [10, 12, 15, 41]. They are many and diverse and have been described as associations with hydrocephalus, tethered cord, spinal dysraphism, vertebral anomalies, sacral agenesis and meningocele, anorectal malformations, cleft lip and palate, polydactyly, transposition of great vessels, neurogenic bladder, bifid scrotum, hypospadias and epispadias, and ectopic kidney. SCT can occur as part of the Currarino triad, when it is associated with anorectal malformations and sacral anomalies. Urogenital anomalies seem to be more common in girls with SCT [42].

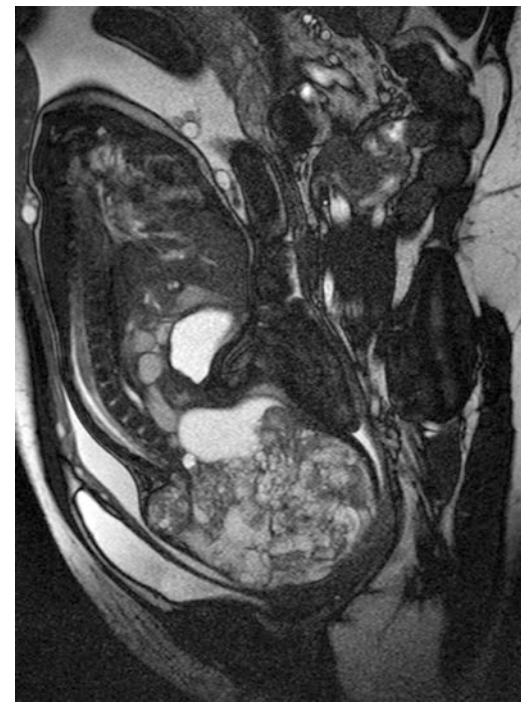

Fig. 39.5 Prenatal MRI at 30 WGA (same patient as in Fig. 39.2)

Vascular disruption defects refer to those involving the interruption or destruction of some part of the fetal vascularization. A vascular disruption sequence has been mentioned by Atis about a rare case of SCT causing multiple fetal disruption defects like cleft lip and palate, limb amputations, and hydrops [43].

In most fetus, the prenatal course is uneventful. However in case of unfavorable evolution, the fetus and the mother can be in danger. Close monitoring helps to predict and prevent these unusual outcomes. Several factors such as tumor morphology (solid vs. cystic), vascularity, tumor growth rate, and the presence of hydramnios have been found to predict outcomes in prenatally diagnosed SCT [44–46].

Benachi suggested a prognostic classification of prenatally diagnosed SCT related to their size, vascularization, and macroscopic appearance on ultrasound with Doppler evaluation. SCT are classified into three prognostic groups: (A) tumor diameter < 10 cm, absent or mild vascularity, and slow growth; (B) diameter > 10 cm with pronounced vascularity, high-output cardiac failure, and rapid growth; and (C) diameter of 10 cm or greater, predominantly cystic with absent or mild vascularity and slow growth. Group A is associated to good maternal and perinatal outcome. Group B is related to poor outcome, and the percentage of mortality as well as fetal and maternal morbidity is high. Group C has a good prognosis although shunting or drainage of the SCT could be necessary. Large fast-growing SCT with rich vascularity are associated with a higher perinatal mortality and morbidity than smaller lesions with mild vascularity [23].

As it appeared that the size of the SCT was not significant enough, several ratios have been developed to make a better prognosis and a follow-up during pregnancy:

The THR ratio is the ratio between SCT volume and fetal head [46, 47]. In case of cystic SCT, only the volume of solid components is taken into consideration. A THR < 1 means no death in utero, while a THR > 1 has a 61% risk of poor prognosis.

The TFR ratio is the ratio between SCT volume and fetal weight [48, 49]. It is best done before 24 weeks of gestational age (WGA). A TFR < 12 means a good outcome, while a TFR > 12 has a poor outcome. The sensitivity of the TFR ratio is >91% and his specificity is ≈ 80% [47, 49].

These ratio are helpful at diagnosis but must be followed during pregnancy to evaluate the growth rate of the SCT. A rapid growth (> 60 cm^3/week for Coleman; > 150 cm^3/week for Wilson; >8 mm/week for Hambraeus) bears a risk of adverse outcome [14, 15, 19, 44, 50, 51] as has a preterm delivery [15]. After reviewing 18 studies including 420 cases, Ayed concluded that a SCT diagnosed at >28 WGA with a delivery >34 WGA has a survival rate of 90% [19, 44, 51, 52].

The macro-microscopic appearance of the SCT is also a part of the prognosis:

The prognosis is better in mature types (98% survival) than in immature (69% survival) and in cystic or mixed forms (73% survival) than in solid (45% survival) [15, 31].

The effects of SCT on fetus are of two types: the compressions due to the volume of the mass that are more important in the internal types (i.e., types III and IV) and the cardiocirculatory disturbances induced by the SCT itself. SCT may parasitize blood supply usually from the mid-sacral artery or sometimes from the internal and external iliac systems. This causes abnormal high flow through enlarged vessels that "steal" blood from the normal vascular stream. The highest risks for fetal death are in the most vascularized tumors, regardless of size [51]. Then the fetus may develop a high-output cardiac failure, an hydrops fetalis, an hemorrhage inside or outside the tumor, a polyhydramnios, and/or a placentomegaly. Should a hydrops appear after 30 WGA, the mortality risk is 25%, while appearing before 30 WGA means 90% mortality [51]. Grossly said without hydrops fetalis and/or polyhydramnios, SCT have 80% survival for a full-term delivery but only 52% survival with a preterm delivery (before 34 WGA) [51].

Inadequate placental flow has been reported to induce the release of vasoactive substances that can gain access to the maternal circulation. They induce endothelial cell damage and lead to maternal pseudotoxemia (Ballantyne syndrome). In

this syndrome, there are signs and symptoms of preeclampsia including hypertension, proteinuria, peripheral edema, pulmonary edema, nausea, and vomiting.

Last but not least, the external SCT have a significant risk of dystocia and may require for a Cesarean section due to the size (>10 cm?) and to the risk of rupture of one of the major vessels running on its surface during labor (Fig. 39.2a, b).

Thus there is a ratio for fetal management in selected cases. Should unfavorable evolution occur, the termination of pregnancy using a Cesarean section has to be considered according to the WGA. Indications for Cesarean section are fetal (hydrops fetalis, cardiac failure) or maternal complications. Early delivery as an alternative management strategy for selected high-risk SCT must weigh the pros and the cons among risk of death in utero and prematurity [53]. The EXIT procedure (ex utero intrapartum therapy) can be an alternative between 28 and 36 WGA for selected cases as long as there is no maternal or placental compromise [54, 55]. The EXIT procedure requires the presence of maternal-fetal specialists, pediatric anesthetists, neonatologists, and pediatric surgeons at delivery to secure stable airway access and ventilation to the baby before clamping the umbilical cord.

Otherwise many techniques have been developed to reduce the volume of the mass or to minimize the risk of bleeding. In case of nonvascular cystic SCT, percutaneous drainage/decompression can be performed under US guidance [56]. Laser coagulation of surface or deep vessels can be done under fetoscopy, under US guidance, or using radiofrequency ablation [57–60]. Radiofrequency ablation is done by a needle inserted through the mother's abdomen into the tumor. Radiofrequency waves are sent through this needle, producing heat into the tumor and destroying the blood vessels that supply it [61, 62]. However it is difficult to control the energy released, resulting in severe collateral damage to the surrounding tissues. Complications have been reported such as severe orthopedic sequelae to the pelvis and sciatic nerve injuries [63]. Radiological techniques of occlusions using coils, alcohol, or tissue adhesive (Histoacryl®) have been used [60].

Adzick first used ex utero open fetal surgery for tumor ablation in 1997 which since then has been followed by others [41, 64–67]. These procedures are at risk for the fetus and for the mother [59]. Thus mandatory criteria for fetal surgery must be followed: accurate prenatal diagnosis, absence of other life-threatening or debilitating anomalies, and procedure without increased risk to the mother's life or for her future fertility [65]. In addition the specific criteria for SCT are blood volume represented by SCT circulation may have exceeded the capacity of baby's lungs to arterialize blood, large venous blood stream from the SCT contributed to a low mixed venous PO2 and pulmonary vasoconstriction, fetal ascites and abdominal distension impairs lung development in utero, resulting in reduced lung volumes and finally to presume that post birth the SCT volume will impair diaphragmatic movements.

39.7 Postnatal Preoperative Cares and Surgery

SCT bears a high risk of fatal issue during and after delivery. It is said to be the "most common cause of neonatal mortality" [68]. Death during the prepartum is related to heavy bleeding associated to trauma on the external vessels, while during the postpartum, major bleeding from deep vessel injuries is involved [10].

Preoperative assessments include postnatal MRI, complete assessment of the spine (mostly in type IV), and blood sampling for αFP, β-HCG, and CA-125. Additionally cross-matched blood should be done to ensure availability in the operating room with extensive coagulation tests as significant coagulopathies are associated with SCT. In case of ureteric compression with subsequent hydronephrosis, renal functions should be done.

Treatment of SCT is mainly surgical. Whenever possible, early excision within the 1st week of life should be the aim as some undifferentiated foci may proliferate with time and become aggressive [51, 67]. Surgery should include total resection of the SCT and coccyx

removal. As to reduce the risk of sharp bleeding in case of enlarged vascularization, control of the presacral artery is required. This can be done radiologically using preoperative radiological embolization [69–71] or by clipping laparoscopically the artery [72–78] if the child's conditions allow it. If not possible, it has to be the first step through an open laparotomy.

The patient is laid in a prone position, a pad being placed under the pubic symphysis. The incision differs according to the surgeon and to the quality of the skin. Historically, the chevron incision has been used but leaves transverse scars causing unpleasant cosmetic results. Posterior sagittal anorectoplasty (PSARP) has also been used [79]. Resecting the skin at that stage is not recommended as we don't know yet how the wound will be closed at the end of the SCT removal. Then the limit between the sacrum and the coccyx is looked for and carefully cut transversally (Fig. 39.6). The presacral artery lies just under the sacrum (Fig. 39.7). It can be a major one and has to be ligated carefully. Its control permits excision with significant reduction of bleeding. We have not required aortic control in any of our patients, even with large tumors. The dissection is carried on cranially surrounding the upper pole of the tumor (Fig. 39.6b). At this point we reach the posterior wall of the rectum that must be dissected carefully. On either side, the gluteal muscles are spread away and sometimes difficult to identify. Then the safest way is to stay in close contact with the tumor without opening it. The lower part of the dissection can be in close contact with the anorectal muscular complex. It is of major importance to avoid lateral dissection to preserve from nerve injury. Skin is closed over drainage(s), but buttock reconstruction after SCT resection is difficult.

Some surgeons prefer to perform a preliminary colostomy before combined abdominosacral excision of large type III and IV lesions to reduce morbidity [80]. The use of ECMO and hypothermic hypoperfusion [81, 82] or cardiopulmonary bypass and ECMO [83] has been described in large SCT resections.

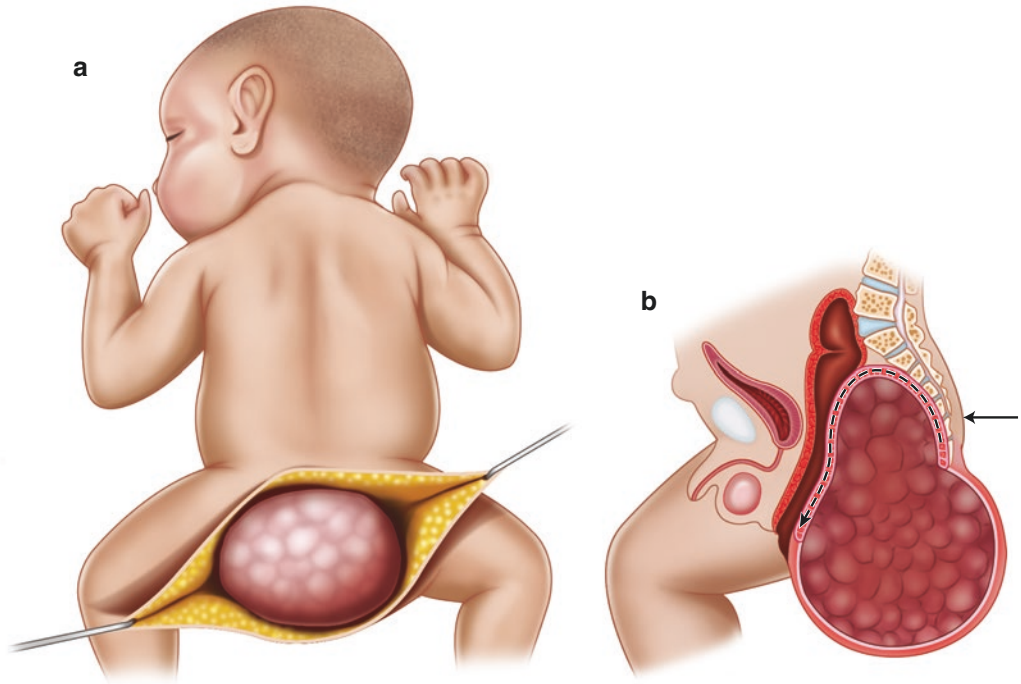

Fig. 39.6 (**a**, **b**) Transverse section between the sacrum and the coccyx (arrows). After section of the coccyx, the dissection goes cranially, surrounding the upper pole of the tumor (**b**)

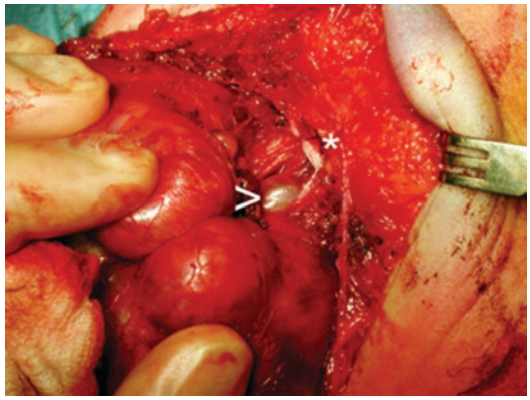

Fig. 39.7 Peroperative view after section of the coccyx. Note the large presacral artery (arrow) lying just below the sacrum (asterisk) (same patient as in Fig. 39.2, operated on Day 2)

39.8 Recurrences and Prognosis

The overall prognosis after SCT removal is good with >90% survival and free of recurrence at 5-year follow-up [10]. However it varies widely according to several factors including early and complete resection without spillage, size of the tumor, and histology. After total macroscopic resection, the prognosis for benign histology is good with 7–22% recurrences but is 37–49% after incomplete resection. However recurrences have been described after macroscopically and histologically radical tumor removal. Thus recurrences need for extensive histology. Recurrence rate is higher if surgery is delayed (>50% recurrences when surgery is done 2–4 months vs. 10–35% if performed before 1 month). A strong argument favors early resection: a shift from initially benign histology toward immaturity or malignancy has been frequently described [10, 67, 84]. The histology of fetal SCT may change in utero and post birth. Graf reported histological maturation in fetal SCT between the initial debulking procedure and subsequent definitive resection [67]. However in these cases, it is unclear whether this was the result of spontaneous in utero tumor maturation or transformation induced by fetal surgery. Malignant recurrence after excision of benign tumors has been reported despite excision of the coccyx [84–86]. Most recurrences occur within 2–3 years [10, 84].

Malignant SCT has a good overall prognosis provided complete surgery is achieved and chemotherapy is administered. A huge improvement with neoadjuvant chemotherapy has been widely described with 5-year survival rising from 49 to 83% [23, 33, 85]. Distant recurrence or metastasis at first resection requires for risk-adapted chemotherapy with a fairly good prognosis [85].

All presacral teratomas do not bear the same risk of malignant evolution. This is the case when comparing the risk of malignant transformation of isolated SCT with that of presacral teratoma in Currarino syndrome. The evolution may differ despite the similar position and appearance. The malignancy-free survival of patients with isolated SCT seems to be lower than for patients with a presacral teratoma associated with Currarino syndrome (80 and 58% after 1 and 2 years in isolated SCT versus 100% after 2 years in Currarino syndrome) [87].

39.9 Follow-Up

Long-term functional sequelae after resection of SCT are relatively common. They mainly affect fecal and urinary continence interfering with the quality of life. In most series, no anorectal or urologic complications occurred in patients with Altman type I SCT [88, 89]. But Dericks considers Altman classification, sex, histopathology, incomplete resection, and age at diagnosis are not risk factors for functional sequelae [8].

Fecal complications can be involuntary bowel movements, soiling, or constipation. Constipation is encountered in 8–50% cases [8, 88, 90, 91]. Soiling is present in 24–27% [8, 88–91]. In a Swedish study on 34 SCT, 40% soiling were found in spite of recto-anal inhibitory reflex present and normal. The authors could not determine if anal incontinence was related to the surgery or to the tumor itself [92]. A very long-term follow-up (mean 30 years) was reported by Rintala: if 88% of patients reported themselves with normal fecal continence, only 27% had completely normal bowel habits. As in other reports, no correla-

tion was found between the impaired anorectal functions and the degree of intrapelvic extension of the tumor [91].

Urologic complications are underappreciated sequelae of the mass effect of SCT and of its resection. Most series report ≈ 30% complaints [8, 88–92]. Patient may have no urinary complaints after surgery, but urodynamic investigations reveal anomalies in 78% of cases including neurogenic bladders specially in the intrapelvic forms [88, 90, 93, 94]. Renal impairment may follow obstructive findings on prenatal imaging related to ureteric compressions by the tumor [93].

Sexual activity after resection of SCT seems to be normal. Males reported normal erectile functions and penetration ability with normal ejaculations. However females had significant lower Body Image Questionnaire results compared to males [95]. Successful pregnancies were reported, and neither of their children had SCT [42]. Some authors mentioned obstetric difficulty due to rigid pelvic outlet in their patients [96, 97], but in a series of 20 pregnancies in women after SCT, 17 children were born by vaginal delivery and 3 required Cesarean section [98].

The common complaint among 40% patients is a cosmetically unacceptable scar [8]. According to Derikx, the size of the tumor (>500 cm^3) bears a significant risk factor for cosmetically unacceptable scar. Fishman has described a technique to improve the cosmetic appearance of scar and buttock after SCT resection [99]. However it must be said that the poor quality of the skin and the need for total resection sometimes impede performing a nice reconstruction and closure (Fig. 39.8).

Orthopedic sequelae after SCT removal have been described [96]. Most patients show normal gait pattern but abnormal kinetics of some ambulatory muscles independently of tumor size.

The role of alpha fetoprotein (αFP) and human chorionic gonadotropin (β-HCG) in the follow-up of SCT is well known [85, 100, 101]. Pauniaho demonstrated that αFP was useful in detecting malignant recurrences, while CA-125 was useful in early detection of recurrences of mature and immature tumors [100]. The mean time required for markers to become normal is by 8–12 months after resection [100, 102]. With no decrease at 6 months, an MRI should be done. Thus, regular monitoring of αFP, β-HCG, and CA-125 is recommended in post-surgical follow-up of SCT. However there is no consensus on the frequency and duration of controls. Several authors recommend that patients undergo serum αFP monitoring every 3 months for more than 3 years after SCT resection [86, 101]. Barreto evaluates monthly the αFP in the first 6 months, every 2 months in the following 6 months, and every 3 months in the second and third years [102].

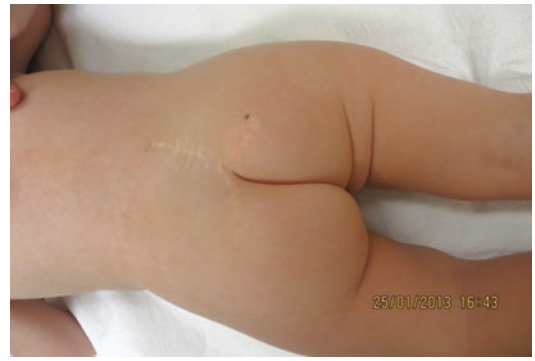

Fig. 39.8 Cosmetic result 4 years post surgery (same patient as in Fig. 39.2)

39.10 Cervical Teratoma

Congenital cervical teratoma represents the second most frequent extragonadal teratoma location after SCT. They are very unusual arising in 1/20,000–40,000 live births [1, 54, 103]. The term epignathus refers to those arising from the oropharynx or palate in the sphenoid region called Rathke pouch [104].

What has been said about SCT is valid for cervical teratoma including cardiovascular complications and fetal hydrops. However according to the location, their masses are likely to cause airway or esophageal compressions. Closure of the esophageal lumen by external compression leads to polyhydramnios and risk of preterm delivery.

Polyhydramnios and hydrops, associated with a large tumor size (>5 cm), have a poor prognosis [105, 106]. Teratoma arising from the face, the pharynx, the palate, or the tongue may occlude the airway leading to respiratory distress at birth, and tracheal intubation can be very difficult or impossible [107–109]. Fetal MRI with 3-D virtual reconstruction (external and internal views of the fetus) provides the best evaluation of the airway compression or distortion.

Then a multidisciplinary planning for delivery must be organized including maternal-fetal specialists, neonatologists, pediatric surgeons, and pediatric anesthetists. Even if the airway appears to remain free of obstruction, Cesarean section is usually necessary with large tumors causing hyperextension of the neck and dystocia [110].

Several procedures have been used to achieve adequate ventilation and oxygenation of the newborn. With airway compression, the best option to ensure a stable airway access is the EXIT procedure (ex utero intrapartum treatment) [111–115]. If antegrade tracheal intubation fails during the EXIT procedure, then a retrograde intubation must be obtained through a tracheostomy [114]. These extreme conditions may lead to 20–30% neonatal deaths [114].

Some teams with experience in ex utero surgery or fetoscopy have been able to reduce the volume of cervical teratoma and successfully free the airway before birth [116, 117].

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Part VIII

Genitourinary

Congenital Ureteropelvic Junction Obstruction

40

Michela Maffi and Mario Lima

40.1 Definition

Primitive or congenital hydronephrosis is a dilation of renal pelvis and intrarenal calyces mostly due to an abnormality of the ureteropelvic junction (UPJ), which results in an inadequate drainage of urine from the pelvis into the ureter. Increased intrapelvic pressure and urinary stasis in the collecting ducts cause progressive damage to the kidney.

40.2 Classification

Several classification systems for urinary tract (UT) dilation have been proposed over time, and some of them are currently used. Perhaps the most basic is the traditional grading system, in which the grade of hydronephrosis is descriptively defined as mild, moderate, or severe [1]. Obviously this is a highly subjective system resulting in poor inter-rater reliability. A more objective system is based on the measurement of the anterior-posterior diameter (APD) of renal pelvis during prenatal age. There is now ample evidence that there is a significant correlation between APD on prenatal ultrasound and the likelihood of pathological dilation after birth, taking into account the fact that the diameter of the renal pelvis increases with gestational age (GA). Mostly accepted thresholds are APD <4 mm in the second trimester and <7 mm in the third trimester. The APD classification is resumed in Table 40.1.

In 1993, the Society of Fetal Urology (SFU) proposed a classification based on the appearance of pelvis, calyces, and renal parenchyma (Fig. 40.1) [2]. In case of monolateral hydronephrosis, parenchymal thickness reduction is considered significant when it is less than half of the non-affected kidney and in case of bilateral hydronephrosis when it is less than 4 mm. The SFU classification is summarized in Table 40.2.

The SFU grading system finds a wide application; however, it emphasizes more intracalyceal and pelvic dilation and does not take into account APD measurement. To overshadow this limit, in 2008, the European Society of Pediatric Radiology has proposed a revision of the SFU classification which includes the introduction of APD measurement [3, 4].

In 2014 a panel of eight societies with a special interest in the diagnosis and management of fetuses and children with UT dilation agreed to collaborate on the development of a unified grading system for perinatal UT dilation (UTD system) and propose a standardize scheme for follow-up evaluation [5]. This is a six-item

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Table 40.1 Definition of antenatal hydronephrosis (ANH) by APD

Degree of ANH	Second trimester	Third trimester
Mild	4 to <7 mm	7 to <9 mm
Moderate	7 to ≤10 mm	9 to ≤15 mm
Severe	>10 mm	>15 mm

grading system that considers the following ultrasound findings in relation to age: ADP, calyceal dilatation, parenchymal thickness, parenchymal appearance, ureter visibility, and bladder aspect. A further prenatal item is represented by unexplained oligohydramnios. In normal fetuses,

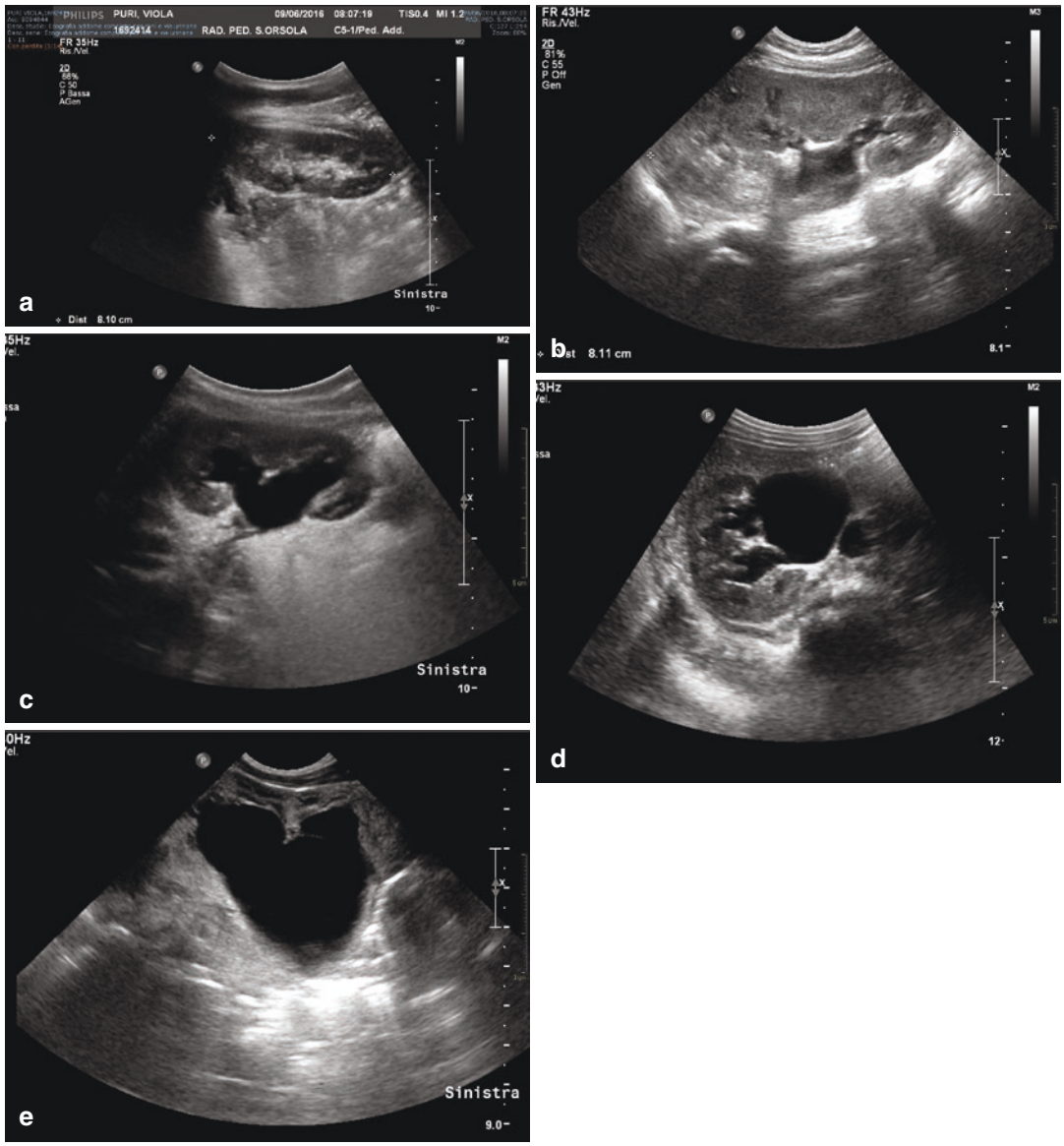

Fig. 40.1 Ultrasonographic appearance of urinary tract dilation according to SFU system. (**a**) SFU grade 0, no splitting; (**b**) SFU grade 1, urine in pelvis barely split sinus; (**c**) SFU grade 2, urine fills intrarenal pelvis/urine fills extrarenal pelvis; major calyces dilated; (**d**) SFU grade 3, SFU gr2 and minor calyces uniformly dilated and parenchyma preserved; (**e**) SFU grade 4, SFU gr3 and parenchymal thinning (segmental 4A or diffuse 4B)

calyceal dilation is absent, renal parenchyma has a normal thickness and appearance, ureter is not visible, bladder is normal, and there isn't oligohydramnios. Normal APD measures <4 mm at <28-week gestation, <7 mm at ≥28 weeks, and < 10 mm postnatally. When UTD is detected antenatally (denoted as A for antenatal), it's possible to identify a low-risk group (UTD A1) and an increased risk group (UTD A2-3). Postnatally detected UTD is denoted by P, and patients are stratified in low-risk (UTD P1), intermediate-risk (UTD P2), and high-risk (UTD P3) groups. The features of each group are summarized in Table 40.3.

Table 40.2 The Society for Fetal Urology Hydronephrosis Grading System (http://www.uab.edu/images/peduro/SFU/sfu_grading_ on_web/sfu_grading_on_web.htm)

	Pattern of renal sinus splitting
SFU grade 0	No splitting
SFU grade 1	Urine in pelvis barely split sinus
SFU grade 2	Urine fills intrarenal pelvis/urine fills extrarenal pelvis; major calyces dilated
SFU grade 3	SFU gr2 and minor calyces uniformly dilated and parenchyma preserved
SFU grade 4	SFU gr3 and parenchymal thinning (segmental 4A or diffuse 4B)

40.3 Embryogenesis

At 4th week of GA, primitive structures such as cloaca and mesonephros have been formed. At 5th week of GA, the ureteral bud, an extroflection of the mesonephric duct, grows in cranial direction until penetrating the metanephric blastema.

The interaction between these structures leads to renal development. The ureteral bud induces the metanephric blastema to form specialized nephrons and is induced to form the pelvis, the calices, and the collecting ducts. From the 10th to the 12th week of GA, urine begins to be produced and to pass in the bladder [4].

From the 18th to the 20th week, virtually all amniotic fluid is made up of fetal urine. Atypical muscular cells, located in the minor calices, act as pacemaker sites. The peristaltic wave propagates through the major calices and activates the muscles of the renal pelvis that push the urine in distal direction. The UPJ represents the transition point in which the pyelic peristaltic activity, characterized by short and frequent waves, turns into ureteral peristaltic activity characterized by wide and slow waves. When the endopyelic pressure overcomes ureteral pressure, the UPJ initially opens, pushing the urine toward the ureter, and then

Table 40.3 UTD classification system

	Prenatal presentation				Postnatal presentation		
APD	16–27 weeks 4 to <7 mm	≥28 weeks 7 to <10 mm	16–27 weeks ≥7 mm	≥28 weeks >10 mm	>48 h APD 10 to <15 mm	>48 h APD ≥15 mm	>48 h APD ≥15 mm
Calyceal dilation	Central or no calyceal dilation		Peripheral calyceal dilation		Central calyceal dilation	Peripheral calyceal dilation	Peripheral calyceal dilation
Parenchymal thickness	Normal		Abnormal		Normal	Normal	Abnormal
Parenchymal appearance	Normal		Abnormal		Normal	Normal	Abnormal
Ureter	Normal		Abnormal		Normal	Abnormal	Abnormal
Bladder	Normal		Abnormal		Normal	Normal	Abnormal
Oligohydramnios	No		Unexplained oligohydramnios		–	–	–
	UTD A1 Low risk		UTD A2-3 Increased risk		UTD P1 Low risk	UTD P2 Intermediate risk	UTD P3 High risk

closes, avoiding the ureteral contraction to cause reflux into the pelvis. A premature stop of ureteral muscle development would lead to an adynamic segment without peristalsis at the UPJ level.

40.4 Etiology and Physiopathology [6]

UPJ obstruction can be dividend in intrinsic and extrinsic forms. In intrinsic forms, a variable portion of UPJ is stenotic or kinked as the ureter enters the pelvis. The urothelial lining is normal but the number of parietal smooth muscular cells is reduced with an increased proportion of collagen between muscle fibers, an increased proportion of elastin in adventitious, and a rearrangement in the orientation of muscle fibers, with predominant longitudinal arrangement. This hypoplastic and adynamic segment is able to discharge urine at low pressures, but cannot adequately respond to an increase in workload with progressive dilation of renal pelvis. The high compliance of renal pelvis in the fetal age and in the first years of life explains the occurrence of severe hydronephrosis not associated with high intrapelvic pressure and secondary renal damage. Other rare forms of intrinsic obstruction are due to the presence of mucous valve or ureteral polyps or the persistence of convoluted fetal ureter. In 10–20% of patients, obstruction of the UPJ is extrinsic, mostly due to the presence of an inferior polar abnormal vessel that intersects the UPJ anteriorly. Extrinsic compression causes a progressive alteration of the ureteral wall, decreasing the number of myocytes, fibrosis and deposition of collagen with consequent stenosis of the lumen. During correction of hydronephrosis due to abnormal vessel, therefore, it is necessary to check patency and function of UPJ after displacement of the crossing vessel. Less frequently, extrinsic obstruction is caused by connective bands or adhesions between pelvis and ureter.

40.5 Epidemiology

The UPJ obstruction has an incidence of 1:500 live births and represents the major cause of primitive hydronephrosis (10–30% of patients with antenatal hydronephrosis are affected by UPJ obstruction) [4]. It is most common in males with an M/F ratio of 2–3:1 and mostly affects the left side (L/R = 2:1). In 15–35% of cases, it is bilateral [7–10].

UPJ obstruction may be associated with other genitourinary anomalies such as horseshoe kidney or be a component of a syndrome such as CHARGE (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies) [11, 12].

40.6 Differential Diagnosis

UPJ obstruction belongs to congenital anomalies of the kidney and urinary tract (CAKUT). All these conditions may present in prenatal age with hydronephrosis as the main feature. CAKUT represent the cause of prenatal hydronephrosis in one third of patients [13]. UPJ obstruction is the most common cause of hydronephrosis, but several other causes of hydronephrosis can be identified:

- Megaureter
- Multicystic dysplastic kidney
- Ureterocele
- Posterior urethral valves
- Ectopic ureter
- Prune-belly syndrome
- Urachal cyst
- Duplex collecting system
- Urethral atresia

40.7 Clinical Manifestation

With the advent of fetal ultrasound, the diagnosis of hydronephrosis is basically prenatal. In patients without early diagnosis, symptoms can be varied and complex. In the neonatal age, a palpable abdominal mass can represent the first and only clinical sign. Classical symptoms may be urinary tract infection, hematuria, and food refusal.

In older children, sometimes, the first episode is a renal colic or a pain localized at flank. In case of bilateral severe hydronephrosis or single

kidney, clinical manifestation can be dominated by symptoms of renal failure.

40.8 Diagnosis

At birth, a diagnostic work-up is required to evaluate the actual presence and entity of dilation, identify the underlying cause, and asses the renal function. The diagnostic tools essential to obtain these information are represented by renal ultrasonography (RUS), voiding cystourethrography (VCUG), and diuretic renal scintigraphy.

40.8.1 Postnatal Ultrasound

Postnatal ultrasound should be performed by the first week of life; RUS performed in the first 48 h of life may underestimate the entity of hydronephrosis due to transient dehydration status with reduced glomerular filtration and diuresis restriction. RUS allows assessment of pelvic and calyceal dilation, thickness of the renal pelvis, possible presence of ureteral dilatation, and the condition of the contralateral kidney and urinary tract. It also provides information on the bladder. In case of UPJ obstruction, the ureter typically has a normal diameter and cannot be visualized during RUS. In case of hydroureteronephrosis, the concomitant presence of ureteral dilation is classified according to the ureteral diameter in grade 1 (<7 mm), grade 2 (7–10 mm), and grade 3 (> 10 mm).

40.8.2 Diuretic Renal Scintigraphy

Diuretic renal scintigraphy is performed by intravenous infusion of a radionuclide, 99mTc DTPA (Tc99m-diethylenetriamine pentaacetic acid) or preferably 99mTc-MAG3 (99mTc-mercaptoacetyltriglycine), followed by the administration of a diuretic (furosemide). While being less accurate in defining renal function than DMSA scintigraphy, the diuretic renal scintigraphy allows to evaluate urinary flow in response to diuretic administration, distinguishing obstructing or non-obstructing forms of urinary tract dilatations. The degree of obstruction is evaluated by calculating the T1/2, i.e., the time needed to eliminate 50% of the radionuclide. A T1/2 greater than 20 min is indicative of obstruction, and a T1/2 between 15 and 20 min is considered doubtful. The T1/2 evaluation is influenced by several factors: technique, hydration status, renal function, and anatomy (Fig. 40.2). Renal scintigraphy should be performed at about 3–4 weeks of life, as kidney immatureness of the newborn results in reduced glomerular filtration and a lower diuretic response.

40.8.3 Voiding Cystourethrography

Voiding cystourethrography (VCUG) consists in acquiring radiographs after filling the bladder with a contrast medium through a transurethral catheter. Adequate bladder filling can be used to detect vesical abnormalities and the presence of passive reflux. The voiding phase shows active VURs, studies the urethral morphology, and evaluates the proper bladder emptying. Voiding urosonography (VUS) is an alternative to VCUG. It is performed by a trans-catheter injection into the bladder of an eco-amplifier contrast medium that allows visualization of any reflux. It offers the advantage of avoid radiation exposure but has limits in providing morphologic informations of the urinary tract.

40.8.4 Intravenous Urography

Intravenous urography allows, in doubtful cases, a better definition of anatomical details. In pediatric age, it is currently underutilized because of high radiation exposure.

40.8.5 Magnetic Resonance Imaging

Magnetic resonance imaging of the urinary system (Uro-RM) can provide accurate anatomical and functional details. It has the advantage of not using ionizing radiation but has the disadvantage of requiring general anesthesia in smaller patients [14–16].

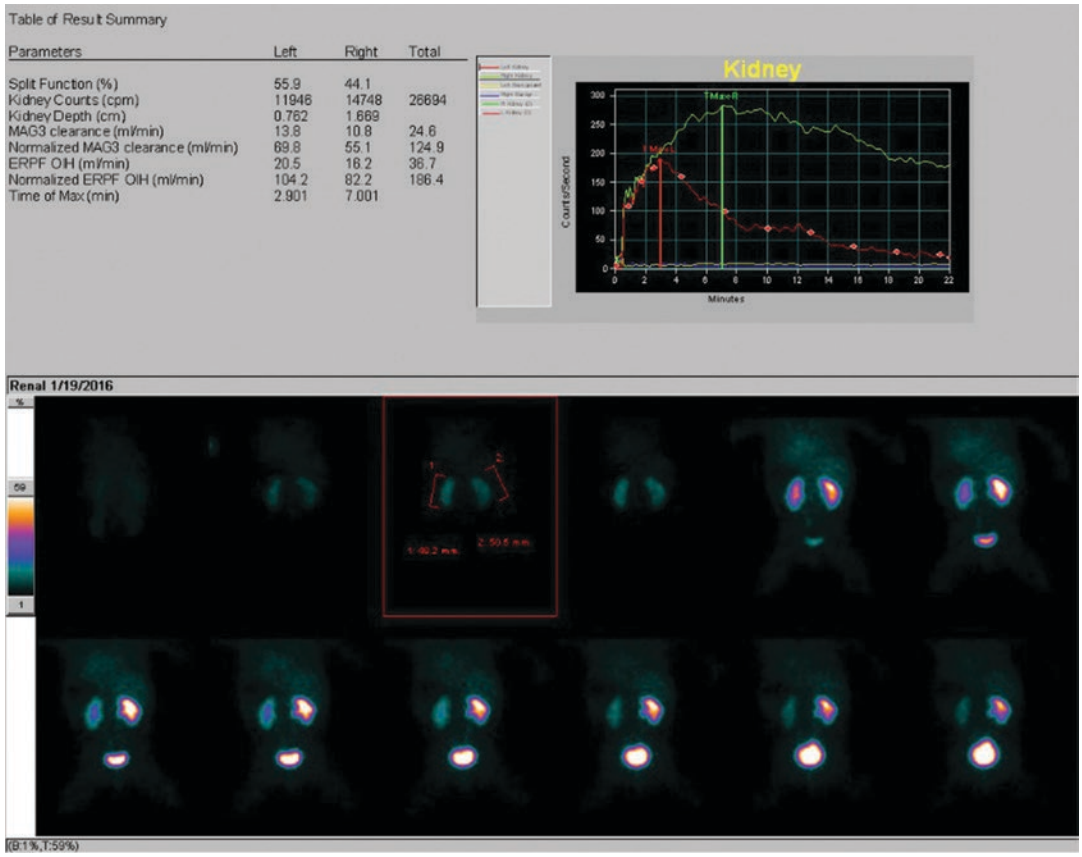

Fig. 40.2 Diuretic scintigraphy showing a persistent stasis of the radiopharmaceutical in the right pelvis

40.9 Postnatal Management According to SFU Classification

40.9.1 SFU I and II Monolateral Hydronephrosis

RUS during the first week of life (>48 h of life) and VCUG at about 1 month. In the absence of VUR, RUS follow-up is performed every 3 months during the first year of life. If VUR is diagnosed, antibiotic prophylaxis is set, and scintigraphic examination to evaluate differential renal function (DRF) is performed at 4–6 weeks. If DRF <40% or there is a worsening of the ultrasound findings, it may be useful to repeat RUS and MAG3 diuretic scintigraphy at 3 months. Conservative treatment is indicated in small children with DRF >40% and good familial "compliance."

Surgery is indicated in cases of DRF <40% with a further reduction of DRF >5% in patients with baseline differential renal function <40%.

40.9.2 SFU III and IV Unilateral Hydronephrosis

RUS during the first week of life (>48 h of life) and VCUG at about 1 month. Antibiotic prophylaxis and MAG3 diuretic renal scintigraphy are performed at 4–6 weeks. In presence of DRF >40%, RUS will be scheduled every 3 months and a MAG3 diuretic scintigraphy at 6 months. In presence of DRF <40%, RUS and MAG3 scintigraphy at 3 months will be scheduled. In case of significant symptomatology, worsening of clinical features, or reduction of DRF >10% compared to the baseline value during follow-up, it is recommended to undergo early surgery.

40.9.3 Bilateral Hydronephrosis SFU III and IV

The management of bilateral hydronephrosis is similar to that of monolateral hydronephrosis of the same degree but varies in the execution time of the VCUG that must be performed during the first 24–48 h of life, to exclude lower urinary tract obstructions (LUTO). In addition, since accurate assessment of differential renal function in a bilateral hydronephrosis is difficult to define, it is desirable to select lower DRF threshold values to indicate surgical correction in order not to further impair renal function.

40.9.4 Criteria for Surgical Correction

The main criteria for surgical correction are:

- DRF <40%
- Reduction of DRF >5%
- Worsening of hydronephrosis
- Severe monolateral hydronephrosis (AP diameter >50 mm)
- Severe hydronephrosis in single kidney
- Severe bilateral hydronephrosis (AP diameter >30 mm)
- Urinary tract infections, symptomatic hydronephrosis

40.10 Management of Hydronephrosis According to UTD System [5]

40.10.1 Antenatally Detected Hydronephrosis

If UTD A1 is diagnosed before 32 weeks, a further RUS at ≥32 weeks is recommended. If the second RUS is normal, no further evaluation is necessary. If UT is persistent after 32 weeks, a postnatal evaluation is recommended whatever is the risk group. After birth, two additional RUS are recommended: the first between 48 h of life and 1 month and the second 1–6 months later. In case of UTD A2-3, the prenatal and postnatal follow-up can be closer, with more than two prenatal RUS and early postnatal evaluation (always at more than 48 h of life).

40.10.2 Postnatally Detected Hydronephrosis

In case of UTD P1, follow-up RUS is recommended at 1–6 months. Antibiotic prophylaxis and VCUG are at discretion of clinician, while functional scan is not recommended.

In case of UTD P2, follow-up RUS is recommended at 1–3 months. Antibiotic prophylaxis and VCUG and functional scan are at discretion of clinician.

In case of UTD P3, follow-up RUS at 1 month, antibiotic prophylaxis, and VCUG are recommended, while functional scan is at discretion of clinician.

Further research will be needed to correlate the UTD classification system risk stratification to other specific clinical outcomes such as surgical intervention, renal function, urinary tract infection, and others. Currently it's possible to convert the existing grading system to the UDT classification. For example, SFU grade 1e2 would be equivalent to UTD P1, SFU grade 3 to UTD P2, and SFU grade 4 to UTD P3.

40.11 Surgical Treatment

In selected and extreme cases, antenatal decompression of hydronephrosis can be considered to prevent dystocic delivery or fetal pulmonary compression.

While in most of cases, surgical treatment can be delayed beyond neonatal age. Nevertheless, following are reported the possible surgical approaches to UPJ obstruction.

40.11.1 Anderson–Hynes Pyeloplasty (Dismembered Pyeloplasty): Open Approach

The almost universally used technique is a dismembered pyeloplasty. It consists of excision of the UPJ stenotic tract, part of the pelvis, and the

proximal ureter. The classical approach is lombotomic extraperitoneal. The patient lays in lateral decubitus and an incision is made at the tip of the 12th rib. Parietal muscles are divided bluntly according to fiber direction. This approach provides direct exposure of the renal hilum. A traction stich is placed in the anterior portion of the pelvis, proximal to the planned section line, and a second traction stich is placed in the anterior portion of the upper ureter, distal to the stenotic tract. These two stiches will act as landmarks to avoid the twisting of the anastomosis. The redundant pelvis is resected, the obstructed UPJ is removed, and the proximal ureter is spatulated on its inferior (posterior) border in order to obtain a wide anastomosis. The anastomosis is performed by placing the first stitch between the inferior part of the spatulated ureter and of the transected pelvis and proceeding up either side with running suture using 6-0 or 7-0 monofilament absorbable sutures. Before completion of the anastomosis, a trans-anastomotic stent is placed [17].

40.11.2 Laparoscopic Approach

The patient lays in slight lateral decubitus. The first 5 mm trocar is placed in the umbilicus, and two additional 3–5 mm trocar are placed in epigastrium (lower rib margin) and in the lower inferior quadrant (iliac crest) of the side to be treated. The pelvis can be reached after mobilization of colic flexure or with transmesocolic approach. Once the pelvis is suspended, the pyeloplasty is performed following the principles of the open technique.

40.11.3 Retroperitoneoscopic Approach

This approach follows the principles of the open approach. The patient is placed in lateral decubitus. The skin incision, for the first 5 mm trocar, is performed at the tip of the 12th rib. Two further 3 mm trocars are placed, at the spino-costal edge and immediately above the iliac crest, respectively. The kidney is approached posteriorly, and the pelvis is identified and isolated. The procedure is then performed as in open approach. In newborn, retroperitoneoscopic approach is limited by the little working space.

40.11.4 Robotic Surgery

Robot-assisted approach is similar to laparoscopic approach, but it provides a greater precision and wider degrees of freedom than conventional laparoscopic instruments. Nevertheless, robotic instruments are still too big (8 mm for Da Vinci Xi and 5 mm for Da Vinci Si but with limited movements and variety of tools) and require too much distance from each other (at least 6–7 cm) to be placed in a newborn, so neonatal experiences are still limited.

40.11.5 One–Trocar–Assisted Pyeloplasty (OTAP)

One-trocar-assisted pyeloplasty is a technique that combines the principles of open approach with those of retroperitoneoscopic minimally invasive surgery (Fig. 40.3). This technique provides retroperitoneoscopic access to the renal loggia using one 10 mm trocar for operative optics, subsequent GPU identification, exteriorization through the surgical incision, and pyeloplasty following the Anderson-Hynes open technique [18].

The surgical incision, about 1 cm length, is made at the tip of the 12th rib. Through the incision, the retroperitoneal space is reached, and the Gerota fascia is opened. The self-anchoring 10 mm trocar is introduced, and CO2 is insufflated, with an 8 mmHg pressure and a 0.5 L/min flow. The working space is created with the help of a laparoscopic swab; the ureter is identified and isolated using the psoas muscle as a landmark. Following the ureter, the lower renal pole and the pelvis are identified. A rubber band is introduced to surround the ureter, and it is exteriorized together with the UPJ. If the pelvic dilation is severe, it can be emptied by an evacuation puncture. The technique proceeds as in the open

approach with the resection of the obstructed tract and the redundant pelvis followed by the suture with 6-0 or 7-0 monofilament absorbable suture. Before the completion of anastomosis, a trans-anastomotic stent such as Mazeman-Porges or a J-J or Pippi-Salle stent is placed. The pelvis is then replaced in the retroperitoneal space, and the anastomosis is checked endoscopically.

If a pyelostomic or nephrostomic stent has been placed, it will be removed, in the fifth post-operative day, while the J-J stent will be removed by cystoscopy after 4–6 weeks.

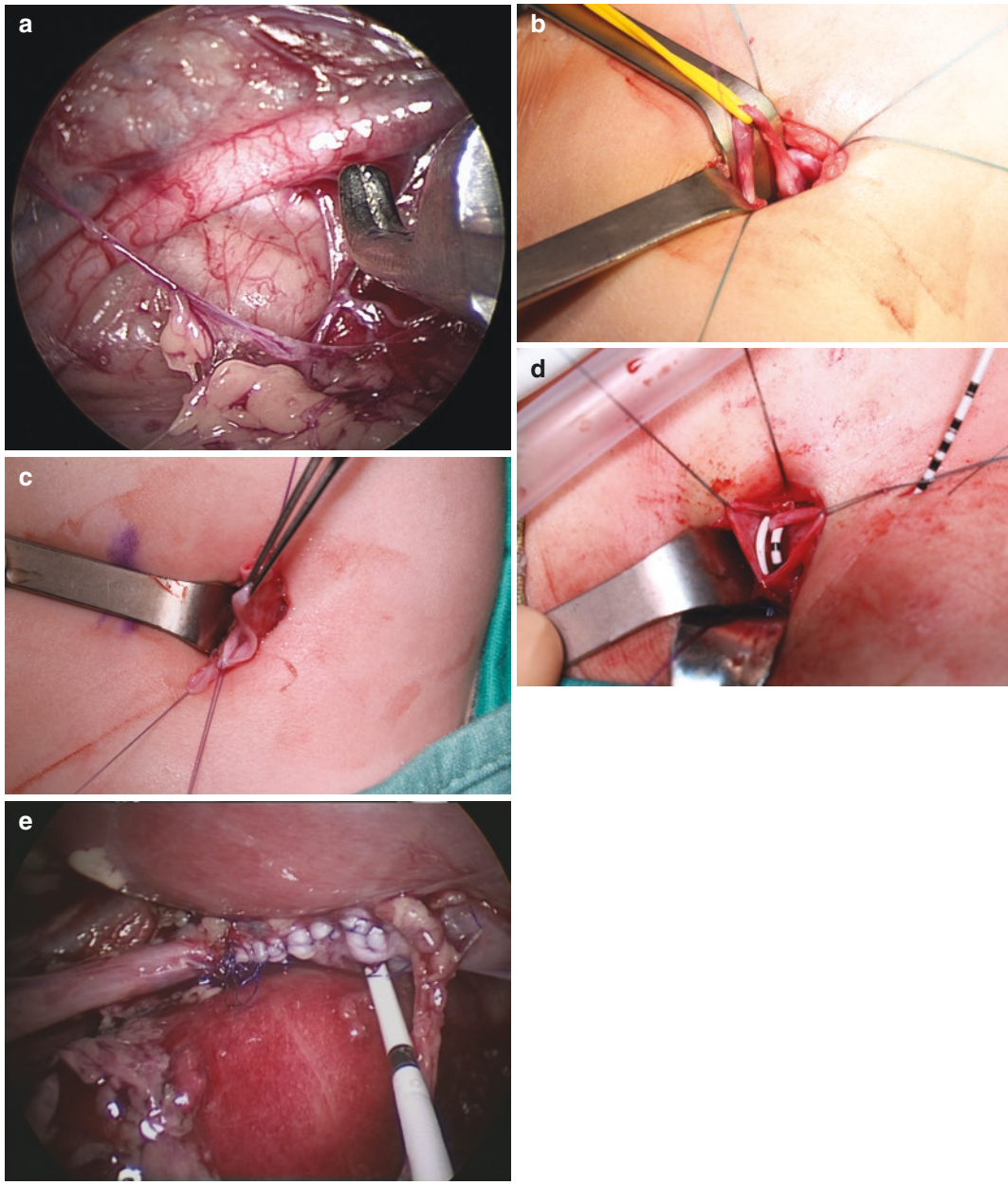

Fig. 40.3 One-trocar-assisted pyeloplasty – OTAP. (**a**) Endoscopic view of the ureter that is identified and isolated; (**b**) exteriorization of the UPJ; (**c**) removal of the stenotic tract and starting of the anastomosis; (**d**) ureteral stent placement; (**e**) endoscopic check of the pyeloplasty at the end of the procedure

40.11.6 Postoperative Follow-Up

RUS is indicated 4–6 weeks after surgery. If the investigation detects an improvement (reduction of the hydronephrosis), seriated RUS is performed at increasing time intervals (initially every 3 months, then annually, and every 2–3 years) [19]. If the follow-up RUS does not show any improvement, a MAG3 scintigraphy is indicated to evaluate the possible recurrence of obstruction.

40.11.7 Complications

Outcomes of open dismembered pyeloplasty are excellent, with resolution of the obstruction in 90–95% of cases, including newborns [20, 21]. Among the possible early complications of intervention, the most frequent is anastomotic leakage with retroperitoneal urinoma formation. Therapy is conservative with or without drainage and antibiotic coverage. The most significant long-term complication is represented by the recurrence of obstruction, which may require re-intervention (5% of cases).

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Multicystic Dysplastic Kidney

41

Michela Maffi and Mario Lima

41.1 Introduction and Definition

Multicystic dysplastic kidney (MCDK) is the most common cystic renal anomaly found in children and the second cause of palpable mass in neonates after hydronephrosis. The kidney is characterized by the presence of multiple non-communicating cysts in absence of normal parenchyma.

41.2 Epidemiology

The estimated incidence of MCDK ranges from 1 in 1000 to 1 in 4300 live births, and males are slightly more affected than females (M/F = 2.4:1) [1]. The MCDK is generally unilateral with the left side more affected than the right one, but there are cases of bilateral MCDK which are mostly incompatible with life since renal tissue has minimal or no activity. In 60–80% of cases, it is diagnosed prenatally [1, 2].

41.3 Etiology

The etiology of MCDK is still not clarified; however, there are two predominant theories.

According to the first theory, pelvic-ureteral atresia leads to severe obstruction with massive hydronephrosis and MCDK, but according to others, the result would be a major hydronephrosis and not cystic dysplasia [2].

The second theory argues that MCDK derives from an altered interaction between the ureteric bud and metanephric blastema [3].

The interaction between the metanephros and the ureteric bud stimulates organogenesis that hesitates in the formation of the nephrons and collector systems. When this interaction is altered, the final architecture of the renal parenchyma will be subverted.

A recent study identified some genes to be mutated in children with MCDK: CHD 1L, ROBO2, HNF 1B, and SALL1 genes [4].

Another less accredited theory attributes a role to exposure to teratogens such as viral agents (cytomegalovirus, adenovirus, enterovirus) or medicaments during pregnancy (antiepileptics) that can cause malformations of the urinary tract among which MCDK [1].

41.4 Associated Anomalies

The incidence of associated anomalies ranges from 5 to 48% [1, 2, 6]. MCDK can be associated with several anomalies involving the contralateral urinary tract such as rotational or positional anomalies, hypoplasia, areas of dysplasia, vesicoureteral

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reflux (VUR) (7–26%), ureteropelvic junction obstruction (UPJO) (1.5–5%), ureterovesical junction obstruction (2%), ureterocele, horseshoe kidney, or genital anomalies [1, 2, 5–10].

Extrarenal associated anomalies include heart defects, esophageal or intestinal atresia, neural tube defects (myelomeningocele), and aneuploidy.

41.5 Diagnosis

41.5.1 Prenatal Diagnosis

About 60–80% of cases of unilateral MCDK are detected with prenatal ultrasound. The classical appearance of MCDK is an abdominal mass consisting of multiple thin-walled cysts of different size, not communicating with each other (Fig. 41.1). The kidney is usually enlarged and irregular, with no visible pelvis, atretic or absent ureter, and small or absent renal artery. Parenchymal tissue between the cysts is often hyperechogenic, and the kidney may reduce in size during pregnancy.

Sometimes the ultrasonographic appearance can be confused with an important hydronephrosis, but in this case, the cysts communicate each other and parenchyma can be seen. Rare case of Wilms tumor, multilocular cyst, or cystic mesoblastic nephroma can have a similar aspect to MCDK.

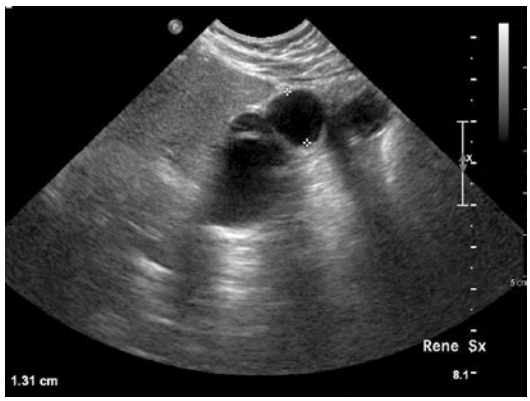

Fig. 41.1 RUS in MCDK showing multiple noncommunicating cysts

41.5.2 Postnatal Presentation

The patient may be totally asymptomatic, and the diagnosis can be done occasionally during an ultrasound examination performed for other reasons.

The most common clinical presentation is a palpable abdominal mass in the neonatal age. The surface is typically irregular in contrast to what happens in case of hydronephrosis or polycystic kidney disease. The contralateral kidney, if not dysplastic, is generally enlarged by compensatory hypertrophy.

41.6 Natural History

The natural evolution of the MCDK is the spontaneous involution. The complete involution may take place during fetal life and is greater in early life. The rate of involution ranges from 35 to 62% by 10 years of age, and if complete involution does not occur, the MCDK may decrease in size (30–44%) or remain stable (13–34%). Initial size less than 5–6 cm seems to be predictive of complete involution [1, 2, 6].

The RVU, frequently present in the contralateral kidney, is in 90% of cases of low grade (<of grade III) and very rarely requires treatment [11].

The MCDK was once accused of being the cause of hypertension. In fact different studies showed that only a very small proportion of patients develop hypertension with a rate ranging from 1.5 to 6% [2, 10, 12–14], but above all, nephrectomy resulted in the resolution of hypertension in 25–50% of cases [3].

Among the theoretical risks of MCDK is malignant degeneration. In particular it has been suggested an association with the occurrence of Wilms tumor. Again, although some cases have been reported, several reviews reported no malignancies in patients with MCDK [2, 11, 15]. We can argue that the total risk of Wilms tumor in MCDK is not increased if compared to the general population and not sufficient to indicate a prophylactic nephrectomy in a healthy patient.

41.7 Management

According to these data, the most correct approach in case of MCDK is a conservative management based on ultrasound monitoring of the kidney and the management of associated anomalies of the contralateral kidney. Currently the debate regards imaging modality, frequency, and duration of follow-up. In particular, the questioned topics involve the need for a confirmatory renal scan and for a routine voiding cystourethrogram (VCUG) and the frequency and duration of ultrasonographic follow-up.

In the past years, a routine renal scan was performed to confirm absence of function of the affected kidney (Fig. 41.2). Recently, in order to avoid radiation exposure, several studies have investigated the benefits of carrying out this investigation, concluding that renal ultrasounds (RUS) are able to diagnose almost all cases of MCDK, so renal scan should be reserved for doubtful cases [16].

Similarly, VCUG should be reserved to patients with contralateral hydroureteronephrosis or signs and symptoms of a UTI as most cases of VUR in MCDK with normal RUS are not clinically significant [2, 5, 17].

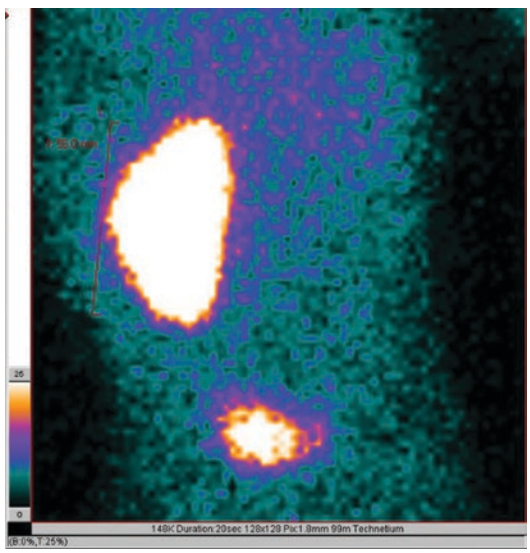

Fig. 41.2 DMSA renal scan showing absence of function of right kidney affected by MCDK disease

A possible algorithm recommends a postnatal RUS and one at 1 year of age with any other imaging investigation guided by any abnormality of the contralateral urinary tract, abnormal blood pressure, or increase in dimension of MCDK [2]. Another more widely accepted algorithm recommends performing RUS at birth, 4 weeks, 2 years, 5 years, and 10 years of age [18]. In all cases, follow-up should be completed by routine blood pressure measurement, urinalysis to detect proteinuria, and renal function studies (e.g., serum creatinine) especially in patients with contralateral abnormalities that may develop chronic renal disease [19, 20].

Currently, nephrectomy is not part of the normal management of MCDK; however, it can be indicated in selected cases:

- Symptoms caused by compression: large or increasing in size MCDK, can lead to intestinal compression. Although it has been called into question the possible decompression, nephrectomy is still one option for treatment.
- Other symptoms: in a minority of cases, the patient may complain of pain, hematuria, recurrent infections, and hypertension. This can also be an indication for surgery [21].
- Equivocal diagnosis: in case of uncertainty, it should be considered that the patient may have another potentially life-threatening disease such as cystic Wilms tumor [22].

41.8 Nephrectomy

The approach to the kidney is traditionally extraperitoneal although it can also be approached transperitoneally. The nephrectomy can be performed with open or minimally invasive surgery, laparoscopic or retroperitoneoscopic, and robotic.

In the open approach, the patient lays in the lateral decubitus with the shoulders rotated slightly forward and the pelvis rotated slightly back. The incision is performed at the apex of the 12th rib. Parietal muscles are divided by blunt dissection following fibers direction. Then the Gerota fascia is opened exposing the kidney. Vessels and ureter are then isolated and dissected. The evacuation by puncture of the cysts can facil-

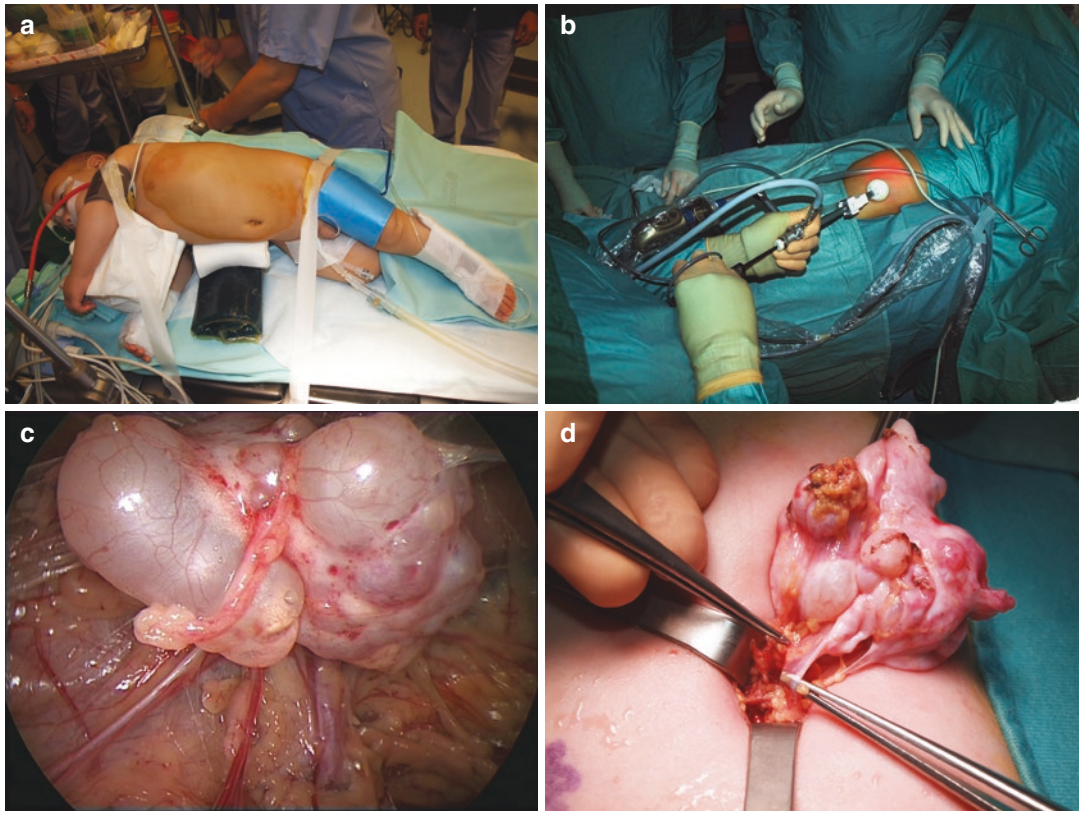

Fig. 41.3 One-trocar-assisted nephrectomy: (**a**) patient position; (**b**) operative setup and trocar placement; (**c**) retroperitoneoscopic appearance of MCDK; (**d**) exteriorization of the MCDK

itate the identification of the hilum and thus the removal of the kidney.

The minimally invasive approach can be retroperitoneoscopic with the patient in the prone position or laparoscopic. In our institute we usually perform a video-assisted retroperitoneoscopic approach through a single access (Fig. 41.3) [23]. The patient position is the same of the open approach, and the incision is performed in front of and above the apex of 12th rib but has minimum extension, just to allow the insertion of 10 mm self-anchoring trocar. The working space is created by blunt dissection with the help of a laparoscopic swab. The kidney is identified and, after emptying the cysts, pulled out through the incision and removed as in open surgery. It should be noted that in case of ipsilateral RVU, it is essential to remove the ureter as distal as possible and suture the residual stump.

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Vesicoureteral Reflux

42

Michela Cing Yu Wong and Girolamo Mattioli

42.1 Definition

Vesicoureteral reflux (VUR) is an anatomical and/or functional disorder characterised by backflow of urine from the bladder into the ureter and, sometimes, in the renal collecting system. Urinary tract infection (UTI) associated with VUR predisposes the child to acute pyelonephritis and possible subsequent renal scars, hypertension and renal failure [1–3]. VUR can be primary or secondary to a urethral obstruction (e.g. in case of posterior urethral valves—PUVs). PUVs are a congenital obstruction of the posterior urethra and are considered one of the few life-threatening congenital anomalies of the urinary tract found during the neonatal period [4].

42.2 Epidemiology

VUR is the most common urologic anomaly in children and affects 1% of children [1–3]. The true prevalence is hard to determine as VUR can also be asymptomatic. The prevalence of VUR in non-symptomatic children has been estimated at 0.4–1.8% [5]. Among infants with prenatal hydronephrosis on ultrasonography (US), the prevalence of VUR is 16.2% [6]. The prevalence of reflux is statistically greater in girls (23%) than boys (16%) for anatomical reasons [6]. Siblings of children with VUR have a 27.4% (3–51%) risk of also having VUR, whereas the offspring of parents with VUR have a higher incidence of 35.7% (21.2–61.4%) [6].

Within children with UTIs, the incidence of VUR is much higher (30–50%, depending on age). UTIs are more common in girls than boys due to anatomical differences [1]. By the age of 6 years, 2% of boys and 8% of girls will have experienced a UTI [7]. Most infections occur during the first 2 years of life, with boys dominating during the first 6 months and girls thereafter [8, 9]. Specific risk factors for acute pyelonephritis and renal scarring in patients with VUR include a higher grade of reflux, dysfunctional voiding/elimination, recurrent pyelonephritic episodes and delayed initiation of antibiotic therapy [10]. Untreated recurrent UTIs may have a negative impact on somatic growth and medical status of the child. It is important to underline that renal scarring in patients with VUR is the result of both the congenital dysplasia and acquired postinfectious damage [10].

Primary VUR is a disease with a good spontaneous resolution. It depends on age at presentation, sex, VUR grade, laterality, mode of clinical presentation and ureteral anatomy [11]. Age <1 year at presentation, lower grade of reflux (grades 1–3), asymptomatic presentation with prenatal hydronephrosis or sibling reflux and

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single ureter are associated with significantly earlier resolution of reflux. Spontaneous resolution is low for bilateral high-grade reflux [11].

Secondary VUR is usually caused by the presence of PUVs. As this disorder develops early in gestation, the bladder and upper urinary tract are exposed to high pressure throughout development. Despite optimal treatment, PUVs in children could result in renal failure in almost one-third of cases [12]. The incidence of PUVs has been estimated of 2.2 in 10,000 births, with up to 62% being diagnosed prenatally [4, 13]. Despite their rarity, PUVs present such a severe insult to the upper urinary tract that they account for almost 17% of children with end-stage renal failure [14, 15].

42.3 Clinical Presentation and Diagnostic Pathway

VUR clinical presentation could be variable. The clinical pictures are [1]:

1. Prenatal hydronephrosis.
2. Siblings and/or offspring of patients with VUR.
3. Febrile urinary tract infections/pyelonephritis.

42.3.1 Prenatal Hydronephrosis

The detection of congenital anomalies has increased because of the widespread use of routine second trimester US. One of the most frequently detected abnormalities is the dilation of the foetal renal collecting system, affecting 1–4.5% of all pregnancies [16–18]. The prenatal detection of pelvis dilation is not always associated with pathological conditions; in fact, these findings may instead reflect normal physiology [17]. It is important to distinguish prenatal sonographically evident renal pelvis (SERP) from hydronephrosis, which consists also in calices dilation [16].

Up to 64–94% of foetuses with prenatal SERP will ultimately have no identifiable postnatal urologic abnormality [19–21]. There is a significant increase in risk per increasing degree of prenatal hydronephrosis [20]. Several studies have tried to assess the threshold for diagnosing foetal hydronephrosis associated with persistent renal anomalies [22–24]. The most commonly accepted values are those described initially by Corteville and colleagues: an anterior-posterior diameter (APD) greater than or equal to 4 mm before 33 weeks' gestation or 7 mm after 33 weeks' gestation allows the identification of 100% of foetuses that ultimately will have impaired renal function or require surgery [24].

To characterise the dilatation of the collecting system and correlate foetal hydronephrosis with postnatal clinical relevance, the Society for Fetal Urology (SFU) developed a grading scale for foetuses older than 20 weeks' gestation [25] (Table 42.1):

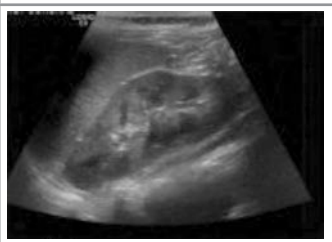
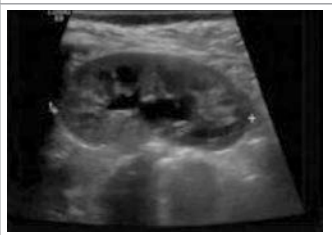
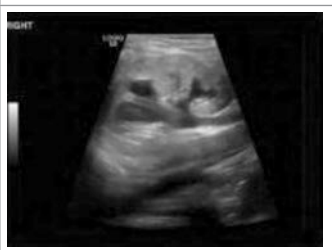
- Grade 0: no hydronephrosis.
- Grade 1: the renal pelvis only is visualised.
- Grade 2: hydronephrosis is present when a few but not all calices are identified in addition to the renal pelvis.
- Grade 3: hydronephrosis requires that virtually all calices are seen.
- Grade 4: hydronephrosis may have a similar appearance of the calices as grade 3 but, when compared with the normal side, the involved kidney has parenchymal thinning.

Neither the SFU grading scale nor APD has the ability to specifically identify pathological cases. They remain indicators of 'potential' disease [26].

In the presence of PUVs, antenatal US commonly demonstrates a distended thick-walled bladder and a dilated posterior urethra (keyhole sign), associated with monolateral/bilateral hydroureteronephrosis and sometimes oligohydramnios. This disorder may account for up to 10% of all prenatally detected hydronephrosis [13].

After the birth, physical examination is usually normal. Basic serum laboratory exams, specifically creatinine, are not necessary for children with unilateral prenatal hydronephrosis, but

Table 42.1 Hydronephrosis grading on ultrasound imaging

SFU grade	Patterns of renal sinus splitting		Grade	APD at >20 weeks gestation/ calyceal dilation (13)
SFU 0	No splitting			n/a
SFU 1	Urine in pelvis barely splits sinus		1	1 cm Normal calyces
SFU 2	Urine fills intrarenal pelvis or urine fills extrarenal pelvis and major calyces dilated		2	1–1.5 cm calyces are normal

(continued)

Table 42.1 (continued)

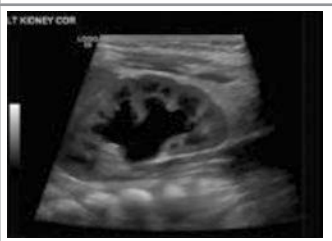
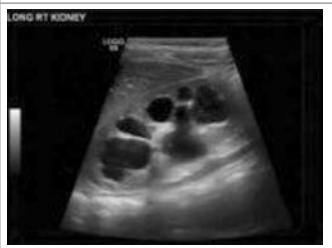
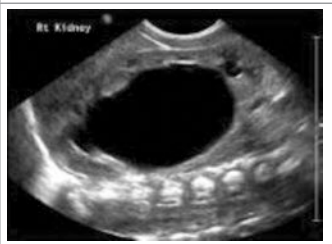
SFU grade	Patterns of renal sinus splitting		Grade	APD at >20 weeks gestation/ calyceal dilation (13)
SFU 3	SFU grade 2 + minor calyces uniformly dilated and parenchyma preserved		3	>1.5 cm slight caliectasis
SFU 4 SFU grade3 + parenchyma thinning			4	>1.5 cm moderate caliectasis
			5	>1.5 cm with severe caliectasis and thinning of the renal cortex <2 mm thick

Table 42.1 [refers to 23, 24]—SFU hydronephrosis grading
SFU Society for Fetal Urology, *APD* anterior-posterior diameter

should be mandatory on those with bilateral significant hydronephrosis associated with distended bladder and increased renal echogenicity as the risk of bladder outlet obstruction (e.g. in case of PUVs) is higher with a more severe disease process [26]. The initial serum creatinine reflects maternal renal function, but it could be useful as baseline value. Serum creatinine for a term newborn should be 0.4 mg/dL by day 7 of life [26].

Imaging includes postnatal renal and bladder US, voiding cystourethrogram (VCUG) and diuretic renal scintigraphy [21, 27]. If PUVs are suspected, the postnatal US and VCUG should be performed immediately as the risk of renal insufficiency is high [26]. In the presence of PUVs, the VCUG will demonstrate a dilated posterior urethra and trabeculated bladder, often vesicoureteral reflux, and the valve leaflets themselves could be detected [4, 15]. It is important to have a voiding view of the urethra without the catheter in order to make a complete evaluation of the urethra and to document all cases of valves [4, 15].

Current SFU guidelines suggest that a prenatal hydronephrosis diagnosed in the second trimester that resolves on repeat ultrasound in the third trimester does not require postnatal evaluation, while it is required in any cases of prenatal hydronephrosis in the third trimester [28].

The postnatal US ideally should be performed between 5 and 30 days, as performing it in the first 2 days of life may underestimate the degree of hydronephrosis due to the newborn's oliguria [1, 26]. It is commonly recommended that a follow-up ultrasound after 1 month is necessary to confirm resolution. In infants with two normal successive scans, VUR is a rare entity, and, if present, it is likely to be low grade [1, 16, 27].

US cortical abnormalities (as cortical thinning or increased echogenicity) are more common in high-grade hydronephrosis and warrant the use of VCUG for detecting VUR and/or PUVs [1]. VCUG for VUR evaluation is recommended also in patients with bilateral high-grade hydroureteronephrosis, duplex kidneys with hydronephrosis, ureterocele and abnormal bladders, because the likelihood of VUR is much higher.

42.3.2 Siblings and/or Offspring of Reflux Patients

The screening of siblings and offspring of patients with VUR is very controversial. Siblings of patients with VUR are at greater risk of having reflux compared to the general population. It seems that the incidence of sibling VUR is maximal in patients who are younger than 3 years old. In symptomatic siblings younger than 3 years old, reflux is usually high grade and associated with a higher incidence of renal scarring [29]. The screening is recommended in siblings younger than 3 years old of index patients with grades III–V VUR [29]. In older asymptomatic siblings of index patients, the incidence is very low, and the observation alone is the preferred option [30]. Other authors suggest the necessity of screening all siblings of index patients with VUR as the risk of nephropathy and renal scarring is present also in asymptomatic older siblings [31].

42.3.3 Children with Febrile Urinary Tract Infections/ Pyelonephritis

UTIs are the most common bacterial infections in young children with an incidence of renal scarring of 15%. Children with VUR are significantly more likely to develop pyelonephritis and renal scarring compared with children without VUR [32]. Infections caused by *Escherichia coli* are the most common, although, in the first year of life, *Klebsiella pneumoniae*, *Enterobacter* spp., *Enterococcus* spp. and *Pseudomonas* spp. are more frequent than later in life [33].

Signs and symptoms of UTIs are usually nonspecific, especially in newborns. In young children fever may be the only symptom of UTIs. In newborns UTIs may manifest themselves as sepsis with nonspecific signs and symptoms as poor weight gain, appetite loss, anorexia, vomiting, poor sucking, irritability, lethargy, convulsions and hypothermia [34]. In older children, lower urinary tract symptoms include dysuria, frequency, urgency, malodorous urine, incontinence,

haematuria and suprapubic pain for the upper urinary tract, fever and flank pain [34].

The physical examination should be complete, covering nutritional aspects, growth and psychomotor development. Laboratory tests include C-reactive protein, blood cell counts and renal function, and, in severe cases, blood cultures should also be taken [34]. Diagnosing UTIs requires appropriate collection of uncontaminated urine sample for uranalysis and urine culture. It is recommended to collect urine in a clean manner in children who are toilet-trained, while in infants and younger children, urine should be obtained by urinary catheterisation or suprapubic aspiration [35]. Urine culture remains the reference standard for diagnosing UTIs, even if the results are not immediate [35]. Significant UTIs are characterised by more than 105 CFU/ml of voided urine [34].

In patients with UTIs, imaging techniques are very important. The most effective diagnostic strategy for children with UTI has been debated for several years, but no consensus has yet been reached. Renal US is the first-line imaging exam if a UTI is suspected. It is useful for detecting renal abscess, hydronephrosis, congenital abnormalities and sometimes stones, but it has a lower sensitivity for diagnosing pyelonephritis than dimercaptosuccinic acid renal scan—DMSA [35].

Two possible imaging strategies have been proposed for the diagnosis of VUR in patients with UTI: the bottom-up method (VCUG and, if positive, a DMSA scan) or the top-down method (DMSA scan and, if positive, VCUG) [34, 36, 37]. The American Academy of Pediatrics guideline recommends that VCUG should not be performed routinely after the first febrile UTI [38]. The EAU/ESPU guideline recommends that, for infants under 1 year of age, VUR should be excluded by VCUG and/or DMSA scan [1]. A VCUG is usually delayed for 2–4 weeks after successful UTI treatment to assess the presence of VUR and/or PUVs. Grade III, or higher, is significantly associated with a higher risk of renal cortical damage, and a DMSA scan should be considered to assess for renal scarring [33]. Usually a delay of 4–6 months is needed following acute pyelonephritis to allow acute reversible lesions to resolve in order to detect definitive renal scarring [35].

42.4 Imaging

The aim of the diagnostic work-up should be to evaluate the overall health and development of the child, the presence of UTIs, renal status, the presence and grading of VUR and the presence of low urinary tract obstruction. A basic diagnostic work-up comprises a detailed medical history (including family history), physical examination including blood pressure measurement, urinalysis (assessing proteinuria), urine culture and serum creatinine in patients with bilateral renal parenchymal abnormalities [1]. Currently there is no consensus regarding the best imaging approach after the first episode of febrile UTI. In this context, Williams et al. suggest a simple and direct approach: (1) renal and bladder US in all children and (2) VCUG and/or DMSA for children with abnormal renal tract sonography.

42.4.1 Renal and Bladder Ultrasound (US)

Renal and bladder US is a non-invasive tool and provides reliable information regarding bladder wall, kidney structure, size, parenchymal thickness and collecting system dilation [1]. US is considered the first-line imaging exam in paediatric population because of the lack of radiation, low cost and easy access [26]. A good hydration of the child should be required during the US, and thus he is allowed to eat and drink normally prior to this study [26]. As said, in patients with prenatal hydronephrosis, the postnatal US ideally should be performed between 5 and 30 days, as in the first 2 days of life, the neonatal oliguria may lead to underestimate the degree of hydronephrosis [1, 26], while when PUVs are suspected, the US should be performed immediately as the risk of renal insufficiency is higher [26]. The following features must be carefully evaluated: renal parenchyma and size, degree of hydronephrosis,

presence of associated ureteral dilation, duplicated collecting systems, ectopic ureters or ureteroceles and bladder anatomy [1, 16].

42.4.2 Voiding Cystourethrogram (VCUG)

VCUG is required to evaluate the anatomy and capacity of the bladder, bladder neck and urethra and to detect VUR (Figs. 42.1 and 42.2) [26]. In the international scientific panorama, no agreement on performing VCUG routinely has been achieved. In fact, on the one hand, VCUG is considered the gold standard as it better characterises VUR and permits evaluation of the urethra and bladder [2]; on the other hand, an inappropriate number of negative VCUGs and radiation exposure could be avoided [39]. Lee et al. suggest this radiologic exam should be required only if the US has one of the following three findings: presence of hydroureter, renal dysmorphia or duplication [39]. In 1985, the International Reflux Study Committee introduced a uniform system for the classification of VUR. It is based upon the extent of filling and dilation by VUR of the ureter, the renal pelvis and the calyces [40] (Table 42.2):

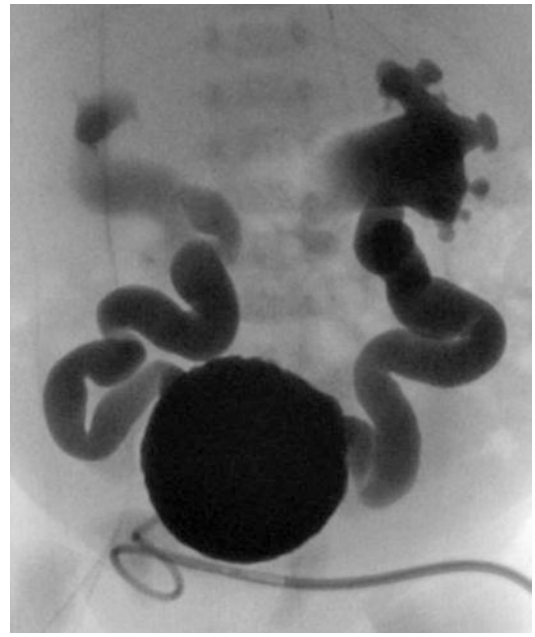


Fig. 42.2 CUM image of a newborn of 3 days of age with PUVs and consequent bilateral reflux

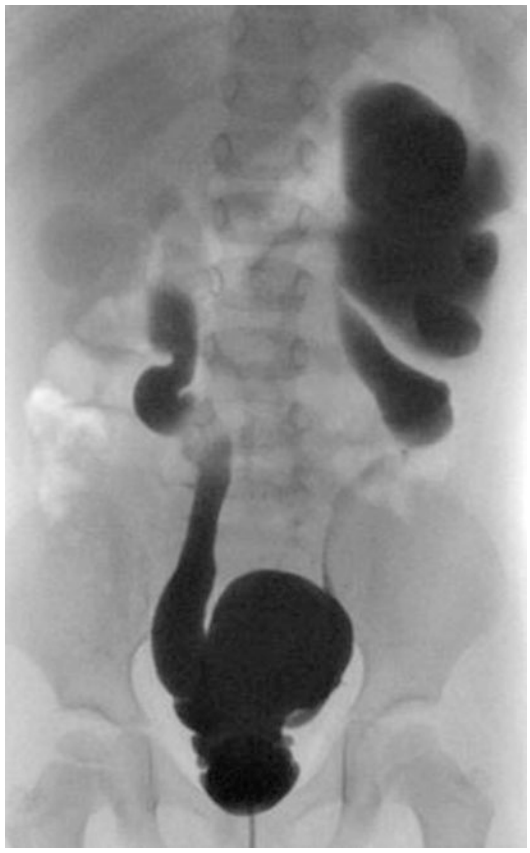
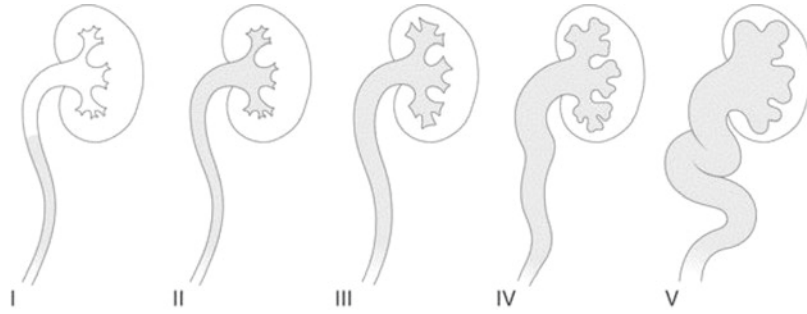


Fig. 42.1 CUM image of a bilateral reflux in a 2-year-old girl with recurrent UTIs and reflux nephropathy

42.4.3 Renal Cortical Scintigraphy (Dimercaptosuccinic Acid (DMSA) Renal Scan)

Renal cortical scintigraphy with DMSA is the gold standard for diagnosing renal scars and pyelonephritis [2]. DMSA is the best nuclear agent for visualising the cortical tissue and for evaluating the differential function between the kidneys. In fact, DMSA is taken up by proximal renal tubular cells and in areas of acute inflammation or scarring; DMSA uptake is poor and appears as cold spots. DMSA is important to detect and monitor renal scarring [1, 41].

Table 42.2 Grading system for VUR on VCUG, according to the International Reflux Study Committee [refer to 1, 36]



Grade I	Reflux does not reach the renal pelvis; varying degrees of ureteral dilatation
Grade II	Reflux reaches the renal pelvis; no dilatation of the collecting system; normal fornices
Grade III	Mild or moderate dilatation of the ureter, with or without kinking; moderate dilatation of the collecting system; normal or minimally deformed fornices
Grade IV	Moderate dilatation of the ureter with or without kinking; moderate dilatation of the collecting system; blunt fornices, but impressions of the papillae still visible
Grade V	Gross dilatation and kinking of the ureter, marked dilatation of the collecting system; papillary impressions no longer visible; intraparenchymal reflux

In 2004, Hansson et al. introduced the top-down approach, which consists of performing a DMSA scintigraphy in all patients with the first UTI and later performing VCUG only in those patients with defects on DMSA scintigraphy [42]. Following this approach, a great number of unnecessary VCUGs are avoided and less than 0.05% of children with damaged kidney is missed [42].

42.4.4 Echo-Enhanced Cystosonography (CSG)

Echo-enhanced CSG has been proposed as an alternative exam to VCUG. It is a safe imaging tool, which allows the detection of VUR without the exposition to ionising radiation. Excellent results have been described with the use of US echo-enhancement agents made of galactose suspension as SH U 508A in paediatric patients [43–47]. CSG has a diagnostic accuracy superior to 90%, and it seems that CSG may also help to evaluate disease in patients in whom there is a high suspicion for VUR but a negative VCUG image, because it can be repeated without additional radiation exposure [47]. CSG can be an alternative to VCUG under the following conditions:

- First diagnosis in females.
- VUR monitoring both during antibiotic prophylaxis and after endoscopic treatment and/or vesicoureteral reimplantation.
- Stenotic megaureters and/or ureteroceles already diagnosed and treated or not treated by endoscopy or transvesical surgery.
- Diagnosis of VUR in transplanted kidneys [46, 47].

42.5 Treatment

There are two approaches for VUR therapeutic management [1]:

1. Conservative approach
2. Surgical approach

42.5.1 Conservative Approach

The aim of the conservative approach is to prevent febrile UTI and scar formation, considering that approximately 20% of those children who experience one infection will have a repeat episode [1, 48]. The conservative option is based on the knowledge that VUR can be resolved sponta-

neously, especially in young patients with low grade; and it includes watchful waiting, antibiotic prophylaxis, bladder rehabilitation and bowel management [49].

In scientific literature, the use of antibiotic prophylaxis has always been very controversial because of the lack of properly randomised and controlled studies. For a long time, evidence regarding the efficacy of prophylactic therapy to prevent recurrences after the first episode of UTI has been lacking for the infant population [48]. Several studies have prospectively observed children with reflux on and off prophylaxis and found similar rates of infection between the groups [50–54]. In 2014 the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial was published. It is a randomised, double-blind, placebo-controlled trial of prophylaxis with trimethoprim-sulfamethoxazole in children with VUR that was diagnosed after a first or second febrile or symptomatic urinary tract infection [55]. According to this study, antibiotic prophylaxis reduces the risk of recurrences by 50% compared to placebo. Moreover, it seems that children with bladder and bowel dysfunction at baseline and children whose first infection is febrile derive particular benefit from prophylaxis.

Another controversial aspect is the occurrence of renal scarring in children with and without prophylaxis. It seems that the scar occurrence does not differ significantly between the two groups [55].

Finally, several studies have shown VUR resolution after treatment for bladder and bowel dysfunction (BBD), which underlines the important correlation between the treatment of BBD and higher success rates of surgical VUR treatments, as well as medical therapy, biofeedback and behavioural treatment [56, 57].

42.5.2 Surgical Approach

Surgical approach should be distinguished between primary VUR and secondary VUR treatment (VUP treatment).

42.5.2.1 Primary VUR Surgical Treatment

Surgical treatment is usually reserved for patients with high-grade VUR, recurrent UTI despite antibiotic prophylaxis and noncompliance with prophylactic antibiotics [58]. Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation.

Endoscopic VUR Treatment

Since its first clinical application in VUR in 1984 by O'Donnell and Puri [59], endoscopic treatment has gained great popularity among paediatric urologists, particularly after dextranomer/hyaluronic acid (Dx/HA) copolymer approval by the US Food and Drug Administration (FDA) in 2001. Over the years, a number of different tissue-augmenting substances have been evaluated in clinical practice: polytetrafluoroethylene (Teflon), bovine collagen, polydimethylsiloxane (Macroplastique), autologous chondrocytes, synthetic calcium hydroxyapatite, Dx/HA copolymer (Deflux) and polyacrylate-polyalcohol copolymer (Vantris) [59–67]. Using cystoscopy, bulking agents are injected beneath the intramural part of the ureter in a submucosal location, elevating the ureteral orifice and the distal ureter so that competence is increased. The lumen is consequently narrowed, preventing urine reflux into the ureter, while still allowing the urine's antegrade flow [68]. Two possible techniques have been described: subureteral transurethral injection (STING) and hydrodistension implantation technique (HIT). STING technique was first introduced by Matouschek in 1981 [69] and subsequently popularised by O'Donnell and Puri in 1984 [59]. STING consists of inserting the needle 2–3 mm below the ureteric orifice at 6-o'clock position and advancing it for another 3 mm (Fig. 42.3). The intention is to create a 'crescent-shaped' ureteric orifice [69, 70]. HIT technique was first described by Kirsch in 2004 [71]. In this procedure, the lumen of the distal ureter is distended by hydrostatic pressure, and the bulking agent is injected 4 mm into the submucosa of the mid/distal ureteral tunnel at the 6-o'clock position (Fig. 42.3). The aim is to

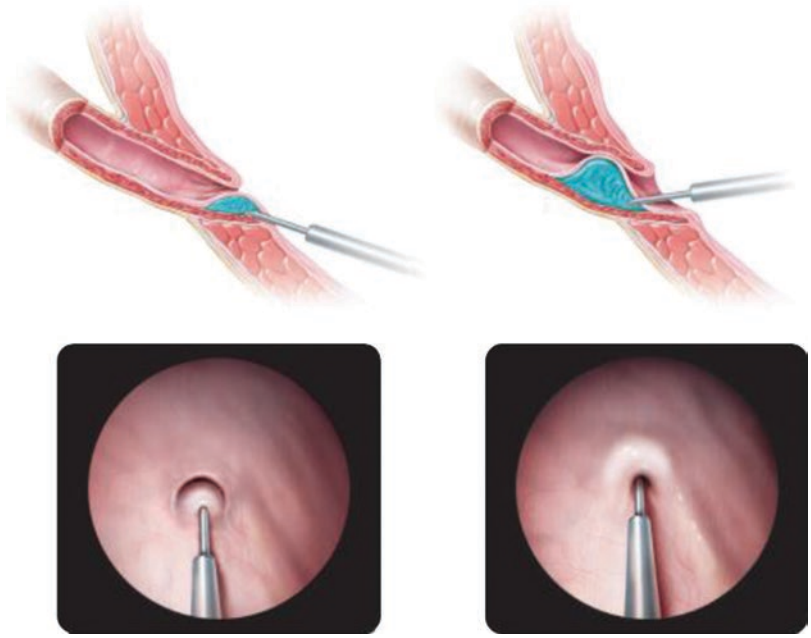


Fig. 42.3 STING technique on the left and HIT technique on the right (from G. Lackgren and A.J. Kirsch (2010). Surgery illustrated Surgical atlas: endoscopic treatment of VUR [72])

convert the ureteric orifice into a volcano-shaped mound upon completion of the injection [70, 71]. It seems that HIT is superior to STING technique for resolution of VUR after Dx/Ha injection [70].

According to a meta-analysis conducted in 2010 [73], within 5527 patients and 8101 renal units, VUR resolution after one endoscopic treatment with Dx/HA is 78.5% for grades I and II reflux, 72% for grade III, 63% for grade IV and 51% for grade V. If the first injection is unsuccessful, the second treatment has a success rate of 68% and the third treatment 34%. The overall success rate with one or more Dx/HA injections is 85%. The success rate is correlated to the preoperative VUR grade, and it is significantly lower for duplicated (50%) versus single (73%) systems and neuropathic (62%) versus normal (74%) bladders [73].

Some studies have shown that, after endoscopic Dx/HA injection, there is a high recurrence rate which may rise as high as 20% in 2 years [74, 75]. These findings have led to research for new substances with a higher long-term efficacy, and, for this reason, polyacrylate-polyalcohol copolymer has been introduced. It is a non-biodegradable tissue-augmenting substance, which may lead to the better stability of the injectable material and avoids VUR recurrence, also after 3 years of follow-up [76–78].

Complications after the endoscopic procedure are infrequent and relate mainly to the obstruction of ureterovesical junction and the development of a new contralateral VUR after treatment of unilateral VUR [78].

Endoscopic approach is a safe procedure with low risk of complications, and it is currently the method of choice among most urologists and parents for children over the age of 1 year [58, 79].

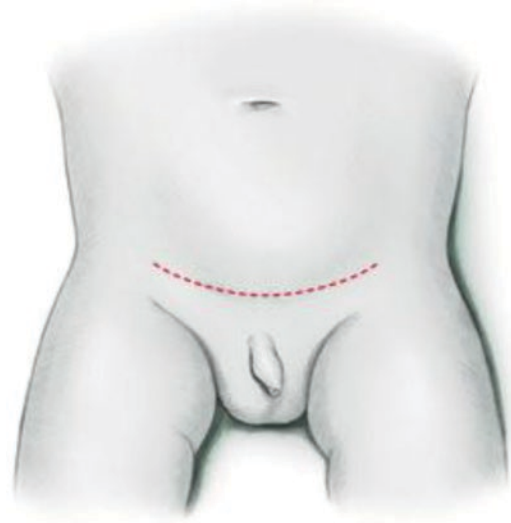
Ureteral Reimplantation

Various intravesical and extravesical techniques have been described for the surgical correction of VUR. They are all based upon the basic principle of lengthening the intramural part of the ureter by submucosal implantation of the ureter to create a 4–5:1 ratio of submucosal tunnel length to ureteral width. The most widely used technique is the intravesical Cohen cross-trigonal reimplantation [80]. The main concern with this procedure is the difficulty of accessing the ureters endoscopically if needed when the child is older [1]. Success rate currently ranges between 95% and 98%. Other reimplantation techniques which

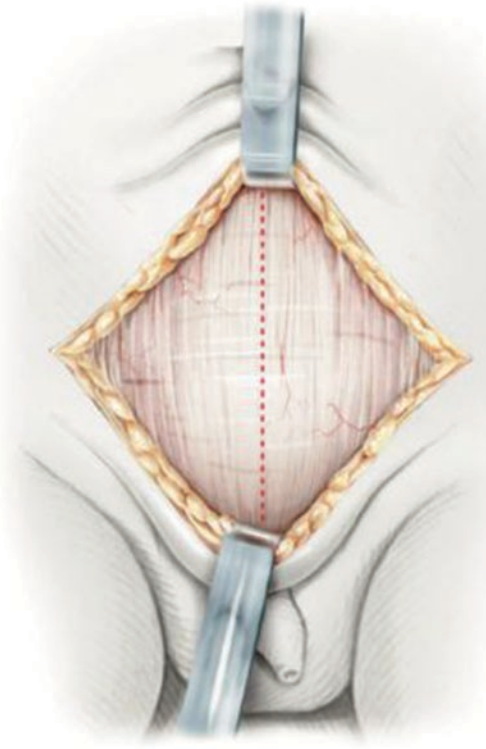
have been described are Politano-Leadbetter suprahiatal reimplantation [81], Glenn-Anderson infrahiatal reimplantation [82] and Lich-Gregoir extravesical reimplantation [83]. VUR surgical treatment has been described also with laparoscopic and robotic approaches. Lakshmanan et al. were the first to describe laparoscopic extravesical reimplantation in humans [84]. A novel minimally invasive cross-trigonal ureteral reimplantation technique under pneumovesicum was reported by Yeung in 2005, and it is now widespread with a high success rate (92–94%) [85–87].

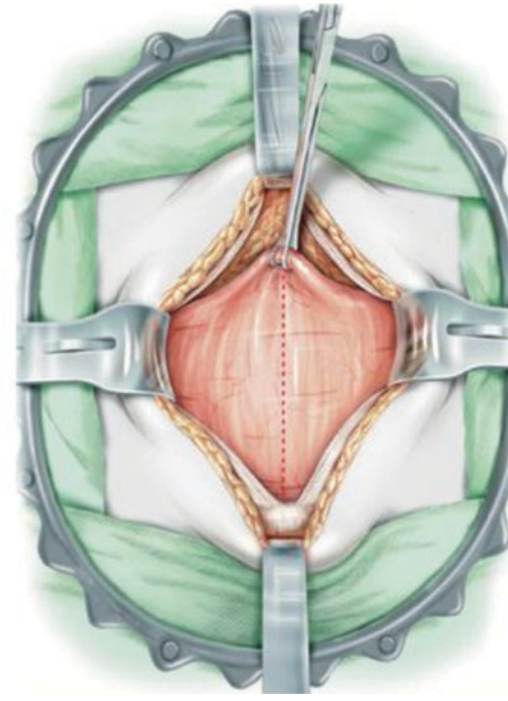
Cohen Reimplantation

Cohen described the intravesical cross-trigonal reimplantation in 1975 [80]. The procedure is illustrated in the following figures (from Mure, P.-Y. and Mouriquand, P. D.E. (2004), Surgical Atlas The Cohen procedure. BJU International, 94: 679–698. doi:https://doi.org/10.1111/j.1464-410X.2004.05083.x) [88]:

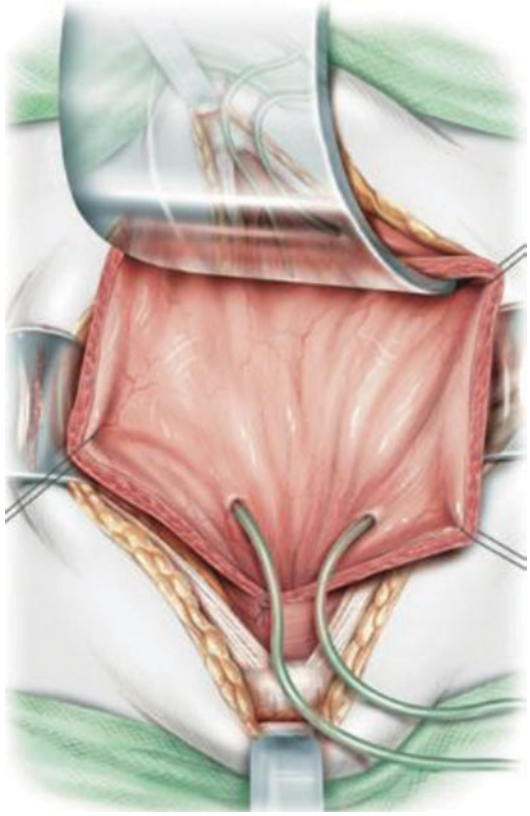


1. A transverse suprapubic incision is made 2 cm above the pubic symphysis.

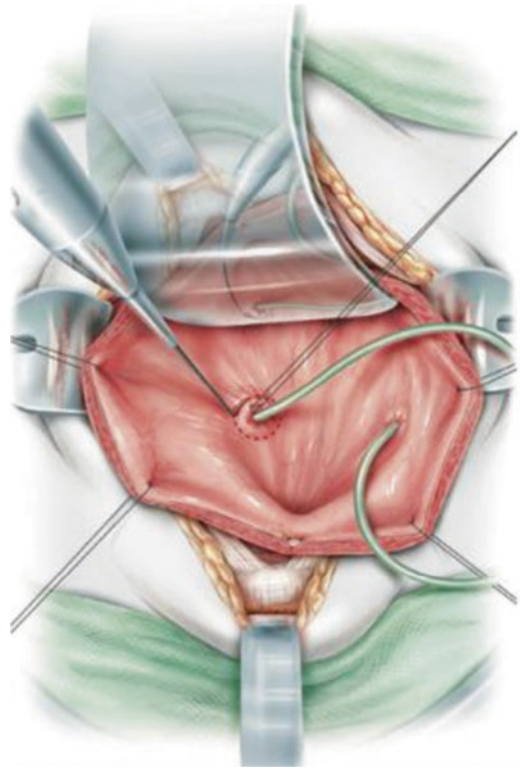




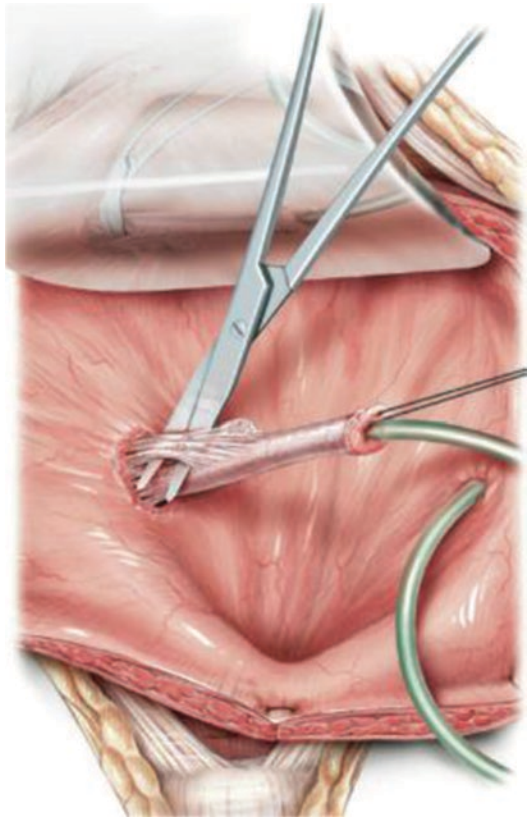
2. The rectus and the bladder are opened vertically in the midline.



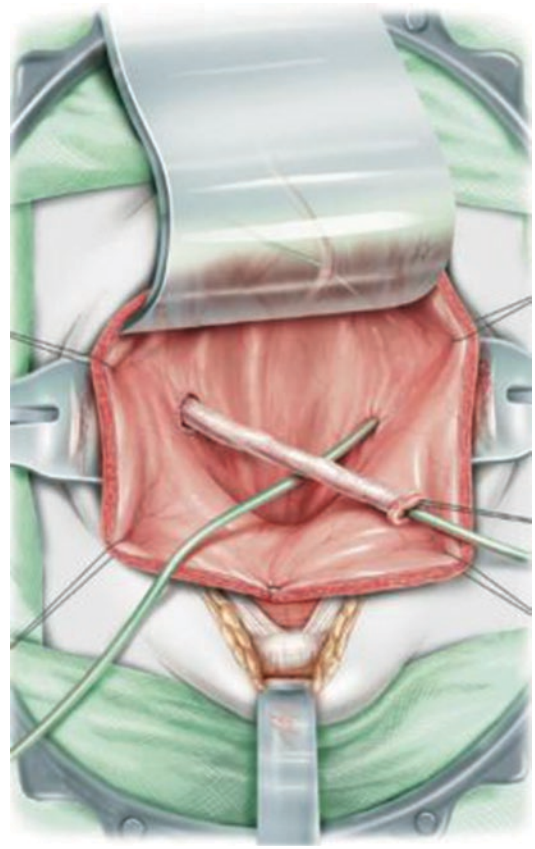
3. Two or three stay sutures are placed on each side to expose the bladder. To expose the trigone, one or several swabs are put inside the bladder and retracted upwards. A 3/0 or 4/0 absorbable suture is placed at the lowest point of the vesicostomy, to prevent the incision downwards into the bladder neck and the urethra. A feeding tube (usually 4F) is inserted into each ureter.



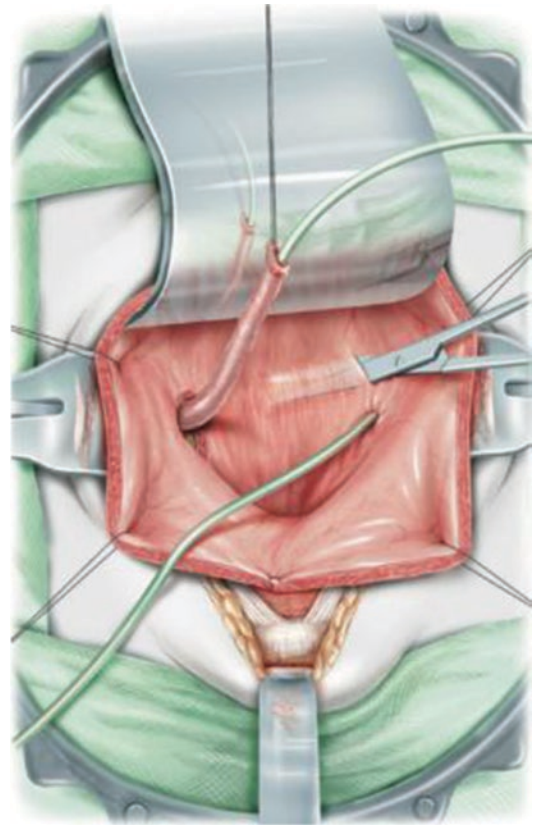
4. A stay suture is placed around each ureteric orifice and tied over the feeding tube, the ureteric orifice is circumcised with diathermy and the distal 2 cm of ureter can be mobilized.



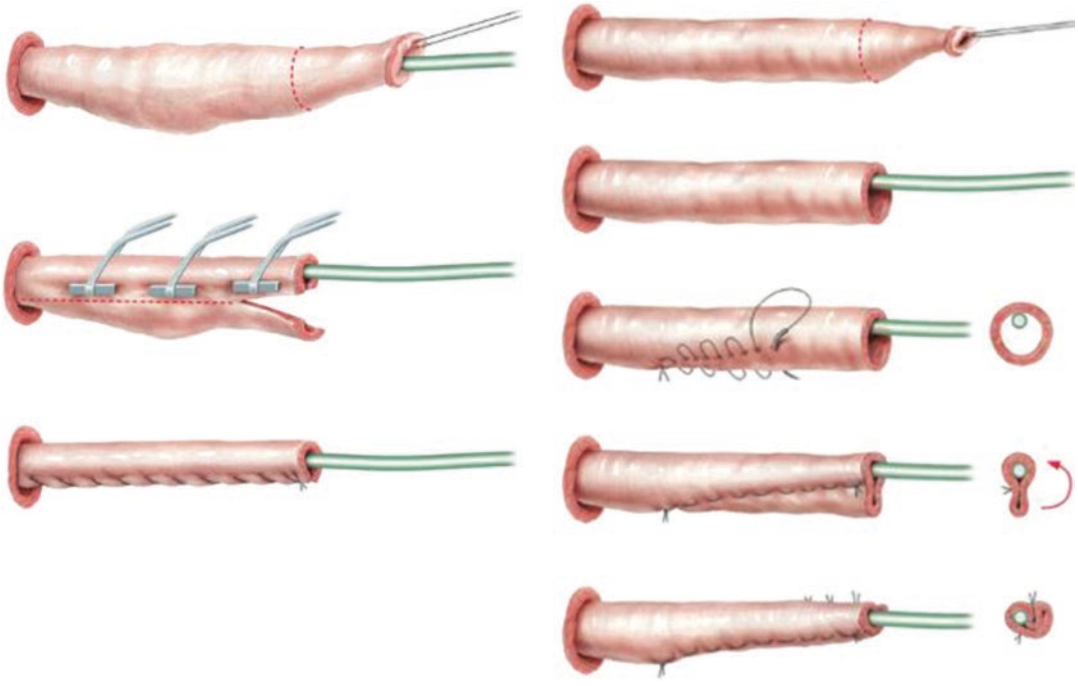
5. It is essential to enter the correct plane between the bladder and the transparietal ureter, commencing below the orifice, using Reynolds scissors. Muscle fibres are grasped with fine forceps, coagulated and divided. The fibres should be coagulated some distance from the ureter, to avoid damaging its blood supply.



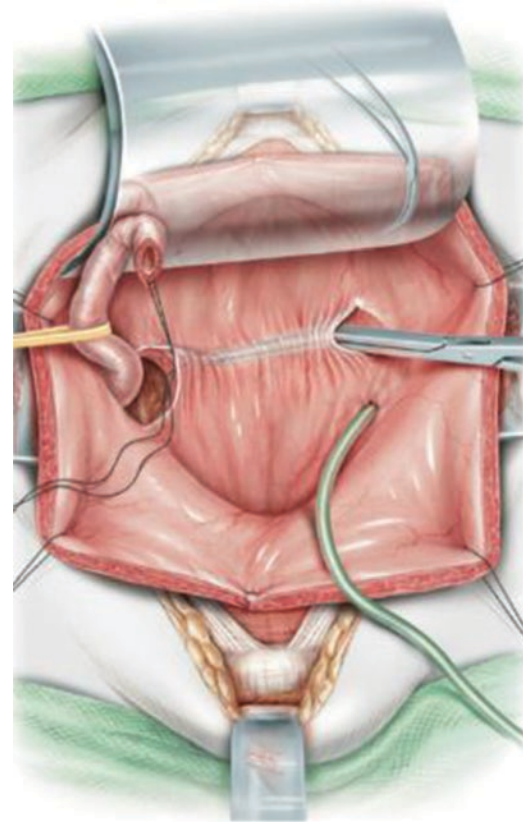
6. The dissection continues progressively, circumferentially until the ureter is completely freed.



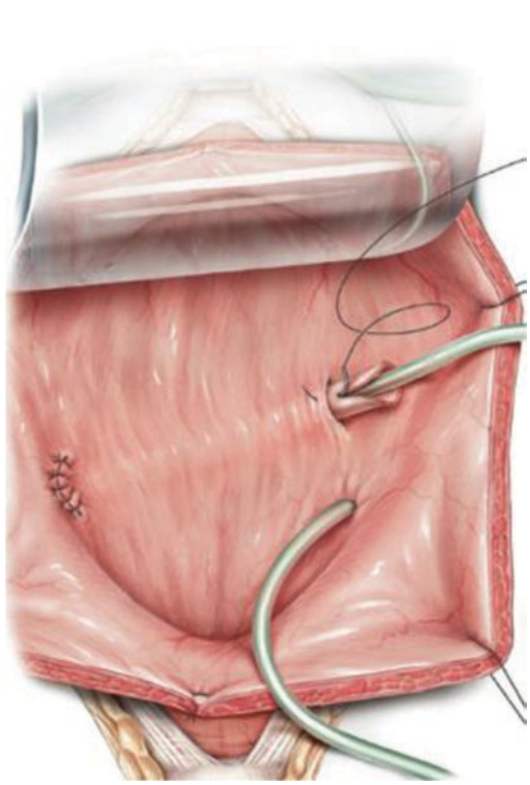
7. The submucosal tunnel is then formed; it is usually a horizontal tunnel, crossing the midline of the posterior surface of the bladder, just above the trigone.

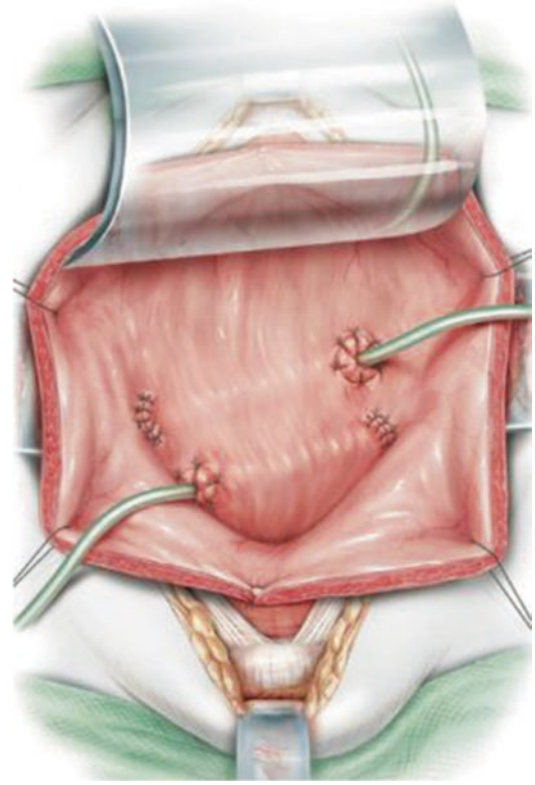


8. The length of the submucosal tunnel should be at least five times the ureteric diameter (Paquin's rule) [89]. If this cannot be fulfilled, modelling of the ureter should be considered and there are two possibilities. On the left, the figure describes the Hendren's technique in which the calibre of the ureter is reduced by excising a strip of ureter [90]. On the right, the figure describes the Kalicinski's technique, in which the calibre of the ureter is reduced by infolding the ureter [91].

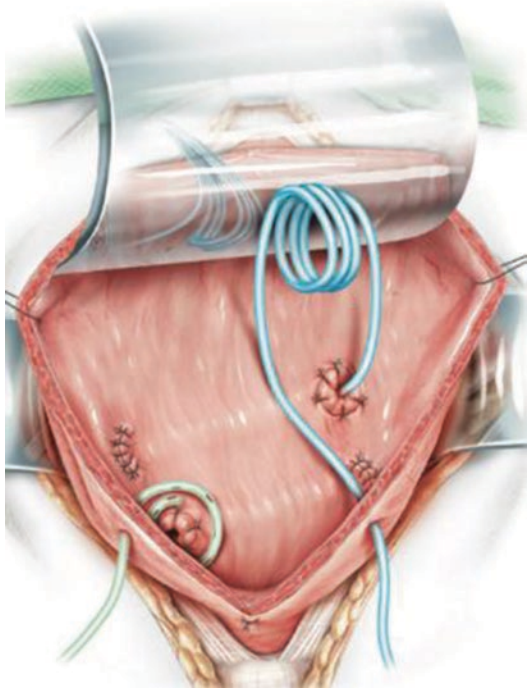


9. The site of the new ureteric orifice is selected and the bladder mucosa lifted from the underlying bladder muscles with a pair of Reynolds scissors, starting either from the hiatus or from the new ureteric orifice. The tunnel should be wide enough to allow easy insertion of the ureter, with no constriction. A similar procedure can be used for the opposite ureter in case of bilateral reimplantation.

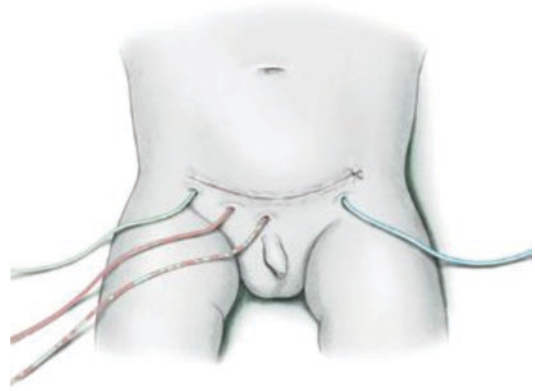




10. The 5/0 absorbable suture anchors the ureter to the bladder muscles and the ureterovesicostomy is completed with interrupted 6/0 absorbable sutures.



11. For some surgeons, an infant feeding tube or JJ stent is inserted into the reimplanted ureter and exteriorised through the bladder wall, the rectus muscle and the skin, using the punch of a suprapubic catheter. The feeding tube is left in position for 2 days or for 10 days if the ureter has been remodelled. There is no consensus on the efficacy of drainage of the reimplanted ureter, and some surgeons do not leave any drainage. The bladder is drained either by a transurethral catheter for 5 days or by a suprapubic catheter.



12. The bladder is closed with a 3/0 or 4/0 suture (interrupted or continuous). The prevesical and subcutaneous spaces are drained by a suction drain. The abdominal wall, the subcutaneous tissues and the skin are then closed.

42.5.2.2 Secondary VUR Surgical Treatment

The treatment of secondary VUR consists in relieving the obstruction and pressure on the urinary tract, with care to maintain normal bladder and renal function for as long as possible [4]. The surgical approach comprises also foetal intervention which should be proposed to parents of foetuses with oligohydramnios after 18 weeks' gestation and severe bilateral hydronephrosis, but with 'normal renal function' [92]. It is important to underline that amniotic fluid is necessary for normal lung development, and its absence may lead to pulmonary hypoplasia, causing a life-threatening problem [1]. The main technique utilised for foetal intervention is the vesicoamniotic shunting, whereby a double pigtail stent is introduced percutaneously via a trocar, under ultrasound guidance and maternal local anaesthetic. An alternative is foetal cystoscopy, whereby a trocar is placed inside the foetal bladder under

ultrasound guidance and the foetoscope is advanced into the foetal bladder in an antegrade fashion and valves visualised and ablated [13].

After birth, a catheter drainage of the bladder is inserted, with close monitoring of serum electrolytes and renal function, and antibiotics administration to prevent UTIs [4]. Primary valve ablation is considered the treatment of choice for PUVs, while controversy exists regarding the vesical or supravesical diversion and delayed valve ablation [93]. Actually, at the moment, it seems that there are no significant differences in the major outcomes between those children treated by initial vesicostomy and those who have undergone primary fulguration [93].

Primary Valve Ablation

Nowadays, after catheter drainage, if hydronephrosis and creatinine improve, the best practice guidelines suggest planning endoscopic valve ablation when the child is medically stable [4].

Cystoscopy is performed, and after filling the bladder with saline, the suprapubic region is compressed with Credé's manoeuvre to fully dilate and visualise the posterior urethra. There are two main types of PUVs detected during the urethroscopy: types 1 and 3. Type 2 was originally defined by Young in 1919 but was later determined to be an overclassification [94, 95]. Type 1 PUVs are descripted as a valvelike lesion oblique to the urethral axis, the most important finding of which is a connection of the lesion to the verumontanum at the 5 and 7 o'clock positions with the formation of posterolateral folds (Fig. 42.2). Type 3 PUVs are described as a membrane or diaphragm with a hole present in its centre (Fig. 42.4).

Small paediatric cystoscopes and resectoscopes are nowadays available either to incise or to resect the valves at the 5, 7 or 12 o'clock position, or at all three positions, depending on the surgeon's preference [1]. Valve ablation can be performed both with cold knife ablation and diathermy hook, even if it seems that the first one has lower rate of urethral stricture than the latter one. After valve ablation two complications can occur: urethral stricture and valve residual [96]. After 3 months a VCUG or a second cystoscopy is performed in order to demonstrate the effectiveness of the treatment [1].

Vesicostomy

A temporary vesicostomy is considered in newborn too small (under 2000 g) and in those

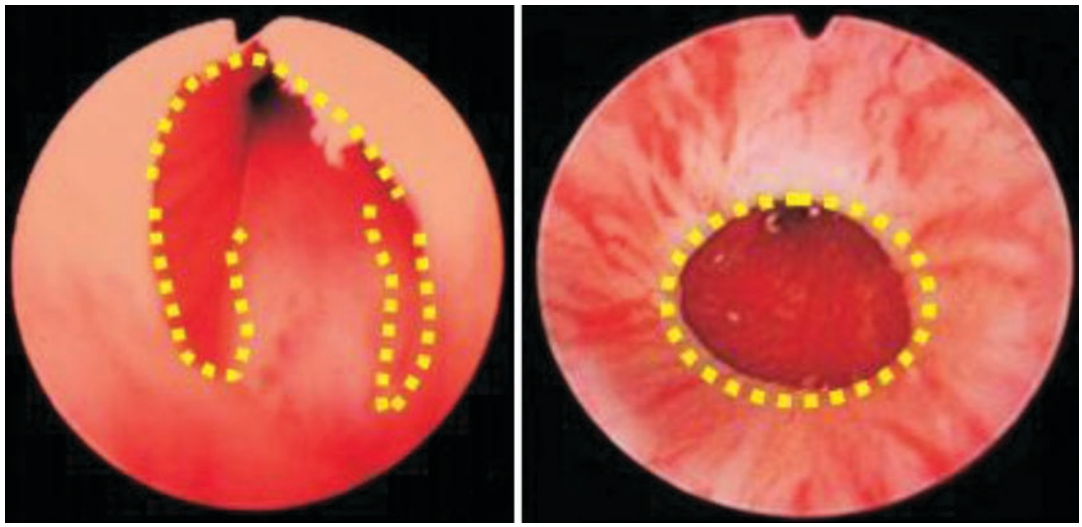


Fig. 42.4 On the left, endoscopic findings of type 1 VUPs and on the right endoscopic findings of type 3 VUPs (From Nakai H et al. Aggressive diagnosis and treatment for posterior urethral valve as an etiology for vesicoureteral reflux or urge incontinence in children. Investig Clin Urol. 2017 June;58(Suppl 1): S46–S53) [95]

patients with worsening of hydronephrosis and creatinine despite the bladder catheter drainage [1, 4]. Vesicostomy is a surgical procedure which protects the upper urinary tract, decreases hydronephrosis and improves kidney function in more than 90% of patients [97]. In literature, there has been a long debate regarding the bladder function after vesicostomy. Some authors concern that vesicostomy lead to reduced bladder compliance and capacity, but nowadays no valid data are available [98, 99]. Finally, it seems that vesicostomy is more advantageous than bilateral loop cutaneous ureterostomy because it enables free drainage of urine and avoids a completely defunctionalised bladder [98].

High Urinary Tract Diversion

High urinary tract diversion comprises high loop ureterostomy, ring ureterostomy, end ureterostomy or pyelostomy. Diversion may be suitable if there are recurrent infections of the upper tract, no improvement in renal function and/or an increase in upper tract dilatation, despite adequate bladder drainage. Nowadays this surgical option has got few estimators as the bladder results completely defunctionalised [98].

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Ureterocele

43

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43.1 Definition and Demographics

Ureterocele (UC) is a cystic dilatation of the terminal, intravesical portion of the ureter.

The incidence of UC is not well established. Different autopsy studies indicate a wide occurrence rate of 1 in 500 to 4000 children. UC are 3–7 times more common in females than males and more frequent in Caucasians than Blacks. There is a slight left-sided predominance, and bilateral UC occurs in approximately 10% of cases.

UC can vary in size and location, while various anatomical features may be associated with UC, including the presence of duplication anomalies, vesicoureteral reflux (VUR) into the ipsilateral lower pole ureter or contralateral renal unit, and presence of a cystic dysplastic moiety pertinent to the UC (see Classification paragraph).

43.2 Embryology

There are several theories that have been postulated to explain UC formation, with lack of a singular explanation that fits the variability found in UC.

Chwalla [1] theorized that a delay in rupture in Chwalla's membrane, which separates the Wolffian duct from the urogenital sinus, would result in stenosis of the orifice and in aneurismal-type dilatation of the distal ureteral segment. This theory of obstruction fits well with UC having a stenotic orifice, actually the majority, but does not adequately explain the embryology of those with normal or patulous orifices.

Tanagho [2] postulated that the distal ureteral lumen is delayed in formation and, therefore, results in ureteral expansion as result of hydrostatic pressure.

Additionally, Stephens [3, 4] proposed an intrinsic muscular defect in the wall of the ureter which results in dilatation of the terminal portion and UC formation. Examining the musculature of the intravesical portion of ectopic ureters associated with UC, deficiency of the terminal musculature has been observed, compared with ectopic ureters without UC.

43.3 Classification

Traditionally UC are classified according to location of ureteral orifice, as described by Ericsson in 1954 [5]:

- *Simple* if the UC is entirely contained within the bladder.
- *Ectopic* if the UC extends into the bladder neck or posterior urethra.

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Stephens [3, 4] has provided a more pathophysiologic classification, dividing UC into four categories:

- *Stenotic* UC corresponds to the simple UC of Ericsson's classification; it is entirely contained into the bladder and has a small orifice that can vary in size and, therefore, in the degree of distension of the UC itself.
- *Sphincteric* UC is an ectopic UC in which the orifice is located within the internal sphincter mechanism (bladder neck or proximal urethra); the orifice can be normal or large in size with relative obstruction occurring, except during time of voiding with relaxation of the internal sphincter mechanism.
- *Sphincterostenotic* UC has a orifice located within the sphincter mechanism and, in addition, the orifice is stenotic; as a result UC does not empty during voiding and hence tends to be large and tense and may act as a ball valve into the bladder outlet and cause obstruction.
- *Cecoureterocele* has an orifice located within the bladder; however, a "cecum" or a tongue of UC extends submucosally into the urethra.

The best classification to date is based on the report of the Committee on Terminology, Nomenclature and Classification of the Urology Section of the *American Academy of Pediatrics*. It subdivides UC based on the number of ureters that drain the kidney pertinent to the UC, the location and the extent of UC, and the additional anatomic distortions of the UC:

- *Duplex system* UC is pertinent to the upper pole of a completely duplicated collecting system.
- *Single system* UC is pertinent to a single ureter draining the kidney.
- *Intravesical* if the UC and its orifice are located entirely within the bladder.
- *Ectopic* if the UC and its orifice extend beyond the trigone to the bladder neck or outside of the bladder to involve the urethra.

Ectopic UC constitutes 60–70% of UC in pediatric age, 70–80% being associated with duplicated systems. The contralateral upper tract of a duplicated system with UC is likewise duplicated in 30–40% of cases. Ectopic UC are mostly associated with the upper pole ureter of a duplex system but also could be present in a single system. Intravesical UC are usually associated with single systems, but, rarely, they may also be pertinent to the upper moiety of a duplicated system, especially in males.

43.4 Presentation

In the last decades, the widespread use of prenatal ultrasound (US) has significantly modified mode of presentation and patient age at time of diagnosis. Currently UC is diagnosed at neonatal evaluation of prenatally detected hydronephrosis in 75% of cases. Therefore age at presentation is within the first week of life, with less than 25% presenting later, after urinary tract infection. Most often in the past, rarely today, sepsis, hematuria, urinary incontinence, and/or flank pain can be also present at presentation. A palpable mass may also be the first sign of UC, resulting from an obstructed dilated upper pole (obstructive UC with stenotic orifice) or distended, obstructed bladder.

Bladder outlet obstruction (BOO) can be caused by a tense UC which acts as a ball valve into the bladder neck or by a cecoureterocele which elevates the floor of the bladder neck submucosally or a distal mucosal lip which blocks the BOO. Because most UC become compressed upon voiding, obstruction usually does not occur. The most common cause of urethral obstruction in the little girl is urethral prolapse of a UC, the so-called dumbbell UC, presenting as perineal mass (Figs. 43.1 and 43.2).

43.5 Diagnosis

Antenatal ultrasound, performed after the 16th gestational week, is able to detect fetal hydronephrosis, often associated with UC (Fig. 43.3a); after the 30th week of pregnancy, the UC can be occasionally demonstrated within the fetal bladder as well (Fig. 43.3b).

However, in the majority of cases, definitive diagnosis can be achieved only postnatally.

The goals of diagnosis are (1) to identify the ureterocele, define the side involved, and evaluate the status of both ipsilateral and contralateral kidneys and the condition of the bladder and (2) to detect the presence of VUR and of contralateral malformations.

The diagnostic workup relies on the use of US, voiding cystourethrogram (VCUG), nuclear scan, and cystoscopy, if required. In the past intravenous pyelogram (IVP) was an important diagnostic tool to better study urinary tract anatomy, nowadays almost completely superseded by MR urography.

Postnatal US, done to confirm a prenatal suspicion or because of symptoms or as routine screening, reveals a well-defined cystic intravesical mass (Fig. 43.4a). This can be followed into a dilated ureter in the bony pelvis and into upper pole hydroureteronephrosis, if duplication is present. Hydronephrosis, thickness, and echogenicity of renal parenchyma can be also evaluated (Fig. 43.4b).

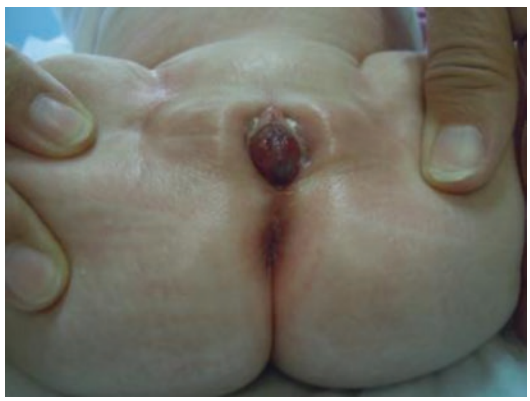

Fig. 43.1 UC prolapsing through urethra, presenting as perineal mass

After US, voiding cystourethrogram is an important part of the evaluation of patients with UC, given its frequent association with reflux. The ipsilateral lower pole system of a duplication with UC is refluent in 40–50% of cases (Fig. 43.5a). The contralateral system is affected by reflux in approximately 15–25% of cases as well. VCUG provides information also regarding the quality of detrusor backing of the UC; in fact with poor detrusor backing, a diverticulum-like effect is seen. In 15% of cases, reflux can be observed into the UC, most often with cecoureteroceles or those with a patulous orifice located in the bladder neck. Single system intravesical UC are less likely associated with refluent units (Fig. 43.5b).

Renal scintigraphy should be used to evaluate renal function (especially of the upper pole moiety if a duplex system is suspected) and eventual degree of obstruction and to detect renal scarring (Fig. 43.6). Technetium 99m (99mTc) diethylenetriamine penta-acetic acid (DTPA) and mercaptoacetyltriglycine (MAG3) scans provide reasonable assessments of function and obstruction. Since 99mTc dimercaptosuccinic acid (DMSA) scans result in renal tubular labeling and are unaffected by obstruction, they are more sensitive to low levels of renal function and are sometimes helpful in detecting occult duplex anomalies and small kidneys associated

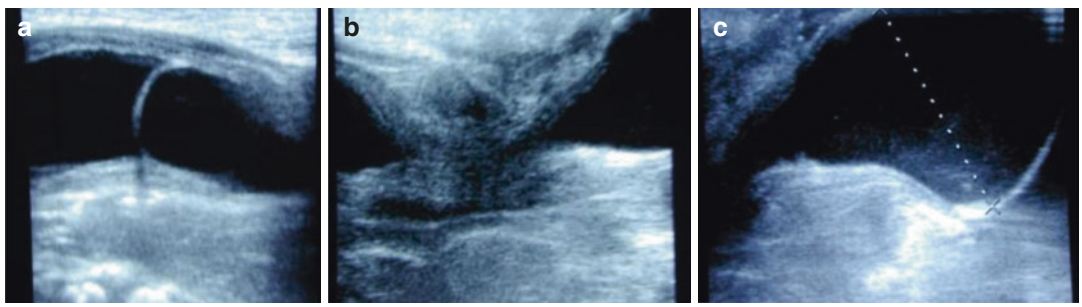

Fig. 43.2 Dumbbell UC: US images of intravesical (**a**), urethral (**b**), and perineal (**c**) portions (Photos are courtesy of Dr. A.A. Caldamone)

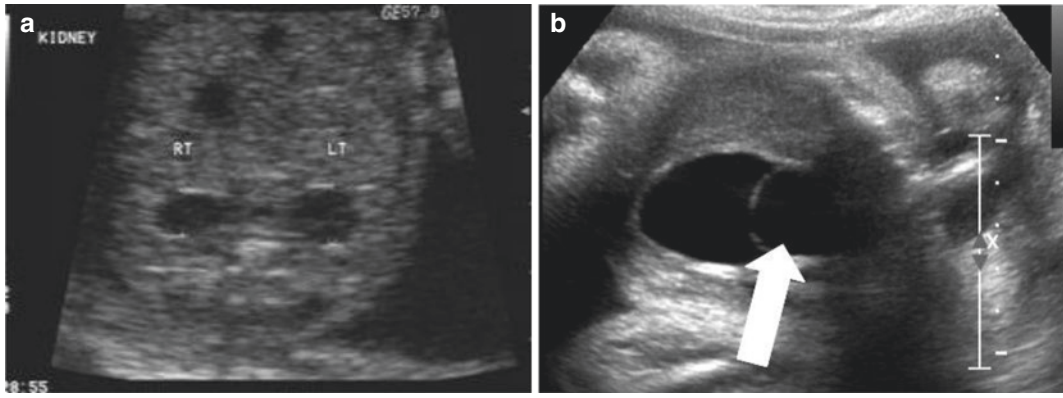

Fig. 43.3 Prenatal US showing bilateral hydronephrosis (**a**) and a UC (white arrow) within the distended bladder (**b**)

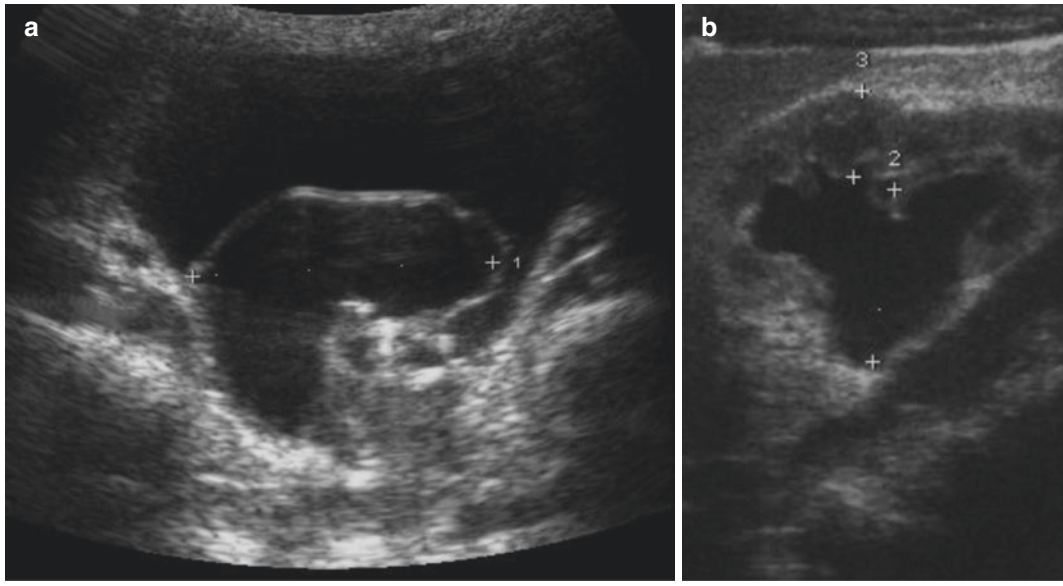

Fig. 43.4 Neonatal US showing a big UC inside the bladder (**a**) and hydronephrosis of upper pole (**b**)

with ureteral anomalies that are not identified by other techniques [6].

The upper pole of a duplex kidney or a solitary kidney is considered nonfunctioning when its contribution to the overall renal function is less than 10%. Obstruction is considered in cases of severe hydroureteronephrosis that suggests poor drainage of the upper pole or kidney. To assess upper pole/kidney obstruction, a diuretic renography with Furosemide is usually performed.

Intravenous pyelogram was the most important diagnostic step in the past. Nowadays the progress of ultrasonography and of nuclear medicine imaging has made this examination obsolete in most cases, although when the anatomy is confused, it may still play a role. Anatomy of upper and lower tract and renal functionality can be detected. When the associated upper tract parenchyma functions adequately, the presence or the absence of a duplication anomaly can be easily visualized and the typical "cobra head" deformity in the bladder can be observed, resulting from opacified urine surrounded by a radiolucent halo representing the UC wall (Fig. 43.7).

Due to the fact that the most of associated upper pole segments are dysplastic and,

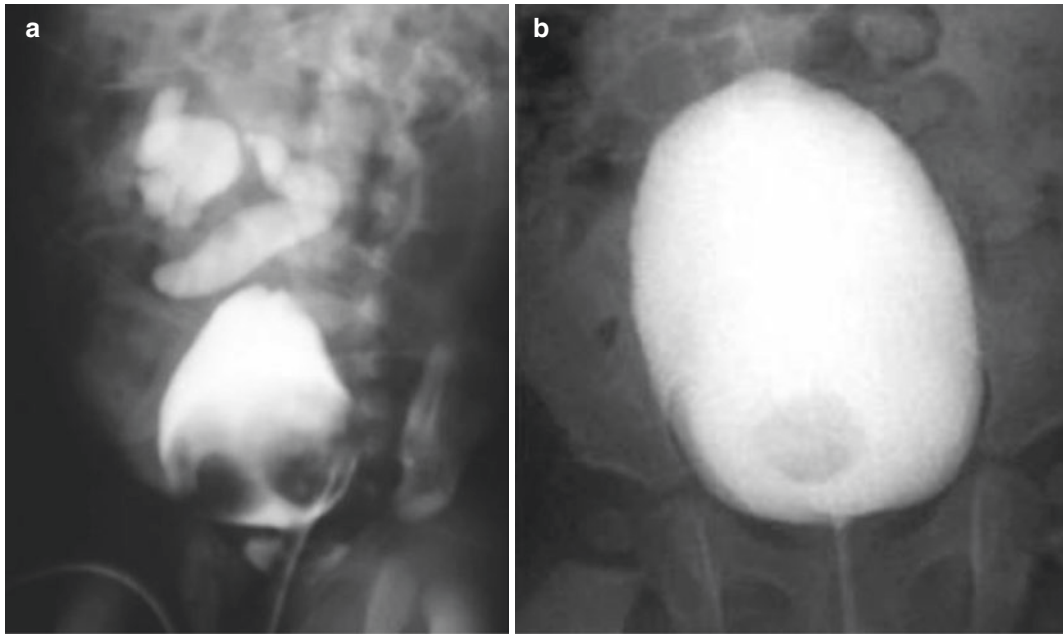

Fig. 43.5 VCUG showing grade 5 reflux into the lower system and a two-lobes UC inside the bladder (**a**); VCUG showing absence of reflux and intravesical UC seen as a filling defect (**b**)

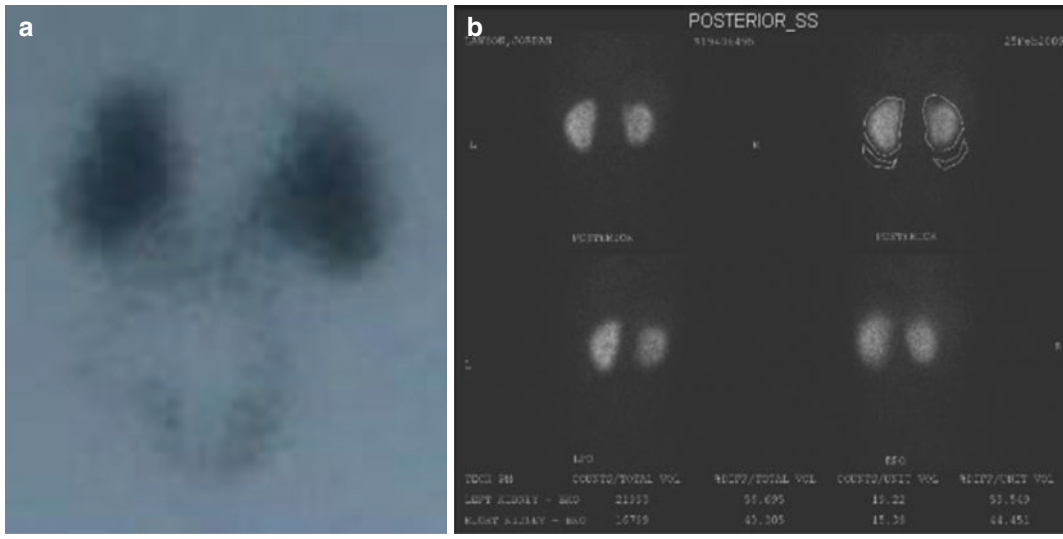

Fig. 43.6 MAG3 scan showing functioning single system kidneys (**a**) and nonfunctioning upper pole in a right duplicated system (**b**)

therefore, poorly functioning at best, radiological findings are often indirect. If the function of the pertinent parenchyma is not adequate to opacify the collecting system, the effects of the hydronephrosis on the associated lower pole structures are visible. The opacified collecting system of the affected kidney usually has too few calyces and lacks an upper pole infundibulum. When the upper pole moiety is hydronephrotic, it will tend to push the lower pole moiety laterally and

inferiorly producing the classic "drooping lily" effect. A dilated upper pole hydroureter may force the lower pole pelvis and ureter laterally and cause distal lower pole ureter to appear tortuous as it becomes more closely intertwined with the dilated upper pole ureter. As the bladder fills with contrast material, a negative shadow will be created by the UC filled with unopacified urine, in the earlier films.

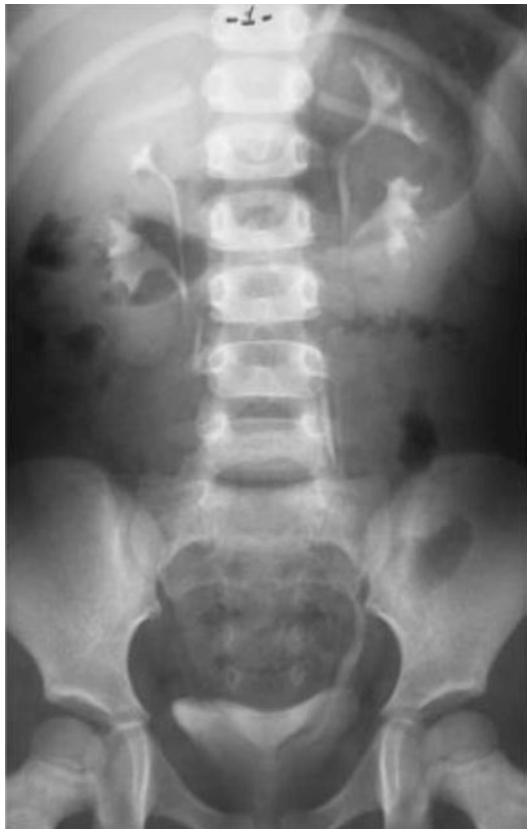

Fig. 43.7 IVP in bilateral duplex system associated with small bilateral intravesical ureteroceles

Cystoscopy is an important diagnostic tool to confirm or define UC location (Fig. 43.8) and kind of system; it is fundamental before performing endoscopic treatments (transurethral incision or puncture of UC as well as endoscopic correction of eventually associated reflux). The bladder should be examined both when full and when completely empty because compressible UC may not be evident in a full bladder or may appear as a bladder diverticulum. On the contrary, the dilated distal end of an ectopic ureter or megaureter may elevate the trigone, creating the cystoscopic appearance of a so-called pseudo-ureterocele.

43.6 Management: Introduction

Multiple treatment strategies are available for pediatric UCs; consensus on the best initial approach is lacking; therefore the treatment of this uropathy remains a matter of debate. Historically, aggressive treatments were the rule to prevent renal damage secondary to infections and obstruction. However, treatment objectives

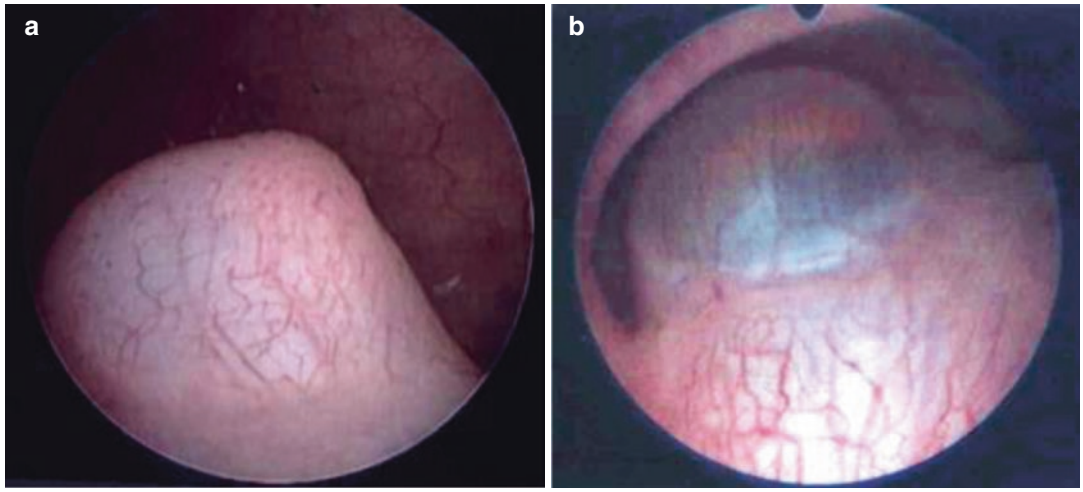

Fig. 43.8 Cystoscopic picture of intravesical (**a**) and ectopic UC (**b**) (Photos are courtesy of Dr. A.A. Caldamone)

and timing have changed through years and since the advent of prenatal diagnosis, which modified natural history of this malformation. Current treatment strategies tend toward a more conservative approach, because it appears the same functional results can be achieved [7].

The goals of treatment are:

- Prompt decompression of obstructed urinary tracts with infection.
- Elimination of any potential source of infection.
- Relief of significant obstruction of the upper tract and/or the BOO.
- Elimination of clinically significant reflux.
- Preservation of renal function (including functional moiety of a duplex system).
- Restoration and maintenance of continence.
- Prevention and treatment of any bladder wall deficiency (diverticula, poor detrusor backing).
- Minimization of the number of surgical procedures and surgical morbidity [8, 9].

However, the means of accomplishing these objectives still remain a significant challenge in modern pediatric urology. Practice patterns are widely variable, and no randomized controlled trials exist to guide management decisions [10, 11]. Moreover to compare methods is difficult because each patient can have a different clinical history, so no single method of treatment suffices for all cases and management needs to be individualized [12]. The selection of a treatment modality, including nonoperative management, endoscopic ureterocele decompression, upper pole nephrectomy, high or low ureteroureterostomy, and excision of the ureterocele with ureteral reimplant, can therefore only be based on the balance between potential risks inherent to the condition and the summation of published results for a multitude of therapeutic alternatives [13, 14]. Also surgeon's preference weights on the choice, even if each surgeon should be skilled in multiple approaches. Ultimately, the decision to treat (and when to treat) is difficult as every patient is unique: the optimal management of UCs remains controversial and begins with the same algorithm used in all patients, namely, evaluation of the history, physical examination, imaging, and discussion with the family [15].

Over the past 40 years, the management of ectopic ureteroceles has significantly changed. Initially, it was thought that upper pole partial nephrectomy alone was optimal, or, in rare cases, nephrectomy if the entire kidney was essentially nonfunctioning. Over time many of these patients required further surgery, leading to the adoption of a single-stage upper pole partial nephrectomy, total ureterectomy of the upper pole ureter, ureterocelectomy or marsupialization, and unilateral or bilateral ureteroneocystostomy based on the involvement of each ureter in the ureterocele [16].

In recent years, conservative management of asymptomatic patients without obstruction has shown that these patients remain free of symptoms, hydronephrosis tends to resolve as ureterocele collapses, and vesicoureteral reflux tends to disappear spontaneously. Transurethral puncture (TUP) has become a popular, safe, and minimally invasive procedure. However, concern exists regarding new-onset reflux after puncture and the frequent need for subsequent interventions. Although more invasive procedures such as upper pole partial nephrectomy or reimplantation are safe and associated with a low percentage of complications, they may not always be necessary (Fig. 43.9) [7].

The first point to be decided is whether patients really need intervention or can be managed conservatively. Indeed, the present aim is to achieve goals of treatment and avoid complications, with the fewest possible interventions. In fact, doubts have recently arisen as to whether early diagnosis, often prenatal, leads to unnecessary interventions [7]. Current trends are away from single-stage open reconstruction (heminephrectomy, ureterocele excision, bladder base/neck reconstruction, and ureteral reimplantation) and oriented toward conservative management and minimally invasive approaches [9].

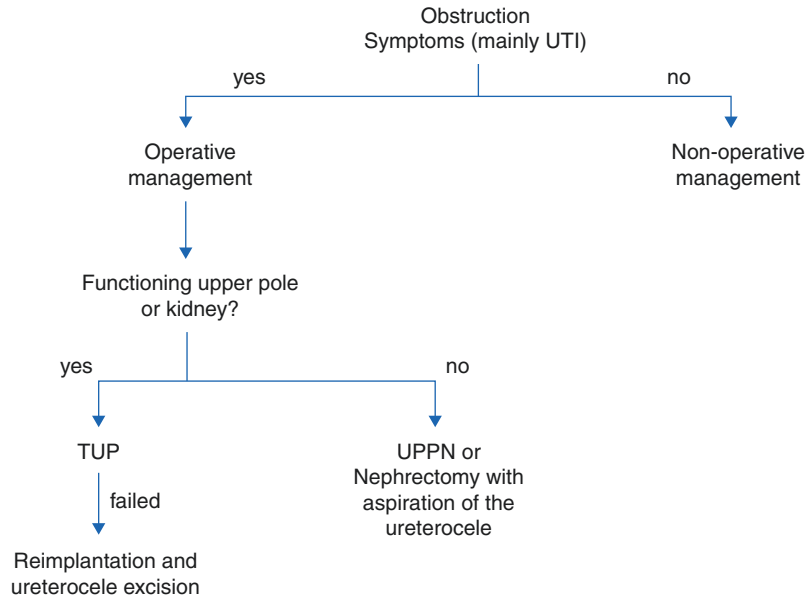

Fig. 43.9 Initial therapeutic protocol. *TUP* transurethral puncture, *UPPN* upper pole partial nephrectomy, *UTI* urinary tract infection (from Gander R et al.) [7]

43.7 Nonoperative Management

Under specific circumstances, UCs themselves require no surgical therapy. Because the majority of UCs are detected antenatally and patients are often asymptomatic at birth, the lack of a significant urinary tract obstruction could prompt consideration of nonoperative management (Table 43.1) [14].

Shankar et al. [17] reported 14 of 52 patients with UC who were managed conservatively. Their selection criteria for nonoperative management were nonfunctioning upper pole moieties, nonobstructed lower poles, absent or low-grade VUR to the lower pole, and no BOO. Patients with upper pole function >10% were considered for surgical intervention. After a median follow-up of 8 years, no patient underwent surgery or had a UTI. The authors estimate that a further seven patients—or a total of 27% from the original cohort of 52—might have also been managed expectantly.

Coplen and Austen [18] reported on a cohort of eight children with UCs associated with cystic dysplastic moieties, four cases with single systems and four with duplex systems, who underwent no surgical management. In all children, the cystic dysplastic moiety involuted resulting in decompression. Reflux into the ipsilateral renal unit and into both the ipsilateral and contralateral renal units resolved. A third patient with ipsilateral reflux did not undergo follow-up cystography, as she was clinically well; thus, it was assumed that the reflux resolved. During a mean follow-up of 36 months, only one child had a UTI.

Han et al. [19] reported 13 cases initially managed conservatively. In contrast to Shankar et al., they stated that functioning upper pole was not a criterion for surgical intervention; those patients were evaluated with MAG3 to determine adequate drainage. If high-grade obstruction was present, patients were managed surgically.

Gander et al. [7] agree with Han et al. that patients with a functioning upper pole who are managed conservatively should be carefully evaluated for obstruction. Based on their results and the previously studies, they suggest that asymptomatic patients without obstruction can be safely managed conservatively and followed up with US. Special attention should be paid to patients with a functioning upper pole to detect obstruction during follow-up; mercaptoacetyltriglycine is probably the best tool for this purpose.

Also Direnna and Leonard's [20] study supports a nonoperative course in selected patients.

Table 43.1 Review of nonoperative management of ureteroceles (from Pohl HG) [14]

Reference	Presentation (*n*)	Indications for nonoperative management	Antibiotic prophylaxis	Follow-up	No. undergoing surgery	No. UTI	VUR resolution (*n*)	Hydronephrosis resolution/MCDK involution
Shankar et al. [17]	Prenatal (14)	<10% function lower pole	Yes	Median, 8 years (range, 1.6–128 years)	0	0		Resolution in 6/14
		Nonobstructed lower pole						
		Lower pole VUR ≤3						
		No bladder outlet obstruction						
Coplen and Austin [18]	Prenatal (8)	Multicystic dysplasia	–	Mean, 3 years (range 1.2–4.5 years)	0	1		Involution of MCD in 8/8
Han et al. [19]	Prenatal (10)	Nonobstructed upper pole	Yes	Median, 3.42 years (range, 1–8 years)	Progressive obstruction (1)	3	Ipsilateral lower pole VUR grade III (2)	Involution of dysplastic unit (3)
	UTI (3)	Multicystic dysplasia			UTI (3)		Ipsilateral lower pole VUR, grade IV (3)	Resolution of hydro (6)
Direnna and Leonard [20]	Duplex (6)	Lower pole VUR ≤3	Yes	Median, 5 years (range 1–11 years)	0	0	Ipsilateral lower pole VUR, grade ≤ III (4)	Resolution of hydro (6)
	Single (4)	Nonobstructed lower pole						VUR resolved (2)
		No bladder obstruction						

UTI urinary tract infection, *VUR* vesicoureteral reflux

The authors admit that this cohort represents a minority of the patients diagnosed prenatally with UC but underscores the importance of individualizing the management of prenatally detected UCs.

In summary these studies suggest that a subgroup of patients presenting with nonobstructive noninfected ureteroceles, especially but not exclusively in presence of a nonfunctioning dysplastic moiety, rarely require surgery, even if low-grade reflux is present. In conclusion, according to new trends proposed in the literature, the most successful therapeutic approach to prenatally diagnosed ureteroceles without symptoms or signs of obstruction appears to be nonsurgical. However, any patient being managed conservatively should be followed, and the development of BOO, symptomatic UTI, or significant worsening of upper tract obstruction should prompt consideration of operative intervention [9]. We underline, however, that this subset of cases are only a small percentage.

43.8 Surgical Management

It is currently beyond any doubt that patients with significant obstruction or symptoms require surgical intervention.

43.8.1 TUP

Although a fraction of patients with minor urinary tract obstruction may present as older children, the vast majority today in developed countries are diagnosed on prenatal ultrasound, making early treatment in the neonatal period the new standard. In addition to changes in patterns of diagnosis, improvements in pediatric anesthesia and endoscopic technology and technique have resulted in an increasing shift of the timing of intervention toward younger ages [21]. Thus, patients requiring UC surgery are younger, and younger patients are better able to tolerate an endoscopic approach than more complex surgical techniques [22].

Indeed endoscopic UC decompression is a widely used, minimally invasive method of achieving timely UC decompression and decreasing the risk of UTI while avoiding, or at least postponing, extensive trigonal surgery in infants [9]. Moreover it is a relative simple and quick procedure, which can be performed as one-day surgery (Fig. 43.10).

Endoscopic puncture represents the treatment of choice in several clinical scenarios, both in the urgency and in the elective setting.

For patients with UC presenting at birth with systemic infection and azotemia, or high-grade obstruction, or prolapse of the ureterocele through the urethra with BOO, endoscopic incision is the initial therapeutic approach of choice. This permits immediate decompression of the renal system and faster resolution of sepsis and, in a part of cases, can be the only treatment necessary.

In the elective setting, essential preoperative considerations include UC type and position, upper tract anatomy and function, and presence of associated ipsilateral and/or contralateral VUR. In the past, management has been based primarily on UC position, with endoscopic intervention preferred for intravesical UCs and upper tract approach or complete reconstruction used for ectopic, duplex system UCs. Reoperation rates have often been used as a primary outcome measure to evaluate the success of TUP. Indeed endoscopic puncture offers the greatest potential as a definitive treatment of patients with intravesical single-system ureteroceles. Successful decompression without reflux may be achieved in 70–80% of such cases [10, 23]. Nonetheless, several investigators broadened the use of endoscopic puncture to include ectopic UCs [13, 23–26], whereas others combined endoscopic puncture with ureteral bulking agent injection in the setting of associated high-grade reflux [27].

TUP represents an effective short-term correction of upper pole obstruction but may not represent definitive therapy in most cases of ectopic UC ([26, 28, 29] [23, 24]). Many children require repeat puncture for adequate decompression or,

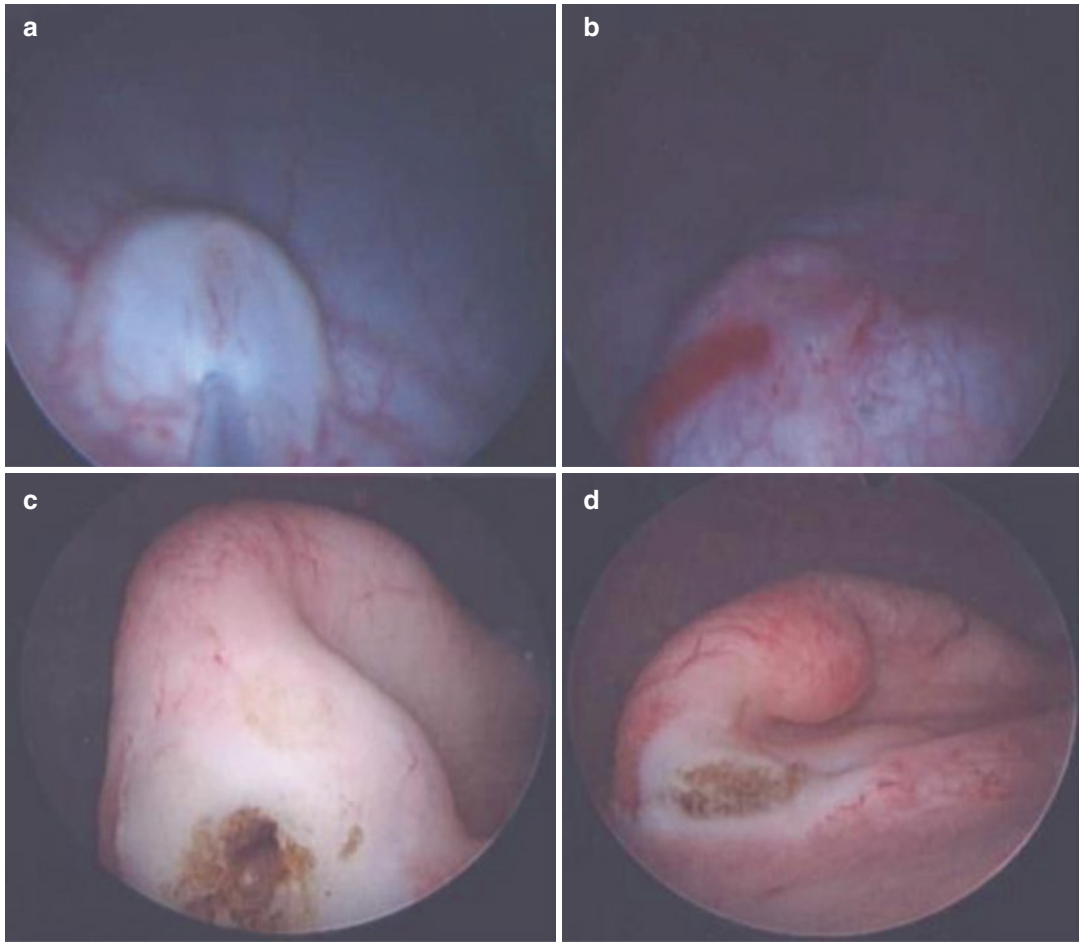

Fig. 43.10 TUI of intravesical UC (**a**) and its decompression after puncture (**b**). Another case of intravesical UC just punctured (**c**) and decompressed (**d**) (Photos are courtesy of Dr. A.A. Caldamone)

more commonly, subsequent reconstructive surgery for persistent obstruction, recurrent infection, or persistent or de novo reflux. Furthermore, incision or puncture may increase the likelihood of future surgery in patients with no preoperative reflux, perhaps because of procedure-related de novo reflux, although this remains unclear [24, 27]. In light of these concerns, an upper tract approach has traditionally been used for ectopic UCs [9]. However, [13] showed no difference in outcomes regarding UC location, leading the authors to suggest that differentiating between orthotopic and ectopic UCs is clinically useless. Anyway, even in cases needing secondary surgery, TUP obviates obstruction, allows a better functional evaluation of the kidney or pole involved by the UC, and, in case of subsequent bladder surgery, reduces the need for ureteral tapering [8].

Although much of the discussion surrounding the management of UCs focuses on the decompression of the upper urinary tract or upper pole moiety, management of any VUR into the ipsilateral lower pole or contralateral renal unit must also be considered. Also, VUR that is created by endoscopic decompression of the UC has the potential to further complicate management [14]. In effect, there is still concern about new onset or worsening of reflux after primary puncture. Some evidence suggests that endoscopic puncture may be used irrespective of the presence of reflux and that minimally invasive techniques may be used

to treat children with VUR either inherent to a duplex system or resulting from previous endoscopic puncture [9]. However, VUR after puncture can be also managed conservatively because it tends to disappear. If treatment is required due to symptomatic VUR, endoscopic injection could be a first option [7].

Adorisio and colleagues [30] applied TUP in 46 consecutive cases irrespective of the presence of reflux. Among 14 patients who had prepuncture VUR, 10 had spontaneous resolution in follow-up, and the remaining 4 were corrected with endoscopic injection. Five of 46 patients developed de novo reflux into the ipsilateral upper pole moiety. Two of these experienced spontaneous resolution, whereas two underwent endoscopic correction.

Regarding endoscopic puncture in the setting of poor or absent UC moiety function, the risk of subsequent morbidity (e.g., UTI, urolithiasis, hypertension, malignancy) conferred by leaving a nonfunctioning UC-associated moiety in vivo is not well understood [9]. For symptomatic patients with a nonfunctioning or a minimally functioning upper pole (considered if upper pole function contributes <10% to total renal function), UPPN has always been considered a definitive and safe option. However, even if associated with good results, it may not always be necessary. The cystic dysplastic upper pole tends to involute, and no higher incidence of infections or complications has more recently been observed. Thus, the question arises as to whether UPPN is really necessary in these patients [7]. Chertin and colleagues [31, 32] examined the long-term morbidity associated with a nonfunctioning or poorly functioning moiety left in situ after endoscopic puncture. Their data support the fact that conservative approach may not contribute to additional morbidity or subsequent need of heminephrectomy.

Postoperative care and follow-up after TUP is highly individualized. Hospitalization with intravenous antibiotics and monitoring may be necessary after acute decompression in the setting of systemic infection. In the elective setting, it is frequently an outpatient procedure.

Postoperative imaging should include US and VCUG at 4–6 weeks. Prophylactic antibiotics are often used until postoperative imaging is completed to assess for VUR [9].

43.8.2 Technique

Several cystoscopic devices and techniques have been used to decompress the UC and the urinary tract accordingly.

In recent years, endoscopic puncture has supplanted incision as the preferred technique [10, 11]. Several different methods of endoscopic decompression exist, such as electrocoagulation, Collins knife incision, and, most recently, laser incision.

Endoscopic puncture is typically performed with an 8-Fr or 10-Fr endoscope and flexible 3-Fr monopolar wire electrode (Bugbee-type endoscopic electrode). The cutting current should be set high enough to ensure a clean puncture. The bladder should be incompletely filled to achieve maximal UC distension for puncture. Intravesical UCs should be punctured with a single shot, close to the base, in a declivous position, allowing collapsed tissue and some intravesical ureter to establish an antireflux valve. Incising distally on the UC, close to the bladder floor, should prevent postoperative reflux [8, 9]. For ectopic UC, a single puncture of the intravesical portion of the UC can be made just proximal to the bladder neck [9]. In the past a further incision at the urethral level was considered to be necessary to remove any potential flap that might obstruct the bladder outlet. Afterwards no adverse effects have been reported by leaving the intraurethral extension of the UC intact, if a good decompression of the intravesical portion was obtained [8].

43.8.3 Laser

The use of laser during cystoscopic procedures in pediatric patients was first described to ablate posterior urethral valves (PUV) by Ehrlich in 1987 [33] using neodymium-doped: yttrium aluminum garnet (Nd:YAG) laser. He reported his experience in a small cohort of six boys (age

7–20 months), performing the procedure in an antegrade manner through cutaneous vesicostomy. Since that time, it has been utilized only sporadically and only to treat PUV, with infrequent case series. In 2000, Bhatnagar et al. [34] reported on a cohort of 23 older boys (age 3 months–9 years) with PUV, still using the Nd:YAG laser.

The first to use laser technique to decompress UC in pediatric patients was Marr in 2002 [22]. He treated 14 patients, using either potassium titanyl phosphate or holmium:yttrium aluminum garnet (Ho:YAG) laser, reporting a 100% decompression rate. The laser decompressed thick and thin ureteroceles, and no endoscopic retreatment was necessary. Marr was also the first to use Ho:YAG laser in pediatric patients [22].

The Ho:YAG laser has been the newest technologic advance in the endoscopic treatment of ureteroceles in children [35]. The Ho:YAG laser is a solid-state, pulsed laser that emits light at 2100 nm. It combines the qualities of the carbon dioxide and Nd:YAG lasers providing both tissue cutting and coagulation in a single device. Since the holmium wavelength can be transmitted down optical fibers, it is especially suited for endoscopic surgery. Tissue ablation occurs superficially, providing for precise incision with a thermal injury zone ranging from 0.5 to 1.0 mm. This level of coagulation is sufficient for adequate hemostasis [36]. Ho:YAG laser in contrast to Nd:YAG laser has the advantages of greater precision, shallower penetration, less variability between different tissues, and less potential for thermal tissue injury [21].

The first author to report an extensive use of Ho:YAG laser and comparing it to electrofulguration was Mandal in 2013 [37], even if he did not treat UC cases. His is the largest pediatric series to date reporting laser treatment of PUV in a cohort of 40 boys (mean age 24 months), comparing these patients in a nonrandomized retrospective manner to 40 boys who underwent electrofulguration. They noted significantly shorter operative times and higher rates of spontaneous voiding after catheter removal, as well as nonsignificant trends toward lower rates of refulguration, urethral stricture, and incontinence in those children treated with laser ablation. Despite this encouraging evidence, the mean age for this study was 24 months (range 3–60 months) with no neonates [21, 37].

Indeed, the literature contains only few reports of laser ablation in neonates (defined as <28 days old) for either urethral valves or ureterocele. The first report was in [38] by Biewald and Schier, who treated with Nd:YAG laser 13 patients with PUV. The first authors to treat newborn for UC were Jankowski and Palmer in 2006 [35]. They treated four patients with five UC, with Ho:YAG laser. Two patients had ectopic UCs, both of which were associated with a duplicated collecting system. One patient had an intravesical UC, and one had bilateral intravesical UCs that were punctured simultaneously. Four of the five UCs (80%) were adequately decompressed after one attempt as determined by the postoperative US and VCUG findings. One patient required a second puncture of the UC at 46 days of age because of incomplete decompression. None of the patients experienced intraoperative or postoperative complications from transurethral laser puncture of the UC, including bladder perforation, bladder neck or urinary sphincter injury, or urinary tract infection. None of the four patients developed new VUR after laser puncture. Both patients with intravesical UCs did not demonstrate preoperative or postoperative VUR. One of the two patients with an ectopic UC demonstrated VUR before and after UC treatment; the other child never demonstrated VUR. In a more recent series by Pagano [21], Ho:YAG laser was used to treat eight newborn with UC and nine with urethral valves. Among patients with UCs, all demonstrated partial or complete decompression of the UC and improvement in hydroureteronephrosis at 3 months. No patient had change in VUR (either new-onset, worsening, or resolution) postoperatively; however, three patients had persistent VUR that ultimately required ureteral reimplantation, all of which were into lower pole moieties of duplicated systems. The relatively small sample size limits drawing wider conclusions for general adoption in the pediatric urologic community, yet to our knowledge this is the

largest series to date on the use of Ho:YAG laser in the neonatal population.

The use of laser fibers in the neonate has several advantages compared with other more-established modalities.

One advantage is that the laser fibers are smaller, which is advantageous in the smaller anatomy of the neonate [35]. From a technological standpoint, improvements in cystoscopic and optic technology have allowed for the construction of smaller cystoscopes over time while maintaining excellent visualization. The laser fiber lends itself well to these small cystoscopes as the small caliber fibers can fit well through the working channels of the instruments and still allow for some irrigation flow [21]. In Pagano's [21] series small laser fiber (200 μm) were used to decompress UC in newborns and, as reported, that allowed a more accurate puncture while still allowing for discrete tissue destruction by vaporization. Although small Bugbee electrodes can still be used with small neonatal cystoscopes, in Pagano et al. experience, laser fiber offers greater precision and control [21]. On the other side, Jankowski and Palmer used a larger fiber (365 or 550 μm) except in one case (200 μm). The only one failed attempt at decompression occurred using the smaller laser fiber, which was then successfully decompressed with a 550 μm fiber. As the size of the laser fiber has a direct correlation with the puncture size of the UC, this may explain why retreatment was required in the only patient treated with the smaller fiber [35].

Another benefit is that the laser fiber does not have the thermal effect beyond the point of incision site compared with the Bugbee electrode. This allows for precise puncture of the UC, and, if necessary, multiple, small punctures can be made rather than one comparably large puncture with the Bugbee electrode [35]. Laser energy not only maintains the advantages of good hemostasis comparable to coagulation electrosurgery but also has the advantage of less thermal tissue damage and earlier re-epithelialization of tissue. These advantages have lent themselves to the adoption of the laser elsewhere in urologic practice, including as a common modality for treatment of urethral and ureteral strictures [21].

An additional, more theoretical, benefit is that the energy supplied by the laser vaporizes the treated tissue rather than just simply cauterizing, incising, or puncturing the tissue as performed with electrocautery, stylet, and cold knife incision, respectively. This may allow for the small incision made by the laser not to reseal compared with the other conventional techniques [35]. The probability of the incision resealing is less than puncture, conventional incision, or electrocautery [22].

One known potential risk of transurethral decompression of a UC is iatrogenic VUR. Previous studies have reported rates of iatrogenic reflux ranging from 18 to 27%, with traditional techniques. The precision and small hole afforded by laser puncture may decrease the incidence of iatrogenic reflux [35]. However, additional procedures must be performed to confirm this hypothesis.

43.9 Fetal Intervention

Fetal lower urinary tract obstruction (LUTO) is a rare and complex disease entity that carries with it a high degree of neonatal mortality and long-term morbidity. With the advent of fetal US in the early 1970s, fetal intervention—initially vesicocentesis, later vesicoamniotic shunting (VAS), and more recently fetal cystoscopy—has been proposed to reduce mortality and limit or reverse renal injury for these patients. However, the benefits of fetal intervention remain controversial. Outcome data in studies of fetal intervention in LUTO are often confounded by small samples sizes, limited follow-up data, and variations in criteria for intervention [39].

One of the major challenges in understanding the role of fetal intervention in the management of LUTO is the heterogeneity of urinary tract and renal pathology in LUTO itself. While PUV is the predominant etiologic mechanism of LUTO, other processes, including urethral atresia, urethral stenosis, obstructing UCs, and prune belly syndrome, are reported with some frequency. The severity of obstruction is also highly variable and dependent on the underlying mechanism of

obstruction. Added to the complexity of LUTO are also variations in renal pathology. Animal and human data strongly support the hypothesis that the developing kidney is uniquely susceptible to injury from obstruction of urinary flow. Thus, variability in the degree of obstruction and the gestational age at the onset of obstructed urinary flow are likely to have a direct impact on the severity of renal damage. The resulting secondary renal dysplasia or cystic dysplasia can occur unilaterally or bilaterally and is often undetectable until later in gestation. Other primary renal developmental anomalies, such as renal hypoplasia or glomerulocystic disease, are reported frequently in LUTO [39, 40].

In an attempt to better define subsets of patients that would benefit from fetal intervention, a LUTO classification system was developed at the Texas Children's Fetal Center in 2012 that incorporated (1) fetal urinary biomarkers of renal injury, (2) amniotic fluid levels as a surrogate for the severity of obstruction, and (3) imaging studies to identify signs of renal dysplastic or cystic changes (Table 43.2) [41].

For patients with low risk of either renal disease or pulmonary hypoplasia (Stage 1), intervention was not recommended. Patients with signs of severe LUTO felt to be at high risk for either progressive renal injury or pulmonary hypoplasia, but without evidence of severe preexisting renal damage (Stage 2), underwent VAS; some cases required serial VAS placement. For those patients who at the time of evaluation had evidence of severe LUTO with established renal disease (Stage 3), fetal intervention was individualized and often based on bladder capacity and bladder refilling after vesicocentesis [39, 41].

Once the decision to intervene has been made, the next question is: "how?" Fetal vesicostomy achieves the task but is now out of date [42]. Vesicoamniotic shunting (VAS) could work, but there is still a high incidence of dislodgement, and shunt technology has not been updated for the last 20–25 years. In utero fetal cystoscopy is emerging as a new and exciting modality but is clearly technically challenging. Most of current experience is with valve ablation of PUV, which can often be difficult in the newborn, especially in the premature, growth-restricted babies, let alone in even smaller fetuses. In addition, valve ablation is not always adequate to decompress the urinary tract, resulting in persistently dilated upper tracts and deteriorating renal function. The in utero setting of a desperately compromised fetus with severe obstruction and a limited window of time compound this difficulty [39].

Normally UC are unilateral and may cause only ureteral obstruction. However, although uncommon, a large, bulging, or prolapsing UC may cause BOO [43]. Usually, when fetal BOO from UCs is diagnosed, the fetus is monitored in

Table 43.2 Proposed classification of fetal lower urinary tract obstruction (LUTO) according to severity (from Ruano R et al.) [41]

	Stage I (mild LUTO)	Stage II (severe LUTO, with prenatal findings suggestive of preserved fetal renal function)	Stage III (severe LUTO, with prenatal findings suggestive of fetal abnormal renal function)
Amount of amniotic fluid	Normal	Oligohydramnios or anhydramnios	Oligohydramnios, but usually anhydramnios
Echogenicity of fetal kidneys	Normal	Hyperechogenic	Hyperechogenic
Renal cortical cysts	Absent	Absent	Can be present
Renal dysplasia	Absent	Absent	Can be present
Fetal urinary biochemistry	Favorable	Favorable within three consecutive evaluations	Not favorable after three consecutive evaluations
Fetal intervention	Not indicated	Indicated to prevent pulmonary hypoplasia and severe renal impairment	May be indicated to prevent pulmonary hypoplasia but not postnatal renal impairment; further studies are necessary

The disease can progress from Stage I to Stage II and then to Stage III during pregnancy

utero, and then at birth an endoscopic incision of the UC may be done. Fetal intervention should be considered in the presence of severe BOO, which may result in bilateral renal damage, oligohydramnios, pulmonary hypoplasia, and neonatal death. Indications are sonographic findings suggestive of progressive obstruction such as increasing bilateral hydronephrosis, hyperechogenic kidneys, and significant reduction of amniotic fluid volume [44, 45].

In 2001 Quintero [45] wrote that prenatal treatment of bladder-outlet obstructing fetal UC constituted an important landmark in minimally invasive fetal therapy, expanding the applications of this approach for the in utero correction of birth defects. Anyway, the value and limitations of that novel prenatal intervention were yet to be proved.

As for PUV, treatment options include repeated amnioinfusions, placement of a vesicoamniotic shunt, ultrasound-guided percutaneous needle incision, or, more recently, fetal cystoscopic laser incision [43, 46]. It is obvious that, compared to percutaneous needle puncture, endoscopic visualization of the UC has the major advantage of allowing precise selection of the size and site of the UC puncture and to protect the bladder wall from damage [44].

The first to report fetal cystoscopic laser incision of UC was Quintero in 2001 [45]. Under general anesthesia the bladder of the fetus was accessed percutaneously under ultrasound guidance with a 3.5 mm trocar. Fetal cystoscopy showed a cecoureterocele extending from the right side of the bladder floor (bladder neck) to the urethra. The UC was incised without complications with a Nd:YAG laser (Surgical Laser Technologies, Montgomeryville, PA, USA) using a 400 μm contact fiber both at the level of the urethra and bladder, with immediate decompression of the lesion. As a result of the treatment, amniotic fluid volume increased, pregnancy proceeded until term, left kidney function was preserved, and pulmonary hypoplasia from oligohydramnios was avoided. Unfortunately, right kidney function could not be preserved. Earlier intervention in future cases may be warranted but only in cases where bladder-outlet obstruction and oligohydramnios are present.

The second experience with fetal endoscopy was that of Montebruno in 2015 [47], who reported the successful use of fetoscopy to treat a case of prolapsed UC in a 26-week female fetus, causing intermittent BOO and oligohydramnios. In this clinical case, however, the UC was prolapsed through the external urethral outlet protruding from the vulva; therefore, there was no need to access the fetal bladder. Under maternal local anesthesia and sedation, and fetal intramuscular analgesia and immobilization, a 3 mm trocar was percutaneously introduced into the amniotic cavity. By direct vision, the UC emerging between major labia of the vulva was identified and perforated under combined endoscopic and US control, by gently touching with a diode laser fiber at power settings of 10 W, with successful and persistent decompression of the UC and progressive reduction of the upper tract dilatation. Amniotic fluid remained normal throughout the whole pregnancy.

In 2016 [44] Persico et al. reported two additional cases of fetal UC treated by cystoscopic laser decompression. In the first case, a standard 3.3 mm uterine entry was used. The ureterocele was incised under endoscopic vision using a 400 μm diameter diode laser fiber, with a power output of 10–15 W, with UC decompression and subsequent improvement in hydronephrosis and restoration of normal amniotic fluid volume. For the second case, a new approach was adopted using an all-seeing-needle 1.6 mm endoscope. A 200 μm diameter Ho:YAG laser fiber, with a power output of 10–15 W, was used to incise the UC, achieving decompression of the UC, improvement in hydronephrosis, and restoration of normal amniotic fluid volume.

The experience from Persico et al. suggests that effective fetal cystoscopic laser treatment of an UC under direct vision can be carried out using an instrument with a much smaller diameter (1.6 mm) than the standard 3.3 mm fetoscopic access, and this approach provided an equally good endoscopic view while retaining the ability to use a laser fiber. Up to date there are no previ-

ous reports on its use for the intrauterine treatment of fetal UC. The diameter of the instrument used for intra-amniotic access is particularly important in fetal surgery because it has been shown to be directly related to the risk of premature rupture of membranes, a common complication of intrauterine procedures. The minimally invasive technique described in this report, using a fine needle which allows for good endoscopic views and provides a working channel for a laser fiber, has many potentials for wider application in the field of prenatal intervention [44].

43.10 Lower Tract Approaches

Lower tract approaches to pyeloureteral duplex system anomalies have traditionally included total reconstruction and superior moiety (SM) salvage procedures, such as ipsilateral ureteroureterostomy (IUU) and ureteropyelostomy.

43.10.1 Total Reconstruction (Fig. 43.11)

During previous years, total reconstruction was infrequently recommended in infants because of the risk of damaging the bladder. Concerns about lower urinary tract reconstruction include persistent reflux or obstruction from reimplantation procedure, urinary incontinence from bladder-outlet injury, and risks to leave hypofunctioning or dysplastic renal segments.

In the past there was general agreement that this form of procedure carries an increased risk of voiding dysfunction, although several authors have shown that voiding dysfunction is part of the disease in many patients, even when the patient is not operated on. However, with recent standards of care at present, some authors advise this approach which could be performed safely at any age without consequences for bladder function, even if its role for the prevention of urinary incontinence is questionable up to now [13, 48, 49].

Ureteral reimplantation via Cohen's method is highly successful to stop reflux. Nonetheless, while the procedure still represents the most effective and consistent approach for achieving single-stage cure of VUR, it is not 100% effective [49–51]. Beganovic et al. [52] reported persistent VUR in 13% of cases and a secondary surgery rate of 36% during long-term follow-up of 53 patients. Therefore, total reconstruction should be limited to cases of preoperative multiple or high-grade VUR [49, 50, 53].

Few attempts have been made to simplify this surgical procedure. On the one hand, Gran et al. [54] proposed avoiding the upper tract approach and also reimplanting the ureter of the nonfunctioning pole; none of their 16 patients developed any problems during an average follow-up of 5 years. This result was confirmed by

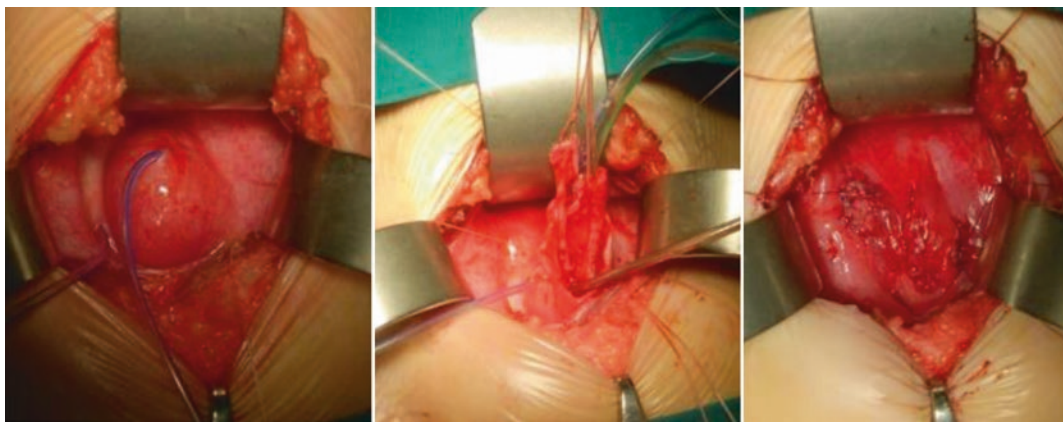

Fig. 43.11 UC excision and reimplant in duplex system intravesical UC

Wang et al. [55]. On the other hand, IUU has been reported as a viable option, even in cases in which there is a marked discrepancy in diameter between the donor and recipient ureter [56, 57]. Finally, others have suggested avoiding UC excision and bladder neck reconstruction and, instead, performing the whole procedure via an extravesical approach [10, 58].

Furthermore, one of the demanding points of reconstruction is reported to be the removal of the posterior mucosal wall inside the distal ureterocele and the repair of thinned-out posterior bladder wall, in order to provide adequate muscular backing. The complete mobilization of the distal lip of ureterocele is in some cases difficult because it extends deep in the urethra and removal of the mucosa brings risks to injure sphincter mechanisms or even create urethrovaginal fistulas in female patients. In these instances Shimada et al. [59] suggested to cut the distal edge of the UC in order not to leave valvular structure and fulgulate posterior mucosal epithelium instead of complete removal of the mucosal layer.

43.10.2 Superior Moiety Salvage Procedures

Some investigators have shown that SM salvage procedure (IUU, ureteropyelostomy) recovers only a modest percentile of overall renal function and may contribute to overall surgical morbidity in some patients. Vates and colleagues [60] reported that an average decrease in overall renal function among the 31 patients who underwent partial nephrectomy was only 2.25%.

When obstruction of the upper pole moiety is the only feature encountered with duplex system UCs, anastomosis between the upper and lower pole ureters is an appealing approach, particularly, as poorly or nonfunctioning upper poles do not require removal [14]. Therefore, IUU is an increasingly used alternative for children with pyeloureteral duplication in whom the obstructed moiety has significant functionality [9, 61, 62]. Furthermore, the application of laparoscopic and robot-assisted techniques for IUU has caused renewed interest in the application of UU in the management of ectopic duplex ureters. UU offers a theoretical advantage over heminephrectomy by preserving any functioning upper pole renal parenchyma and avoiding potential morbidity from renal surgery, including damage to the more viable lower pole moiety. Hence, minimally invasive IUU can be an excellent option in carefully selected patients. Though, Vates et al. [60] argue for judicious use in the setting of absent SM function, high-grade recipient ureteral VUR, and massively dilated donor ureter.

Conventional laparoscopic IUU is feasible and has been described [63, 64]. However, the delicate intracorporeal suturing and fine reconstructive techniques necessary for the repair with current conventional laparoscopic instruments remain challenging for other than expert laparoscopic surgeons [65]. Therefore, overall clinical experience with minimally invasive IUU remains limited, and published data describing outcomes and complications are sparse. Most investigators reserve IUU for children without IM VUR in order to avoid introducing reflux into a functioning but anatomically abnormal upper pole moiety [62, 63, 66]. However, a few centers have begun using IUU for the management of duplex anomalies irrespective of the degree of ureteral dilatation, SM functionality, or presence of ipsilateral reflux [57, 67]. Reimplantation of a refluxing lower pole ureter along with concomitant IUU is also a successful technique on the whole, although persistent VUR may be seen [56, 57].

Several case series report successful robotic-assisted IUU procedures: the advantages of robotic approach include superior exposure and visualization, tremor filtration, motion scaling, and wrist-like instrumentation with a highly magnified three-dimensional image, which may convey a potentially decreased risk of complications while improving cosmesis with smaller port incisions [61, 68–70]. Moreover, given the technical difficulties associated with conven-

tional laparoscopic suturing, robotic-assisted surgery may reduce the learning curve and increase the prevalence of performing minimally invasive surgery for IUU on infants and children with ectopic ureters [71]. These features increase surgeon dexterity by almost 50% in comparison to conventional laparoscopic surgery and have been shown to decrease skills-based errors by 93% [72]. This is particularly important in complex procedures like IUUs that require precise suturing to establish a watertight anastomosis. Furthermore, in studies comparing robotic-assisted to open pediatric IUUs, pyeloplasties, and extravesical reimplantations, patients in the robotic group presented comparable operative times, estimated blood loss, and complication rates with slightly shorter lengths of hospital stay and higher rates of improved hydronephrosis or drainage during initial follow-up imaging [73–75]. However, the use of robotic-assisted procedures in the pediatric population was initially limited due to concerns regarding operating the robot in smaller working spaces. Only few reports currently exist analyzing the use of robotic-assisted procedures exclusively in infants [76–78]. Nevertheless, as it has increasingly been demonstrated to be feasible and safe, the role of robotic surgery in the pediatric population has expanded.

43.11 Upper Tract Approaches

Upper tract approaches to pyeloureteral duplex system anomalies have traditionally included pyelopyelostomy, ureteropyelostomy, and SM heminephrectomy. The first two are seldom used because they seem to offer no advantage compared with SM heminephrectomy and may portend a higher morbidity [9, 60].

43.11.1 Heminephrectomy with Partial Ureterectomy

Heminephrectomy is traditionally considered a more definitive surgery compared to IUU, and it is appropriate for children with ectopic duplex system UC without VUR and is definitive in 85% of such cases [26, 28, 79]. Heminephrectomy has been referred to as the "simple" approach, favoring excision of a poorly functioning upper pole moiety over lower tract reconstruction with IUU (Fig. 43.12).

As reported by Michaud [80], it offers theoretical advantages over UU by avoiding distal ureteral dissection and potential pathology associated with leaving the upper pole moiety including hypertension from renal dysplasia and pyelonephritis. However, concerns with the use

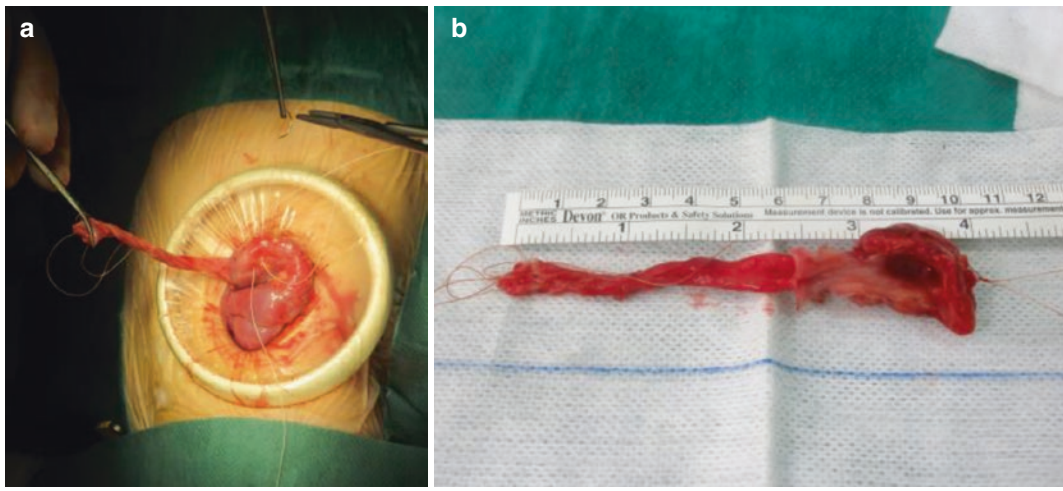

Fig. 43.12 Heminephrectomy with partial ureterectomy: isolation of proximal dilated ureter (**a**) and removed displastyc upper pole, dilated pelvis, and ureter (**b**)

of heminephrectomy include loss of renal function from damage to the lower pole moiety, continued or new-onset lower pole VUR, and the need for reoperation on the distal ureter.

Several studies have shown the utility of heminephrectomy, especially in children with absent SM function and absence of preoperative ipsilateral VUR. Potential suboptimal outcomes include ipsilateral hemi pole functional loss, UTI caused by persistent VUR, de novo VUR, and need for additional surgery. However, only few long-term data exist with respect to long-term functional renal outcomes after minimally invasive SM heminephrectomy.

Laparoscopic retroperitoneal [81–86], laparoscopic intraperitoneal [31, 32, 55, 87–90], robotic retroperitoneal [91], and robotic intraperitoneal [92, 93] approaches have been described with respect to heminephrectomy. There are several advantages offered by these approaches compared with open surgery. First, the innocent pole is not directly manipulated as it is often in open surgery, which requires mobilization of the kidney from surrounding structures and downward traction for exposure. Such maneuvers risk torsion of the renal pedicle and consequent injury or thrombosis of innocent pole vasculature [85, 94]. In contrast, a laparoscopic approach is performed with the kidney in situ with minimal traction on the pedicle [82]. This approach may reduce the risk of remnant pole vasospasm or vascular injury [70]. Furthermore, minimally invasive approaches offer a shorter hospital stay and an improved cosmesis with comparable operative duration [95].

Transperitoneal and retroperitoneal laparoscopic heminephrectomy are comparable with respect to operative duration, hospital stay, and analgesic requirements, and both are superior to open surgery in these respects [31, 32, 83, 93]. Laparoscopic intraperitoneal heminephrectomy seems to be a faster, safer, and easier procedure to perform in children compared to laparoscopic retroperitoneal approach due to a larger operative chamber available, a good overall exposure of the anatomy of the kidney, and its vascularization and the possibility to remove the entire ureter near the bladder dome in refluxing systems avoiding to leave a refluxing ureteral stump [96, 97]. Moreover, in retroperitoneal laparoscopic heminephrectomy one significant risk factor leading to the possibility of conversion is the age of the child; the risk is greater in the younger age group, especially in the first 6 months of life [84, 86, 98]. Hence, the spatial limitations of the narrow retroperitoneal working space in children younger than 12 months and the difficulty of removing the entire ureter near the bladder dome lead some authors to recommend the retroperitoneal approach in patients older than 12 months who need an upper or lower pole heminephrectomy with partial ureterectomy [97]. However, retroperitoneal laparoscopic heminephrectomy allows direct access to and excellent exposure of the kidney and its pedicle as well as minimal in situ mobilization of the kidney and surrounding structures. Moreover, this technique decreases the risk of intraperitoneal organ injury and postoperative adhesions, which is of paramount importance for the future of our pediatric population [99].

The robotic intraperitoneal technique is preferred by some authors [9, 93], in part because of the superior three-dimensional visualization and magnification afforded by the robot, in part because of the articulating instrument that allows for the use of only two small robotic working ports in most cases, in part because this procedure seems to be associated with low complication rates [92]. Moreover, robotic technology allows more accurate distinction of the vascular and anatomic plane between upper and lower poles of the duplex system, as well as an improved ability to preserve innocent pole vasculature, parenchyma, and ureter. Specifically, Malik and colleagues [100] reported that robotic intraperitoneal technique allows easy and efficient identification of the ureters. Therefore, the authors do not require the placement of a retrograde ureteral catheter preoperatively, avoiding additional instrumentation.

However, heminephrectomy does not frequently represent a curative intervention for children with duplex system anomalies and VUR. Husmann and colleagues [26, 28] found that in children with ectopic ureterocele in whom

preoperative VCUG shows reflux, both endoscopic incision and heminephrectomy are definitive in only 16% of cases. Several studies have shown a prevalence of de novo ipsilateral lower pole or contralateral reflux of 40–50% after upper tract surgery [19, 26, 28, 101].

As reported [16], there is an increase in postoperative reflux after the use of heminephrectomy alone when compared to the three other surgical approaches (lower tract reconstruction LTR, simultaneous upper and lower tract approach, and staged lower tract reconstruction). Although heminephrectomy was a definitive procedure in some patients without reflux at presentation, many who underwent heminephrectomy, leaving the ureterocele intact, went on to require later bladder surgery for either recurrent UTI or persistent reflux.

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Posterior Urethral Valves: Fetal and Neonatal Aspects

44

Lisieux Eyer de Jesus and João Luiz Pippi-Salle

Posterior urethral valves (PUV) are the most common form of urethral obstruction. The disease occurs in 1:5000–1:8000 live male neonates [1]. PUV are a significant cause of perinatal mortality and one of the most common causes of kidney failure in infancy and childhood (a third of the patients suffering from PUV progress to terminal kidney failure during life, and PUV constitute 15% of children undergoing renal transplantation). Grade 5 kidney failure is rare (7:1,000,000 neonates), but is determined almost exclusively by PUV/fetal urethral obstruction and bilateral renal hypoplasia/dysplasia. Survival of such neonates in dialysis is possible in modern referral centers: around 80% survive till preschool age [2], but at the cost of a very high morbidity and the need for renal transplantation in young children.

The purpose in this chapter is to explore the aspects of PUV during fetal life and infancy, especially in what concerns diagnostic and therapeutic interventions on the disease.

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44.1 PUV: Definition and Physiopathology

PUV are mucosal leaflets that determine partial obstruction on the proximal (posterior) urethra. Their embryological origin is controversial.

PUV were classified by Young [3] into three types (Fig. 44.1):

1. Type I, the most common (approximately 95%): A membranous incomplete leaflet in a caudal and anterior direction, shaped as a crescent moon, with the concavity facing the verumontanum, where from it originates.
2. Type II, nowadays considered clinically insignificant: The bicuspid valves assume a cephalic direction from the verumontanum to the bladder neck.
3. Type III (approximately 5%): A membranous concentric perforated diaphragm located in the posterior urethra, near to the *verumontanum*.

Recently a unifying concept was proposed by Dewan and Goh [4], suggesting that PUV are in fact a unique disease, caused by a congenital obstructing posterior urethral membrane (COPUM) that originates from the caudalmost end of the Wolffian duct when the duct fuses with the developing cloaca (4th gestational week). The persistent membrane obliterates in a variable fashion, determining various degrees of obstruction, affecting the development of the kidneys,

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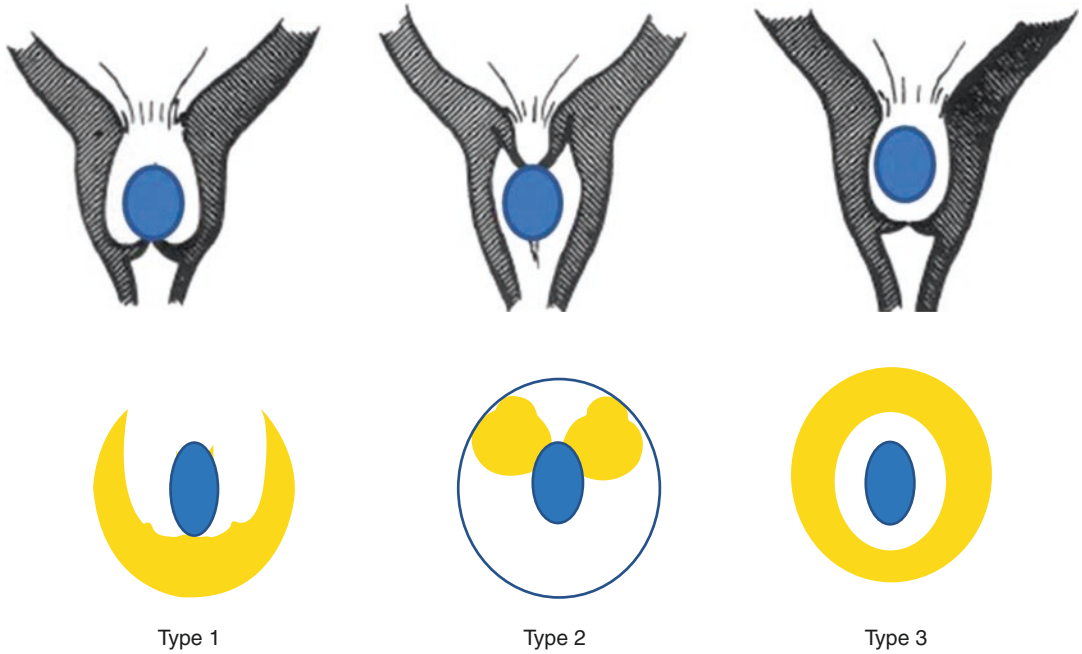

Fig. 44.1 Posterior urethral valves, types (schematic). Superior line: anatomical view, coronal cut. Inferior line: endoscopic view (valves in yellow). Verumontanum: blue circles

ureters, and bladder. For these authors COPUM should be differentiated from Cobb's collar, a transverse partial obstruction located near the external urethral sphincter.

Fetal response to urethral obstruction is characterized by hyperplasia and hypertrophy of the muscular bladder wall. The functional and anatomical reactive modifications of the detrusor, together with increased deposition of specific collagen types, determine progressive thickening, muscular hyperactivity, and loss of bladder compliance. Early in gestation, the bladder presents as an enlarged fluid-filled structure (megacystis) and evolves to a thickened, low-capacity, low-compliance, pseudodiverticular organ.

Bladder emptying occurs at expense of high pressures from fetal life. Back pressure determines hydroureteronephrosis, frequently associated with parenchymal atrophy. Either vesicoureteral reflux or functional obstruction of the terminal ureters can occur secondarily to high bladder pressures, detrusor hypertrophy, and low bladder compliance.

The ongoing obstruction in the developing kidneys can determine structural abnormalities, namely, uni- or bilateral dysplasia. The distal tubules are the most affected, resulting in a limited concentrating capacity and a pseudoaldosteronism-like polyuric syndrome that persist temporarily or permanently after relieving the obstruction (post-obstructive diuresis).

As fetal urine is the main component of the amniotic fluid, severe urethral obstruction during fetal life may determine oligohydramnios from the second trimester of pregnancy. The severity of oligohydramnios has prognostic and therapeutic implications and has to be monitored during pregnancy in fetuses with images suggestive of PUV. The decreased amount of amniotic fluid causes secondary pulmonary hypoplasia, as the normal development of the lungs depends on the aspiration of amniotic fluid. Oligohydramnios may also cause morphological abnormalities, especially clubfeet and, in severe cases, face deformities (Potter's face). Severe cases of PUV can lead to prenatal fetal death. Figure 44.2 illustrated many features of dysmorphic urinary tract associated with PUV.

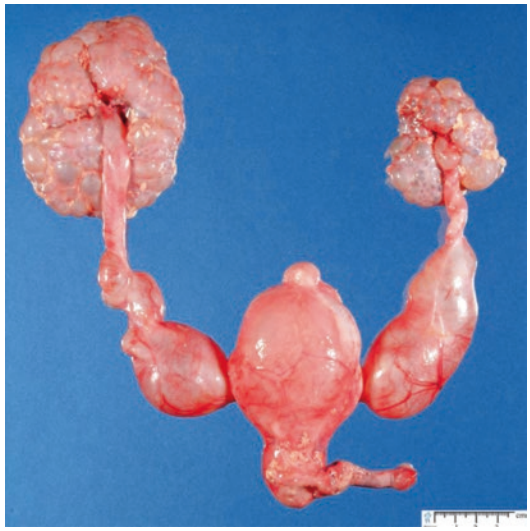

Fig. 44.2 Autopsy of a fetus with severe PUV (bilateral renal dysplasia, hydroureteronephrosis, thickened detrusor, and dilated posterior urethra)

44.2 PUV: Prenatal Aspects

Prenatal ultrasonography is now routine, with at least three evaluations in the first, second, and third trimesters. PUV is commonly diagnosed from the 16th gestational week, after formation of the kidneys and predominance of urine as the foremost component of the amniotic fluid, although some signs may be seen earlier, especially in severe cases.

The disease is normally perceived during the second trimester, from a constellation of symptoms (male gender, bilateral hydroureteronephrosis, megacystis, dilated posterior urethra, and oligohydramnios). The main ultrasound signals to suggest PUV are:

1. Male fetus (PUV is exclusive of males).
2. Oligohydramnios, which is also a poor prognostic sign.
3. Megacystis (defined as ≥7 mm longitudinal bladder diameter in the first trimester and fetal bladder longitudinal diameter ≥gestational age (weeks) + 12 mm in the second and third trimesters [5]). Early diagnosis suggests a worse prognosis [6]. Megacystis is present in <1% of the gestations, and most persistent cases are due to PUV (Fig. 44.3). The differential diagnosis of fetal megacystis is between obstructive problems (mainly PUV), transitory maturational phenomena and a component in syndromic fetuses. A dedicated ultrasonographist should be attentive for the fact that, from the second trimester, failure of bladder emptying for 45 min suggests obstruction [1].
4. Thickened bladder/megacystis.
5. Bilateral hydroureteronephrosis is typical, but approximately 15% of the fetuses present unilateral dilatation.
6. Renal dysplasia (hyperechogenic kidneys, multiple cortical cysts, loss of corticomedullary differentiation).
7. Dilatation of the posterior urethra (keyhole sign), which is detectable in half the cases of PUV, but presents low specificity (may be detected in 1/3 of non-PUV lower urinary tract obstruction (LUTO) cases [1])—Fig. 44.4.

Fetal MRI may also document the same findings (Fig. 44.5). The main differential diagnoses are prune belly syndrome, other urethral obstructions of the posterior urethra (stenosis and atresia), urethral anterior valves, syringocele or diverticula, obstructive prolapsing ureteroceles, congenital megalourethra, severe vesicoureteral reflux associated with detrusor-sphincter dyssynergia [7], and megacystis-megaureter-microcolon associations.

As mentioned before the pregnancy needs to be closely monitored in any fetus suspected of PUV, in order to detect the two main fetal complications of the disease:

1. Oligohydramnios (that suggests secondary kidney damage and dysplasia and is directly related to lung hypoplasia and fetal respiratory insufficiency). Oligohydramnios is the trigger to consider intrauterine therapy for PUV cases.
2. Fetal ascites or perinephric urinoma, normally secondary to the rupture of a renal calix secondary to back pressure. Bladder rupture is exceedingly rare.

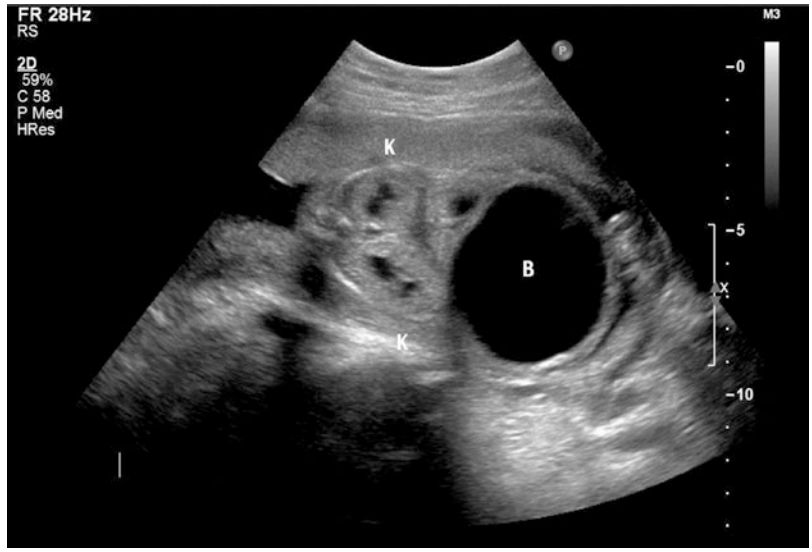

Fig. 44.3 Ultrasound of 17-week fetus with megacystis caused by PUV (*K* kidney, *B* bladder)

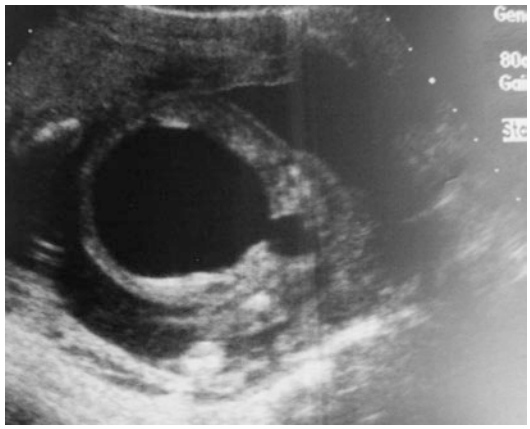

Fig. 44.4 Ultrasound in a fetus with megacystis and keyhole sign in a bladder with thickened detrusor

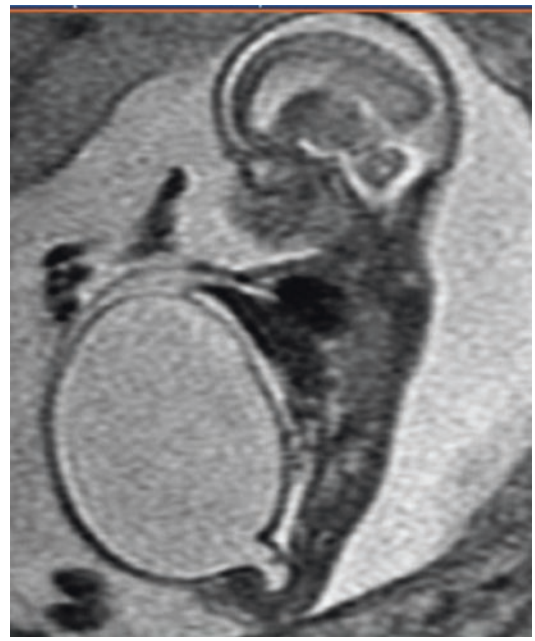

Fig. 44.5 Fetal MRI, posterior urethral valves, showing megacystis and posterior urethral dilatation

Future renal prognosis is mainly determined by signs of kidney dysplasia, especially hyperechogenicity, cortical cysts, and loss of corticomedullary differentiation [8, 9] (Fig. 44.6). Total parenchymal area/cortical volume before decompression has also been suggested as a prognostic marker, but no prenatal nomograms are available till now [8, 10, 11]. Lower urinary TGF-β1, TNF-α, and microalbumin suggest better prognosis, as well as progressive lowering of these markers after decompression [12]. Recently some authors have suggested that certain genetic markers (copy number variants) may also affect kidney prognosis in PUV cases [13]. Fetal urinary/amniotic peptide profile is also being researched in search of prognostic markers for fetal urinary obstruction [14].

There is also some evidence that antenatal detection of PUV allows a better prognosis [15], possibly to planned delivery in better equipped centers, where the neonates may

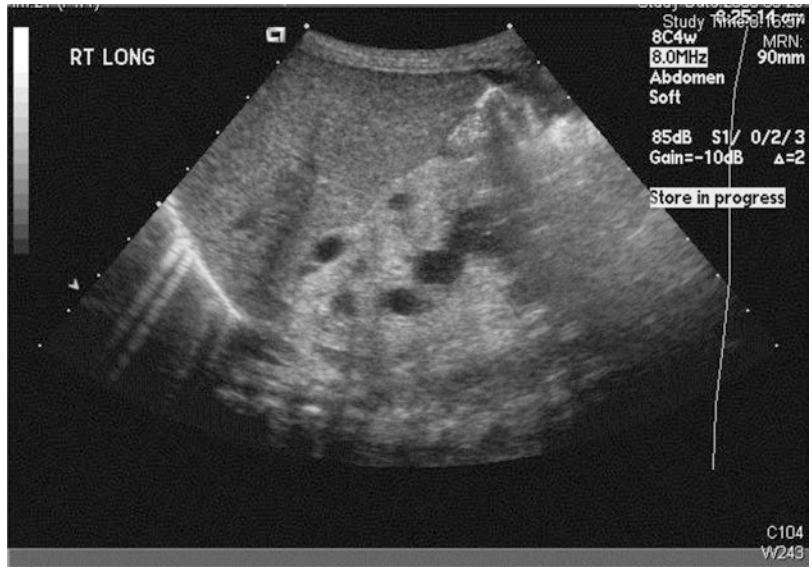

Fig. 44.6 Postnatal ultrasound of baby with PUV (hyperechogenic kidney and cortical cysts)

receive expert nephrological care, including dialysis as needed. Also, there is a clear bias in the literature as unfavorable cases are randomly born in underdeveloped countries, while in developed ones, fetal diagnosis of severe disease leads to abortions, therefore selecting favorable cases.

Fetal intervention to treat PUV may be done by:

1. Repeated vesicocentesis.
2. Vesicoamniotic shunting (VAS).
3. Intrauterine antegrade transvesical laser valve ablation (ITVLA).
4. Amnioinfusion (indicated in late pregnancy to avoid premature births in cases of severe late oligohydramnios).
5. Intraperitoneal shunting as a treatment for severe fetal ascites (uncommon).

VAS or ITVLA may be considered only in singleton pregnancies with early, severe, or progressive oligohydramnios in genetically normal fetuses unaffected by other severe malformations. A careful discussion with the parents is needed. Maternal risks are to be considered. In addition these interventions offer no guarantee of recovery of renal function for the future baby. Fetal therapy for PUV does succeed to prevent pulmonary insufficiency, but less so to avoid kidney failure.

The pertinent literature reporting prenatal interventions suffers from several biases, namely, analysis of small populations, high taxes of voluntary termination (including after prenatal treatment), and different criteria for fetal selection. Recent research comparing nonintervention, VAS and ITVLA, in severe LUTO cases suggests that:

(a) The probability of perinatal survival increases in the intervention groups, possibly due to better postnatal pulmonary function.
(b) Renal function tends to be better in the first semester of life only in the ITVLA group [16].

Prenatal intervention should not be offered to fetuses affected by irreversible fetal kidney failure, as suggested by ultrasound and analysis of fetal urine, obtained by transabdominal transuterine puncture of the fetal bladder. Table 44.1 describes the most common markers to evaluate fetal kidney viability (Table 44.1) [1].

VAS and ITLVA are better indicated for a second trimester fetus with oligohydramnios and favorable urinary markers. Both VAS and ITVLA offer better perinatal survivals (mostly as a consequence of avoiding respiratory insufficiency

Table 44.1 Fetal urine markers obtained by repeated bladder aspirations

Fetal urinary prognostic marker	Favorable values
Sodium	<100 mEq/L
Chloride	<90 mEq/L
Calcium	<8 mg/dL
Osmolality	<200 mOsm/L
Protein	<20 mg/dL
β2-Microglobulin	<6 mg/L

secondary to PUV) and, probably, lower rates of postnatal kidney failure, considering that the fetuses selected for the procedures are among the PUV cases with viable renal function. Even so, both methods have been unable to eliminate the risk of future kidney failure, possibly because fetal intervention is done after the embryological period of embryological kidney formation, therefore does not prevent renal dysplasia.

VAS was the first successful fetal treatment for PUV. A double pigtail catheter is transabdominally inserted into the fetal bladder, communicating the organ with the amniotic cavity. The procedure is minimally invasive and may be done under local anesthesia. An ultrasound-guided Seldinger-like puncture method is used. The mother's abdominal and uterine walls and the fetal abdominal and bladder walls are punctured. A guidewire is inserted. A double-coil catheter is inserted over the guidewire. One extremity of the catheter is located inside the fetal bladder. The other end extrudes through the fetal abdominal wall into the amniotic cavity. The risks to the mother are relatively small, including premature membrane rupture, premature labor, and chorioamniotic infection. The main risks for the fetus are dislocation of the catheter (spontaneous, driven by fetal growth or pulled by the fetus), bladder prolapse, and iatrogenic gastroschisis (Fig. 44.7).

The limited success, the complications with VAS and the proper nature of the method (palliative shunting that excludes fetal bladder cycling) and the recent technological progress gave rise to ITVLA, a newer proposal to treat fetal PUV. In this case maternal and fetal anesthesia are needed. The fetal bladder is accessed through an endoscope that perforates serially the mother's abdominal and uterine walls and the fetal abdominal and bladder walls. Once inside the bladder wall, the endoscope is then used to antegradely ablate the urethral valve with laser. Prospective series of ITVLA are still rare, but the results suggest fetal survival higher than 50%, elimination of pulmonary hypoplasia, normalization of amniotic fluid and bladder anatomy, and postnatal adequate kidney function in approximately ¾ of the patients [17–19]. Obstetric problems with ITVLA are the same as with VAS. The procedure does not have the risks of catheter migration/dislodgement, obstruction, extra-anatomical positioning, and iatrogenic gastroschisis. Theoretically ITVLA is also advantageous to provide a more physiological development of the cycling bladder. Serious urological complications (urethral fistulae and stenoses) have been reported [19].

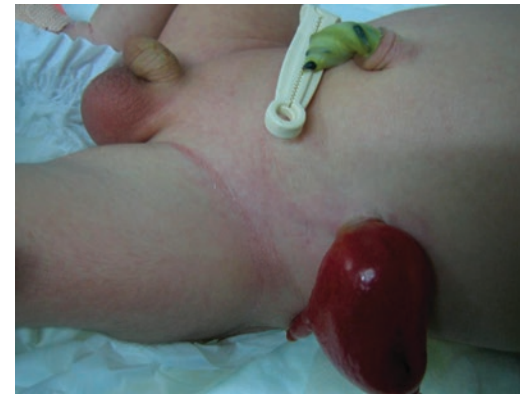

Fig. 44.7 Bladder prolapse in a shunted baby with PUV

44.3 Postnatal Management

Most cases of PUV are antenatally diagnosed and have bilateral hydroureteronephrosis associated with a thickened detrusor on postnatal ultrasound. In cases with oligohydramnios and renal and/or pulmonary hypoplasia/insufficiency, Potter facies features may be present. Male babies with an antenatal diagnosis of LUTO should be delivered in hospitals with neonatal intensive care unit (NICU) and specialized nephro-urological pediatric care available. Pulmonary insufficiency may associate with the

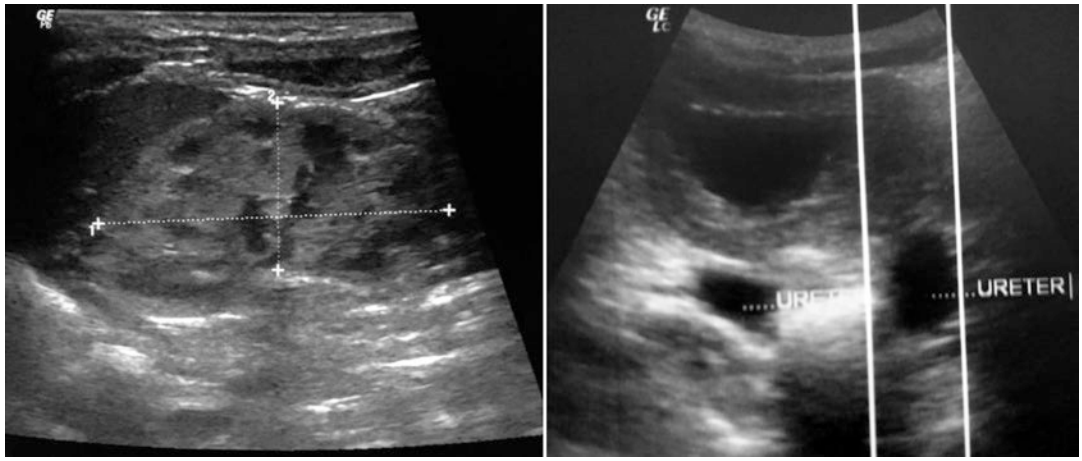

Fig. 44.8 Perinatal ultrasound (left, hyperechogenic dysplastic kidney; right, thick bladder and bilateral ureteral dilatation)

need for ventilators and prematurity is common. Respiratory insufficiency is usually seen after pregnancies complicated by severe oligohydramnios without fetal intervention. Pneumothorax may result from the attempts to ventilate such babies.

In patients without prenatal diagnosis, the most common presentation of the disease is perinatal sepsis secondary to urinary tract infection (UTI). Of note, neonates with UTI do not present with typical signs as seen in older children. The baby may present with sepsis, failure to thrive and refusal to feed, all of them nonspecific signs of UTI.

Urinary retention, abnormal flow and voiding problems are always present in neonates with PUV. One should not discard this diagnosis because the baby seems to void adequately, although usually with weak stream and high post-voiding residuals [20].

The physical examination of the baby may be unremarkable. The dilated kidneys may be palpable, as well as the bladder. Even an empty bladder may be palpated, because of the thickened bladder wall. Some babies present problems that are secondary to oligohydramnios (Potter facies, clubfeet) or to fetal intervention. Associated malformations are uncommon.

Any male neonate presenting with bilateral hydroureteronephrosis is suspect of PUV. Also, any male babies presenting with UTI/urinary sepsis should be investigated with ultrasound, and if hydroureteronephrosis and a thickened bladder is present, diagnosis of PUV should be entertained. The following management is warranted:

1. The children must be submitted to a confirmatory ultrasound examination as soon as possible after birth (Fig. 44.8).
2. Any male babies suspected of having PUV must be catheterized as soon as possible after birth. Catheters without balloons are preferable, as the balloon irritates the trigone and those catheters show worse drainage as compared to non-ballonated catheters with the same diameter. Catheterization may be difficult: The catheter may curl and stop at the dilated posterior urethra. In this case Coudé catheters may be of help. An open-ended catheter can also be inserted passing over a glidewire (Seldinger-like technique). Some authors have suggested the usage of double-J catheters [21], but they need to be inserted over a guidewire, which may be difficult without sedating the child and without using an endoscope. Most term neonates can be catheterized with a 5–6 Fr tubes. Prematures and small-for-age babies may need smaller catheters. Cystostomies are not indicated, except in

exceptional circumstances, when no other way to catheterize is possible.

3. After drainage post-obstructive diuresis may occur, requiring careful replacement and electrolyte monitoring. Nephrological consultation is advised to manage such patients.
4. The creatinine serum values after catheterization must be serially followed. One should remember that the baby's creatinine reflects partially the mother's values in the first days of life. As a rule, during the first week, creatinine values are relatively higher than the normal and decrease gradually to the normal childhood values. Only after the first week serum creatinine reflects exclusively the kidney function of the child. Two important concepts to retain are (a) creatinine nadir, defined as the lowest measured serum creatinine and (b) velocity to reach creatinine nadir. Generally speaking, the faster the child reaches the creatinine nadir, the better the prognosis. For many authors, a nadir >0.85 mg/dL (>75 μmol/L) during the first year of life signals bad prognosis for the renal function in the future [22].
5. As mentioned above the metabolic conditions of the child are also to be monitored, especially diuresis, as post-obstructive diuresis can occur. The child may present severe polyuria that may attain >4 mL/kg/h. Venous gasometries and evaluation/treatment of acidosis are needed, as well as serum electrolyte evaluation. There is a risk of dehydration in the absence of compensatory intake. Severe cases of PUV typically present dysfunction of the distal nephron and may show pseudohypoaldosteronism (metabolic acidosis, hyponatremia, and hyperkalemia).
6. The gold-standard exam to diagnose PUV is the voiding cystourethrogram (VCUG) that should be performed immediately after stabilizing the baby (Figs. 44.9 a–c). The exam not only demonstrates the valves but also diagnoses bladder problems and secondary vesicoureteral reflux. Transperineal ultrasound was recently reported as a good investigation alternative, with the advantages of being feasible without removing the baby from the NICU, being painless and posing no risks of infection and no exposure to radiation. However, there are disadvantages such as the need for expertise and clear demonstration of the urethral and bladder anatomy [23]. Transperineal ultrasound is the only image exam capable to visualize the PUV per se (Fig. 44.10).

44.3.1 Treatment

44.3.1.1 Valve Ablation

The treatment of PUV involves endoscopic valve ablation with cold knife (preferable) (Fig. 44.11), electrocoagulation with bugbee or hook electrodes and laser fulguration [24, 25]. The valves should be ablated at 12–5–7 o'clock positions. Warm irrigation fluid should be used in order to avoid hypothermia in babies. Forceful ablation of the valves with a Whitaker hook (insulated crochet needle) or Fogarty balloon catheter may be used if appropriate endoscopic equipment is not available or if the patient presents a high risk for anesthesia, as this procedure may be done at the NICU with local transurethral anesthesia [26]. Circumcision should be done concurrent to ablation, as the procedure minimizes the occurrence of postoperative UTIs [1]. Most authors suggest doing a voiding cystourethrogram post ablation but often postpone it if the baby is voiding well, the hydronephrosis decreases, and creatinine is stable.

44.3.1.2 Urinary Diversion

Vesicostomy should be used whenever valve ablation is impracticable due to lack of adequate instrumentation or in very small babies (prematures) with a small caliber urethra. One should not hesitate to do this procedure in such cases as forceful instrumentation of a small urethra can traumatize it and cause strictures, a challenging problem in infants. Although considered a simple procedure, vesicostomies are prone to stenosis if not done properly. The opening at the bladder dome should be wide as the thickened detrusor precludes prolapse.

44.3.1.3 High Diversion

The indication of high diversions (high ureterostomies and pyelostomies) is controversial

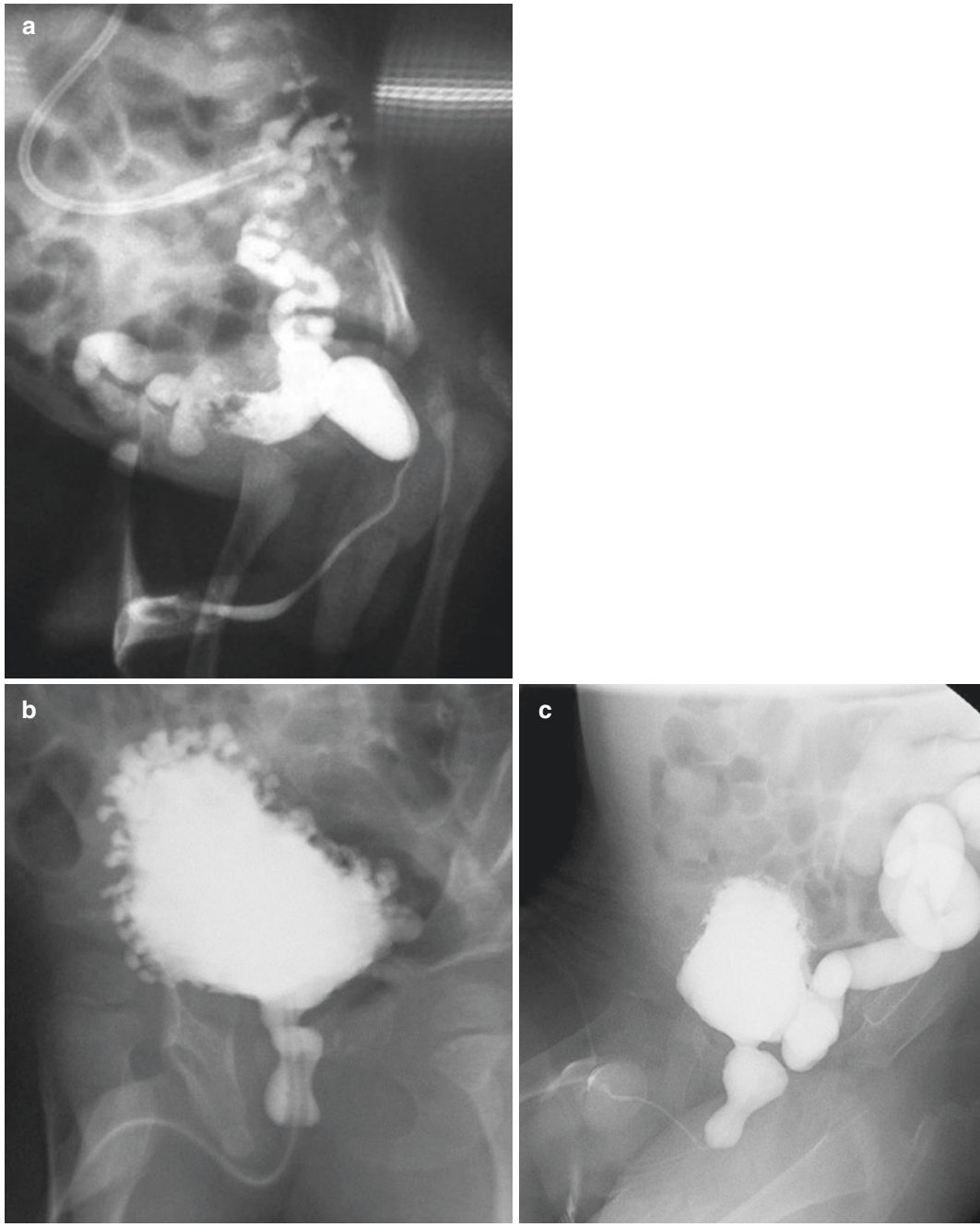

Fig. 44.9 (**a**) PUV – dilated posterior urethra (larger than the bladder!) and bilateral vesicoureteral reflux. (**b**) Trabeculated bladder and typical dilation of posterior urethra and no vesicoureteral reflux. (**c**) PUV and left vesicoureteral reflux associated with dysplastic kidney

although, in our opinion, they are beneficial in some cases. Patients in significant renal failure may benefit from cutaneous ureterostomies, and they prevent UTI and further deterioration of renal function. They have been classically used in those patients that do not recover kidney function after an adequate period of decompression, those with persistent severe dilatation after

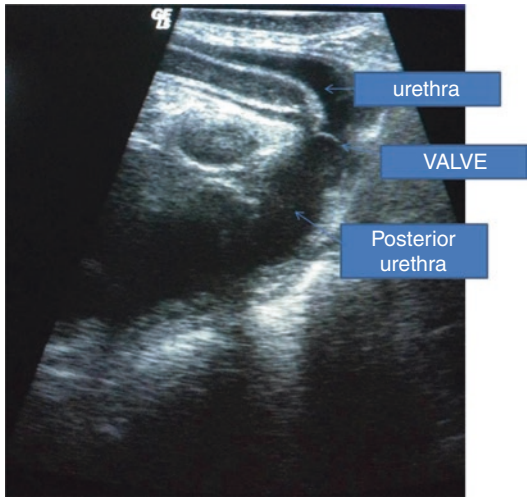

Fig. 44.10 Transperineal ultrasound, demonstrating posterior urethral valves

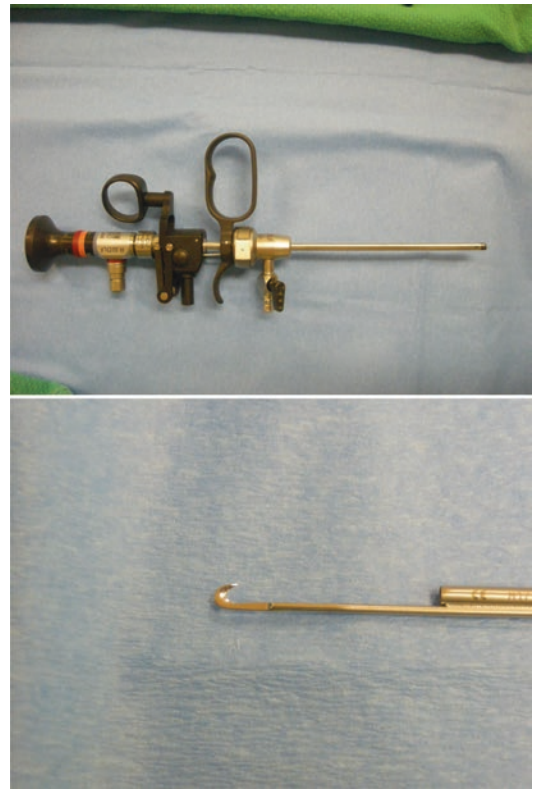

Fig. 44.11 Neonatal resectoscope and hook cold knife: Preferred way to ablate PUV

decompression, or children presenting untreatable urinary sepsis after antibioticotherapy and bladder decompression. In addition there is evidence that, although it does not prevent progression of renal failure, this occurs more slowly, postponing the need for dialysis or transplant to a later stage in life [27]. High diversions imply building stomas that may be difficult to deal with, as they are too high to be protected by diapers and do not adapt well to urinary bags. Besides, they may be socially stigmatizing. In addition, future surgical undiversion can be challenging, in order to avoid kinking or devascularization of the ureter. Other authors believe that patients that do not respond to catheterization and/or vesicostomies have irreversible kidney damage that will not improve by high diversions. Occasionally the persistent dilatation of the high tract may occur due to "pinching" of the distal ureter by the thickened detrusor. Initial treatment with anticholinergics is warranted in such cases, but if unsuccessful we should not hesitate to perform a high diversion. Some authors suggest the use of Sober Y ureterostomy (Fig. 44.12) to avoid bladder defunctionalization, but this procedure is more demanding (same as pyeloplasty) which can be problematic in an unstable uremic patient, the usual candidates for such intervention.

Despite the various controversies and disadvantages of high diversions, some patients, especially those presenting severe renal damage which would be candidates to kidney transplantation during infancy or children living in countries without transplant availability, need special considerations. For those children high urinary diversion seems to prolong life of the native kidneys and to postpone the need for transplantation [27].

After successful valve ablation, urodynamic bladder problems are expected. Secondary hyperactive low-compliant low-capacity bladders are typical of young children presenting with PUV. Polyuria complicates the clinical scenario. Bladder hyperactivity may be treated with oral anticholinergics, and some groups have demonstrated that systematic treatment from neonatal age is advantageous [28]. One should resist temptation to augment PUV bladders as most will eventually self-augment themselves due to progressive

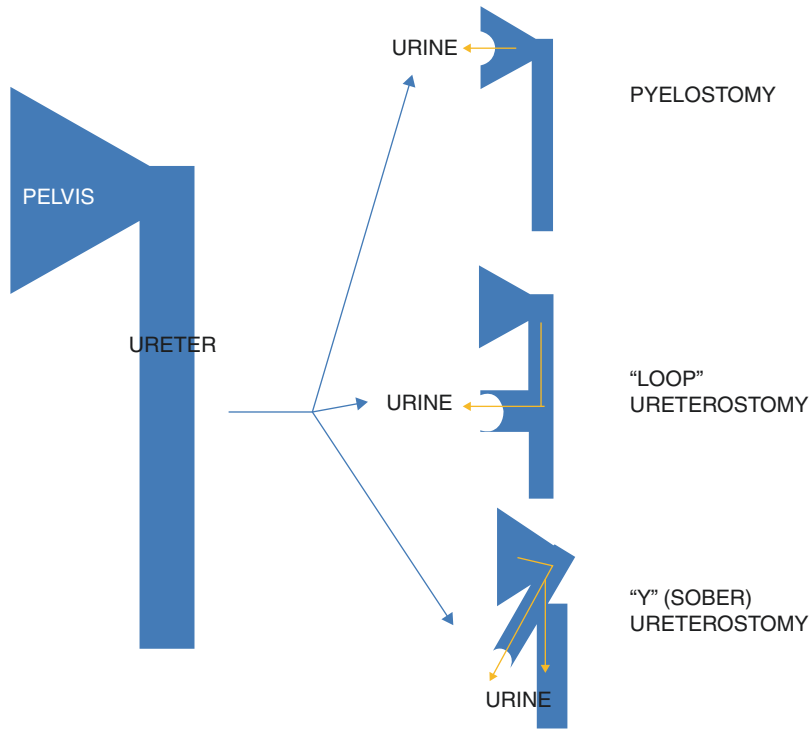

Fig. 44.12 Diagrammatic representation of high diversions

detrusor failure that usually occurs late in childhood or puberty.

Bladder neck hypertrophy is also common and may be treated with alpha-blockers. Bladder neck incision may be proposed. In this case the risk of iatrogenic incontinence is difficult to evaluate, as wetting is quite common in those children, due to bladder dysfunction and polyuria.

Vesicoureteral reflux is present in 30–50% of PUV cases and resolves in most patients after treatment of the urethral obstruction and urodynamic bladder problems. A special group are the patients presenting the so-called VURD syndrome (unilateral severe vesicoureteral reflux associated with ipsilateral kidney dysplasia). Some authors believe that this nonfunctional kidney-ureter system serves as a pop-off mechanism protecting the other functional kidney from pressure backflow. Although this idea has not been proved, this nonfunctional system should not be resected, except in the presence of untreatable repetitive UTI. The dilated ureter and pelvis may serve as urothelial bladder augmentation whenever needed, and simple ipsilateral kidney functional exclusion is not a reason for ablative surgery.

Kidney failure presents in approximately 30% of PUV patients. Terminal kidneys distribute among age groups, typically neonates (cases presenting severe antenatal oligohydramnios), toddlers (surviving neonatal period, especially after multiple UTI episodes), school-aged children (typically 7–8 years old), and young adults, soon after puberty and postpubertal growth.

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Hydrometrocolpos

45

Devendra K. Gupta, Shilpa Sharma,
and Kashish Khanna

45.1 Introduction

Hydrometrocolpos (HMC) is a rare genitourinary condition found in females in which the uterus and vagina are grossly distended by retained vaginal secretions or urine. It is caused by excessive vaginal secretions and distal vaginal obstruction [1, 2]. The condition can be recognized early during the antenatal period with prenatal ultrasound (USG) and fetal magnetic resonance imaging (MRI). The reported incidence has increased to 1/16,000 live births with the growing use of these antenatal investigative modalities.

HMC presents at the two peaks of age in children, initially during the neonatal period, when there is a high vaginal secretion under the influence of high maternal hormones, and then at early puberty with production of estrogenic hormones. The distal vaginal obstruction is mostly due to imperforate hymen, followed by the presence of a transverse vaginal septum, and less commonly due to the vaginal atresia of the distal two third of the vagina [3, 4].

45.2 Definition

The word Hydrometrocolpos is derived from the Greek terms hydro which means water (fluid); metro, tubular structure (uterus); and colpos, vagina. Hydrometrocolpos refers to distension of the uterus and vagina by fluid other than blood or pus [1–4]. Vagina distends much more than the uterus. The accumulation of blood or pus in both the vagina and the uterus is called hematometrocolpos or pyometrocolpos, respectively. Sometimes, only the vagina gets distended, and the uterus is not distended by fluid, blood, or pus; it is then called hydrocolpos, hematocolpos, or pyocolpos, respectively.

45.3 Embryopathogenesis

During the second month of fetal life, the Mullerian ducts develop as tubular invaginations parallel to mesonephric ducts [5]. The caudal ends form the uterus and vagina and fuse in the midline to meet the urogenital sinus (UGS). The distal portion of the fused Mullerian ducts is temporarily occluded completely by a solid cord of cells, the Mullerian tubercle, the caudal end of which becomes the hymen [6].

Failure of degeneration of the epithelial cord in the Mullerian tubercle results in imperforate hymen. Persistence of a portion of the solid cord of cells in the fused Mullerian ducts above the hymen results in vaginal atresia. Transverse septum of the vagina results from incomplete coalescence of vacuoles that develop as the epithelial cord begins to degenerate [1, 2, 4].

The retained fluid in HMC is usually serous or mucoid with large numbers of desquamated

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epithelial cells and leukocytes. Secondary infection of the vaginal fluid, usually with colonic organisms, is not uncommon and is a real risk to life [4]. HMC is classified into two types on the basis of its contents:

- **Secretory**: mucoid viscid material secreted by cervical uterine glands.
- **Urinary**: urine is collected in the vagina due to a valvular flow of urine to vagina.

It is expected that both the estrogenic stimulation and the vaginal obstruction must coexist before HMC develops. If the fetal reproductive tract is sufficiently stimulated by maternal hormones, a newborn infant having the vaginal obstruction will develop HMC. If there is lower level of maternal hormones, the obstruction though present may remain unnoticed until puberty. It is probably due to this reason that in most patients, HMC though congenital in origin is not symptomatically manifested until hematocolpos is superimposed at the time of the menarche [2].

45.4 Antenatal Diagnosis

Antenatal diagnosis of HMC may be associated with oligohydramnios. It may initially be misdiagnosed as a large bladder [7]. USG shows a large retrovesical septate hypoechogenic mass in the fetal abdomen. Fetal MRI helps in detailed assessment of fetal urogenital anomalies [8]. Postaxial polydactyly in the fetus associated with a retrovesical cystic structure provides a great suspicion of HMC-associated syndromes.

45.5 Classification

Hydrometrocolpos has been classified into five types on the basis of the type and level of obstruction [1–3]. Two third of the cases are associated with imperforate hymen or type I HMC. Table 45.1 summarizes the classification of HMC.

45.6 Clinical Presentation

Neonatal/early presentation: About 80% of the cases present in the first 3 months of life. The typical presentation in a neonate is abdominal distension of the lower abdomen along with a palpable lower midline mass usually as a surgical emergency. Occasionally, the newborn baby girl may also present with a bulging hymen and an absence of vaginal orifice [1–3, 9].

The baby is usually sick due to the gross distension and associated sepsis due to purulent material as content of the HMC. The upper vagina usually takes the brunt and becomes enormously dilated with the contents. The less distensible and thick muscular uterus is involved to a lesser degree, but it is always larger than the normal size. The mass may extend up to the costal margin and may cause life-threatening respiratory distress.

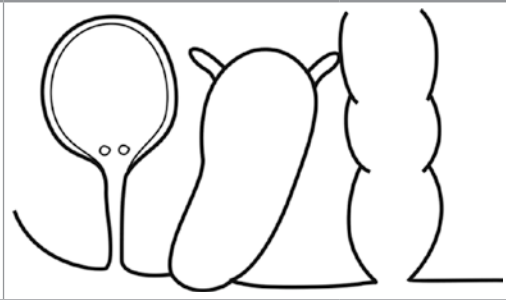
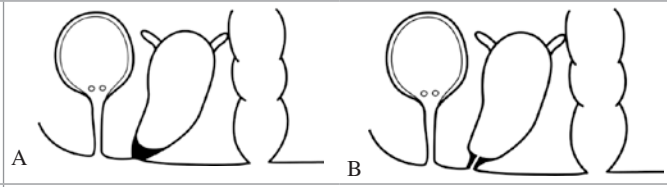
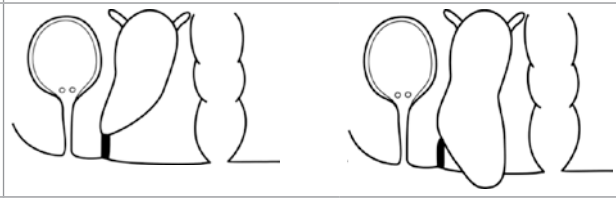
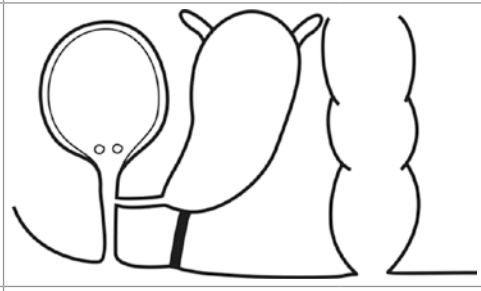
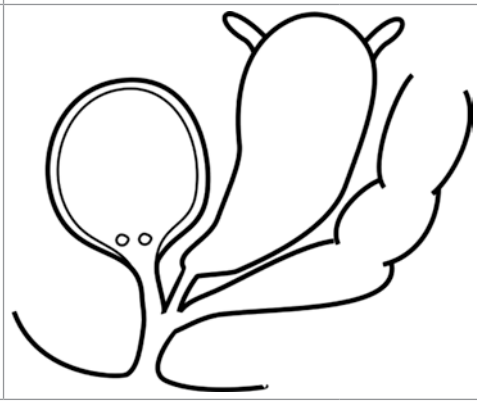
The mass is so large that it may cause obstructive or compressive features on the surrounding structures in the pelvis, leading to urinary retention and constipation [10]. The presence of the distended vagina may kink the urethra and compress it causing acute urinary retention. Compression of the ureters at the pelvic brim results in hydronephrosis and hydroureter.

Compression of the great vessels like inferior vena cava and iliac vessels causes cyanosis, edema, and ecchymosis of the perineum, lower extremities, and abdominal wall. The rectum is usually not affected. However, rarely, constipation may result after HMC.

On perineal examination, a bulging hymenal membrane may be seen. This may be due to imperforate hymen or a bulging transverse vaginal septum. Per rectal examination (if feasible) will reveal a pelvic mass felt anteriorly. In high vaginal atresia or UGS, two perineal openings will be seen. A single perineal opening points toward common cloaca with HMC.

In vaginal atresia, the location where the vaginal orifice should be located may be retracted upward into the pelvis due to the enlarging upper vagina escaping from the small pelvis into the more capacious abdominal cavity [1, 2].

Table 45.1 Classification of types of hydrometrocolpos

Type	Description	Subtype	
I	Low hymenal obstruction	Imperforate hymen	
II	Midplane transverse membrane or septum	A—Without communication B—With a small orifice as communication	
III	High obstruction with distal vaginal atresia	A—Without any perineal swelling B—With perineal swelling	
IV	Vaginal atresia with persistence of the urogenital sinus		
V	Vaginal atresia with cloacal anomaly		

Infection of the dilated tract with collection of fluid is the real risk and cause of high morbidity and mortality in such babies. Most newborns with HMC would present with an infected system, septicemia, respiratory distress, and fever. The infected fluid needs to be drained out urgently to improve the general condition and save the baby.

Late presentation: At puberty, the girl may present with amenorrhea, cyclical abdominal pain, and an abdominal mass secondary to hematocolpos as a result of onset of menarche or HMC. On rare occasions, there may be leukorrhea through a pinpoint opening in the hymen. Adults may present with inability to consummate and infertility.

45.7 Associated Anomalies and Syndromes

About 50% of newborns with HMC are stillbirth [1]. This may probably be due to the other associated anomalies and disorders. The most common and serious are genitourinary anomalies. HMC may present as a part of other disorders (Table 45.2).

The phenotypic overlap of BBS and MKS, both autosomal recessive syndromes, including HMC and postaxial polydactyly in the neonatal stage may cause confusion for appropriate diagnosis. Re-evaluation at a later age for mental retardation, obesity, and retinitis pigmentosa leads to the diagnosis of BBS. Also, uterine, ovarian, fallopian tube, and renal anomalies are more common in BBS than in MKS. By contrast, upper reproductive tract anomalies are not seen with MKS.

HMC may present as a part of **VACTERL** association or may also present as a chromosomal disorder. Interstitial deletion of chromosome 8q21.11-q24.13 was reported to be associated with trichorhinophalangeal syndrome type II (Langer-Giedion syndrome) [13].

HMC may rarely be associated with Mullerian dysgenesis syndrome, staphyloma of the eye, severe hydrops, vertebral segmentation anomalies, lung hypoplasia, corpus callosum hypoplasia, and single umbilical artery [14].

Table 45.2 Hydrometrocolpos and associated anomalies and syndromes

Congenital anomalies		
I	Genitourinary system	Bicornuate uterus, double vagina, duplication of uterus and vagina, bifid clitoris, congenital urethral membrane, double ureter, ureteral stenosis, urethral atresia, renal agenesis, ambiguous genitalia
II	Gastrointestinal	Anorectal malformation, esophageal atresia and tracheoesophageal fistula, duodenal atresia, paraesophageal hiatal hernia, and congenital aganglionosis
III	Cardiac	Congenital heart disease (CHD)
IV	Vertebral	Vertebral segmentation anomalies
Syndromes		
I	McKusick-Kaufman syndrome	Vaginal atresia, HMC, postaxial polydactyly, hydrops fetalis hexadactyly, congenital cardiac anomalies [11, 12]
II	Bardet-Biedl syndrome	The same as MKS with retinal dystrophy or retinitis pigmentosa, obesity, nephropathy, mental disturbance
III	Ellis-van Creveld syndrome	Chondrodystrophy with polydactyly
IV	Langer-Giedion syndrome	Multiple exostoses, learning difficulties, short stature, unique facial features, small head, and skeletal abnormalities

45.8 Investigations

Apart from routine blood and urine tests, investigations to confirm the diagnosis and the type of anomaly and also to plan the management are done and include:

1. **X-ray—**on **plain X-ray of the abdomen**, a mass may be seen in the lower abdomen and pelvis displacing the small intestinal loops into the epigastrium. Neonatal peritoneal calcifications along with the ascites may be seen in HMC secondary to imperforate hymen, without the evidence of gastrointestinal tract obstruction [15].

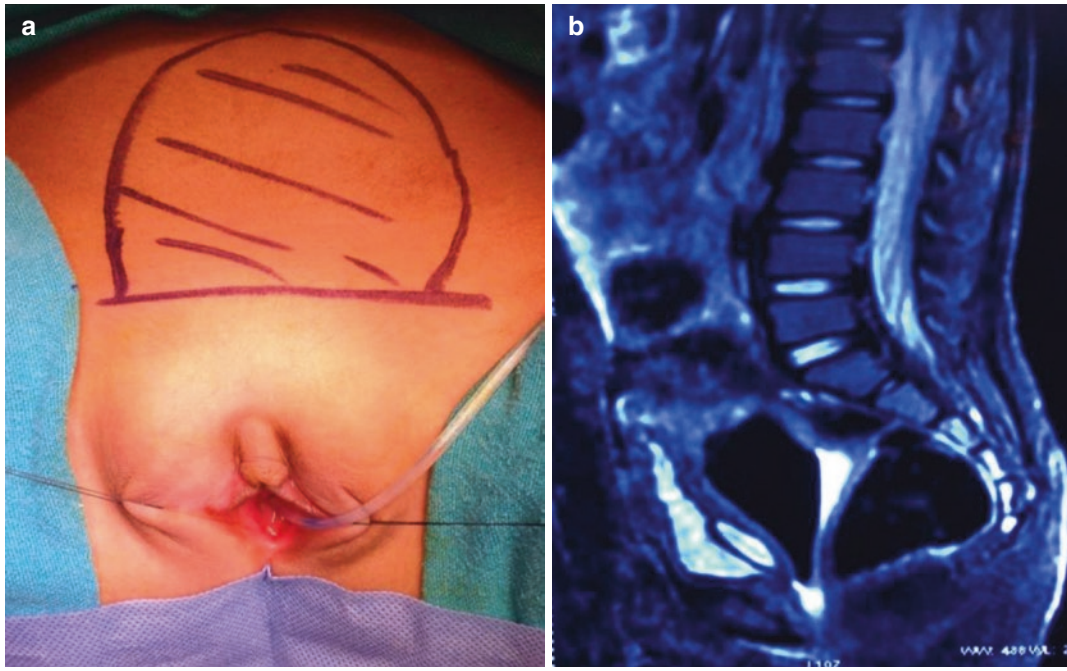


Fig. 45.1 (**a**) A 6-month-old girl with huge abdominal lump and no vaginal orifice in the perineum (hydrometrocolpos due to distal vaginal atresia). (**b**) MRI suggestive of bifid hydrometrocolpos with obstruction due to distal vaginal atresia

2. **Skeletal X-rays** and digital skiagram may be done to identify vertebral and limb anomalies.
3. **USG**—to identify dilated vagina and upper urinary tract anomalies. A trans-perineal USG can help measure a caudally placed obstructive vaginal septum. USG after bladder drainage may help in the diagnosis of HMC [16, 17].
4. **Retrograde genitourethrogram (RGU), micturating cystourethrogram (MCU), and dye study**—to identify the urogenital sinus and its communication with vagina.
5. **Endoscopy**—to delineate the anatomy and the length of common channel (C.C) in cases of cloaca and UGS.
6. **Intravenous urography, CT scan, and MRI**—to delineate anatomy while planning corrective surgery (Fig. 45.1).
7. **Echocardiogram**—to rule out cardiac anomalies.
8. **Renogram studies**—renal function studies to rule out associated renal abnormalities.

45.9 Management

The treatment of HMC is surgical. However, medical management is required to treat the infection, build up the baby, and make her fit for surgery. The type of procedure and the timing of surgical intervention will depend upon the severity of the condition, the type of anomaly, and the age at presentation.

Early neonatal surgery is indicated when a grossly distended HMC presents with a bulging hymen. It is often associated with complications like abdominal mass, urinary obstruction, constipation, sepsis, dehydration, and even respiratory distress. Laparotomy is indicated in patients with high vaginal obstruction and for the treatment of abdominal complications or the associated anomalies. Temporary decompression by needle aspiration or an abdominal tube or a flap vaginostomy may be required to drain the infected material from the vagina. Early drainage in neonates facilitates drainage of the infected material and thus reduction of the chances of sepsis.

Table 45.3 Management algorithm for hydrometrocolpos

	Type I	Type II		Type III	Type IV	Type V
Diagnosis	Imperforate hymen	Transverse vaginal septum		Vaginal atresia	Urogenital sinus	Cloaca
Initial procedure				Vaginostomy (indwelling catheter/flap)		
Subtypes		A—Low/ bulging	B—With a small orifice	Agenesis of lower vagina	UGS/cloaca	
					Common channel length <2.5 cm	Common channel length >2.5 cm
Treatment options	Hymenectomy or hymenotomy	Cruciate incision/ excision and repair, with post-op dilatation		Abdominoperineal pull-through of vagina	TUM or PSARVUP	PSARVUP + vaginal replacement

UGS urogenital sinus, *TUM* total urogenital mobilization, *PSARVUP* Posterior sagittal anorecto-vagino-urethroplasty

Surgery in the prepubertal age is done to allow natural passage for menstrual flow and create a passage for sexual activity and for psychosocial reasons.

Preoperative resuscitation—The newborn should be nursed in head-up position and resuscitated with oxygen, IV fluids, IV antibiotics, incubator care, nasogastric tube decompression, a Foley's catheterization of urinary bladder, and the rectal syringing (in cases associated with constipation). In the presence of a huge distended HMC in a sick neonate, a preliminary drainage by puncturing the vagina under USG guidance may be done for 24–48 h prior to corrective surgery [18]. Alternatively, the hymen or the vaginal septum (type I and II anomaly) can be incised under the USG guidance or even under vision in experienced hands. An USG-guided bilateral tube nephrostomy helps in quick relief from obstructive uropathy in sick neonates.

The following algorithm simplifies the management of this complex condition (Table 45.3).

45.10 Surgical Options

First requirement is the early drainage of the fluid from the closed cavity. The management is simple with low type I and II anomalies. In these cases, drainage procedures alone may be curative. At the most, some of the patients may require postoperative dilatation for a few months. However, the patients with type III, IV, and V HMC anomalies are usually obstructed and often infected. Thus, an initial drainage procedure to drain the dirty infected fluid, followed by a definitive repair later on, is the preferred option. Various surgical options are:

1. Drainage procedures.
   a. Hymenotomy/hymenectomy
   b. Vaginostomy (perineal/abdominal)
2. Abdominoperineal repair of vagina
3. Total urogenital mobilization (TUM)
4. Vaginal pull-through with posterior sagittal anorecto-vagino-urethroplasty (PSARVUP)
5. Vaginal replacement

Drainage procedures—In type I/II, drainage procedures are the definitive treatment. In all other types/in pyometra, drainage of the retained/infected material is the first stage in treatment.

Hymenotomy/ hymenectomy—A bulging membrane in an infant with imperforate hymen or transverse septum of the vagina may be incised without anesthesia. However, excision is preferable if the hymen is thickened or the patient is an adolescent. Hymenotomy may resolve the acute renal failure caused due to obstruction by HMC. The patency of the opening is maintained by the initial use of a drain followed by repeated dilatations [1].

Steps of hymenectomy with illustrations are given in Fig. 45.2.

A contrast study may be performed to delineate the internal anatomy. The vagina is drained for about 2–3 weeks. This is a simple, bedside procedure which can be performed in the intensive care unit if the baby is sick. The depth can be pre-assessed by needle puncture and USG. It can

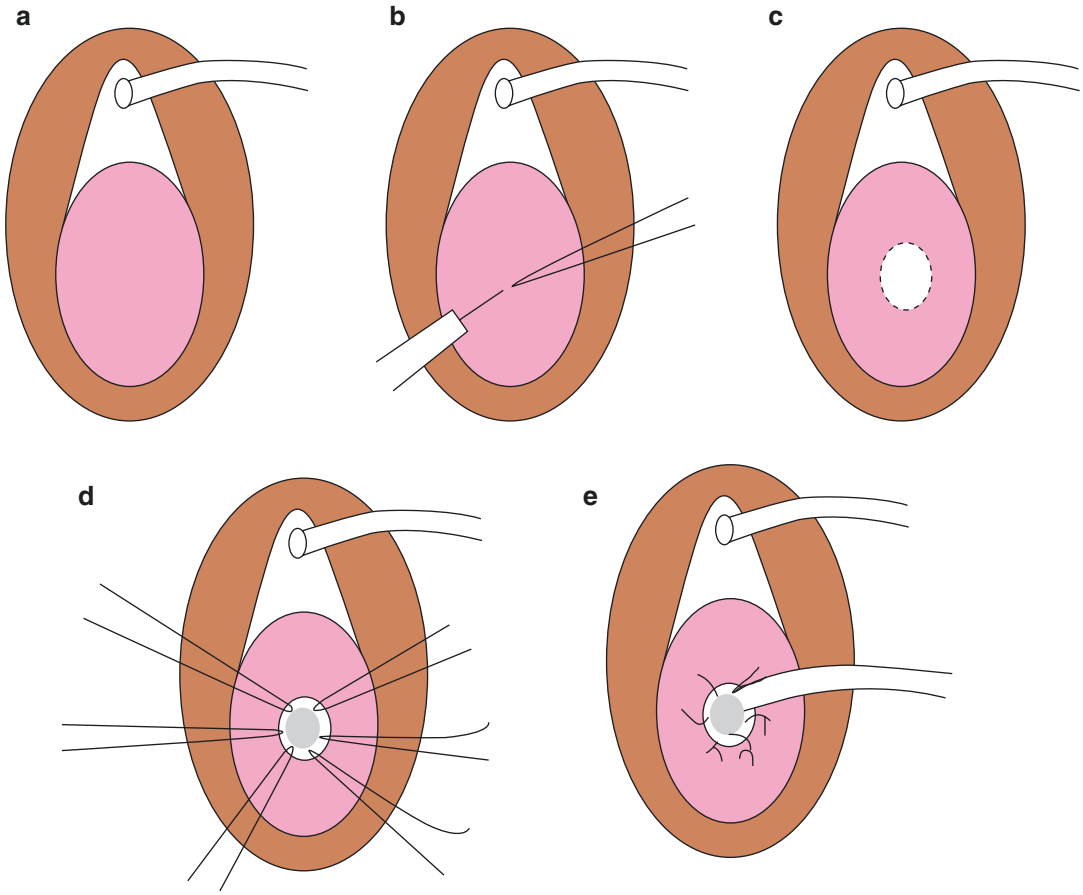


Fig. 45.2 Steps of hymenectomy (to be redrawn)

also be performed under GA in the operation theater. Antibiotics should be given for 5–7 days.

Vaginostomy—It serves as a temporizing drainage procedure for cases with infected fluid, usually as the first stage of treatment for type III, IV, and V HMC-infected cases.

- **Perineal vaginostomy** [1] (Fig. 45.3) is done through the perineal route in type II:
  (a) When a low transverse vaginal septum is present (between the lower one third and upper two third of the vagina) and is seen as a bulge at the perineum.
  (b) In some patients, a pinpoint vaginal orifice may be visible that may be surgically enlarged and oversewn with the placement of a catheter for about 2 weeks, in the vagina for establishing the drainage.
- **Abdominal vaginostomy** (Fig. 45.4) may either be in the form of an **indwelling catheter** or a **tube**:
  – An indwelling catheter has certain disadvantages like infection; encrustation and also the need to keep the tube in situ, requiring frequent catheter changing; and an inconvenience to the child.
  – Alternately, a U-shaped flap of the vagina is made into a shape of a tube that provides drainage through the natural tract and is fixed to the abdominal wall and the skin. A tubed or the flap vaginostomy avoids the long-term use of any indwelling catheter and at the same time provides an effective drainage. It also provides an easy access for performing the dye studies to outline the anatomy before doing a definitive surgery [1].

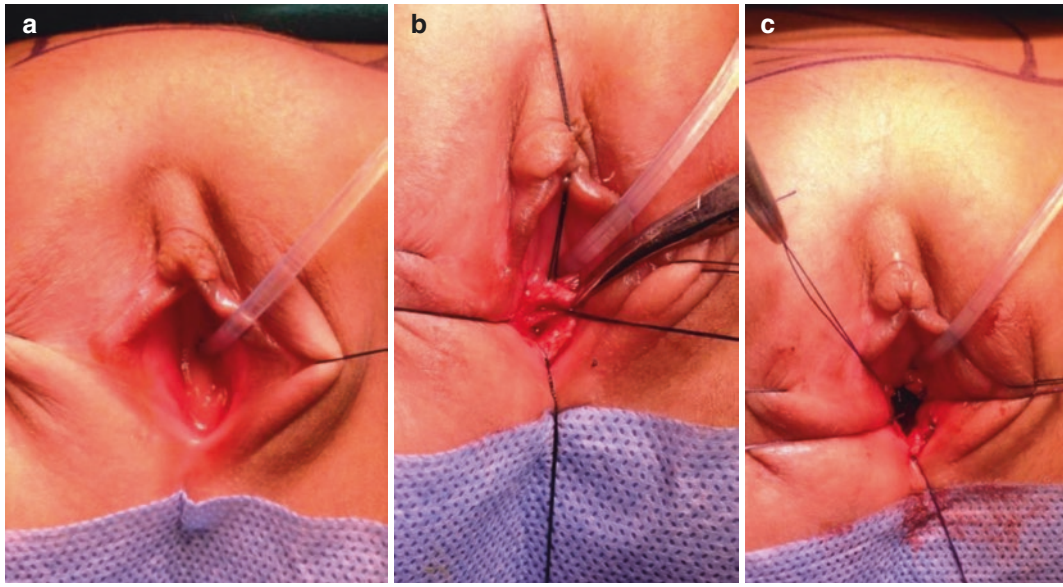


Fig. 45.3 Perineal vaginostomy in a girl with hydrometrocolpos due to transverse vaginal septum

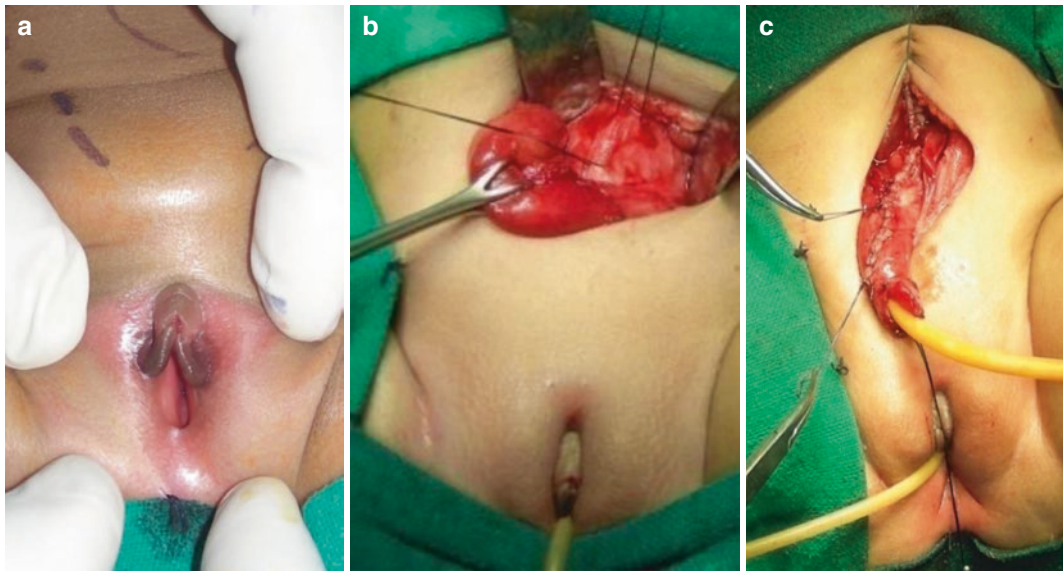


Fig. 45.4 Abdominal tube vaginostomy in a girl presenting with infected hydrometrocolpos with urogenital sinus, causing urinary obstruction and septicemia

45.10.1 Abdominoperineal Repair of Vagina [1, 2]

In a few cases of type II (transverse vaginal septum) and most type III (atresia of lower vagina), following initial vaginostomy and drainage, the vagina is exteriorized onto the perineum by an abdominoperineal combined vaginal pull-through. The normal upper vagina is pulled down and is sewn with the perineum in place. If required, a Barrow's skin pedicle flap can be added to reach the vaginal wall, falling short by about 1–1.5 cm. A Silastic catheter drains the vagina from below, and another

catheter drains the HMC from above (kept for a week).

For type III–V HMC (atresia of the lower two third of the vagina, UGS or common cloaca), an abdominal route is preferred for doing the vaginostomy. In type V HMC associated with cloacal anomaly, an additional right transverse colostomy is also required during the first stage of surgery.

45.10.2 Total Urogenital Mobilization (TUM) [1, 2]

In type IV, if the common channel of the UGS is found to be less than 2.5 cm long on endoscopy and the dye study, a disconnection of the vagina and the urethra may be done by posterior sagittal anorectoplasty (PSARP) route. The vagina may be exteriorized onto the perineum, while the UGS can be made to function as the main urethra. However, the authors have most of the time found it difficult to mobilize the dilated vagina and bring it down if there had been a history of infected HMC.

UGS can also be mobilized by total urogenital mobilization (TUM) to bring the urethra and the vagina both on to the perineum. If the vaginal introitus is narrow, it can be widened by placing a Barrow's skin pedicled flap in its posterior wall.

45.10.3 Vaginal Replacement and Posterior Sagittal Anorecto–Vagino–Urethroplasty (PSARVUP) [1, 2]

In patients with UGS with the common channel length more than 2.5 cm and in patients with HMC with cloacal malformation, a vaginal replacement would be required. First by PSARP route, the rectum can be bisected or lifted off from its bed to approach the vagina direct from behind (PSARVUP). The fistulous communication of the UGS, between the urethra and the vagina, is divided and suture repaired, and the vagina is freed. In cases with infected HMC, the vaginal wall is very much thick and also adherent with the pelvic structures; thus it is almost impossible to achieve length and bring it to the perineum by using the posterior sagittal route. Thus, there is a need for vaginal substitution.

Bowel vaginoplasty is done for cases with longer common channel more than 2.5 cm. A loop of sigmoid colon or an ileum is used for vaginal reconstruction in patients with a narrow distal vagina, or if the vagina has retracted following its repair, flaps of perineal skin may be used to contribute to the distal vaginal segment. A Barrow's skin flap is the most commonly used procedure. An inverted "Y" incision is given with the vertical limb of Y going inside the vaginal introitus for a cm or so in the posterior midline wall. The V-shaped perineal skin with an intact blood supply is created and mobilized sufficiently. It is then advanced in the vagina and sutured to the margins of the incision edges in the introitus.

Many surgeons have used free skin graft over a vaginal mold, a cylinder of a prosthetic patch (Silastic or Gore-Tex), or the buccal mucosa graft with a mesh to form the neo-vagina. Retractions and graft contraction are common with these procedures. Surgical expertise and experience with a large number of cases are a requisite to undertake these surgeries. It has been seen that the vaginoplasty with flaps is prone to shrinkage and needs repeated dilatations. The results are more favorable when performed at puberty at the time of menarche or just before marriage.

In patients with cloacal abnormality with duplication of vagina and HMC, a vaginal switch procedure is also an option for vaginal reconstruction.

45.11 Results and Follow-Up

Regular follow-up visits to look for complications like vaginal infection, retraction, tube dislodgement, neo-vaginal stenosis, mucosal prolapse, and perineal excoriation are important. Vaginal dilatations may be required till marriage, though frequency may decrease. Girls may come with menstrual irregularity, endometriosis, and infertility.

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46 Different Sexual Development (DSD)

Maria Marcela Bailez

46.1 Introduction

Nearly 1 in 4500 infants is born with abnormalities of the external genitalia.

Detection of the abnormality is usually immediate at birth and is followed by a cascade of events beginning with disclosure of genital anomaly to the expectant parents followed by the time-consuming diagnostic evaluations.

Patients with ambiguous genitalia mostly present in the newborn period requiring a multidisciplinary team which involves a pediatric surgeon/urologist to assign the sex of rearing as soon as possible after a thorough genetic, anatomic, functional, and socioeconomic workup.

DSD is defined as congenital conditions in which development of the chromosomal, gonadal, or anatomical sex is atypical [1, 2].

According to the Consensus Statement on Management of Intersex Disorders, optimal clinical management of individuals with DSD should comprise the following: (1) gender assignment must be avoided before expert evaluation in newborns; (2) evaluation and long-term management must be performed at a center with an experienced multidisciplinary team; (3) all individuals should receive a gender assignment; (4) open communication with patients and families is essential, and participation in decision-making is encouraged; and (5) patient and family concerns should be respected and addressed in strict confidence.

Contemporary management sees DSD decision-making as multifaceted, involving many different factors (none to the exclusion of the others), including etiology, fertility, and most likely gender outcome [3].

46.2 Presentation and Diagnosis

External genitalia exam includes the gonadal palpation and perineal exam; both are the key to choose the sequence of diagnostic procedures to reach an etiologic diagnosis.

It is important to visualize both faces of the phallus, looking for the urethral orifice, defining its localization and aspect. Inguinal and perineal palpation looking for gonads is the other diagnostic key.

Each patient needs to be considered in an individual basis.

Traditionally DSD patients were classified into three groups based on gonadal structure:

- Presence of two well-defined ovaries with ambiguous or male external genitalia (female pseudohermaphroditism; now called overvirilized XX female). These patients have a 46 XX karyotype, and virilization of the external genitalia results from exposure to high level of androgens in utero, while they have female

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internal genitalia. Congenital adrenal hyperplasia (CAH) is the most common disease in this group and accounts for 50–80% of all the cases of ambiguity, depending on the population analyzed. The most common enzymatic defect is 21-hydroxylase deficiency. The incidence of 21-hydroxylase deficiency is 1 in 15,000–40,000 newborns. Other defects are 11-hidroxylase (hypertension) and 3-b-oldehydrogenase or aromatase.

- Presence of two well-defined testicles with ambiguous or female external genitalia (male pseudohermaphroditism; now called undervirilized XY male). These patients have a 46 XY karyotype, and ambiguity of the external genitalia results from a failure of the masculinization androgenic action of the male fetus. This can be due to a failure in androgenic synthesis or in the biological response. This group includes rare defects of the biosynthesis of testosterone, defect of the 5-alpha reductase (enzyme that converts testosterone in dihydrotestosterone) and partial androgen insensitivity syndrome (partial defect of androgenic receptors). It is important to recognize that patients with a 46 XY karyotype and dysgenetic testicles are sometimes included in this group in the literature.
- Presence of incomplete differentiated gonads or coexisting ovarian and testicular tissue with ambiguous or female external genitalia. This is a heterogeneous group with one common factor which is a structural defect in gonadal differentiation with or without a chromosome alteration. Patients with mixed gonadal dysgenesis, testicular dysgenesis, and true hermaphroditism (now called ovotesticular disorder of sex development) are included in this group.

The possibility of the ambiguous genitalia to virilize can be estimated after an hCG test or an appropriate stimulation trial with testosterone or topical DHT. This can be estimated by demonstrating the increment of the penile dimensions or indirectly by the dosage of androgen-sensitive circulating substances (SHBG). Its values are reduced if the patient tissues present sensitivity for the virilizing effect of androgens.

Molecular biology techniques are more sensitive and specific tests for assessment of the tissue sensibility to androgens but not always available.

Histology is only required for diagnosis in patients with abnormal gonads (G3).

Except for gonadal biopsy or resection, no other surgery is performed in the neonatal period. Most of the reconstructive procedures, although done early, are not recommended after the first month of life.

Evolution of practice in the last years tends to postpone surgery. Sex assignment does not mean inevitable surgical intervention. Each case needs to be considered in its own terms. Preservation of tissue, particularly gonadal tissue, and maintenance of the integrity of the body as whole are aspects to care and receive higher priority.

The role of surgery consists in (1) gonadal treatment, (2) feminizing genitoplasty, and (3) urethral/penile reconstruction in the undervirilized child.

46.3 Role of the Surgeon

The surgeon plays an important initial role in the interdisciplinary group that an institution is obliged to have to take care of these complex patients. He not only needs to take care of the best operative techniques for better functional results but also manages the proper information (after conscious discussion of the group) to be given to parents and family. The use of improper words and misinformation may result in irreversible sequela. In our opinion, the surgeon has to be very well informed and participate actively in the preoperative workup before taking contact with the family.

46.4 Gonadal Treatment

Gonadal histology (biopsy or gonadectomy) is required in selected DSD patients with abnormal gonadal development like gonadal dysgenesis.

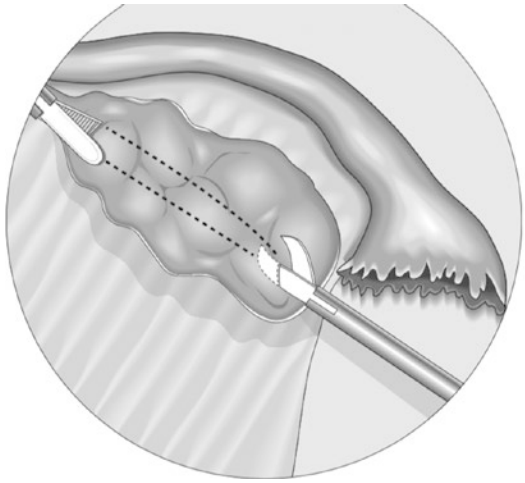

Fig. 46.1 Scheme of gonadal biopsy

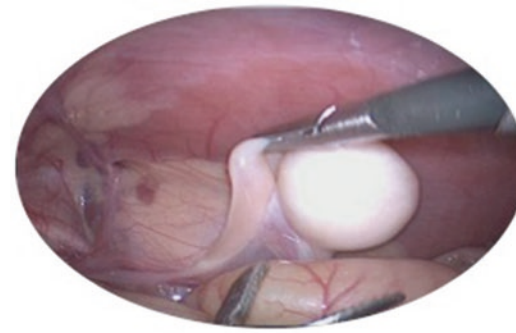

Fig. 46.2 Intraoperative view of ovotestis

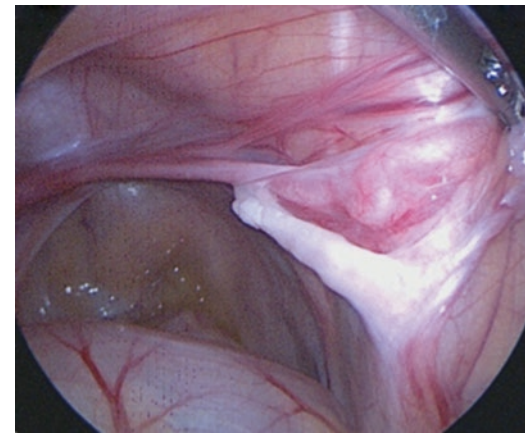

Fig. 46.3 Intraoperative view of streak gonad

The existence of a Y chromosome is associated with a higher risk of developing germ cell tumors as gonadoblastoma.

Gonadal biopsies must be taken along the longitudinal axis of the gonad as both ovarian and testicular tissues may be found at the polar ends of the gonad (Fig. 46.1). Patients with Ovotesticular dysgenesis may have an ovary (O) and testicle (T), bilateral ovotestes (OT), and an O and OT (Fig. 46.2).

Surgical management in DSD should also consider options that will facilitate the chances of fertility. Ovarian component of ovotestes may be separated and the testicular tissue removed, using zoom lens, although it must be kept in mind that these gonads need to be followed closely.

If a streak gonad is recognized like in most patients with 45 /0 46 XY gonadal dysgenesis, it is removed without prior biopsy together with the surrounding peritoneum and the ipsilateral gonaduct (Fig. 46.3). This gonad has to be removed, avoiding previous biopsy, as it has 25–50% chances to develop a gonadoblastoma and/or dysgerminoma and as there is the possibility of an in situ tumor at the time of the procedure. It is usually associated with an intra-abdominal or inguinal dysgenetic testicle, which is removed at the same time in patients with female sex assignment. Although there is the same risk of malignancy in the contralateral gonad (dysgenetic testicle), it may biopsied and preserved in the scrotum of patients with male sex assignment because this gonad is functional.

The highest tumor risk is found in TSPY (testis-specific protein Y-encoded)-positive gonadal dysgenesis and partial androgen insensitivity (PAIS) with intra-abdominal gonads, whereas the lowest risk (5%) is found in ovotestis and complete androgen insensitivity (CAIS).

To analyze the spectrum of gonads of the DSD patients that we treated and assess the incidence of germ cell tumors, we conducted a prospective and observational study of DSD patients who underwent gonadal surgery. Age, sex assigned, scale of external masculinization (EMS), karyotype, molecular analysis, surgical approach, and pathology of the gonads were analyzed.

Patients were divided into three groups: chromosomal dysgenesis (G1), 46 XX gonadal dysgenesis (G2), and 46 XY gonadal dysgenesis (G3) (Table 46.1).

Table 46.1 Classification of DSD analyzed

Chromosomal DSD	46,XY DSD	46,XX DSD
45,X and variants (Turner)	**Gonadal disorders**	**Disorders of gonadal development**
47,XXY and variants (Klinefelter)	Partial/complete dysgenesis	
		• Gonadal dysgenesis
45,X/46,XY (mosaicisms)	DSD ovotesticular	• Ovotesticular DSD
46,XX/46,XY (chimera)	Testicular regression	• Testicular DSD
	Androgen biosynthesis or action disorders	**Excess of extragonadal androgens**
	• Mutation of AR (androgen receptor)	*Congenital adrenal hyperplasia (21OHD)*
	Others	
	• Malformations	• Other enzymatic deficits
	• Hypogonadotropic hypogonadism	• Maternal androgens
		Others
		• Malformations

Group	Number of Gonads	Streak	Ovotestes	Dysgenetic Testes	Testicle	Ovary	Tumors
1	89	52	5	32			6 8,3 %
2			10	15		4	1 6,6%
3	59	10		41	8		8 16 %

Fig. 46.4 Summary of results

More than half of the gonads were intra-abdominal and were treated laparoscopically using 3 or 5 mm instruments. All streak gonads were removed, avoiding previous biopsy. We always waited for the result of biopsy before removing any other gonad than a classical streak.

In total 94 patients with a mean age of 56.42 months (range, 2–216) were analyzed (Fig. 46.4).

46.4.1 G1

Forty-eight patients (19 with a Turner syndrome) with a mean age of 105 months (2–216) were included in G1. The karyotype was 45 X0/46 XY in 87.5% of them. Male sex was assigned in 19, with a mean of 7.26 EMS (1–10). Histological analysis of 89 gonads was completed identifying 52 streak gonads, 32 dysgenetic testes, and 5 ovotestes. Six germ cells tumors (GCT) were found in four patients.

46.4.2 G2

Fifteen patients with a mean age of 27.6 months (2–180) were included in G2. Male gender was assigned to six with a mean EMS of 6.82 (range, 4–8.5). Twenty-nine gonads were analyzed: 10 ovotestes, 15 dysgenetic testes, and 4 ovaries. Bilateral gonadoblastoma was found in a 6-month-old patient with bilateral ovotestes.

46.4.3 G3

Mean age of the 31 patients in G3 was 69.71 months (5–192). Five of them had an SF-1 NR5A mutation, 6 a WT1, and 6 a complete and 3 a partial androgen insensitivity syndrome. A new mutation in the SRY (p.MET64VAL) gene was identified in two sisters. Male gender was assigned in ten with a mean EMS of 4.52 (range, 1–10). Fifty-nine gonads were analyzed, identifying 41 dysgenetic testes, 10 streak gonads and 8 testes. Eight GCT were found in five patients (16%) (seven in streak gonads and one in a dysgenetic testicle).

We concluded that DSD patients with gonadal dysgenesis have a wide variability. The incidence of gonadoblastoma is not negligible in patients 46 XY and even feasible in 46 XX. The incidence of GCT was 8.3, 6.6, and 16% in G1, 2, and 3, respectively (Fig. 46.4). Early histological analysis and monitoring of these patients are mandatory. To our knowledge, this is the first report of bilateral gonadoblastoma in ovotestes at a very early age.

Although we used to schedule simultaneous gonadal and genitalia procedures with good results encouraged by the laparoscopic better visualization and quicker access to intraperitoneal, actually we prefer to avoid resection of any gonad except a classical streak before having definitive histology and postpone genitalia surgical procedures.

Sex may be assigned prior to laparoscopy in patients with 45 XO/46 XY gonadal dysgenesis. This is based on a functional and psychosocial basis in combination with the results of the karyotyping, HCG testing, and interview of the parents.

We have never found functional ovarian tissue in these patients.

Patients with ovotesticular dysgenesis do not have such a classical pattern, and definitive histology is often necessary for sex assignment. Although the most common karyotype is 46 XX and the most common gonadal combination ovary/ovotestes, each case is unique and should be treated on an individual basis. Sometimes the macroscopic aspect of the gonad and gonaduct as well as the result of a frozen section biopsy strongly favors gonadectomy in patients with previous sex assignment. There is an advantage of a laparoscopic approach in these patients requiring secondary pelvic exploration, especially because many of them are potentially fertile.

An additional role of laparoscopy is excision of Mullerian structures, prostatic utricle, and orchidopexy in patients raised as males. In patients with a symptomatic utriculus, removal is best performed laparoscopically to increase the chance of preserving continuity of the vas deferens.

An inguinal approach may be indicated in patients with palpable gonads. We still prefer a laparoscopic approach in most of them as it enables not only better visualization of potential Mullerian structures but also allows for treatment of a patent peritoneal sac, when removing the gonads, with better cosmetic results. In addition, most of these patients have asymmetric gonads with one of them being intra-abdominal. We reserve the inguinal approach for XY patients with symmetric palpable gonads introducing the telescope through the associated hernia sac in order to rule out the presence of Mullerian structures.

Nowadays the resection of testicles in CAIS patients is postponed after spontaneous breast development that occurs because of the peripheral conversion of androgens to estrogens in puberty.

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Congenital Anomalies of the External Male Genitalia

47

Francesco Di Lorenzo, Neil Di Salvo, and Mario Lima

This chapter is aimed at describing the main congenital disorders of the external male genitalia (penis, scrotum, and testis) in order to enable the reader a prompt recognition of such malformations in newborns. The latter is fundamental when formulating potential surgical planning which is almost never carried out in the neonatal period. Recognizing and then planning the correction will surely allay parental anxiety. Description of the corrective surgical techniques goes beyond the purposes of this chapter. We will therefore tackle the anatomic description, etiology, initial evaluation, and timing of treatment of these anomalies. As for all congenital anomalies, a good basic knowledge of the embryologic development of the male genitalia is necessary in identifying and understanding their etiology.

The presence of the Y-chromosome, more precisely its "sexual-specific" region, that is to say the sex-determining region (SRY) which consists in a single couple of genes, is essential in starting the transformation of the undifferentiated gonad into the testis.

The biochemical stimulus for differentiation of the external genitalia, which takes place between the 9th and 14th week of gestation, is given by testosterone that is produced by the Leydig cells of fetal testis tissue.

In the first trimester, these cells are induced by placental human chorionic gonadotropin (HCG). After the first trimester, during the rest of gestation, fetal testosterone secretion is maintained by activation of the fetal pituitary gland through production of the luteinizing hormone (LH). The hypothalamus-pituitary gland-testis axis goes on until the first 4 months of life. Throughout all this period, both antenatally and postnatally, external genitalia continue to grow. Second reactivation of the abovementioned axis during puberty will again promote penile, scrotal, and testicular growth and transformation.

The undifferentiated primitive fetal structures from which external genitalia arise are essentially three: the genital tubercle, the genital folds, and the labioscrotal folds. The first becomes the penile glans in males and the clitoris in females; the urogenital folds will progressively close in a cranio-caudal direction thus becoming the penile shaft with the proximal urethra in the inside; and finally the labioscrotal folds will differentiate into the scrotum and the labia majora in males and females, respectively.

From this brief description, it is easy to understand that a good function of the fetal hypothalamus, pituitary gland, and Leydig cells with a subsequent appropriated timing of activation is fundamental.

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47.1 Penile Agenesis (Aphallia)

The absence of the penis, in male individuals with normal scrotum and testicles, a perineal (anorectal) urethral meatus, without chromosomic and endocrine anomalies, is one of the most rare, serious malformations of the genitourinary tract. This pathology affects 1 every 1–3 million of live newborns with only a few cases reported in literature. It is an atypical expression of caudal regression and embryonically the result of a missed formation of the genital tubercle and folds, which is an initial and fundamental step in the development of the penis (Fig. 47.1).

Based on the localization of the urethral meatus in relation to the anal sphincter, we can distinguish the following types (Fig.47.2):

- Post-sphincteric (urethra-anal fistula) 60%
- Pre-sphincteric (prostatic-rectal fistula) 22%
- Urethral atresia (vesico-rectal fistula) 12%

In the remaining cases, the urethra ends anteriorly to the scrotum or even above the pubic symphysis.

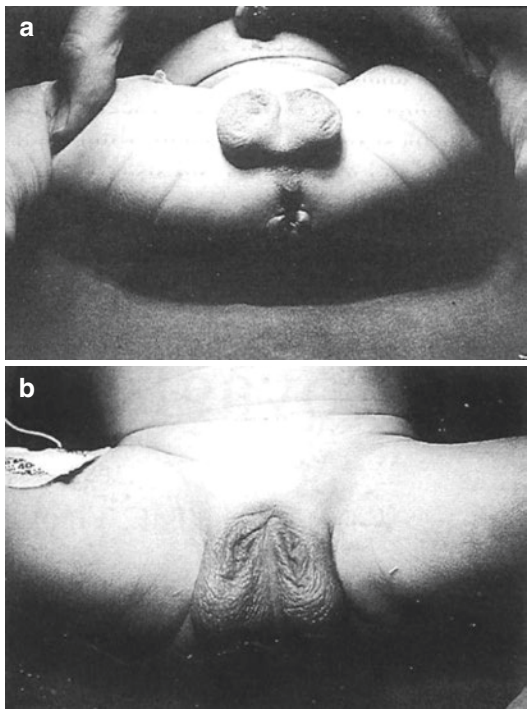

Fig. 47.1 (**a**, **b**) Patient affected from penile agenesis

In more than half of cases, penile agenesis is associated with other malformations: genitourinary (54%) such as urethral valves or atresia, cryptorchidism, vesicoureteral reflux, cystic renal dysplasia, and horseshoe kidneys; digestive such as esophageal and duodenal atresia, anorectal malformation, and Hirschsprung disease; scheletric (phocomelia and vertebral anomalies); and cardiovascular.

On a prognostic level, the more proximal the meatus in relation to the anus, worse are the associated malformations and therefore higher morbidity and mortality. For instance, in cases of very short urethras, the bladder neck structures often may be lacking or even totally missing, thus resulting in continence dysfunctions. On a clinical level, the patient affected by true penile agenesis presents a regular chromosomic pattern and normal scrotum and testis whose endocrine function is conserved. A frequent finding is the presence of a cutaneous appendix near the anus.

In most cases diagnosis is easy and obvious; nevertheless a buried penis, an intrauterine amputation of the penis, and a severe posterior hypospadias are sometimes confused with this pathology.

In the past, all children affected by aphallia were gender-reassigned; this viewpoint was due to the difficulty of surgical reconstruction of a functional penis and urethra. The routine standard approach was to remove the male gonads and create a functional female genital and urinary tract. Reconstruction was accomplished by creation of a neovagina using a colonic segment. Recently several doubts have arisen about this approach, because of the increasing awareness of testosterone imprinting on the brain which leads to significant psychosocial issues as the child matures. Therefore the choice of not gender reassigning the child is nowadays considered an option. In these cases early reconstruction of the lower urinary tract and penis should be carried out. In both cases though, long term counselling involving a multidisciplinary team including behavioral medicine specialists, endocrinologists, psychologists, urologists, and social workers should be provided.

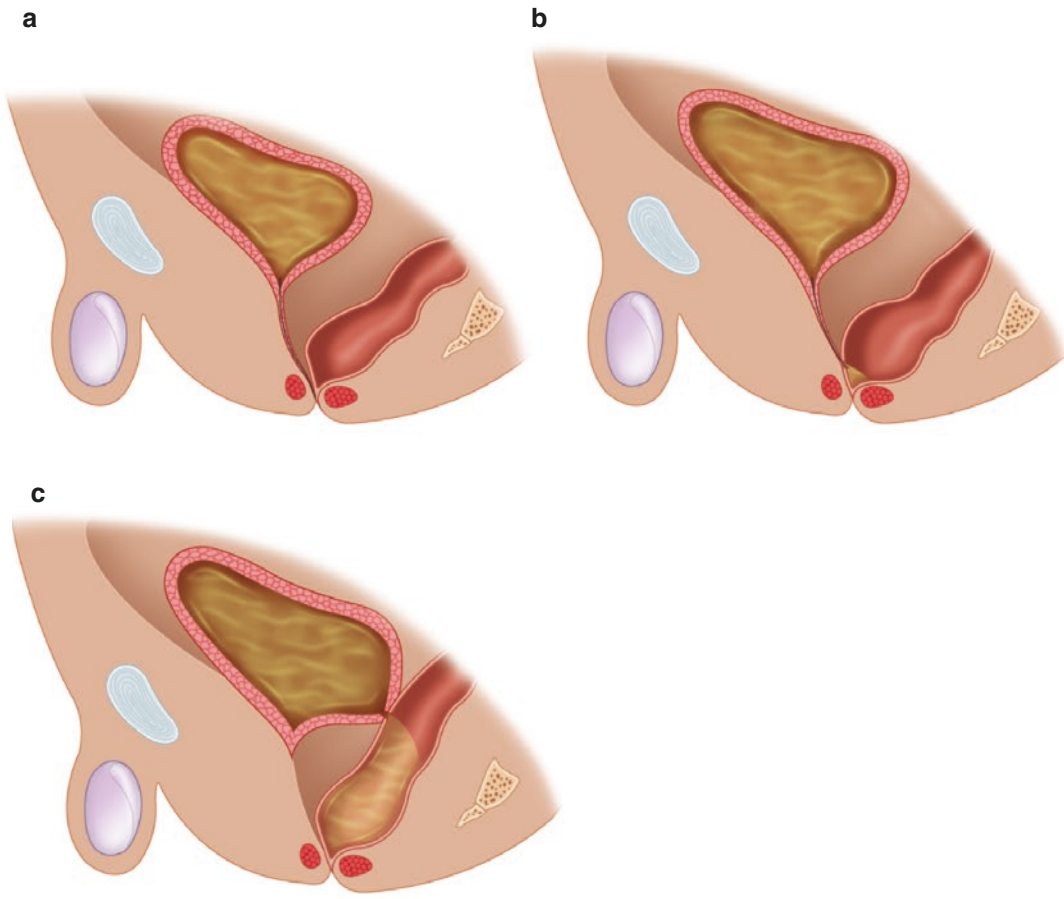

Fig. 47.2 (**a**) post-sphincteric penile agenesis (urethra-anal fistula); (**b**) pre-sphincteric penile agenesis (prostatic-rectal fistula); (**c**) urethral atresia (vesico-rectal fistula)

47.2 Micropenis

Micropenis is defined as a morphologically normal penis whose length is 2.5 standard deviations (SD) inferior than the reference for age with testis present in the scrotal sac, thus eliminating any doubt of genital ambiguity. A low stimulation by androgens is the cause of a poor development of the penis. On the etiopathogenetic basis, there are basically two conditions that can lead to such conditions:

- Functional anomaly of the hypothalamus-pituitary gland axis with subsequent insufficient induction of Leydig cells with low production of testosterone.
- Peripheric insensibility to testosterone.

The majority of patients affected by micropenis are able to produce LH, follicle-stimulating hormone (FSH), and testosterone after exogenous stimulation with gonadotropin-releasing hormone (GnRH), demonstrating full functionality of the pituitary gland and the testis. Furthermore, these patients' penis respond to both topical and systemic administration of testosterone. It is evident from this that the problem is localized in the hypothalamus. Nevertheless, since a central lesion may be associated with multiple hormonal defects that could determine disastrous effects, a pediatric endocrinologist should be consulted as soon as a diagnosis of micropenis has been formulated. He or she will carry out anterior pituitary and endocrine testicular function testing. In cases in where testicular failure is diagnosed and the testis can-

not be palpated (ambigous genitalia), laparoscopy should be carried out to determine the presence or nonpresence of testicular tissue in the abdomen.

Systemic medical therapy must be given early in the first year of life in order to accomplish satisfying results even though timing of hormonal stimulation with testosterone is controversial.

Alternatively, a 3% testosterone cream can be used topically; however, absorption is variable and posology has not yet been precisely defined.

47.3 Buried/Hidden Penis

Congenital buried penis in children is a relatively rare and poorly known pathology. It can be defined as a congenital deficiency of penile shaft skin often associated with a tight foreskin (phimosis), resulting sometimes in the urine dilating the preputial "reservoir," still called preputial bladder. Congenital buried penis is a separate entity from the acquired one even in children, as it happens after early circumcision. Some authors refer to this condition as trapped penis. This condition can create such an important psychological involvement both in the parents and the pediatric patient. Functional problems can arise since it can be responsible for recurrent urinary tract infections and balanitis or dysuria. Surgical correction is difficult with sometimes disappointing results.

Urination issues, recurrent infections, or a strong demand from the parents and patient seem to be the major surgical indication for correction of this pathology, certainly after the child has started to walk and has lost most of the prepubic fat pad even though this surgery can be performed safely in children from 3 months of age. It is reasonable to treat this pathology as the majority of penile pathologies in children, between the 12th and 24th month of life, before the school starting age.

47.4 Duplication of the Penis (Diphallia) and Bifid Penis

Duplication of the penis or diphallia represents another rare malformation (1 every five million live births). The most plausible hypothesis is an early division of the pubic tubercle beginning from the fifth week of gestation, even though an incomplete fusion of the genital tubercle has been suggested. Clinically it can appear in different forms from a simple duplication of the penis glans up to a complete duplication of the entire penis, associated with a urethro-vesical duplication (Fig. 47.3). In the complex "exstrophy-epispadias," there is an apparent diphallia. Nevertheless it is more appropriate to refer to these cases as "bifid penis" since two corporal bodies are well distinguishable and separated with their own hemi-glans.

The treatment of this form is always preceded by a precise preoperative evaluation of the genitourinary tract. The principles that surgeons must follow when choosing which penis to save are based on the morphology and erectile function of both the units.

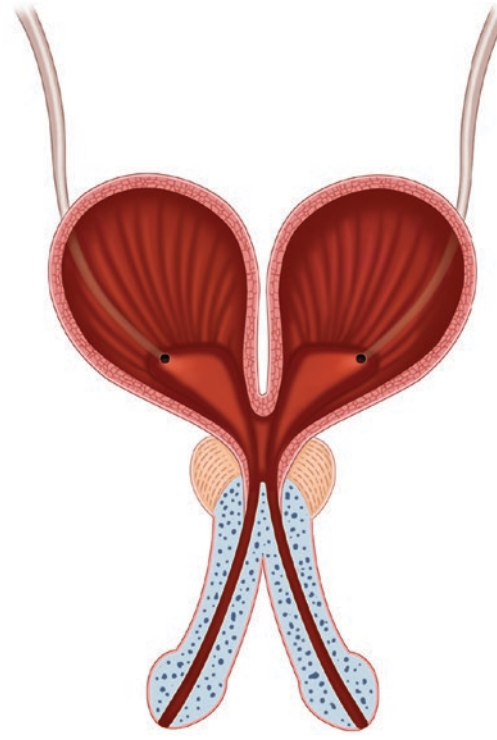

Fig. 47.3 Complete duplication of the penis with consensual urethra-vesical duplication

47.5 Scrotal Agenesis

Congenital scrotal agenesis (CSA) is an extremely rare congenital anomaly (Fig. 47.4). It is associated with a male karyotype. Bilateral testes are present in a cryptorchid or ectopic position, and external androgen-dependent structures, including the penis, are normal. A possible explanation for this condition is an arrest in primary scrotal development: the most likely explanation for CSA is a failure of the labioscrotal fold to develop at all. Physical examination should attempt identification of the presence and location of the testes and diagnose other congenital anomalies including facial anomalies, developmental delay and cognitive impairment, nystagmus, clinodactyly, cardiac septal defects, anterior displaced anus, and clubfoot. Surgical construction of the scrotum may be attempted by various techniques. In infants with scrotal agenesis, it is important that the child not be circumcised because the prepuce is invaluable for scrotal reconstruction.

47.6 Penoscrotal Transposition

In the penoscrotal transposition, the base of the penis is located below the higher insertion of the two scrotal hemisacs (Fig. 47.5). It is often associated with posterior hypospadias and other congenital anomalies especially of the urinary tract but also of the digestive and cardiovascular system, sometimes extremely serious and incompatible with life. From a clinical standpoint, penoscrotal transposition can present in the complete or minor form (as bifid scrotum) in which the urethra is not constantly involved.

Surgical correction consists in mobilizing the two hemisacs with rotation and advancement flaps and repositioning them below the penis, or, alternatively, a tunneling of the penis can be performed on the central line. Generally it is advisable to procrastinate an eventual urethroplasty after scrotal correction.

47.7 Bifid Scrotum

It is due to a missed fusion of the genital folds along the scrotal septum. It is often associated with severe forms of hypospadias (scrotal and perineal ones) and ambiguous genitalia. It rarely presents as an isolated malformation. Surgical correction is obtained by rotating below in the missing septum an anterior skin flap and suturing it with the two hemisacs (Fig. 47.6).

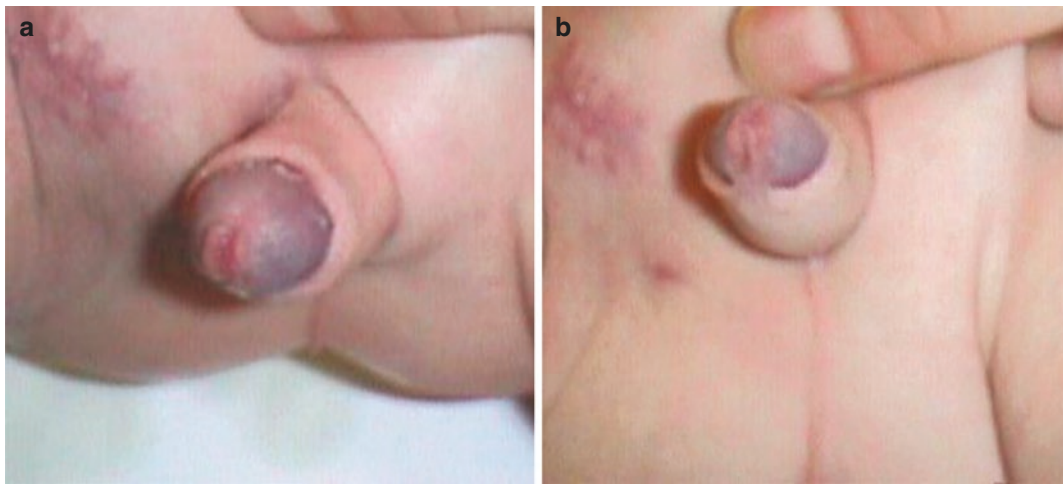

Fig. 47.4 (**a**, **b**) A patient with scrotal agenesis

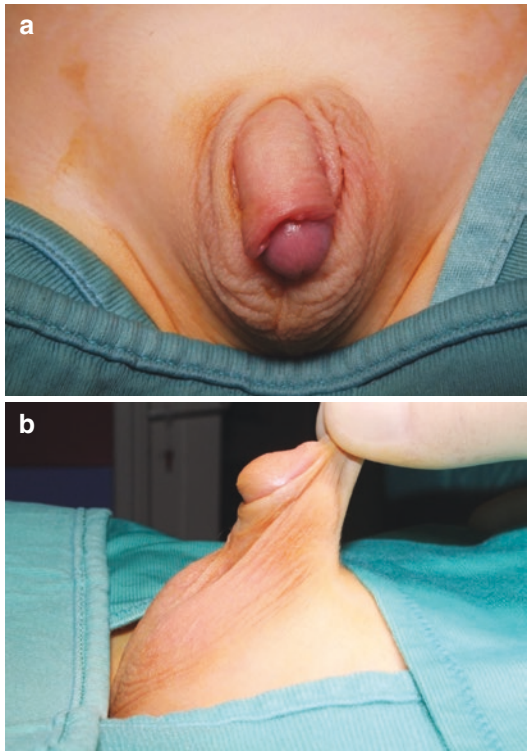

Fig. 47.5 (**a**, **b**) Penoscrotal transposition. The patient also presented a posterior hypospadias

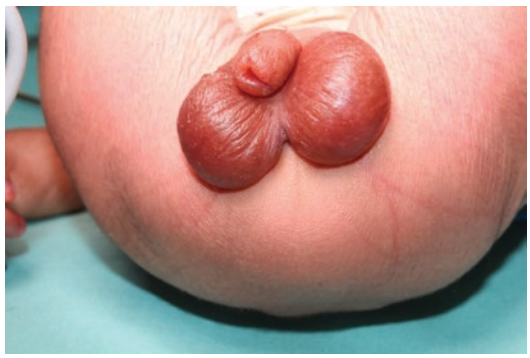

Fig. 47.6 Patient affected from bifid scrotum. In this particular case, he also presented steno-atresia of the urethra and a high anorectal malformation (pouch colon)

47.8 Ectopic Scrotum

The anomaly can be uni- or bilateral, complete or incomplete. The ectopic scrotum can be seen in many areas, starting from the inguinal canal up to the buttock, medially to the inferior limb.

Embryonically it is believed that ectopic scrotum develops due to a defect in the gubernacular development. Also an anomalous migration or division of the labioscrotal folds has been advocated. Careful physical examination to localize the testes and upper urinary tract imaging with ultrasounds, in order to diagnose a likely associated urinary malformation, is recommended.

The testis in the hemisac can be normal or atrophic. In the latter case, it will have to be removed at time of surgical correction. The exact timing of surgery is usually between 6 months and 3 years, basically determined by the association with undescended testis and therefore the necessity to perform an orchiopexy.

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Part IX

Nervous System

Surgical Treatment of Central Nervous System Malformations

48

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48.1 Introduction

The surgical treatment of CNS malformations is a big challenge for neurosurgeons. The developing technologies, from the new radiological imaging techniques as well the surgical armamentarium, and the improving of knowledge of such diseases, have dramatically changed the opportunity to treat the different malformations with best results and quality of life for patients and family.

The neuroendoscopy, for example, has radically changed the surgical approach to many CSF-related diseases, giving, in some cases, the opportunity to treat the hydrocephalus in a minimally invasive and more physiological way. The new biomaterials such as resorbable plate and screws have changed the possibility for the surgical management of craniofacial disease. Endoscopic endonasal approach (EEA) has radically changed the approach to the lesions of the skull base; with a transnasal endoscopic approach, you can reach every skull base.

Authors of this chapter intend to describe the current state of art in the surgical management of CNS malformations basing on their experience and reviewing the pertinent literature (Table 48.1).

48.2 Hydrocephalus and CSF-Related Disturbances: Etiology and Management

48.2.1 Hydrocephalus from Aqueductal Stenosis

Cerebrospinal fluid, (CSF) flows from the two paired and symmetrical lateral ventricles to the third ventricle, unpaired and situated on the midline, through the foramina of Monro, and then to the fourth ventricle. The narrow channel which connects the third and fourth ventricles is the aqueduct of Sylvius.

Aqueductal stenosis is the most common cause of congenital hydrocephalus, but a stenosis can be present in the neonatal period or even later in the adolescence. The male/female ratio is 2:1.

Aqueductal stenosis can be congenital or acquired and is present in about 50% of patients with congenital hydrocephalus and in 15–20% of patients with hydrocephalus.

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Table 48.1 Surgical procedures for CNS malformations in children 1996–2016

Procedure	*N*	%
Neuroendoscopy	1444	25.15
Shunting procedures	2086	36.2
Craniofacial repair for craniosynostosis	1415	24.6
Excision of encephalocele	83	1.4
Posterior fossa decompression for Chiari type I anomaly	434	7.5
Surgery for dysraphic state	293	5.1
Fetal surgery	3	0.05

48.2.1.1 Embryology

The aqueduct of Sylvius develops about the 6th week of gestation. Embryologically, the brain starts out as a tubular structure. As the brain grows, the inner tube remains as a series of interconnected cavities termed as ventricles.

The ventricular system closes in Stage 12 (26–30 days of gestational age) at the end of neurulation; in Stage 15 (35–38 days of gestational age), the evaginations of the cerebral hemispheres develop with enlargement of the lateral ventricles, the third ventricle, and the foramen of Monro.

During Stage 20 (51–53 days of gestational age), the choroid plexuses develop a secretory epithelium; the leptomeninx is beginning to form a potential subarachnoid space, and the roof of the fourth ventricle perforates. Due to the growth of contiguous structures (mesencephalon, corpora quadrigemina, and crura cerebri) in this period, the aqueduct of Sylvius narrows.

48.2.1.2 Anatomy

The aqueduct is a narrow irregular channel situated in the dorsal midbrain between the posterior commissura and the lamina tecti posteriorly and oculomotor, trochlear nuclei, medial longitudinal fasciculus, and red nuclei anteriorly.

Its lumen ranges normally from 0.2 to 1.8 mm and its length averages 11 mm. This explains why it is considered the critical point of the CSF pathway.

In his experimental studies, Jacobson noticed that the laminar flow of CSF through the aqueduct is very important and it is secured by its particular shape. Therefore a change of its shape will alter the flow rate and the flow pattern.

For this reason it is clear why a severe stenosis results in increased intracranial pressure, (ICP) and it explains why a change of the shape of the aqueductal lumen, which produces a mild stenosis, may result in an important flow alteration with subsequent further damage of the lumen and the establishment of a pathological pressure gradient between the supra- and the infratentorial compartments.

48.2.1.3 Classification

From the anatomical standpoint, the aqueductal stenosis can be defined as intrinsic (primary) or extrinsic (secondary). There are multiple causes of obstruction, but their morphological differentiation is often impossible.

The possible etiologies are:

- DEVELOPMENTAL: forking, narrowing, transverse septum.
- GENETIC: Bickers and Adams syndrome, an X-linked recessive chromosomal anomaly, accounts for approximately 7% of male hydrocephalus. It is characterized by stenosis of aqueduct, mental retardation, adducted thumbs, and spastic paraparesis. As for all X-linked recessive diseases, only males are affected, but the disease is transmitted through the females of the family. In addition to the X-linked inheritance, an autosomal recessive pattern has been identified in families in which both sexes are affected. Hydrocephalus may also be present in a number of major and minor chromosomal aberrations affecting chromosomes 8, 9, 13, 15, 18, or 21.
- MALFORMATIVE: cysts of the posterior fossa and of the tentorial incisural, spina

bifida, or hydranencephaly where aqueductal stenosis is primary or secondary in origin.
- CHEMICAL: trypan blue, salicilyte, cuprizone, if taken by the mother during pregnancy, vitamin B and folic acid deficiency in early gestation and vitamin A deficiency in newborn.
- INFECTIOUS: aqueductal gliosis due to bacterial or viral intrauterine or postnatal infections (50%) (toxoplasmosis, CMV, syphilis, rheo-, paramyxo-, arboviruses, influenza).
- VASCULAR: vein of Galen aneurysms, intracranial hemorrhages in premature and newborn as well as in adults.
- NEOPLASTIC: (extremely rare) posterior fossa, brain stem, and pineal region tumors.
- and sometimes cryptogenetic.
- DEVELOPMENTAL STENOSIS: Developmental stenosis represents the 10% of the etiology of hydrocephalus in newborn. Incidence rate is 0.5–1 on 1000 births.

- **Aqueductal agenesia** (complete or partial) in which small ependymal nests represent the consequence of an abnormal infolding of the neural plate. It is very rare.
- **Aqueductal forking** in which the aqueduct is splitted in two or more irregular channels that can be blind, independent, or communicate with each other.
- **Aqueductal occlusion** due to the formation of an ependymary septum at its lower tract.
- **Aqueductal stenosis** where a gliotic proliferation, which develops in areas of the aqueduct without ependymal lining "denuded areas," narrows its lumen.

48.2.1.4 Diagnosis

Prenatal sonograms, in utero MRI, postnatal cranial ultrasound, and head CT and MR represent the diagnostic tools to detect aqueductal stenosis.

Fetal Diagnosis

The early antenatal diagnosis still remains as a diagnostic challenge, since the diagnosis of ventriculomegaly or hydrocephalus may not become apparent until 18 weeks of gestation. Aqueductal stenosis is usually diagnosed in the second or third trimester of pregnancy.

The prenatal detection of fetal hydrocephalus has traditionally relied on sonographic measurements of ventricles. The most useful measurement is the transverse atrial width, which is normally between 4 and 8 mm with an upper limit of normal at 10 mm. The utility of the measurement is based on the fact that the atria are easily identified, and the measurement is nearly constant between 15 and 35 weeks of gestation. Prenatal sonographic data include also the biparietal diameter, size of the third ventricle, the ratio between laterals and third ventricle, and thickness of the frontoparietal cortical mantle.

The finding of fetal ventriculomegaly requires a prompt evaluation that begins with a concerted effort to rule out additional anomalies.

For those patients diagnosed before the legal limit of abortion, there is urgency to complete the work-up to allow an informed parental decision. The maternal gestational history is reviewed for previous outcomes, early drug exposures, and unexpected illnesses, and the family history is reviewed for X-linked hydrocephalus and neural tube malformations.

Ultrasound evaluations alone can miss important anomalies, which will affect the outcome, so ultrafast fetal MRI has been developed as a more anatomically precise modality for prenatal neuroimaging. There is no apparent risk to the mother or fetus from the radiofrequency pulses or the magnetic field. Therefore, ideally, an MRI scan is obtained and interpreted by an experienced pediatric neuroradiologist to rule out any additional CNS anomalies.

Amniocentesis is performed for viral cultures, chromosomal analysis, and alpha-fetoprotein levels.

Postnatal Diagnosis

On CT scan, blockage at the aqueduct is assumed when the lateral and third ventricles are enlarged proximal to the obstruction, and the fourth ventricle is relatively small.

An MRI examination, in T1 and T2 sequences, with 3-mm-thick, contiguous midline sagittal sections, will reveal the presence of an aqueductal stenosis and its etiology.

At aqueductal level, the "flow void" signal produced by CSF flow pulsations, in T2 images, appears hypointense in comparison with ventricular CSF. This is considered the most important radiological sign of aqueduct patency.

It is important to notice that in aqueductal shape modifications, the increase of flow velocity may result in a void signal with a false diagnosis of aqueductal patency on MRI examination.

Another and more reliable method to study the CSF pathways is the cardiac-gated cine MRI.

48.2.1.5 Prognosis

The prenatal detection of hydrocephalus has facilitated obstetric care but presents a source of uncertainty for the family and a challenge for the team counseling parents regarding their fetus.

It is clear that fetal ventriculomegaly with associated abnormalities have a poor outcome. In cases of ventriculomegaly associated with infections, chromosomal abnormalities and severe CNS and extracranial abnormalities, the poor prognosis may influence the family's decision to continue the pregnancy. The outcome of isolated fetal hydrocephalus, however, is variable.

Published studies of neonates with aqueductal stenosis have noted variable outcomes, with normal development seen in 24–86% of cases. The prognosis of aqueductal stenosis depends on the following: the extent of venticulomegaly, how early during gestation it becomes evident, and its progression with time. However, it is not possible to predict in an affordable way if the baby will be mentally handicapped or not and, if yes, to which extent. Fetuses with aqueductal stenosis have a good survival rate, because they usually do not have associated abnormalities. Males with X-linked hydrocephalus generally have a less favorable prognosis.

Prenatal factors such as progression, degree of cortical mantle thinning to less than 1.5 cm, and in utero duration of greater than 4 weeks contribute to a worse prognosis. On the other hand, those with mild isolated ventriculomegaly of less than 12 mm have an excellent prognosis.

48.3 Arachnoid Cyst

Arachnoid cysts are collections of CSF in the subarachnoid space. They are relatively closed spaces with a very poor fluid circulation inside them and throughout the entire subarachnoid space.

The anatomy of the subarachnoid space and cisterns, described first by Vesalius in 1555, had a thorough description by Yasargil (Microsurgical anatomy of basal cisterns,1984, Georg Thieme Verlag Vol I).

Many of the subarachnoid cisterns can be considered anatomically distinct compartments. After normal development, there is a continuous exchange of CSF from one compartment to another, via trabeculated porous of various sizes.

These apertures and communications may become plugged and partially or totally obliterated by various mechanisms (infection, hemorrhage, etc.).

Various cystic lesions may be observed in different regions of the intracranial and spinal spaces.

48.3.1 Sylvian Cyst

They are cavities located in the temporal region. They may assume huge proportion, and they may extend as far as a whole hemisphere. We describe three forms (Galassi et al. Surg Neurol 17:363–9, 1982).

1. Internal cyst (mesial to the temporal lobe). It is a small, biconvex cyst, located in the anterior temporal tip. Classically no mass effect is present.
2. Internal and external to the temporal lobe. They usually involve the proximal and intermediate segments of sylvian fissure. There may be a mass effect on ventricular structures and/or cranial nerves.
3. Huge almost hemispheric cyst. They involve the entire sylvian fissure with normally marked shift of the midline structures.

Surgical indication depends on signs of raised Intracranial pressure (ICP) and/or compression of cranial nerves. In case of huge volume, the surgical treatment must be considered.

If seizures are the only sign the surgical indication is controversial.

Marsupialization of the cyst with the cisternal space is the recommended procedure.

In some cases, especially in very young babies, a temporary shunting procedure may be effective.

Marsupialization can be done by microsurgical technique and by neuroendoscopy (see chapter on Neuroendoscopy).

48.3.2 Suprasellar Cyst

They are cavities located in the suprasellar space. They may be arachnoid cysts or a neuroepithelial cysts realizing a true hamartoma.

Signs are related to hydrocephalus or endocrine dysfunctions like precocious puberty.

In older children or adults, signs of increased ICP may be difficult to identify. For example, seizures, lipotimia, or episode of raised arterial blood pressure may mask a real state of IIC.

Surgery is mandatory in almost all cases of suprasellar cyst.

Today the gold standard is the endoscopic approach with marsupialization of the cyst into ventricles and cisterns.

48.3.3 Convexity Cyst

They are mild volume cavities on the surface of the brain mainly located on the outer surface of the parietal lobe, rarely on the mesial one.

Signs are related to local mass effect on cerebral gyri and sulci.

Seizures are frequent. Focal headache is described.

Surgical indication is controversial and based on the volume of the cyst and the frequency of the seizures.

Microsurgical marsupialization with subarachnoid space is the technique of choice.

48.3.4 Interhemispheric Cyst

They are complex malformations involving the brain, corpus callosum, and commissures.

They may be associated with hydrocephalus. In the neonatal period, the signs of raised ICP are frequently observed.

Surgical indication depends on hydrocephalus. Temporary CSF diversion by shunting of the cyst is the best tool.

Secondary the shunt may be removed after the endoscopic marsupialization of the cyst into the ventricle.

48.3.5 Septum Pellucidum, Velum Interpositum, and Quadrigeminal Cyst

Rarely these cysts have mass effect and disturb the CSF circulation.

Surgical indication is quite rare.

Quadrigeminal cyst may disturb CSF circulation in the aqueduct causing mild hydrocephalus. Endoscopic approach with third ventriculostomy resolves the hydrocephalus without approaching the cyst. In some cases, endoscopic marsupialization of the cyst via the ventricle is feasible.

48.3.6 Posterior Fossa Cyst

The Dandy–Walker complex must be excluded from the arachnoid cyst of the posterior fossa.

The so-called Dandy–Walker variant must also be excluded.

The Blake's pouch is a retrocerebellar cystic evagination of the posterior tela choroidea, without agenesis of the cerebellar vermis.

Rarely the posterior fossa cysts are symptomatic.

Even very huge retrocerebellar cyst rarely disturbs the CSF dynamics.

In some cases, overcrowding the posterior fossa, a supracerebellar cyst may induce the herniation of the cerebellar tonsils, becoming symptomatic. In like manner, a retrocerebellar cyst or

a Blake's pouch may push down and occlude the cisterna magna and become symptomatic.

In these cases an osseous anomaly with a reduced volume of the posterior fossa explains the presence of the symptoms.

Microsurgical marsupialization (supracerebellar or cerebellopontine angle cyst) and endoscopic approach (retrocerebellar) are the best techniques to resolve these problems.

48.3.7 Spinal Cyst

Arachnoid cysts may be located into the spinal canal at various levels.

Their volume is small, but they might grow with a mass effect on the spinal cord and/or root and become symptomatic in a short period.

Scoliosis may be a revealing sign.

There can be true arachnoid cysts, but a connective basal membrane is often found at histological exam realizing the so-called leptomeningeal cyst.

Direct microsurgical approach by laminotomy and marsupialization of the cyst is mandatory if neurological signs are present.

48.4 Management of Hydrocephalus and CSF-Related Disturbances

48.4.1 Neuroendoscopy

Neuroendoscopy appeared at the beginning of the last century and started modifying general neurosurgery during the last 20 years, thanks to technological progress of optical fibers. Besides radically changing the neurosurgical treatment of hydrocephalus, nowadays neuroendoscopy is an alternative and effective treatment for other intracerebral and periventricular lesions located in the third and the lateral ventricles, such as arachnoid and colloids cysts.

Furthermore neuroendoscopy allows biopsy and sometimes removal of intra- and paraventricular tumors, including vascular malformation and hypothalamic hamartoma (HH), and is currently used in rare subtypes of hydrocephalus.

In pediatric age, the high incidence of hydrocephalus, isolated or associated with almost all the cerebral lesions, makes neuroendoscopy a valid and suitable tool for multimodal treatment.

First of all endoscopic third ventriculostomy (ETV) is today recognized as the gold standard treatment of obstructive hydrocephalus, both in children and infants, with an overall success rate in a range of 65–85% in many published series, depending on the institution, patients' age, definition of failure, origin of hydrocephalus, indication, and follow-up period.

Obstructive hydrocephalus due to aqueductal stenosis in children older than 1 year is characterized by 98% of patients shunt-free after ETV.

ETV remains as a controversial hydrocephalus treatment option with high failure rates in pediatric patients with a history of myelomeningocele (MMC). In some cases ETV can be performed with success rate of almost 50%. The procedure should be delayed until the patient completes 1 month of age. At Saint Louis Fetal Care Institute, overall ETV success rate was 11/24 (45.8%) in patients who underwent fetal MMC repair. Young age (less than 6 months) and late gestational age (GA) at time of fetal MMC repair (after 23 weeks GA) were predictors for ETV failure [1]. In patients more than 6 months of age after shunt failure has been shown to have a good long-term success (approximately 80%) [2].

ETV in Dandy–Walker malformation can be an effective means to achieve reduction in hydrocephalus and is a recommended line of treatment [3].

Hydrocephalus in Chiari 1 malformation is a known entity with a complex etiology which is a matter of great debate. However the use of ETV in Chiari 1 malformation is spreading mainly because it causes reduced hampering of the physiological pathways of CSF flow and absorption [4].

ETV may be considered the first treatment of choice for the forms of hydrocephalus that are multifactorial and associated with complex craniosynostosis. Hydrocephalus should be managed before

cranioplasty and offers less risks of skull growth impairment and infections than shunt, but its long-term success rate is reported to be 60%. So, a close clinical monitoring is mandatory because of the high failure rate of ETV in these patients [5, 6].

The role of ETV in tumoral hydrocephalus is primary: in literature series, ETV was found to have a success rate of 70–90% and has been recommended as the ideal treatment for hydrocephalus in such cases [7]. Posterior fossa tumors with hydrocephalus must be treated first by ETV, followed by direct approach to the tumor few days later. In our series the ETV success rate in posterior fossa surgery is 78.5%.

ETV for pineal region tumors is regarded as the primary line of intervention with the advantage of not only relieving hydrocephalus but also providing window for biopsy and CSF analysis and to inspect for tumor seedlings and dissemination if any [8].

In infants the number of CSF shunting procedures is being reduced by neuroendoscopy.

Posthemorrhagic hydrocephalus in preterm newborns can be treated too by neuroendoscopy instead of traditional techniques.

Indeed, in all cases of obstructive hydrocephalus (obstruction of the outlets of fourth ventricle, cysts, Chiari malformation, complex craniosynostosis), ETV may be considered the first-choice treatment [5]. In case of shunt failure, ETV can be proposed instead of ventriculoperitoneal shunt revision, achieving 82% success rate of children shunt-free [9]. A significant improvement in our understanding has been contributed by the preliminary results published by The International Infant Hydrocephalus Study Group; this prospective, multicenter comparison of ETV, and shunt success in infants (<24 months old) suggest that shunting has a superior success rate as compared to ETV (66% vs. 88% at age of 6 months), slightly higher than would have been predicted by the ETV Success Score (57%).

Even in shunted children with slit ventricle syndrome, ETV may be considered an alternative choice [10].

48.4.1.1 The Endoscope

Techniques for intraventricular catheter placement may be ameliorated with pediatric neuroendoscopy.

The 9.5 Fr rigid neuroendoscope produced by Storz™ is very useful and versatile in pediatric neurosurgery. Despite very small dimension of external diameter and thanks to a particular optical smallness, this instrument is equipped with a 3 Fr operative channel like that of bigger endoscopes. So it is possible to make the same operations as with the larger endoscopes. The penetration of cortical surface is smaller and less traumatic. During the ventricular tapping, the risk of injuries of ependymal vein is lower.

Moreover in particular surgical situation like narrow foramen of Monro or rigid and small ventricles, this instrument avoid injuries to the neighboring structures. In the third ventricle, in case of huge massa intermedia, the targeting of the stoma is easier, and the penetration of the interpeduncular cistern is possible too.

48.4.1.2 Third Ventriculocisternostomy

It is a standardized technique to open the third ventricle floor to make it communicate with basal cisterns in order to divert the CSF circulation from the aqueduct and fourth ventricle. It is utilized for obstructive hydrocephalus due to aqueductal stenosis on a malformative basis (aqueductal atresia, arachnoid cysts of lamina quadrigemina) and tumoral (posterior fossa, pineal or brainstem tumor, tectal hamartoma) and also in the presence of aqueductal flow disturbance due to hemorrhages or infections.

The surgical technique is standardized in all cases. We used a Storz™ rigid neuroendoscope of 9.5 French, a Fogarty balloon catheter with an outer diameter of 3.2 mm and 30° angulated optic. The camera was oriented with the operative sheet. Under general anesthesia, the patients were positioned supine with the head slightly flexed, and a pre-coronal 5 mm burr hole was made. In infants, the access was performed at the lateral margin of the anterior fontanel.

After opening the dura and the arachnoidal surface, the endoscope was inserted "freehand" without a stilet under direct view control. The presence of mandrin passed inside the operative channel and prevented the passage of small brain particles into the endoscope during the introduction. After the lateral ventricle was reached, the foramen of Monro was identified following the choroid plexus, at the confluence with the venous angle formed by anastomosis of the anterior septal vein and the thalamostriatal vein. The endoscope crossed the Monro to reach the third ventricle. The fenestration was performed in the triangle between the tuber cinereum anteriorly and the mammillary bodies posteriorly, as close as possible to the dorsum sellae to avoid injury to the basilar artery complex (Fig. 48.1). The opening in the floor of the third ventricle was made with a 1 mm coagulator fiber followed by the insertion of a 2 French Fogarty balloon catheter inflated with 0.2 cc of saline solution in the cistern and then withdrawn into the third ventricle (Fig. 48.2). No forceps or blunt technique was used. After the perforation of the floor of the third ventricle, the neuroendoscope was always introduced through the stoma into the interpeduncular cisternal space to open the two layers of the Liliequist membrane to reach the prepontine cistern, after the identification of basilar artery. The endoscope was then retracted (Fig. 48.3). Irrigation was carried out carefully and manually if necessary; no continuous irrigation was used. The whole procedure was always carried out in a "freehand" fashion and took an average time of 30 min.

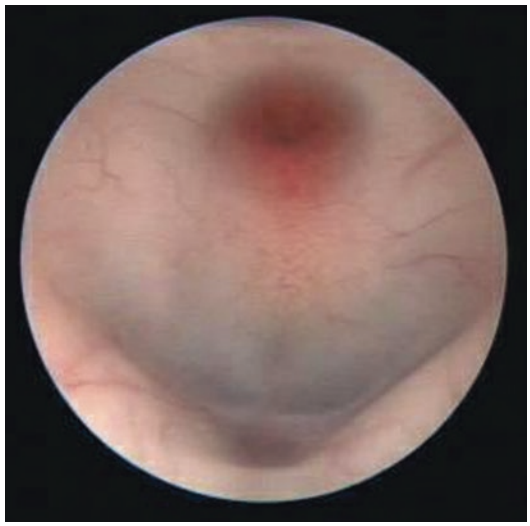

Fig. 48.1 Endoscopic view of the floor of the third ventricle. the tuber cinereum and mammillary bodies are visible

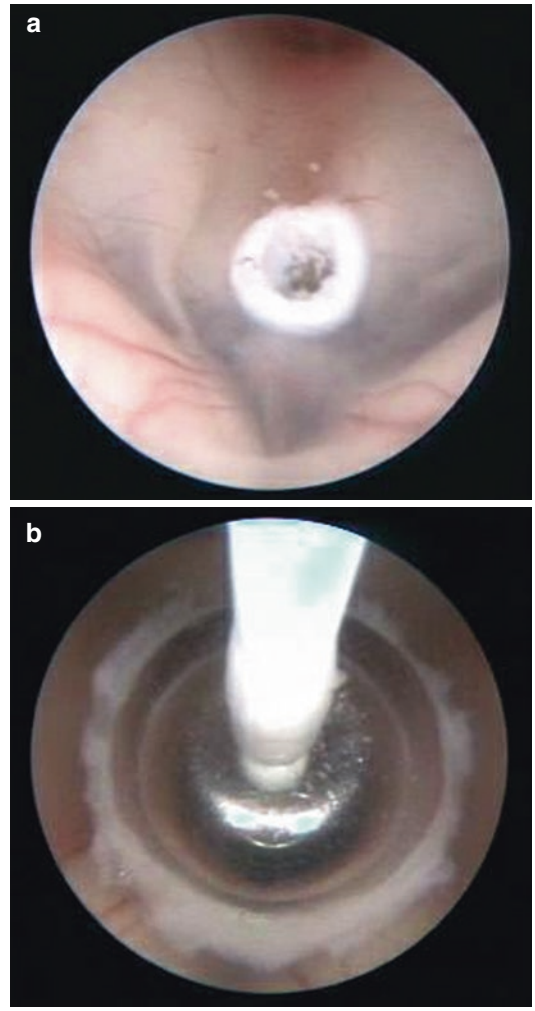

Fig. 48.2 Endoscopic view. (**a**) Opening of the floor by coagulator. (**b**) The balloon of the Fogarty catheter is inflated through the stoma

48.4.1.3 Septostomy

Septostomy consists in opening the septum pellucidum (Fig. 48.4) in case of monoventricular or biventricular hydrocephalus. It is also applied to open pathologic septa inside ventricles in multicystic hydrocephalus [11]. Multistep neuroendoscopic

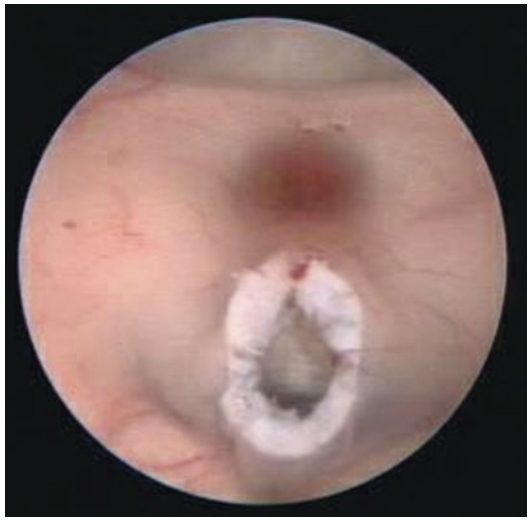

Fig. 48.3 Endoscopic view: the stoma is open between the third ventricle and the interpeduncolar cistern

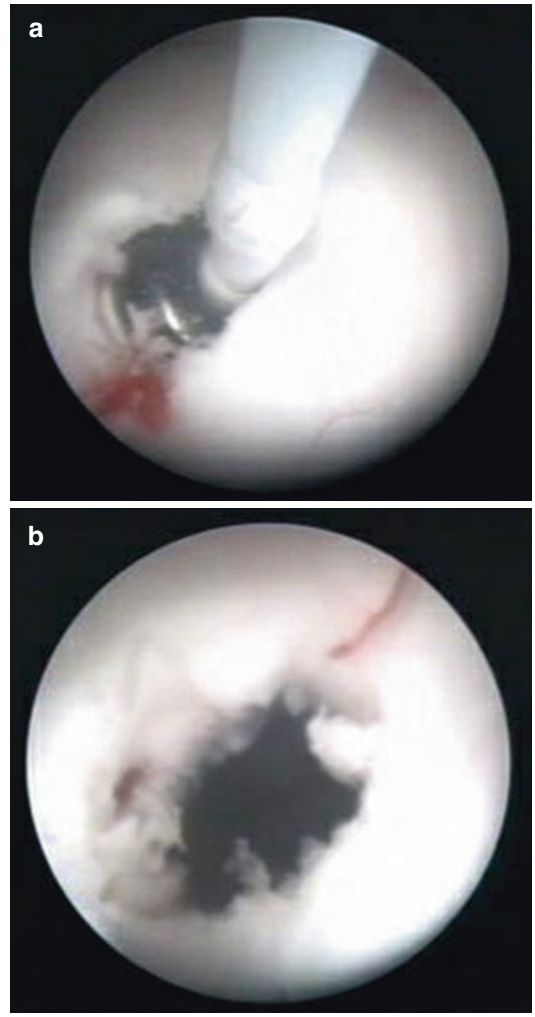

Fig. 48.4 Endoscopic view. (**a**) The Fogarty ballon is pushed through the septum pellucidum. (**b**) Opening between the two lateral ventricles

treatment of multiloculated hydrocephalus reduces the number of intracranial shunts.

To perform the septostomy, a lateral precoronal hole is performed to achieve perpendicular and not parallel access to the septum.

48.4.1.4 Arachnoid Cysts Marsupialization

The technique aims to open the wall of the cyst inside the CSF cisterns and/or ventricular cavities: for example, a temporo-sylvian cyst can be put in communication with optic, internal carotid artery and perimesencephalic cistern (Fig. 48.5). A suprasellar cyst may be fenestrated into the interpeduncular cistern, while an interhemispheric cyst is opened into the ventricular cavities [11]. Posterior fossa cyst (retrocerebellar, pontocerebellar angle, supracerebellar) may be fenestrated into the cisterna magna or into the pontocerebellar cisterns and perimedullary cisternal spaces.

Among reviewed quadrigeminal cistern cysts treated by endoscopic fenestration, complete or partial clinical remission was achieved on average in 88.5% [12–14]; for suprasellar cysts is 89.7% and for posterior cranial fossa 83.3%, similar to the results of craniotomy and cyst shunting, 86% and 90%, respectively [15–19].

The best surgical management of sylvian arachnoid cysts has been discussed and is still controversial. The microsurgical approach results in 88% success rate, while the endoscopic technique in 70%. In our experience, 40 patients have been operated with endoscopic fenestration for middle fossa arachnoid cysts: in 92.5% there was a satisfactory clinical outcome, and in 72.5% patients the cyst was reduced in size or completely disappeared. Endoscopic fenestration failure occurred in 10% of patients (n = 4), necessitating repeat

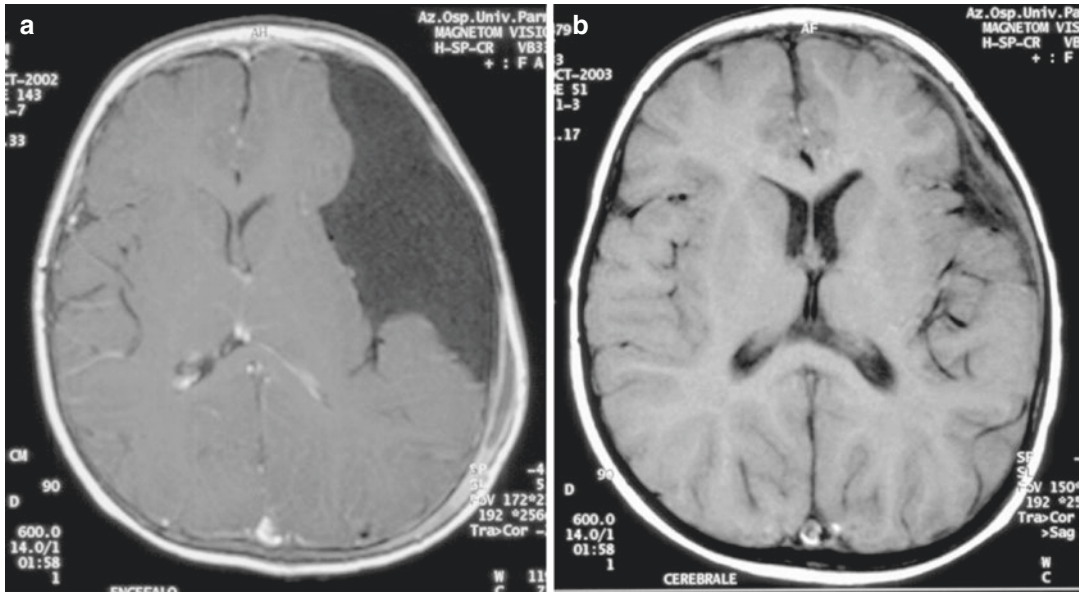

Fig. 48.5 MRI Axial view. (**a**) Huge arachnid cyst in the temporo-sylvian region with compression of the midline structures. (**b**) MRI Axial view: Post operative (endoscopic approach). Note the almost complete disappearance of the cyst

surgical treatment, one with cystoperitoneal shunting and three with a redo-endoscopic procedure [20].

Arachnoid cysts of the cortical and interhemispheric regions are best treated by craniotomy with direct cyst fenestration.

In case of endoscopic surgery failure, redo-endoscopy and direct microsurgical opening of the cyst through craniotomy are to be considered the first instance; cystoperitoneal shunting today represents last-choice surgery.

48.4.1.5 Placement of Catheters

In the presence of virtual ventricles or ventricles with multiple septations, neuroendoscopy enables a catheter to be placed in the selected place, also allowing its connection with an Ommaya reservoir for CSF tapping and/or drug delivering [11].

48.4.1.6 Computer-Assisted Neuroendoscopy

Neuroendoscopy can be utilized together with neuronavigator for procedures in small or virtual CSF pathways as well as for treating deep cystic lesions.

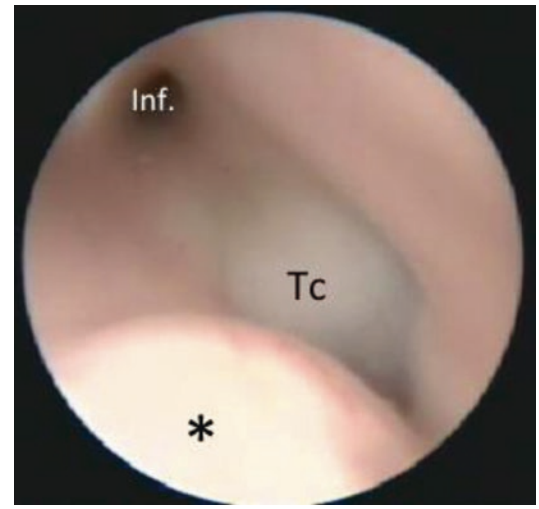

Fig. 48.6 Endoscopic view of Hypothalamic hamartoma (*). Tuber cinereum (Tc), infundibular recess (Inf.)

48.4.1.7 Functional Neurosurgery

Neuroendoscopy can be utilized in epilepsy surgery for the deafferentation of hypothalamic hamartoma (HH) (Fig. 48.6). HHs are rare, non-neoplastic, congenital malformations arising from the inferior hypothalamus and associated

with gelastic and dacrystic seizures, precocious puberty, and cognitive problems. Recent reports indicate that endoscopic disconnection of HHs seems to be safer and more effective than other modalities [21, 22]. In most cases, navigation assistance is recommended because lateral and third ventricles are normal sizes in these patients.

48.5 Shunting Procedures

The evacuation of superficial intracranial fluid in hydrocephalic children was first described in detail in the tenth century by Abu Al-KassimKhalaf Ibn Abbas Al Zaharawi (936–1013) said Abulcassis in Al-Andalous.

In 1893 the first permanent ventriculo-subarachnoid-subgaleal shunt was described by Mikulicz, who proposed a simultaneous ventriculostomy and drainage into extrathecal low-pressure compartment.

Between 1898 and 1925, lumboperitoneal and ventriculoperitoneal, ventriculovenous, ventriculopleural, and ventriculoureteral shunts were invented, but, in most cases, these systems had a high failure rate due to insufficient implant materials.

Artificial CSF valves were proposed in 1948 by Ingrham, by Bush at MIT in 1949 in collaboration with Matson, and by Nulsen and Spitz in Philadelphia. During the 1950s, the Spitz–Holter shunt was developed leading to a tremendous impact on neurosurgical procedures for hydrocephalus.

After the first generation of simple differential pressure valves, which are unable to drain physiologically in all body positions, a second generation of adjustable, autoregulating, anti-siphoning, and gravitational valves was developed.

Many shunt systems also have a flexible flushing chamber (reservoir) which may be housed within the same unit as the valve or may be a separate unit along the shunt, depending on the design of the shunt system. This chamber serves several important purposes. It permits to obtain samples of CSF from the shunt with a needle and syringe and to inject the chamber for testing shunt function and for medical treatment. The chamber also allows the shunt to be "flushed" or pumped. Flushing is accomplished simply by pressing on the skin overlying the flushing chamber.

Assuming that "the best shunt is no shunt," none of the innumerable multicentric trials have showed that any shunting system is more effective than another.

At the moment at least 127 different designs are available but most of these are only clones.

48.5.1 CSF Shunt Valves

48.5.1.1 Differential Pressure Pre-settled Valves

These valves are subdivided in four broad categories: slit valves, miter valves, diaphragm valves, and ball-in-cone valves. These systems have pre-defined operating pressures with three or five performance levels that vary from very low to high. Differential pressure valves open when the intraventricular pressure rise above the precalibrated opening pressure, allowing CSF outflow, and close when the pressure falls below the closing pressure of the valve. The limitation of standard differential valves is that the flow increases when the pressure differential increases (i.e., orthostatic pressure in standing position) leading to overdrainage complications.

48.5.1.2 Anti-siphoning Devices

These devices have been developed by Portnoy et al. in 1973, in the attempt to counteract the complication of overdrainage. The device is implanted below the valve and is responsive to atmospheric pressure transmitted through the skin, in fact, thanks to a small diaphragm that reduces CSF flow when the pressure inside the shunt falls below the atmospheric pressure. The problem is that if it becomes incased by scar tissue, it is unable to sense atmospheric pressure.

48.5.1.3 Programmable Valves

These valves have an adjustable ball-spring mechanism and operate as a differential device with the advantage that it is possible to modify the operating pressure of the valve once it has been implanted by means of an external device with a magnet placed on the skin.

Some authors have not reported a higher efficacy and safety rate of these devices compared to precalibrated valves. Other Authors believe that this type of shunt is superior because "..one cannot know in advance which case will turn out to be complicated…".

48.5.1.4 Flow-Regulating Valves

In these valves CSF flow through the device varies in correlation to the variation of CSF pressure. In attempt to keep the CSF flow rate constant, the mechanism resistance increases as the pressure gradient increases.

In conclusion none of the described types of valve appears to be best for the initial treatment of pediatric hydrocephalus.

48.5.2 Shunt Surgery Techniques

Especially in children the ventriculoperitoneal route is preferred to the ventriculoatrial route because it is easier to place and is followed by less morbidity.

Many studies have been carried out to evaluate the possibility of prevention and reversibility of pathological changes in hydrocephalic brain after shunting.

In experimental models it has been demonstrated that, after early shunting, many damages to the gray (reduction of neuron size, disorientation, dendritic deterioration) and white matter (periventricular edema, axonal damage, demyelinization, gliosis) and brain metabolism can partially recover.

48.5.2.1 External Ventricular Drainage

A short-term CSF shunt device may be needed for hydrocephalus following intraventricular hemorrhage, bacterial infection, or after brain tumor surgery with a high risk of postoperative hydrocephalus.

48.5.2.2 Ventriculoperitoneal Shunt

This is the most popular shunting procedure. The ventricular catheter is placed through an occipital or frontal burr hole and connected to the valve. The distal catheter is tunneled in the subcutaneous space and placed in the peritoneum. The advantages and disadvantages are as follows:

Advantages:

1. Less morbidity from shunt infections.
2. The possibility of placing a length of distal tubing to accommodate the patient's distal growth.

Disadvantage:

1. Peritoneal adhesions or infections.

The risk of seizures, which appears higher with frontal positioning, has been reported to be 5.5% in the first year after placement of a ventricular catheter. The risk rate dropped to 1.1% after 3 years.

48.5.2.3 Procedure

Shampoo the night before the procedure is recommended; before surgery an antiseptic iodine solution is used. It is not proven that hair shaving reduces contamination, so we do not shave the hair.

Under general anesthesia, the patient is positioned supine with the head rotated on the opposite side of the planned implantation. The neck is extended and lifted with a rolled drape positioned underneath, to obtain a straight and flat line between head and abdomen in order to facilitate the subcutaneous passage.

The site of the cranial and abdominal incision should be selected and marked before draping. After an accurate skin preparation (5 min) with iodine solution, the patient must be entirely covered by drapes with the exclusion of a small skin corridor between the head and the abdomen. An adhesive plastic sterile drape is then placed over the exposed skin to avoid contact with the skin surface. Skin incisions must be adequate and the cranial incision should not overlie the valve.

Ventricular catheter can be inserted in the lateral ventricle via the frontal or the occipital horn; which burr hole location is advisable is controversial. Some authors reported that "…shunts inserted via the frontal region functioned significantly longer than parietally inserted shunts".

Frontal burr hole must be placed 2.5–3 cm. from the midline, on the midpupillary line, and 1 cm. anteriorly to the coronal suture, parieto-occipital burr hole at about 7 cm. from the inion. Burr hole size must be adequate to the implanted device and can be carried out with a twist drill.

The peritoneal cavity is approached with a minilaparotomy and a trocar or endoscopically. We prefer a small laparotomy, and the abdominal incision is carried out transversally in the para-umbilical region. Tunnelization should be carried out between the two skin incisions starting from the abdominal incision especially if the implant of a pre-assembled system has been planned. The tunneling instrument must be passed not too deeply or too superficially in order to avoid, respectively, chest or posterior fossa injuries and skin lacerations.

After the tube and reservoir are in place, the dural opening is carried out with low-power monopolar applied to a small brain needle; it should have the same diameter of ventricular catheter to avoid CSF leakage, and the pia is cauterized with bipolar forceps.

The catheter trajectory is determined according to external landmarks. From a frontal approach, catheter is inserted perpendicularly to the skull, aiming the posterior projection of the medial epicanthus. From an occipital burr hole, the target will be the midpoint of the forehead.

Introducing the proximal catheter, it is possible to feel the ventricular cavity entry as a "pop" when the ependyma is breached, with a concomitant gush of CSF.

A right-angled guide allows catheter bending and stabilization before attaching it to the valve. Once CSF is flowing out of the tip of the distal catheter, it is time to insert it into the peritoneal cavity.

Soft tissue should be closed in two layers with careful apposition of the edges.

48.5.2.4 Ventriculoatrial Shunt

This is a less commonly used procedure for the high risk of infection (sepsy, pulmonary embolus, cor pulmonale, nephritis, and death). The shunt procedure is more demanding because the distal catheter is introduced into the transverse facial or jugular vein, and the amount of distal tubing is standard and cannot be adapted to the child's growth.

48.5.2.5 Procedure

It is advisable to prepare a fluoroscopic control in the operating theater. Patient position, skin preparation, and cranial procedure are identical to ventriculoperitoneal shunting procedure.

Drapes are used to cover the patient except for the part of the skin included between the burr hole and the sternal notch. An oblique skin incision is carried out on the neck at half way between the mastoid and the sternal notch. When the platysma muscle has been divided, it is possible to identify the posterior border of the sternocleidomastoid (SCM) muscle and the external jugular vein. Proceeding with deep dissection underneath the SCM muscle, it is possible to identify the internal jugular vein and the common facial vein; they both lie just lateral to the carotid artery. Once the facial vein is isolated and hemostatic lace and silk ties are positioned, a phlebotomy is carried out on it, and the catheter is passed, under fluoroscopic control, into the jugular vein until its tip is placed in the right atrium, just above the tricuspid valve. Once atrial catheter is well positioned, it is trimmed to the appropriate length and definitively connected to the valve.

48.5.3 Shunt Complications

CSF shunting represents the neurosurgical procedure with the highest failure rate. Most complications that require revision of the shunt occur within 6 months to 1 year after surgery.

The main causes of shunt dysfunction are:

- Obstruction
- Infections
- Mechanical problems (migration, disconnection, malpositioning)
- Other complications

Obstruction can occur in any of the components of the shunt device. The ventricular catheter

may be obstructed by choroid plexus tissue or by ventricular wall. Blood cells, bacteria proteins, and other tissue debris may also block the ventricular catheter and/or valve. Moreover, the tip of the peritoneal catheter may be obstructed by loops, fat abdominal tissue, and other abdominal pathologies.

Shunt infection is usually caused by a child's own bacterial organisms. The most frequent organism is *Staphylococcus epidermidis* which is normally present on the surface of a child's skin, in sweat glands, and in hair follicles deep in the skin. These infections are most likely to occur 1 month after surgery and sometimes up to 6 months after the placement of a shunt [23].

Mechanical and other complications are described too. Shunts are very long-lasting system, although their hardware may become disengaged as a result of the child's growth, with migration into the body cavities where they were originally placed. The valve itself rarely breaks down because of mechanical malfunction even if the shunting device may over- or hypodrain CSF. The overdrainage may result in slit ventricle syndrome and/or subdural hepatoma: in these patients cranial vault expansion and/or subtemporal decompression may be needed to achieve ventricular re-expansion.

48.5.3.1 Preoperative Period

Patient should be assessed taking into consideration general medical conditions and the presence of eventual skin problems. Hair shaving is not advised and skin should be prepared with povidone iodine washing.

48.5.3.2 Shunt Procedure

Shunt procedures should be scheduled early in the morning, before other operations. Newborns and infants have the precedence on older children, and no more than four shunt procedures should be performed in a day. The optimal length of a shunt procedure is comprised in 20–40 min; that's why an experienced neurosurgeon should perform the procedure.

In order to reduce the risk of contamination, a surgical team should consist of the surgeon, the assistant, the anesthesiologist, and the circulating nurse only.

Care must be taken to the selection of the shunt, and the sterile package of the device should be open at the very last moment, immediately before the implantation. Testing the valve, when not necessary, is not advisable.

Prophylactic intravenous antibiotic, a cephalosporin of second generation, should be administered 30 min before the skin incision.

To minimize contact with patient skin while passing the distal catheter, only two skin incisions should be performed. A meticulous hemostasis and utilization of intraoperative antibiotic washing is important to prevent bacterial growth. Skin incision should not overlie the valve, so a careful siting of the valve case and a good quality of soft tissue closure preferably in multiple layers are mandatory.

48.5.3.3 Postoperative Period

Care must be taken in head positioning in order to avoid pressure on the valve especially in prematures and newborns. During the period in hospital, which lengths approximately 4 days for the first shunt procedure and 2 days for a shunt revision, patients shampoo twice [23].

48.6 Craniofacial Repair for Craniofacial Dysmorphism

Surgical treatment of craniosynostosis aims to correct the deviated calvarial shape, to stop the compensatory growth, and to modify its effects by normalizing the physiological functions. This can be achieved, but not always completely, by the "dynamization" of the restricted skull growth and the redirection of the abnormally oriented growth vectors.

In some craniosynostosis (scaphocephaly) only affecting the cranial vault, a simple and wide suturectomy allows a passive reshaping, especially in the first 2 months of life, utilizing the released directional vectors of growth with the final result of a good cranial expansion and cosmetic correction.

In other craniosynostosis involving the vault and the skull base simultaneously (e.g., brachycephalies, trigonocephalies, and most plagiocephalies), active reshaping is required by bringing vault regions into the desired position and remodeling shape, orientation, and angles of the orbital bar.

The best time for this kind of correction is between the fourth and the sixth month of life.

On the other hand, the management of complex craniofacial malformations (e.g., Crouzon, Apart, and Pfeiffer syndromes and cloverleaf skull syndrome) is characterized by a multistep surgery. Initial anterior skull and orbital ridge remodeling with expansion and volumetric increase of the anterior cranial fossa aims to resolve the intracranial hypertension, manage breathing and feeding problems, and safeguard brain growth and visual function. Posterior skull expansion is sometimes needed when the occipital regions appear extremely flat; if Chiari type 1 anomaly coexist, occipital foramen and occipital former opening may be combined [24].

The second step is addressed to midfacial advancement, which is performed later, around the fourth year of life. In cases of severe midfacial retrusion, causing psychological problems in preschool age, early maxillary distraction can be performed by means of mechanical devices that provide a progressive advancement and correction of the facial dysmorphism and subsequent enlargement of the nasal airway.

This procedure is sometimes definitive or can prepare the child for subsequent programmed traditional midfacial advancement using the Le Fort III technique.

Successively, when complete growth is achieved, treatment can be completed with rhinoplasty and canthopexy procedures.

48.6.1 Preoperative Assessment

Early surgical correction is extremely important to achieve best functional and cosmetic result: the chance of an optimal aesthetic result decreases with child age, especially after 12 months. Unfortunately, toddlers in first months of life are characterized by “triple precariousness” (large needs, insufficient supplies, inadequate control mechanisms) making necessary and accurate clinical examination to detect concomitant pathologies (e.g., cardiopulmonary system, coagulopathies, etc.) and reduce anesthesiological and surgical risks.

48.6.2 Surgical Procedures

48.6.2.1 Craniectomy and Suturectomy

This technique is only applied in infants in the first months of life which cranial deformities restricted to the vault (scaphocephaly). Goal of surgery is releasing the directional growth vectors in correspondence of the prematurely fused suture in order to allow a harmonic expansion of the brain.

Vertex craniectomies, associated to strip craniotomies along coronal and lambdoid sutures, must be preferred to small suturectomies to avoid precocious reossification. The bony defects will close by the end of the first year when the infant learns to walk.

The advantage of this technique is represented by the possibility of a more precocious correction and a smaller skin incision (linear or “S-shaped” vertex incision) with reduced blood loss; the disadvantages are represented by a delayed cosmetic result.

Posterior plagiocephaly is the less common kind of craniosynostosis, and a differential diagnosis from the more frequent positional plagiocephaly is often required. Posterior positional plagiocephaly responds to "position therapy" or is solved by the use of external orthoses that mold the cranium.

Surgical treatment is reserved only to true lambdoid premature synostosis which consists in a vault reshapening by performing "fan or radial osteotomies."

48.6.2.2 Cranial Vault Remodeling

When an immediate cosmetic result is required for scaphocephaly, more invasive procedures are employed.

Many authors recommend the Marchac and Renier multisegment technique which allows good cranial reshaping and volume expansion. In these cases, in scaphocephalies, we prefer the "pi procedure" described by Jane in 1986 which accomplishes a satisfactory and immediate active remodeling of the cranial vault (Fig. 48.7).

48.6.2.3 Fronto-orbital Advancement and Remodeling

This technique first described by Tessier and successively modified by Marchac is used in various fashions for trigonocephaly, plagiocephaly (Fig. 48.8), brachycephaly, and oxycephaly, to expand anterior cranial fossa and remodel frontal bone and orbital bar.

The procedure is characterized by a bicoronal skin incision, anterior lift of the scalp flap until the orbital rims, elevation of the pericranium, and detachment of the temporalis muscle and of the periosteum until the upper part of the orbital cavities and frontozygomatic process are exposed. A bifrontal bone flap, included between the coronal sutures and a horizontal line about 2.5 cm above the orbital rims, is then outlined and removed.

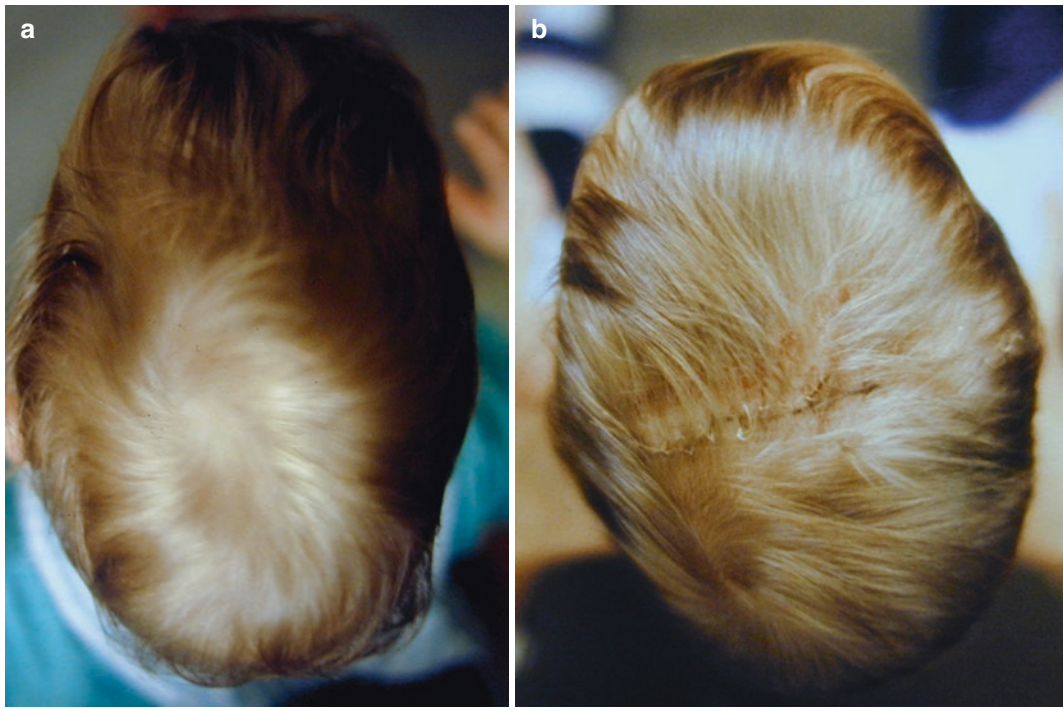

Fig. 48.7 Scaphocefaly (**a**) Preoperative view from above. (**b**) Postoperative appearence after cranial vault remodelling (from above)

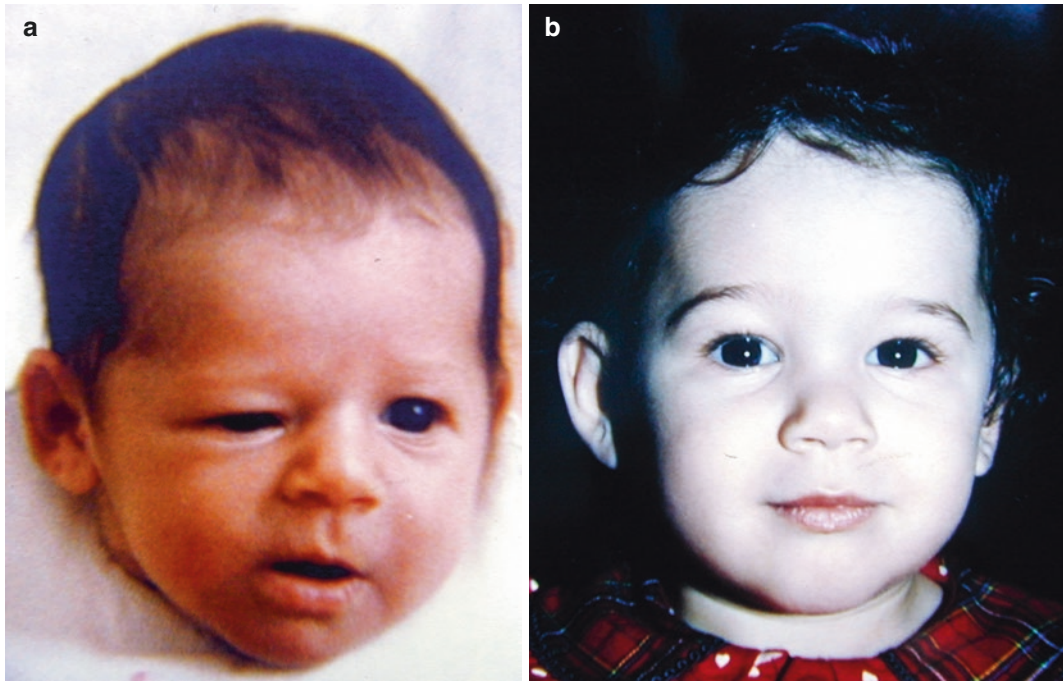

Fig. 48.8 Right anterior plagiocephaly. (**a**) Preoperative view. Note the facial scoliosis. (**b**) Postoperative (at 3 years). Note the symmetry of the craniofacial skull

The fronto-orbital bandeau is removed en bloc, avoiding to open the periorbital capsule, performing multiple osteotomies carried out along the orbital roofs, the frontozygomatic sutures, the lesser sphenoid wing, medially above the frontonasal suture, and along the temporal bone with piezosurgery or a chisel. At this point care is taken to detect dural lacerations and eventually repair them.

The orbital bar is then bent by grooving the inner table or with a bender instrument, reshaped, and repositioned with the new orientation and angle. A good stability especially in brachycephaly (Fig. 48.9) may be achieved with the use of bioresorbable lactic acid polymer plates. After its recontouring, the frontal bone is repositioned and ensured to the orbital bar or leaving it free to "float" on the frontal lobes. The temporal bone defect is filled advancing and rotating anteriorly the temporalis muscle. The bone surface is then covered by pericranium and the scalp is closed in layers.

Treatment of plagiocephaly can also be performed by advancing and remodeling the orbital bar only on the affected side.

48.7 New Minimally Invasive Surgical Techniques for the Treatment of Craniosynostosis

In 1890, Lannelongue published the first corrective action of a craniostenosis (scaphocephaly). From that first surgery, many other surgical techniques have occurred.

Thanks to an increase in knowledge about the etiology of these diseases, we have gone from a minimal technique, how can it be considered mere suturectomy, to a highly qualified remodeling surgery breaks through the cranial vault [25].

Furthermore, in the recent developments on the pathogenesis and non-marginal help brought by new neuroimaging techniques (TC, TC-3D, and MRI), over the past decade, there has been a new turnaround returning to prefer a minimally invasive technique [26]. The aim is to obtain the same result by reducing the morbidity.

This reaches its peak in spring-mediated surgery, in which a simple removal of stitches bind-

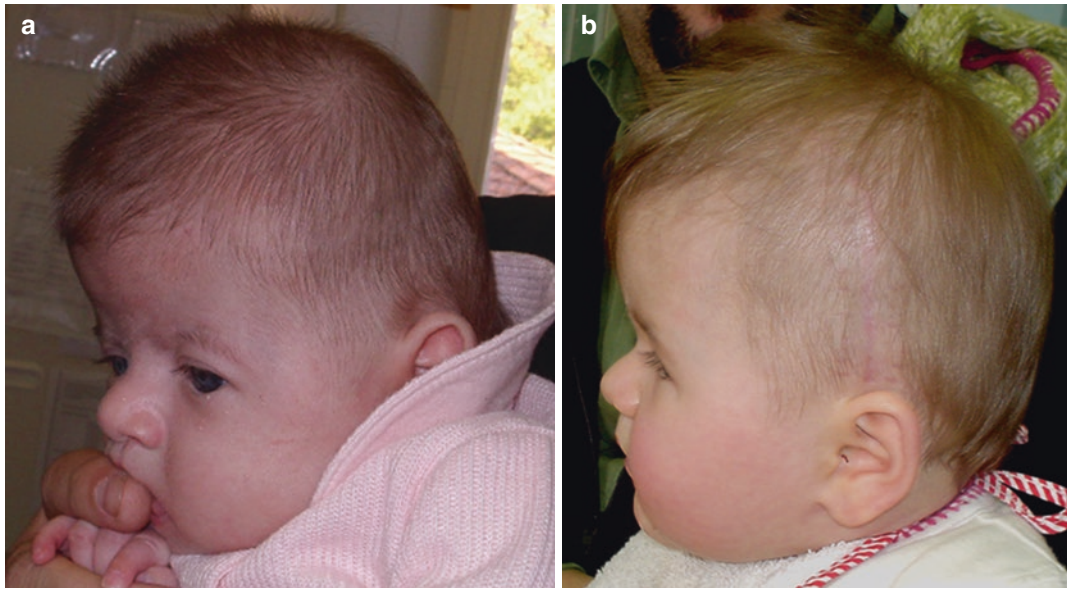

Fig. 48.9 Brachycefphaly. (**a**) Preoperative view. (**b**) Postoperative view after fronts-orbital advancement with bioresorbable plates and screw

ing the dynamic Expander placement in time of a few months will reshape the skull helping us to achieve the desired result.

Since 2007 was introduced at our neurosurgery division the use of dynamic metal expanders (technique introduced in 1997 by Dr. Claus Lauritzen, Sweden) to allow more and more minimally invasive interventions. This new technique involves excision of the pathological suture and the subsequent suture placement of dynamic metal expanders. The weak point of this type of surgery is that such expansion should be removed to achieve results; therefore the small patient should be submitted for a second surgery under general anesthesia [27].

To avoid this, the dynamic Expander 2009 was introduced built with absorbable material (polylactic acid and polyglycolic). Estimated time to complete resorption is 18 months.

In total, from January 2009 to March 2017, 890 patients have been operated with this mini-invasive technique. 497 patients were males and 393 were females. The age of the patients range from 1 to 31 months. The mean age was 9.1 months. The following surgeries were effectuated: 505 only suturectomy (27 with endoscopic technique), 30 suturectomy + metal springs, and 355 suturectomy + absorbable springs. The range of craniosynostosis treated with suturectomy + absorbable springs includes (Fig. 48.10):

- Scaphocephaly 19
- Plagiocephaly 156
- Trigonocephaly 70
- Brachycephaly 38
- Pachycephaly 9
- Multicultural craniosynostosis 51
- Crouzon syndrome 7
- Pfeiffer syndrome 2
- Saethre–Chotzen syndrome 1
- Clover leaf shape of skull

The mean hospitalization time was 5.8 days (range 2–12). The surgical timing was 53′ for placement (range 35′–13′).

As we highlighted the complications, only displacement of three different patients with metallic springs comes to three different diseases: Pfeiffer syndrome, pachycephaly, and anterior plagio-

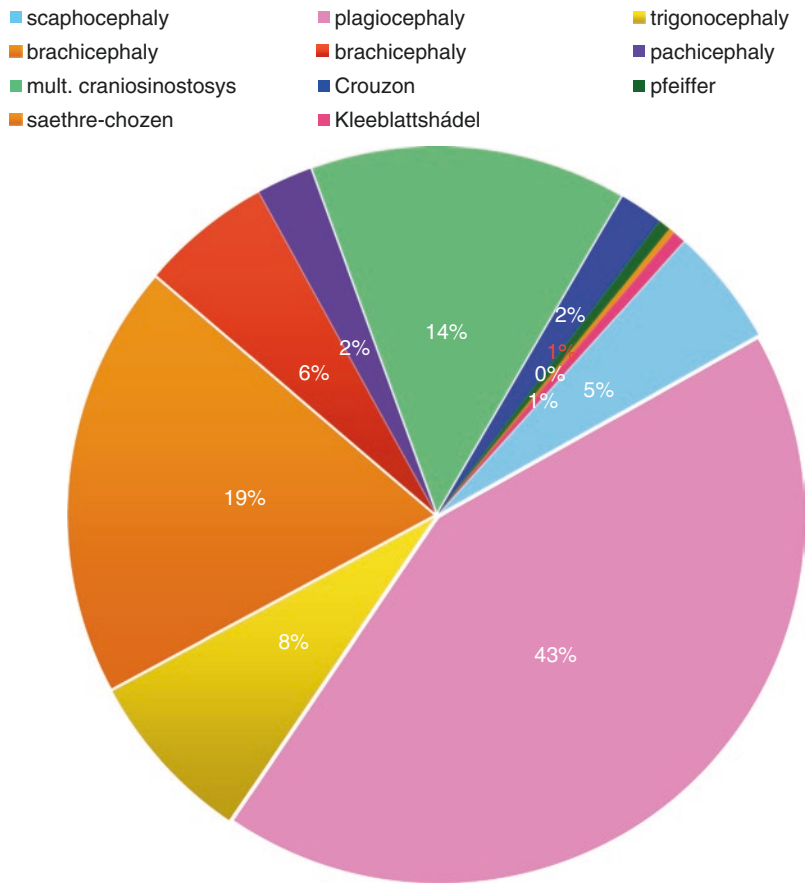

Fig. 48.10 Boy, 6 months at surgery. Clinical outcome on the right photo at 18th month. Minimally invasive technique with absorbable systems

cephaly. The pitfall of procedures was identified and consists in positioning the metal spring hook on the closure sick.

Highlighted benefits compared to the traditional technique are a reduction in blood loss (from 190 to 20 cc) resulting in reduced need for intraoperative blood transfusion, add to that a less postoperative analgesia and the reduction in days of hospitalization with lower costs for individual patient.

The aesthetic and functional results were then evaluated by a team formed by the surgeon and family. These can be clustered as the following:

- Excellent (80%): craniofacial symmetry, normalization of skull shape and size, and aesthetic results that are pleasing to the team.
- Good (13.4%): cosmetic results acceptable to the majority but less than ideal decreed, generally secondary to a slight asymmetric.
- Insufficient (5.7%): presence of an asymmetry evident or a cranial shape/size not acceptable.

In conclusion, the spring-assisted surgery offers in selected cases an excellent expansion of selected areas of the skull, allowing you to expand at the same time to different areas of the skull.

In the simplest of craniosynostosis is recommended the use of minimally invasive surgery with absorbable spring, while in more complex cases of absorbable spring, it is recommended a minimally invasive surgery in more steps (Figs. 48.10, 48.11, 48.12, and 48.13).

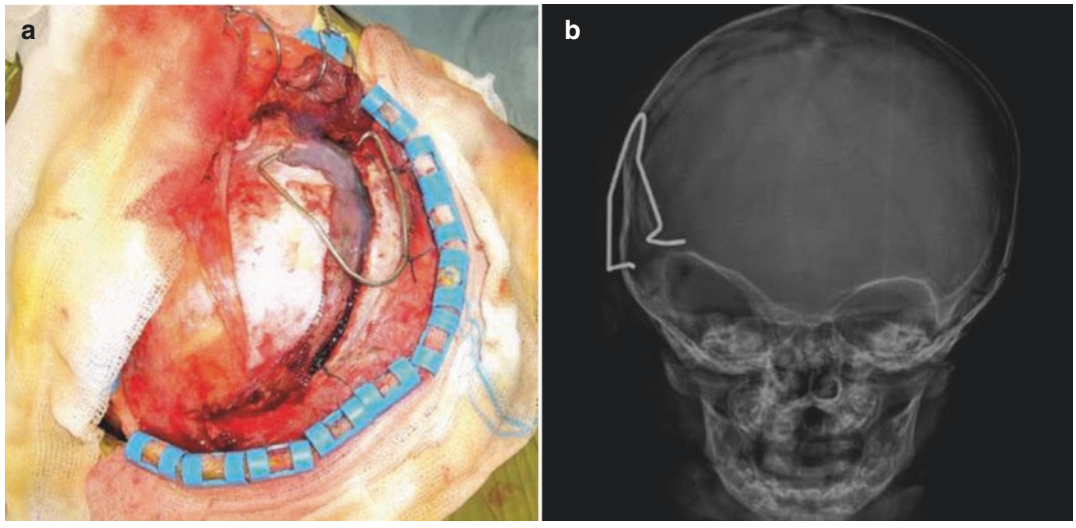

Fig. 48.11 Craniosynostosis treated with suturectomy + absorbable springs

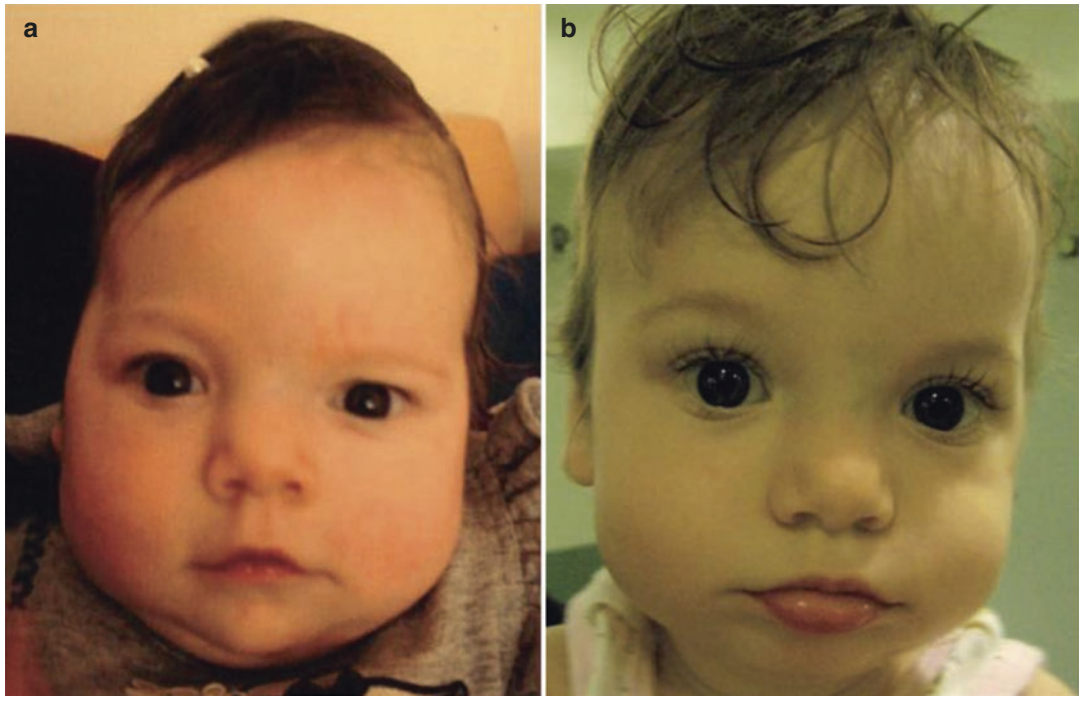

Fig. 48.12 Right plagiocephaly. Minimally invasive technique with suturectomy and placement of metallic dynamic Expander

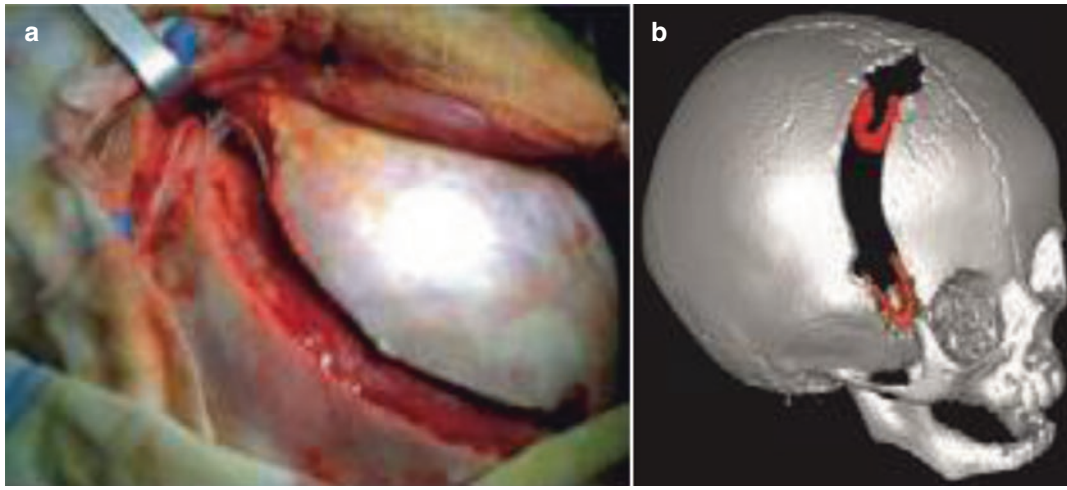

Fig. 48.13 Girl, 6 months at surgery. Clinical outcome with minimally invasive technique at 18th month

48.8 Excision of Cephaloceles

48.8.1 Intrateutoria Cephaloceles

First question is deciding whether to treat or not a newborn with encephalocele. As a matter of fact, all meningoceles should be closed because they do not usually contain brain structures. On the other side, in case of large meningoencephaloceles with large amount of cerebral structures (sometimes exceeding the entire volume of normal brain) and associated malformations, the surgical indication must be discussed with parents because of their poor prognosis. Prognostic factors to be considered are size of the encephalocele, the amount of vital brain tissue, microcephaly, and hydrocephalus associated. In these forms, the neurological outcome is usually dismal because of higher incidence of hydrocephalus and other brain malformations. Goals of surgery are removing the sac with dysplastic tissue, preserving functional nerve structures, and closing the malformation with not-dysplastic skin.

In the early postoperative period, seizures, CSF collections, hydrocephalus, and infection may occur. Seizures are due to the presence of dysplastic and epileptogenic brain structures. It is usual to observe a CSF accumulation into the site of surgery. This "dead space" is to be avoided by compressive dressing: this phenomenon creates a "fifth" ventricle which raises the risk of postoperative hydrocephalus. The hydrocephalus is more common in meningoencephaloceles than in meningocele being due to the loss of supplementary space of CSF accumulation and to coexistent subclinical infections. In case of progressive hydrocephalus, a CSF ventriculoperitoneal shunt is to be placed. Furthermore, in case of CSF collection under the wound, the CSF diversion allows an easier and faster wound healing. In case of hydrocephalus associated with CSF infections, the treatment is external ventricular drainage.

48.8.2 Cranial Vault Cephaloceles

Goal of surgery is cosmetic without trying to remove all the intracranial portion of the content. Skin incision is tailored to the site and extension of the sac; the cranial defect is repaired with autologous bone.

48.8.3 Fronto-ethmoidal or Sincipital Encephaloceles

The encephalocele is to be removed with its whole content by a subfrontal extradural route via an anterior bifrontal bone flap. The craniotomy is

made just above the anterior cranial fossa floor sometimes including a fronto-orbital osteotomy to dissect better the sac in a single-step procedure. After sac excision and watertight dural closure with nonadsorbable suture, a cranial base plasty with peduncolarized autologous periosteum flap is realized to seal the bony defect. A CSF leakage (rhinorrhea and/or CSF "tears") may occur with risk of meningitis avoidable by an external lumbar drainage.

48.8.4 Basal Encephaloceles

The surgical management of transsphenoidal, intrasphenoidal, and transethmoidal cephaloceles is still controversial because of high morbidity, permanent impairment, and mortality especially in neonatal period and infancy. The goal of surgery is the reduction of the prolapsed sac to lessen the traction on the vital structures, preserving their function, and obtaining a watertight dural closure with reparation of the bone defect.

The most important question still remaining is the route of the surgery transcranial versus extracranial. As described by many authors, the transcranial transbasal route via a bifrontal bone flap is followed by higher mortality and morbidity especially in younger patients. On the other hand, since these lesions progressively enlarge, it is best to operate early in order to prevent further damage to the herniated brain tissue, preserve vision, and avoid progressive respiratory distress. Sometimes, urgent repair may be needed in patients with CSF leaks or hemorrhage after inadvertent removal of a cephalocele mimicking a nasal polyp.

So, nowadays the extracranial approach is preferred even in infancy, especially in case of progressive and life-threatening symptoms. Different approaches may be performed: transpalatal, transnasal-transmaxillary, transnasal-transsphenoidal, or combined approaches. In the transpalatal approach, the sac can be easily viewed and dissected by paramedian splitting of the uvula and soft palate and partial osteotomy of the hard palate. The transnasal-transsphenoidal approach uses the well-known technique of pituitary surgery to gain access to the sphenoid bone; this latest surgical technique is highly innovative and allows you to reach all parts of the skull base. In all these techniques, the common principle is not trying to put the whole sac inside the cranium but only to reduce the extent to which it stretches into the nasal cavity and epipharynx to stop traction on vital structures. Closure and reinforcing of the sac is made by application of multiple layers of oxidized cellulose and fibrin glue; the bone defect can be closed by autologous bone powder, nasal septum cartilage, autologous bone of nasal turbinates, and sometimes other heterologous ossification inducers. Reparation may be made through an endoscopic nasal approach, as described in an increasing number of cases reported in literature.

48.8.5 Other Forms of Cranial Dysraphism: Atretic Encephaloceles

A horizontal skin incision in a rhomboidal fashion is made around the sac. The dysplastic skin is removed with the nonvital inner tissue. The intracranial portion, if present, must be left in place. The cranial defect is closed by tubularizing the periosteum which is then covered by autologous bony powder. The skin is closed with nonadsorbable sutures.

48.8.6 Congenital Defects of the Scalp (Aplasia Cutis Congenita)

Smaller lesions can be treated conservatively, waiting for spontaneous healing and epithelialization. Larger lesions must be repaired using rotational skin flaps, sometimes prepared in advance by implanting skin expanders. In cases of massive agenesis of the scalp, desiccation and injury of the brain must be avoided by keeping the lesion moist.

48.9 Chiari Type I Anomaly

48.9.1 Surgical Pathology

The "Chiari anomaly" is defined by herniation of the cerebellar tonsils and medial part of the inferior lobes of the cerebellum below the plane of foramen magnum in different degrees.

Currently, Chiari type I anomaly is characterized by a caudal descent of the cerebral tonsil more than 5 mm under the foramen [28].

Besides the tonsil herniation, Chiari I landmarks are cisterna magna obliteration and reduced or absent CSF flow at the cervicomedullary junction [29].

The physiopathological basis of onset of clinical symptoms in Chiari type I patients is the development of an abnormal pressure gradient between the cranial and spinal compartment at the foramen magnum level [30]. Hence, an intermittent vector of force develops at this level leading to the progressive downward movement of developing tissue through the foramen magnum. If this progressive phenomenon occurs after complete development of cerebellar tonsils, the pressure gradient causes tonsillar herniations and starts spine cavitation that is syringomyelia formation [31].

Though several hypotheses have been proposed to explain its pathogenesis, there is not a single pathogenetic theory. The most accepted theory considers this malformation as the result of a mesodermal defect with consequent undersized posterior cranial fossa and overcrowding of the neural structures.

Indeed, several morphometric studies have shown that patients with Chiari malformation have a posterior fossa volume smaller than normal [32].

In Chiari I patients, the volume of posterior fossa is 23% smaller, and other posterior cranial fossa malformations are described in about 76% of patients [33]: occipital dysplasia, platybasia, occipitalization of the atlas, fusion of cervical vertebrae, Klippel–Feil syndrome (i.e., complete fusion and ossification of cervical spine), basilar invagination, reduced length of the supraocciput, increased slope of the tentorium, reduced length of the clivus, and retroflexion of the odontoid [34].

A variety of other clinical conditions and syndromes have been associated. The most common associated condition are neurofibromatosis type 1 [35, 36] and growth hormone deficiency [35, 36].

The best method to identify the typical aspects of Chiari's malformation and associated abnormalities, including syrinx, hydrocephalus, and craniovertebral anomalies, is definitely the MRI. CSF dynamic studies at the foramen magnum are now routinely used to determine the severity of CSF flow disturbance. The degree of CSF flow disturbance has been shown to correlate with severity and development of clinical symptoms.

Syringomyelia or hydromyelia corresponds to the progressive cavitation of the spine and is associated to Chiari I in 30–76% of cases.

The most common location is the lower cervical spinal cord, followed by the cervicothoracic junction and the upper thoracic region. Holocord syringomyelia is about 20% of the cases, and syringobulbia varies from 1 to 17% [37]. In our experience, syringomyelia is present in 36% of cases, in particular: syringobulbia, 4%; cervical, 35%; dorsal, 15%; cervical dorsal, 27%; lumbosacral, 2%; and holocord, 17%.

A side effect of syringomyelia is scoliosis that is found in 25–50% of subjects presenting Chiari I anomaly before skeletal maturity [38]. The physiopathological explanation of spine cavitation associated with Chiari relies to the abnormal gradient of CSF pressure at the foramen magnum level. The syrinx formation seems to be the result of obstruction of CSF flow at the foramen magnum that increases the systolic pulse wave in the spinal subarachnoid space drawing CSF into the spinal central canal through anatomically continuous perivascular and interstitial spaces [39].

As in our experience, in 10% of cases of Chiari I anomaly, hydrocephalus is associated [34]. Hydrocephalus is not communicating and seems to be due to stenosis of the fourth ventricle outlets (foramen of Magendie and foramens of Luschka). Its consequences are increased by compression of cisterna magna by prolapse

of the tonsils. The mechanism that associates Chiari I with this type of hydrocephalus is double. The presence of hydrocephalus exaggerates the Chiari phenomenon of cerebellar tonsil herniation because of the presence of an enlarged fourth ventricle. On the other side, the tonsil herniation itself may be a concause in narrowing a substenotic Magendie foramen leading to the precipitation of hydrocephalus. In 9% of patients with Chiari I, hydrocephalus and syringomyelia coexist [40].

48.9.2 Posterior Fossa Decompression for Chiari Type I Anomaly

In 1988 the American Association of Neurological Surgeons (AANS) had declared that in Chiari I patients, the posterior fossa decompression is always mandatory in the presence of signs of brainstem dysfunction, questionable in case of mild symptoms and headache, and not recommended in case of asymptomatic patients [41]. Today there is a general agreement to treat Chiari I characterized by cerebellar tonsil prolapse of at least 5 mm down to the foramen magnum with appropriate symptoms. In borderline cases (prolapse of 0–5 mm), surgical indication must be evaluated according to each individual clinical context. In the presence of syringomyelia, surgery is mandatory even in the presence of limited tonsil descent to avoid further enlargement and clinical deterioration [42]. Goal of surgery is to restore normal CSF flow thus reestablishing a pressure balance between intracranial and intraspinal subarachnoidal spaces by decompressing the inferior cerebellum and cervicomedullary region at the level of foramen magnum [43].

Patients are placed in a prone position with slight flexion of the neck to allow for visualization of the occipital bone. A midline vertical incision is made from just inferior to the inion to the C3 level. Myofascial dissection is carried out along the median raphe. Special care must be given in avoiding muscle dissection from C2 level (semispinalis cervicis and multifidus muscle) to prevent cervical instability and to reduce postoperative neck pain. Then, a suboccipital craniectomy is made.

The size of the craniectomy varies from 2×2 cm to 3.5×3.5 cm.

A posterior C1 laminectomy is made of about 2.5 cm. It is not necessary to extend laterally the craniectomy to reduce the surgical risk. A dense, fibrous, and constrictive band covers the atlo-occipital membrane causing intradural compression and arachnoid adhesion.

Several techniques that have been advocated for posterior fossa decompression includes bone decompression only, removal of the atlo-occipital membrane with the outer dura layer [44], intradural extra-arachnoid durotomy with and without duraplasty, intra-arachnoid lysis of the scarring and adhesions around the herniated tonsil [29], coagulation of herniated cerebellar tonsils respecting the integrity of pia and arachnoid [45], resection of cerebellar tonsils with subpial approach in case of very high gliotic tonsils not reduced by simple coagulation [46], as well as opening the foramen of Magendie and obex plugging and section of filum terminale [47].

The treatment of Chiari malformation type 1 with posterior fossa decompression without or with duraplasty is controversial.

Surgical morbidity may occur in form of vertebral artery damage, acute hydrocephalus, cerebellar ptosis, pseudomeningocele, CSF leakage, subdural collections, cervical instability, and acute life-threatening sign of brainstem dysfunction [42].

Indeed, the intradural techniques are associated with increased risk of complications between 15 and 25% [48] including wound infection, CSF leak, pseudomeningocele, meningitis, and complication associated with dural graft. Posterior fossa decompression with extradural lysis of the sclerotic band and opening of the outer dural layer offers a minimally invasive decompression technique with lower risk of complications between 2 and 6% [48].

A number of modern series published by authors like Zerah [49] and Genitori [50] have stressed the good results of this technique which is not followed by the frequent complications and is characterized by shorter hospitalization as

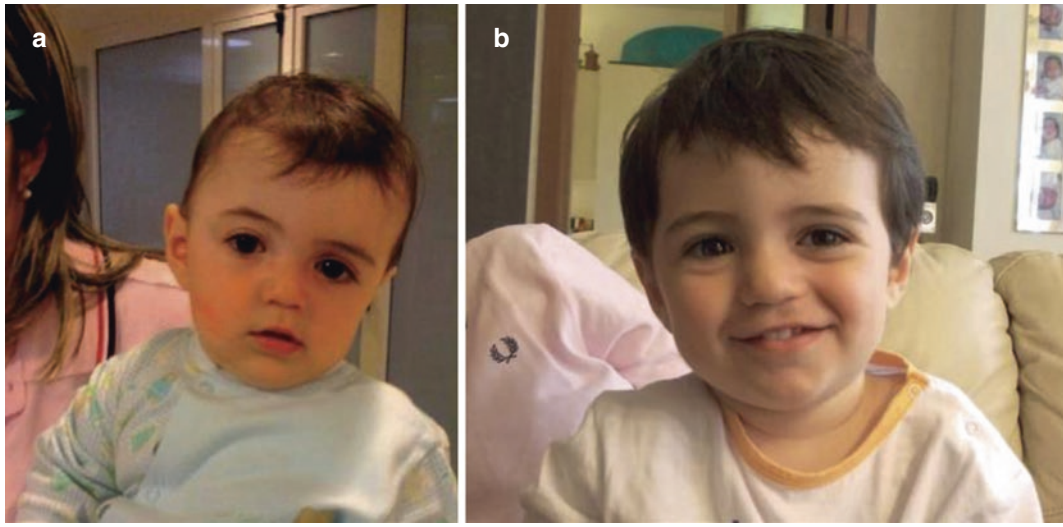

Fig. 48.14 Minimally invasive technology with suturectomy and positioning dynamic Expander reabsorbable material. Left, plagiocephaly

compared with surgical morbidity after surgery characterized by dural opening; surgical outcomes are good both in reducing syringomyelia and in improving its secondary effects like scoliosis (Fig. 48.14). Anyway, in case of clinical and/or radiological Chiari I recurrence or enlargement of syringomyelic cavities, the dural expansion must be considered [50].

Several neurosurgeons have adopted this technique with the caveat that there might be an increased risk of reoperation (12.6% vs. 2.1%).

In our study of 434 patients (from 2000 to 2015), the complication rate occurred using a minimally decompression technique is 1.9% and using intradural technique is 33%. Furthermore, in our experience, it has emerged that the rate of reoperation after extradural technique is 6.5%.

The aim of surgery is clinical improvement and ranges between 61.5 and 93% based on the study being studied.

According to some studies, the most appropriate therapeutic option is posterior decompression with dural plastics as it results in a better clinical outcome.

In fact, the improvement of syringomyelia, reported after posterior fossa decompression with dural plastic, arrives at 91.5% in contrast to the technique without dural opening that reaches 65.7%, although the decompression associated with duroplastic is vitiated by a higher rate of complications, until 40%.

Milhorat and Bolognese [51] have proposed an intraoperative control by intraoperative color Doppler ultrasonography (CDU) to tailor the extension posterior fossa bony decompression and C1 laminectomy and the need of additional steps like duraplasty and shrinkage or resection of the cerebellar tonsils. In first surgical steps, CDU allows to distinguish better all the posterior fossa structures including aberrant vascular anatomy, asymmetrical herniations, and neural displacement; this reduces the surgical risk of error especially in patients undergoing reoperation with a lot of meningo-cerebral scarring [51]. At the end of posterior fossa decompression, CDU serves to control if the CSF circulation and pulsatility are restored by measuring CSF flow velocities and viewing CSF flow directions. The optimal CSF flow to obtain has a peak velocity of 3–5 cm/s, bidirectional movement, and a waveform exhibiting arterial, venous, and respiratory variations [51].

In a recent study, Aaron et al. observed significant CSF flow changes when simply positioning the patient for surgery, using intraoperative MRI [52].

In the past, in the presence of syringomyelia-hydromyelia, some authors have proposed to put a shunt between the fourth ventricle and the

subarachnoidal spaces [53], while others prefer to make a syringostomy by myelotomy [54]. Syringo-subarachnoid shunting by a little catheter has been also suggested even if spinal cord injury after insertion of catheter in the spinal cavity is described [55]. A syringo-peritoneal or pleural shunt has been advocated because of the higher differential pressure compared with the subarachnoidal space [56]. The catheter used is "K" or "T" shaped and 2 mm large. The surgical technique consists in anchoring the catheter to the dura and putting its end in the planned cavity. The insertion of valve device to regulate CSF draining must be evaluated even if it is not usually utilized [43]. The techniques of tunnelization of the distal end of the catheter are the same as described for hydrocephalus shunting surgery. Some technical reports describe the possibility to treat Chiari anomaly by tapping the syringomyelia cavity by a percutaneous aspiration after failure of previous treatment [57].

As regards the associated hydrocephalus, most authors agree that it is the result of impaired CSF circulation within the posterior fossa at the level of the outlets of the fourth ventricle, sylvian aqueduct or arachnoid cisterns. The current trend is to treat the hydrocephalus first and then follow the clinical evolution [58]. Posterior fossa surgery is to be considered in case of onset of Chiari symptoms even if hydrocephalus is solved. The first-choice surgery is endoscopic third ventriculostomy [5]. In our experience, all patients showed a rapid resolution of the symptoms related to increased intracranial pressure.

48.10 Closure of Myelomeningocele (Spina Bifida Aperta)

Delivery by cesarean section is suggested to diminish local trauma to the malformation and prevent the contact of amniotic fluid with the myelomeningocele sac especially if it is ruptured: the amniotic fluid is toxic for the neural tissue, and cases of aseptic ventriculitis are described. The malformation must be protected and kept moist using tulle gras.

At birth a number of precautions have to be taken to avoid hypothermia, hypovolemia, and hypoglycemia. A complete diagnostic work-up must be performed to evaluate the neurological status of the newborn and the associated problems (brain malformation, hydrocephalus, urological and orthopedic impairments).

Surgery must be performed within the first 48 h to avoid septic meningitis, sepsis, and secondary injury to the placode requiring repair. Any delay after 72 h increases this risk to 37% compared to 7% in case of early closure. Neonatal meningitis is a serious complication because it impairs intellectual development.

The neonate is positioned prone with all pressure points on smooth pads in a Trendelenburg position to reduce CSF leaking; warming tables are utilized. Tracheal intubation should be carried out in a donut position if possible to reduce the trauma to the sac. Usual antiseptic drugs (i.e., povidone iodine must be avoided).

Goals of surgery are (1) identification of all anatomical planes according to the well-known embryological physiopathology, (2) reconstruction of the placode, (3) closure of meningeal coverings, and (4) closure of the fascia and skin.

The first step is an incision at the meningo-epithelial junction and dissection of the neural placode under the control of operative microscope. Arachnoidal adhesions between the placode and underlying dura are lysed. Any other associated abnormalities are to be identified and eventually removed (i.e., dermoids, lipomas, neuroenteric cysts, etc.). All residual epidermal and dermal elements must be removed to avoid the future formation of a dermoid or lipoma. At this stage, the placode is tubulized with nonadsorbable suture (Nylon 5/0), and the recurrent spinal roots must be respected. The meningeal layer is then dissected as far as possible to cover the new spinal cord, aiming to maintain it submerged in CSF in order to avoid secondary tethering. Sometimes a duraplasty is created with an autologous flap (periosteum, fascia lata) or more frequently with artificial biocompatible material like PTFE (polytetrafluoroethylene). In a case with a huge kyphosis, kyphectomy is necessary during the first surgery to enable easy

closure of the defect. At the end of the procedure, a myofascial layer is prepared to cover the dura, and the exceeding and dysplastic skin is excised before final closure is made with nonadsorbable sutures (Nylon 3/0). A releasing incision in the fascia laterally away from the defect may be useful to obtain a tension-free closure. In case of large defect, the lumbosacral musculature is useful to create flaps to cover the malformations even if rotational flaps do not often function because of ischemia. Deep dissection of latissimus dorsi may be dangerous because of the risk of damage to retroperitoneal and pulmonary structures.

In the early postoperative period, the newborn must be strictly monitored. The recommended position is Trendelenburg prone or lateral protecting the wound from urine and fecal contamination. Periodical measurement of the cranial circumference and ultrasound tomography are performed to rule out the hydrocephalus. Ventriculoperitoneal shunting is mandatory at first sign of hydrocephalus and/or in case of CSF leakage from the wound and/or brainstem dysfunction related to Chiari II. Endoscopic third ventriculostomy (ETV) achieves good results in secondary treatment of hydrocephalus in such children with shunt dysfunction.

Surgery for Chiari type II anomaly should be considered if at least one of the four Griebel's criteria is present: (1) continuous stridor with respiratory difficulty, (2) recurrent ab ingestis pneumoniae, (3) bradycardia or apnea, and (4) cyanosis. The surgical technique involves wide dissection of the foramen magnum along with posterior C1 laminectomy; a large duraplasty is then constructed using autologous or artificial material. However, this procedure is justified only if the hydrocephalus is well treated; in fact Chiari II may decompensate because of shunt dysfunction [55].

Surgical mortality is near zero, while postoperative complications may be serious. The most frequent is wound dehiscence with CSF leak, followed by local infection (1–1.5%), neonatal sepsis, and all the other complications connected with shunt and posterior fossa surgery.

48.11 Spinal Detethering Technique

48.11.1 Lipomas

- Lipoma of the filum terminale: surgical approach starts by a skin incision in the midline; the subcutaneous is incised with Bovie until the fascia is exposed. Then, paravertebral muscles are dissected off the laminae, and a 1–2 level laminotomy is performed. The use of the surgical microscope is necessary to perform the next surgical step. The dura is opened in a craniocaudal fashion and suspended. The Trendelenburg position of the table allow, at this point, to evitate loss of CSF and to keep the surgical field clear of CSF. The filum lipomatosus is identified, coagulated, and sectioned using the microscissors. Normally after this step, there is a remarkable ascension of the proximal end of the filum. The dura is closed with a 5/0 Prolene running suture. Fibrin glue and oxidized cellulose are positioned on the dura. The laminae are repositioned with care to set it in the normal position and sutured with Vycril 2/0. The fascia is closed. Subcutaneous tissue and skin are closed with resorbable suture.
- Usami et al. [59] described a series of 174 patients treated for lipoma of filum terminale. They found an improvement of symptoms in 50% of patients at 2.1-year follow-up period; one of 85 asymptomatic patients deteriorated (urological deficit). Nine patients presented complications after surgery, eight transient and one permanent.
- In the period between 1994 and 2015, we treated 115 patients with lipoma of filum terminale, 52 were female and 64 male, mean age at surgery was 2.5 years. Thirty-five (30.4%) had skin stigmas and in 24 (20.8%) lipoma of the filum terminale was associated with anorectal malformation. Symptoms at diagnosis were present in 52 patients (45.2%). Two patients underwent first to section of filum terminale externum with no improvement and then to filum terminale sectioning. Symptoms improved in ten patients (19.2%), any clinical

deterioration related to surgery presented. All patients were positioned in Trendelenburg for 3 days and then progressively mobilized to avoid the risk of CSF leakage. In our series four patients presented CSF leakage treated in three cases conservatively with bed rest and compressive medication. Surgical treatment of filum terminale lipoma is a safe procedure with low rate of complications.

- Caudal lipoma (Fig. 48.15): surgical approach starts by a skin incision in the midline. The fascia is exposed. The paravertebral muscles are dissected off the laminas with very careful dissection in the zone of the schisis to not penetrate the dura. A two-level laminotomy is performed above the lesion entry zone in the dura if it is present. The use of the surgical microscope is necessary to perform the next surgical step. The dura is opened in a craniocaudal fashion and suspended. The untethering is achieved by dividing the lipoma below the transitional zone which is identified between the conus and lipoma to avoid neural elements. Often, after division of the lipoma, the cord shows a remarkable degree of retraction. The dura is closed with a Gore-Tex patch using a 5/0 Gore-Tex running suture to avoid retethering the scar and the dural elements. The laminae are repositioned carefully in the normal position.

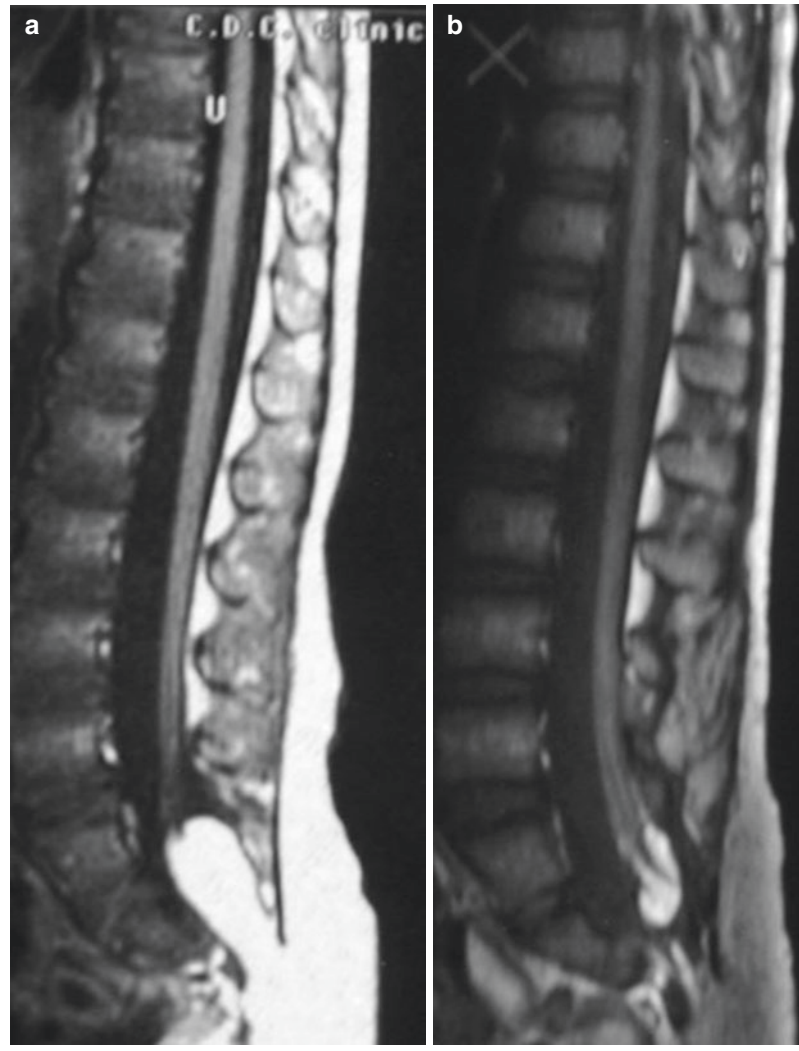

Fig. 48.15 MRI (sagittal view). Dysraphic state. (**a**) Caudal lipoma, preoperative view. (**b**) Postoperative view. Note the detethering of the spinal cord

- We treated 18 patients with caudal lipoma, 10 males and 8 females, mean age of 10 years. Eight patients presented skin stigmas; in four lipoma was associated with anorectal malformations. Urological or motor deficits or both were present in 14 patients at diagnosis time (77.7%). At last follow-up, none of asymptomatic patients presented deficits; four of symptomatic patients showed clinical improvement (28.5%), eight an invariated clinical status (57.1%), and two worsened.
- Lipomyelomeningocele (Fig. 48.16): The initial surgical approach is the same than the other types. At the level of the dura, it may be important to recognize the "normal dura" from the capsule of the lipoma. The lipoma can be dissected and debulked using a CO–laser or ultrasonic aspirator (CUSA) (MzLone 1986). It is not necessary to attempt to debulk the lipoma into the spinal cord since it doesn't increase in size. Careful dissection must be taken at the interface between lipoma and the spinal cord. The filum can be divided after his identification. The detethering, in this case, is from the superficial planes. Nerve roots are horizontalized and cannot be liberated from the lateral surface of the lipoma.
- Pang et al. [60, 61] advocated a total or near-total resection for lipomas with reconstruction of placode to ensure a better long-term outcome. He described a clinical deterioration in 4.1% cases and a low complication rate (0.7%

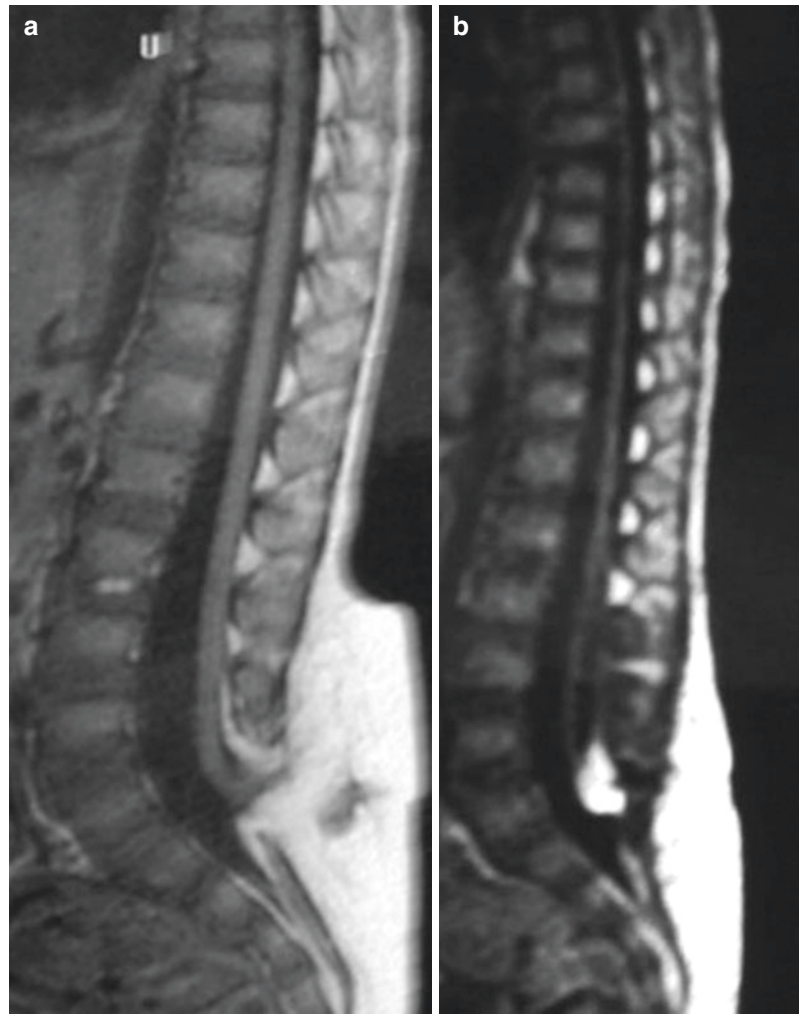

Fig. 48.16 MRI (sagittal view) Dysraphic state. (**a**) Lipomyelomeningocele, preoperative view. (**b**) Postoperative view. The lipoma has not been completely removed, but the spinal cord is detethered

CSF leakage and 1.1% wound complications). In 2010 they compared two groups who underwent, respectively, total or partial resection and found that in short-term follow-up, results were similar: in asymptomatic patients 98% of first group and 94% in the second didn't develop neurological impairment. In symptomatic patients 94% of total resections were improved or stable versus 95% of partial group. The progression-free survival described for total resection was 82.8% at 16 years and 34.6% for partial resection at 10 years.

- In our institution underwent surgical treatment 96 patients underwent surgical treatment with lipomyelomeningocele, 62 females and 34 males, with median age of 4 years. Of these 74 were classified as transitional and 22 as dorsal lipomas. In 77 patients were present skin anomalies as subcutaneous lipoma or other skin stigmas. Neurological impairment was present in 19 patients (14 in transitional and 5 in dorsal lipomas) and urological deficits were in 31 patients (24 in transitional lipomas and 7 in dorsal). In six cases dysraphism was associated with anorectal malformations. All patients except one underwent a partial resection of lipoma. At last follow-up, 19 patients presented an improvement of clinical status (17 in transitional group and 2 in dorsal group). Two patients showed urological deficits without any radiological sign of retethering. The patient who underwent a gross total removal of lipoma worsened; three patients needed a reoperation for retethering after 4 and 6 years after first surgical treatment. Complications were represented by CSF leakage in nine cases, treated conservatively in all by two cases, and local wound dehiscence and infection in seven cases.

48.11.2 Adhesions, Bands, Thick Filum, and Diastematomyelia

- Diastematomyelia (Fig. 48.17): the surgical approach is planned on the base of the radiological evaluation. The aim of surgery is the untethering of the spinal cord, and the technique varies with the two types of SCM. In type I SCM, the osteocartilagineous spur must be removed taking care of tight adhesions between the cord and dura. The skin incision is in the midline extending above and below the lesion. The laminae are dissected off the paravertebral muscles starting where the spinous processes are normal. A minimal laminectomy is begun in a normal area to avoid the risk of a kyphoscoliosis. The bony spur is then progressively exposed and removed after a subperiostal dissection of the septum avoiding lateral movements which can injure the adjacent hemicords. The two dural sacs are progressively exposed, and the dura is opened by an incision encircling the dural cleft and extended toward each extremity. The adhesions between the medial aspect of the hemicord and the dural sleeves must be progressively severed. The closure of the dura is performed with a duroplasty in Gore-Tex patch. In the type II SCM, the procedure is more simple. The dural tube is single, and the two hemicords with the median septum may have three different positions: the first type in

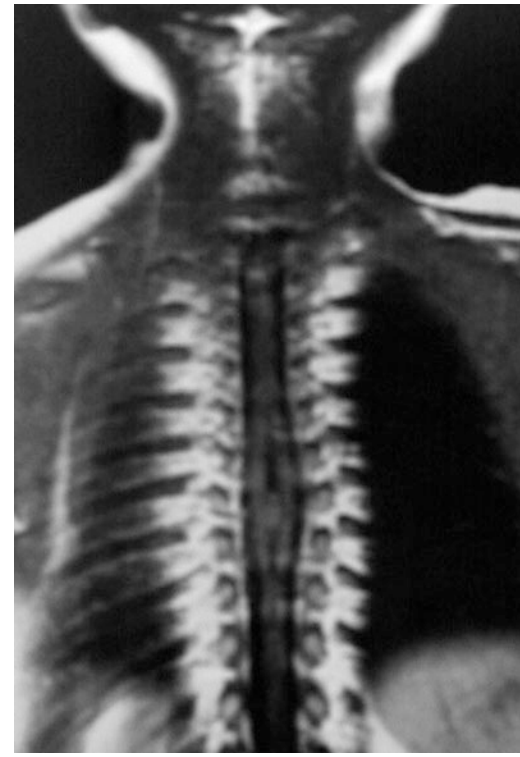

Fig. 48.17 MRI (coronal view). Dysraphic state: dyastematomyelia. Note the split cord malformation

which a complete fibrous septum transfixes the hemicords and is fixed on the ventral and dorsal surfaces of the dura, the second type in which the septum is only ventral fixing the ventromedial aspect of the hemicords to the dura, and the third type where the septum fixing the dorsal aspect of the hemicords (Pang, Neurosurgery 3:451–500, 1992).

- The aim of surgery is to sever the adhesions and remove the septum opening the dura. In the case of ventral septum, the hemicord must be gently rotated to allow the severing from the septum itself. The dura in all cases is closed performing a dural patch in Gore-Tex.
- Patients with diastematomyelia should be investigated for other spinal cord and vertebral anomalies. Filum terminale anomalies could not be detected by MRI as described by Selcuki et al. [62, 63], and failure of untethering procedure could be related to a tight filum terminale which wasn't cut at first procedure [64].
- We treated nine patients with diastematomyelia, seven females and two males, with mean age of 3 years. All but one, in whom the diagnosis was made during pregnancy, were symptomatic. Four patients presented skin stigmas. In five cases was detected by MRI another spinal cord lesion (one caudal lipoma, one dermal sinus, one meningocele manqué, two lipomas of filum terminale). In two patients the surgical procedure was as described above; in one patient the caudal lipoma was debulked, and in six cases only the section of filum terminale was performed. At last follow-up, patient showed a worsening of preoperative clinical status, and none required any other surgical procedure.

48.11.3 Dermal Sinus (Fig. 48.18)

For the dermal sinus tract, the skin is incised around the skin opening. The tract itself is dissected free of the underlined subcutaneous tissues, down to the point where it pierces and penetrates the underlying muscular fascia. Every attempt is made to preserve the tract as the laminotomy is made one or to level above and below the tract as it enters the dura. Then the dura is

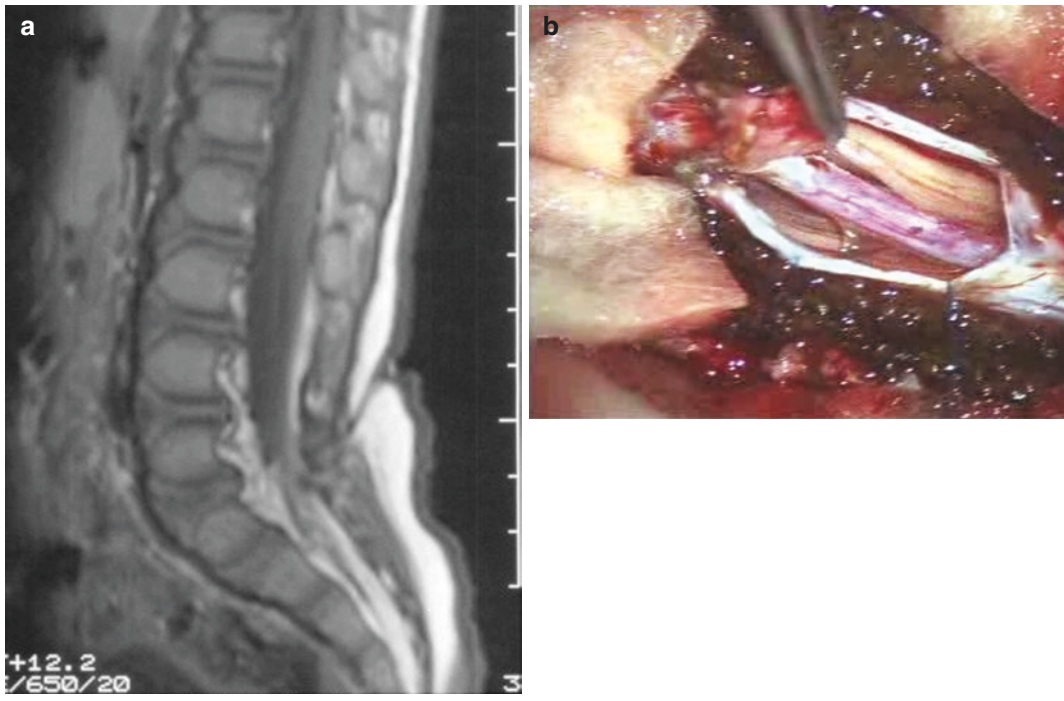

Fig. 48.18 Dysraphic state. (**a**) MRI (sagittal view). Dermal sinus and tract. (**b**) For full color version, see color plate section. Intraoperative view. Note the stalk fixing the spinal cord

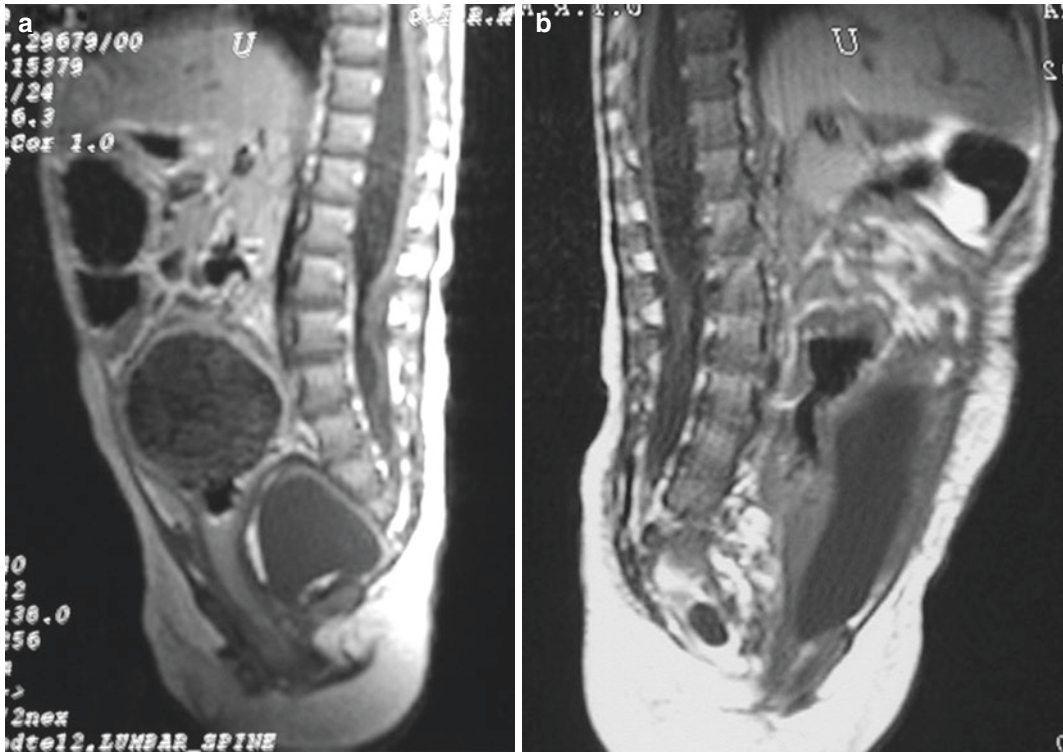

Fig. 48.19 MRI (sagittal view). Dysraphic state. (**a**) Neuroenteric cyst. (**b**) postoperative appearance with removal of the cyst by an anterior approach

opened in the cranial and caudal direction, and two incisions are made around the stock as it penetrates the dura. At this point, the stock is sectioned and removed. Associated lesions such as dermoids and lipomas should be removed with magnification under operative microscope.

Radmanesh et al. [65] described 35 cases of dermal sinus which operated and concluded that early diagnosis and complete resection of sinus is crucial to avoid development of clinical deficits.

We treated 55 patients with spinal dermal sinus, 31 females and 24 males, with mean age of 4 years. Four were previously operated in other institutions. In 43 cases skin anomalies were present; 14 patients presented neurological and/or urological impairment (25%). In six patients were present signs of infection at the time of diagnosis. In 5 cases dermal sinus was associated with fatty filum, in 18 cases with a lipoma, and in 1 case with a split cord malformation. At last follow-up, 50 patients had a stable clinical status and 4 improved. One patient who underwent a gross total removal of transitional lipoma showed a clinical deterioration (Fig. 48.19).

48.12 Fetal Surgery

Fetal surgery represents a multidisciplinary approach to some CNS malformations and tumors diagnosed in utero [66]. Nowadays, these new techniques deal essentially with prenatal hydrocephalus and myelomeningocele [67] and are feasible, thanks to a full collaboration between obstetric surgeon, anesthesiologist, and neurosurgeon [68]. Prenatal imaging by fetal magnetic resonance imaging (MRI) is mandatory to gain a complete and precise evaluation of malformations [69].

48.12.1 Prenatal Hydrocephalus

The incidence of true fetal hydrocephalus ranges from 1 to 4:1000 births [70]. In 70% of cases, other CNS anomalies are associated (holoprosencephaly, Dandy–Walker complex, spina bifida, corpus callosum agenesia, etc.), and in 7–15% of fetuses systemic malformations coexist [10]. In 3–10% of cases, different cromosomopathies have been screened, involving chromosomes 1, 6, 9, 13, 18, 21, 22, or X.

Fetal hydrocephalus may be due to ventricular obstruction (congenital tumors, intraventricular hemorrhage), CNS maldevelopment, or acquired intrauterine damage (infections, hemorrhages) [71]. The most frequent cause of isolated fetal hydrocephalus is aqueductal stenosis [70].

In his "Perspective Classification of Congenital Hydrocephalus (PCCH)," Oi divided prenatal hydrocephalus into four phases according to the gestational age of diagnosis [69]. Phase II (22–31 weeks) corresponds to the the period of "intrauterine preservation"; during this phase if the hydrocephalus becomes progressive, the damage to CNS may be irreversible after birth. Between 22 and 31 weeks of gestational age, the fetal lungs are not developed enough, requiring preservation in the uterus, and it is obvious that the earlier the onset of hydrocephalus, the greater the damage to the developing CNS; hence, the earlier the treatment, the better the results from both motor and cognitive points of view [72]. Thus phase II hydrocephalus is amenable to prenatal surgical treatment [73]. Surgery is suggested only in case of hydrocephalus not associated with other systemic and/or brain malformations because surgical and patient outcomes are better [70]. According to the guidelines of the International Fetal Surgery Registry [74], the ideal candidate to be submitted to fetal surgery should have an isolated hydrocephalus from non-X-linked aqueductal stenosis diagnosed before 28 weeks of gestation and before the cortical mantle thickness is less than 1.5 cm; the hydrocephalus must be moderate to severe and not associated to other fetal brain anomalies on MRI; its progression has been documented by periodical ultrasound tomography; infections and genetic anomalies must be ruled out by amniocentesis. Indeed, fetuses harboring hydrocephalus linked to another CNS malformation (e.g., Dandy–Walker complex, X-linked hydrocephalus, etc.) do not show improved intellectual outcome after fetal surgery [71]. In the case of polymalfomation hydrocephalus, the termination of pregnancy should be suggested to the family. If the hydrocephalus is stable or resolving, the child is delivered at term and then treated [71].

In the past, repeated cephalocentesis was performed to obtain temporary control until delivery was possible [75] even if this technique involved a higher risk of fetus infection, hemorrhage, and porencephaly [70]. Today, fetal CSF shunting surgery is preferred, aiming to obtain a temporary relief from intracranial pressure while waiting for the earliest possible delivery for definitive treatment in better general conditions [71]. Ventriculo-amniotic shunts were proposed by Clewell et al. [76]. This shunting technique is hindered by a high incidence of complications such as catheter obstruction, migration of the device into the amniotic cavity, and infection [70]. Furthermore, fetal hydrocephalus is high pressure but surrounded by a higher intrauterine pressure, which impedes its correct functioning [77]. On this pathological basis, Oi has proposed the use of a fetal ventricular-maternal peritoneal shunt [78]. Bruner has introduced a new type of ventriculo-amniotic shunting to improve the fixation [79]. As a rule, these requirements for such shunts include a safe and simple insertion technique, valid scalp fixation, and a one-way valve to prevent intraventricular reflux of amniotic fluid (Von Kochet al., 2003). As suggested by Cavalheiro et al. [70], endoscopic third ventriculostomy may be considered in case of hydrocephalus due to pure aqueductal stenosis.

48.12.2 Myelomeningocele

Much clinical and experimental evidence shows neurological deterioration in the affected fetus during pregnancy according to the "two-hit"

hypothesis, the first hit being the embryological spinal cord malformation [80]. Some reports have documented normal movement of the lower extremity in fetuses with spina bifida aperta before 17–20 weeks, followed by a fairly complete paralysis in late gestation [81]. This deterioration seems to be due to the exposure of nervous tissue to meconium and amniotic fluid [82] and to direct trauma of the placode from the uterine wall during fetal movements [83]. The amniotic fluid becomes more hypotonic thus more toxic as fetal urine output increases after kidney maturation which takes place after 22 weeks of gestation [84]. Furthermore, there is evidence that the Chiari type II anomaly is also acquired as a result of the continuous CSF leakage from the placode, which leads to progressive hindbrain prolapse [85]. These findings constitute the physiopathological background for myelomeningocele repair in utero [80].

From 1997 to 2003 more than 200 fetal surgical procedures were performed and results showed clinical improvement for the fetus but an increased risk for the mother in term of preterm labor and uterine dehiscence and an increased risk of death or preterm birth for fetus [67].

The first cases were treated by an endoscopic technique pioneered by Copeland et al. [86]. This was performed between 22 and 24 weeks of gestation using a 4 mm rigid endoscope. First, the mother underwent laparotomy under general and epidural anesthesia, with exposure of the gravid uterus. Then, three endoscopic ports were inserted into the maternal uterus (one for the endoscope and two operative channels for instruments). Because of its turbidity, amniotic fluid was tapped until the fetus was completely exposed, and the fluid was replaced by carbon dioxide to maintain ambient intrauterine pressure. After positioning of the fetus, the placode was covered with a maternal split-thickness skin graft because it was not possible to use a standard skin suture. All the reconstruction was sealed by oxidized cellulose and fibrin glue [87, 88]. The surgical results were not satisfactory because fetal morbidity and mortality and maternal morbidity were high: in the four cases treated by Tulipan and Bruner [87, 88], amnionitis, amniotic leakage, uterine dehiscence, placental abruption, preterm delivery, and one death were observed. Furthermore, this technique was only palliative and not curative, as the skin graft was short-lived [86].

Accordingly, the technique of open intrauterine repair was developed, on the basis of experimental models suggesting that most secondary damage takes place during the third trimester of pregnancy [89]. The mother underwent cesarean section under general plus epidural anesthesia at 28–30 weeks of gestation; this anesthetic combination seems to reduce the incidence of unwanted uterine contractions and allows sedation of the fetus too [90]. After the uterus is exteriorized through a Pfannenstiel incision and the fetus and placenta are localized by ultrasound scan, the Tulipan-Bruner trocar is inserted into the uterus [87, 88] to tap most of amniotic fluid which is conserved in warm syringes. A 5 cm incision is made in the uterus and the fetus positioned with the placode in the middle of hysterotomy. The myelomeningocele is then closed using the standard neurosurgical technique with nonresorbable Nylon 7/0 sutures for the placode tubulization and Nylon 5/0 for the skin [90]. During the whole procedure, the fetal heartbeat is monitored by ultrasound and continuous electronic fetal monitoring. The uterus is closed in layers with adsorbable sutures, and the amniotic fluid is replaced, sometimes with saline solution until its turgor becomes similar to the preoperative state, in order to reduce the risk of uterine contractions [90]. The wall of the abdomen is closed in a standard fashion, and the fetus continues to be monitored. The mother is administered tocolytic agents (indomethacin, terbutaline). In the postoperative period, both the mother and the fetus are periodically monitored until delivery by cesarean section, which is usually planned at 34–35 weeks of gestation; delivery is anticipated only in case of uncontrolled amniotic leak or premature contractions, trying to balance, in all cases, the risk of dehiscence of the hysterotomy and iatrogenic fetal immaturity [90]. In the series of 50 cases operated on by Tulipan and co-workers, surgical morbidity was low and included uterine contractions, placental abruption, and amniotic leakage;

uterine dehiscence with prolapse of the fetus into the peritoneal cavity was the most serious. In only one case did premature delivery occur. Surgical mortality in utero involved only one fetus [90] even if, in other series, there is a perinatal mortality of about 6% due to the extreme prematurity [91].

Unwanted side effects of tocolytic therapy are possible in the mother, such as tachycardia, fever, dyspnea, and pulmonary edema [90]. The newborn may show local dehiscence at the site of placode repair, which is usually managed conservatively [90].

The most encouraging surgical results are the lower incidence of Chiari II and of hydrocephalus [90]. Chiari type II anomaly after fetal surgery accounts for only 16% rather than the described incidence of 95% [92–94]. Other studies have shown that hindbrain prolapse is reversed rather than prevented by fetal surgery: postoperative fetal MRI at 3 weeks have well documented the ascent of these structures [95].

Resolution of Chiari II anomaly reduces the incidence of hydrocephalus to 42.7 from 90% [67] thanks to restoration of CSF pathway at the level of the fourth ventricle outlets [96].

Despite a number of experimental and clinical studies to the contrary [80], Tulipan's series did not show any neurological improvement, as the neonates showed neurological impairment exactly corresponding to the level of the defect [90].

In some cases, a secondary, late tethering of the spinal cord has been described because of epidermoid inclusion cysts, which required further treatment [97].

A multicenter randomized controlled trial, the Management of Myelomeningocele Study (MOMS), was conducted from 2003 to 2010 by three different institutions (Children's Hospital of Philadelphia, Vanderbilt Medical University, UCLA) [98]. The selection criteria were the following: singleton pregnancy, evidence of hindbrain hernation, a gestational age of 19.0–25.9 weeks at randomization; level of the defect between T1 and S1, a normal katiotype, US resindency, maternal age of at least 18 years. Were excluded fetus with anomalies unrelated to myelomeningocele, risk of preterm birth, mothers with a body mass index over 35 and contraindication to surgery (i.e. previous hysterectomy). MOMS trial included 183 women and was stopped earlier than planned for the evidence of better outcome for the infants who underwent fetal repair before 26 weeks of gestation. Ventricular shunt placement was less in prenatal group than in postnatal (40% vs. 82%) at 12 months and these infants had a better motor and mental outcome at 30 months of age. An improvement was present also in hindbrain herniation by 12 months and ambulation by 30 months.

Tulipan et al. [99] update the 1 year outcomes for the complete trial and confirmed the benefit of prenatal surgery regard to shunting (44% shunting in prenatal group versus 84% in postnatal group). They identified in the ventricular size a preoperative predictor of shunt-dependent hydrocephalus: there were no benefits related to shunting in fetuses whose ventricles were 15 mm or larger at screening.

In the last years endoscopic third ventriculostomy (ETV) as alternative to shunt has been proposed even in patients who underwent fetal surgical repair. Elbabaa et al. [1] described a series of 60 fetal myelomengocele repairs and analyze factors related to failure of ETV. Successful procedures were related to ventricular size less than 4 mm in utero and ventricular size after surgical repair less than 15 mm, while failure was related to age less than 6 months and repair after 25 week of gestational age.

Brock et al. [15] evaluated the urologic outcome in 56 patients who underwent prenatal surgery and 59 treated postnatal by 30 months of age. They didn't find a significant difference between the two groups (38% rates of clean intermittent catheterization in prenatal group vs. 51% in postnatal group). However they found less bladder trabeculation and reduction of an open bladder neck which significance is unclear.

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Central Nervous System Congenital Tumors

49

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49.1 Introduction

Central nervous system (CNS) tumors are the most common solid tumors in childhood [1]. After the age of 15 years, their incidence in the general population gradually decreases, and they are one of the less common types of tumors in the elderly [1].

A thorough analysis of the epidemiology of CNS tumors reveals that the age differences are not only with regard to the absolute number, and therefore their incidence, but there also are important implications for histology and overall survival [1]. In children, pilocytic astrocytomas, germ cell tumors, and embryonal tumors are much more common than in adulthood, whereas exactly the opposite is true as far as pituitary adenomas, meningiomas, and spinal and cranial nerves tumors are concerned [1].

Those kinds of observations and more are possible, thanks to international and national registries, which collect huge amounts of data. Among them, we refer to the Central Brain Tumor Registry of the United States (CBTRUS), to the International Association of Cancer Registries (IARC—www.iacr.com.fr), and to the data obtained through the AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica—Italian Association for Pediatric Hematology and Oncology). Those data, especially if collected from different countries, are difficult to analyze, and the difficulties increase if we try to assess data about a specific group of CNS tumors in childhood compared with congenital ones. This is because of their rarity and their definition itself. Congenital CNS tumors were first considered as tumors diagnosed during the first 60 days of life of a child [2, 3]. Later, congenital tumors were defined as definitely congenital if already evident at birth; probably congenital if the diagnosis was made within the first week of life; and possibly congenital if the diagnosis was made within the first 4 weeks of life [4]. However, later in the medical literature, congenital tumors of the

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CNS were extended again and were considered as tumors diagnosed in infants younger than 2 months of age [5], and in different series and many case reports, tumors diagnosed up to the first 2 years of life are discussed together with congenital tumors [6–8]. This is because the diagnosis, the clinical presentation, the problems in managing these patients, the surgical complications, and the limitations in oncological treatments are similar. Moreover, we have to consider that the neurons and white matter are not completely mature in infants. Therefore, the clinical presentation of a brain tumor can be delayed because infants are not able to complain or to present specific neurological signs and/or symptoms and the diagnosis is frequently reached only when increased intracranial symptoms appear, often associated with huge tumors whose growth period is unknown.

It is evident that a definition of congenital CNS tumors is complex and it is even more complex if we consider that certain types of tumors, such as teratomas or craniopharyngiomas, are definitely considered as having their origin in the uterus, but their diagnosis, especially for craniopharyngiomas, is only rarely obtained in the perinatal period [9].

The incidence of congenital CNS tumors is difficult to define. If we strictly stay with the definition of congenital CNS tumors as those diagnosed within the first 4 weeks after birth, a reasonable evaluation is probably 0.5–1.5% of all CNS tumors in children [2, 5, 10–15]. If we look at data from the cancer registries, we cannot obtain data referred only to this small group, but we can observe that the incidence of CNS tumors tends to increase after 1 year of age and then it reduces after the teenage (www.iacr.com.fr) [1].

The data from the IACR (www.iacr.com.fr) demonstrate that the incidence of CNS tumors in children younger than 1 year of age in Western countries (the United States and Europe) is around 30–40 cases every million children younger than 1 year of age every year. But if we analyze the same data from the same registries for different countries and continents, the results can be very different. In South America, for example, the incidence can be as low as 1.8 cases in Honduras, but it can then go up as high as 35.5 cases in Chile. Important differences can also be observed in national registries where data are collected distinguishing between different areas, or different population races, or different time frames. New Zealand has an overall annual incidence of 22.9 cases, but if only the data on Maori populations are taken into account, the same value drops to 6.2 new cases for one million children younger than 1 year of age every year. In France, in the regions of Loire-Atlantique and Vendée, the incidence expressed as before is 14.7 new cases every year, whereas in the Gironde, it rises to 73 new cases/year. In Italy, in the region of Piedmont, between 1990 and 1999, 6 new cases as an absolute number were diagnosed, whereas in the same region, there were 23 between 2000 and 2011. In Europe, the median value is considered to be between 30 and 40 new cases a year, but in Norway this value is 79.4 cases vs 11.8 cases in Malta.

Those data taken together are not enough to draw conclusions, but it is possible to speculate that there might be multiple protective and risk factors as far as the risk of developing a congenital CNS tumor is concerned. It appears evident that those factors can be genetical, environmental, and racial.

49.2 Risk Factors

The etiology of CNS tumors is still largely unknown. Many genetic syndromes are associated with the risk of development of CNS tumors. It is grossly estimated that about 5% of these tumors diagnosed in childhood are related to known genetic syndromes [16]. Among them, we can recognize different diseases, first of all the so-called neurophakomatoses.

The tuberous sclerosis complex (TCS) is a dominantly inherited disorder that consists in the mutation of either TCS1 or TCS2 with consequent abnormal differentiation and proliferation of cells, especially in the brain, skin, kidneys, and heart due to an abnormal function of the proteins hamartin and tuberin. Up to 14% of patients in childhood develop subependymal giant cell

astrocytomas (SEGAs), which grow typically in the anterior portion of the lateral ventricles and can produce an obstruction to cerebrospinal fluid (CSF) flow with consequent hydrocephalus and increased intracranial pressure (Fig. 49.1) [17].

Neurofibromatosis (NF) type 1 and type 2 are dominantly inherited disorders due to mutation on chromosomes 17q11.2 and 22q11.2 respectively. Patients affected by NF1 are at a higher risk, in up to 15% of the cases [18], of developing tumoral diseases arising from astrocytes and presenting as pilocytic astrocytomas, especially along the optic pathway or in the brainstem. Plexiform neurofibromas are less common in childhood.

Even rarer in pediatric patients is Von Hippel-Lindau disease, a dominantly inherited disease associated with the risk of developing hemangioblastomas. The most common location is cerebellar, but they can develop along the axis, and it is not uncommon to have multiple lesions [19].

Many other genetic syndromes are associated with a higher risk of developing CNS tumors. We report them in Table 49.1.

In addition to genetic syndromes known to be associated with the risk of developing CNS tumors, many studies were set up to try to understand if exposure to specific factors increases the risk of developing CNS tumors and if genetic mutations not included in known genetic syndromes can play a role in the same direction. When it comes to analyzing this type of parameter in patients affected by a congenital tumor, the studies focus on the exposure within a relatively short time span, which starts the conception and ends with the diagnosis of the tumor in the offspring. Nevertheless, such an analysis is complicated, most are retrospective studies, and are based on interviews. Therefore, they are affected by many biases.

Studies on possible genetic mutation, outside known genetic syndromes, developed during pregnancy or shortly after, have their roots in known cancer risk factors that induce DNA changes and that can produce an alteration in the normal fetal development if the mother is exposed to them, resulting in the so-called congenital

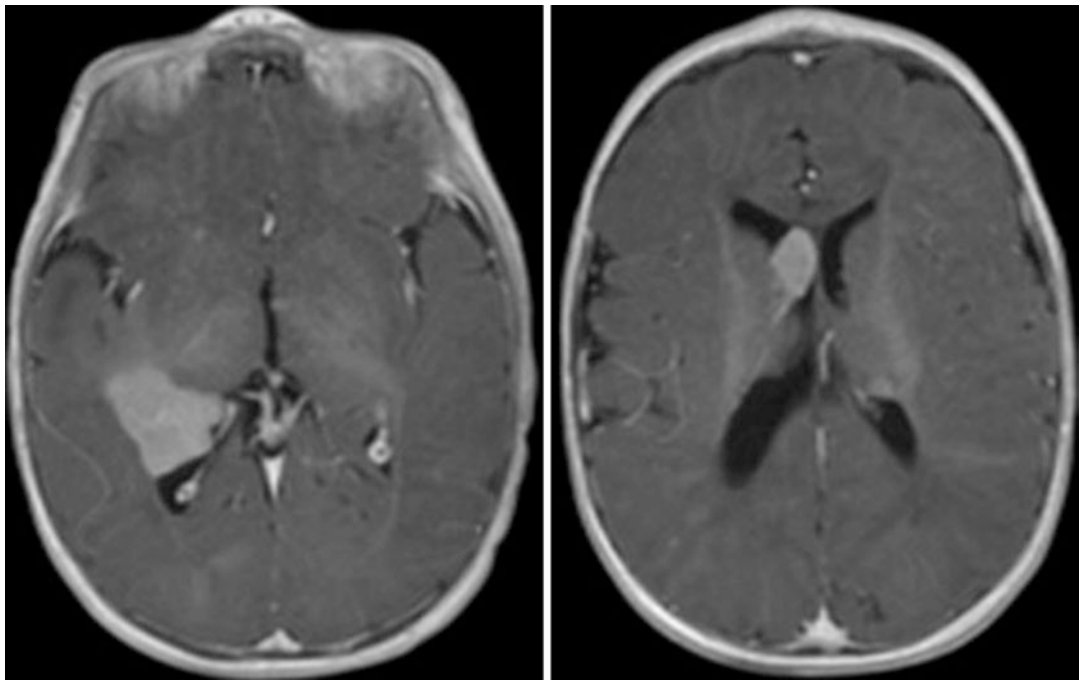


Fig. 49.1 F.B., 5 months old, boy, TSC2 mutation. This patient presents two subependymal giant cell astrocytomas (SEGAs), one in the anterior part of the right lateral ventricle, and one, less common, in the occipital horn of the right lateral ventricle

Table 49.1 The most common known genetic syndromes associated with CNS tumors

Syndrome	Gene	Chromosome	Nervous system	Skin	Other tissues
Neurofibromatosis type 1	NF-1	17q11	Neurofibroma, malignant peripheral nerve sheath tumor, optic nerve glioma, astrocytoma	Cafè-au-lait spots, axillary freckling	Iris hamartomas, osseous lesion, pheochromocytoma, leukemia
Neurofibromatosis type 2	NF-2	22q12	Bilateral vestibular schwannoma, peripheral schwannoma, meningiomas, meningioangiomatosis, spinal ependymoma, astrocytoma, glial hamartias, cerebral calcification	–	Poster lens opacities, retinal hamartoma
Von Hippel-Lindau	VHL	3p25	Hemangioblastoma	–	Retinal hemangioblastoma, renal cell carcinoma, pheochromocytoma, visceral cystic
Tuberous sclerosis complex	TSC1 TSC2	9p34 16p13	Subependymal giant cell astrocytoma, cortical dysplasia	Cutaneous angiofibroma ("adenoma sebaceum"), peau chagrin, subungual fibroma	Cardiac rhabdomyoma, adenomatous polyps of the duodenum and the small intestine, cyst of the lung and kidney, lymphangioleiomyomatosis, renal angiomyolipoma
Li-Fraumeni	TP53	17p13	Astrocytomas, primitive neuroectodermal tumors	–	Breast carcinoma, bone and soft-tissue sarcoma, adrenocortical carcinoma, leukemia
Cowden	PTEN	10q23	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos), megalencephaly	Multiple trichilemmoma, fibroma	Hamartomatous polyps of the colon, thyroid neoplasms, breast carcinoma
Turcot	APC hMLH1 hPSM2	5q21 3p21 7p22	Medulloblastoma Glioblastoma	Cafè-au-lait spots	Colorectal polyps Colorectal polyps
Nevoid basal cell carcinoma syndrome (Gorlin)	PTCH	9q31	Medulloblastoma	Multiple basal cell carcinomas, palmar and plantar pits	Jaw cysts, ovarian fibroma, skeletal abnormalities
Rhabdoid tumor predisposition syndrome	INI1	22q11.2	Atypical teratoid/rhabdoid tumor	–	Renal and extrarenal malignant rhabdoid tumors

anomalies. The strength of this observation is increased by a number of studies reporting that children with tumors are at a higher risk of having associated congenital malformations compared with the general pediatric population not affected by tumors and compared with their siblings [20, 21]. It is feasible to admit that a factor that exerts a teratogenic effect if active during pregnancy might induce genetic mutations responsible for malformations or tumors, or even both in the same patient. According to Mann, the excessive number of malformations found in children with cancer may indicate that in up to 1 in 20 cases, one or more antenatal events may lead to malformation and to a tumor [20].

It is commonly accepted that exposure to ionizing radiation can cause tumors, including CNS tumors and congenital CNS tumors if the exposure happens during fetal life [22, 23]. It is estimated that if embryos or fetuses are exposed to a dose of ionizing radiation of 0.2 Gy, the risk for malformation doubles, as has been extrapolated from studies on rodents [23], even if a dose of as little as 10 mSv (equivalent to 1 cGy = 0.01 Gy) to the fetus can increase the risk of childhood cancer [24]. The general risk for a child exposed during his development in the uterus to ionizing radiation is estimated to be 0.06% for every cGy of radiation [25]. Studies on the Japanese population exposed to that factor reveal that exposure in the uterus to ionizing radiation seems to increase the risk of developing solid tumors more than if the exposure happens to an already born child, who instead is at a higher risk of developing blood cancer [24].

Various substances and general conditions have been studied as possible causes of solid tumors in children born from exposed parents. High birth weight (>4 kg) was analyzed as a possible factor associated with the risk of CNS cancer in children, but results are not the same in different studies, as some authors report an increase in the risk, especially for astrocytomas and embryonal tumors [26, 27], whereas other studies report that it is not [28].

A high level of nitrite intake by the mother during pregnancy with the diet (cured meat, water) has been associated with a higher risk of brain tumor to the child [29, 30], but again different studies report that there is no particular association [30–32]. The Parental exposure to electric and magnetic fields during the perinatal period has been considered as a possible risk for brain tumors in the offspring [33], but it is still a controversial issue and under investigation.

A similar conclusion can be reached for parental occupational exposure or for the exposure to different possible environmental factors [34–37].

On the other hand, when it comes to considering protective factors for CNS tumors, a protective effect has been associated with the intake of vegetables, fruit, folate, and vitamin C in early pregnancy with regard to the risk of PNET in the offspring [32].

49.3 Clinical Considerations

Even if the patients included are not only children younger than 2 months but also those up to 12 months, congenital CNS tumors have some peculiarities that increase their aggressivity, although they may be benign from the histological point of view. Their diagnosis and treatment can therefore be quite difficult.

A first consideration is that when it comes to CNS tumors, and not only congenital CNS tumors, the term “benign” is relative, because it is not always possible to resect them completely depending on their location. Moreover, in the specific case of the young patients we are talking about, there are many problems that make this state more complex.

The clinical presentation and diagnosis of congenital CNS tumors happen frequently because of signs and symptoms of increased intracranial pressure [2, 6, 7] instead of neurological signs and/or symptoms. The reason is probably related to at least two mechanisms that grant to infants the ability to offset the growth of the tumor without clinical evidence of it. The first is the incomplete maturity of neurons and white matter in infants and toddlers [8, 38]. As a consequence, it may be that a tumor growing when the specialized activity of groups of neurons is not yet defined might result in a reorganization of the

activities controlled by those groups of neurons themselves without evident neurological sequelae. Specific neurological signs/symptoms do not appear until the mass reaches a volume that produces a significant neuronal loss. The second mechanism is related to the plasticity of the skull and to its opened sutures and fontanelles. The skull can grow and deform to accept the growing tumor (Fig. 49.2).

The most common clinical presentation according to the literature is intracranial hypertension, such as macrocrania, bulging fontanelle, irritability, and failure to thrive, which account for 42–65% of the reasons to seek for medical advice and consequent diagnosis [6, 21, 38]. Far less common are seizures, cranial nerve palsy, and focal neurology [6, 7, 21, 38]. In our series of 94 patients with a CNS tumor younger than 1 year at diagnosis retrospectively reviewed, the clinical presentation was available for 86 patients, and it resulted in 43 cases (50%) presenting with signs and/or symptoms related to intracranial hypertension.

As observed before, the plasticity of the skull on the one hand and the neuronal plasticity and immaturity on the other result in the ability of infants to offset the growth of the tumor for much longer than older children and adults. The consequences are not only related to a "late" diagnosis but open to more possible considerations. It is not rare that the tumor at diagnosis has already reached considerable dimensions. They are often classified as giant tumors, or they involve more than one lobe at diagnosis (Figs. 49.3, 49.4). Asai et al. [39] reported in their series a mean diameter of tumors at diagnosis of 4.6 cm. Buetow et al. [2] described that 18 cases out of 45 congenital tumors at diagnosis had a volume of more than one third of the whole cerebral volume. A direct consequence is that such huge tumors cannot always be completely surgically resected and that at presentation the patient can have a sudden deterioration of their clinical general and neurological status. A certain number of patients are admitted with a compromised Glasgow Coma Scale. In the series by Oi et al. [21], 66 patients

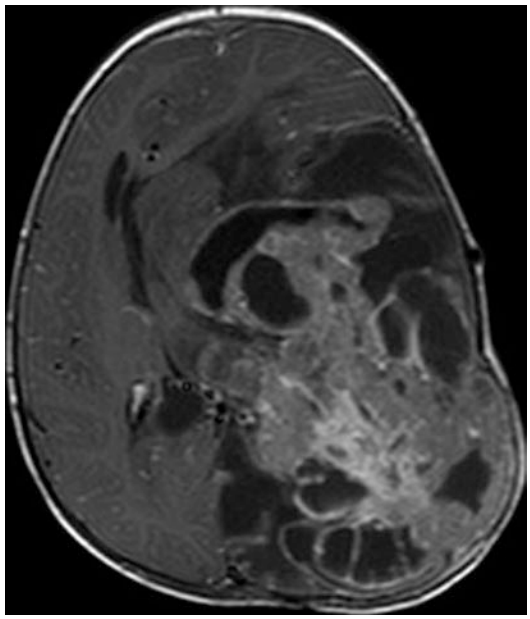


Fig. 49.2 N.R., 8 months old, girl, choroid plexus carcinoma. The tumor grew from the lateral ventricle and completely altered the normal brain. During its growth the tumor induced macrocrania and deformed and thinned the skull

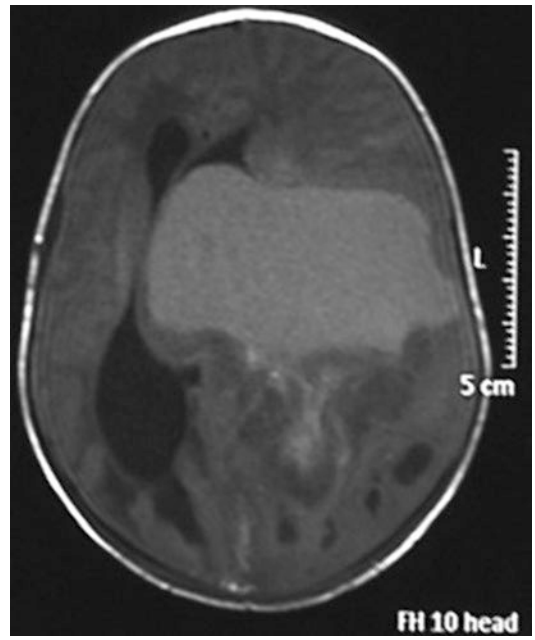


Fig. 49.3 L.L., 1-month-old girl, presenting with macrocrania and increasing head circumference

(21.5%) presented with disturbed consciousness; in the series by Di Rocco et al. [38], impairment of consciousness was reported for 4% of the patients; in the series by Buetow et al. [2], 1 patient out of 45 was lethargic at presentation; Lang et al. [7] described 1 patient out of 16 as being lethargic at presentation. In our series, 7 patients (8.2%) out of 86 presented with a deterioration in the level of consciousness.

Another consideration is that as a consequence of skull plasticity and neural immaturity/plasticity, tumors could develop during the first weeks of life but become clinically evident only later. This observation challenges the rigid definition of Solitaire and Krigman [4], which takes into consideration only congenital tumors diagnosed within the first 4 weeks of life.

The location of CNS tumors in children younger than 12 months differs significantly when compared with the general epidemiology of brain tumors in children. These patients have supratentorial tumors more frequently than infratentorial. A supratentorial location is observed in 60–70% of the cases [2, 7, 21, 38]. In our series, 56 patients (59.5%) out of 94 had a supratentorial tumor.

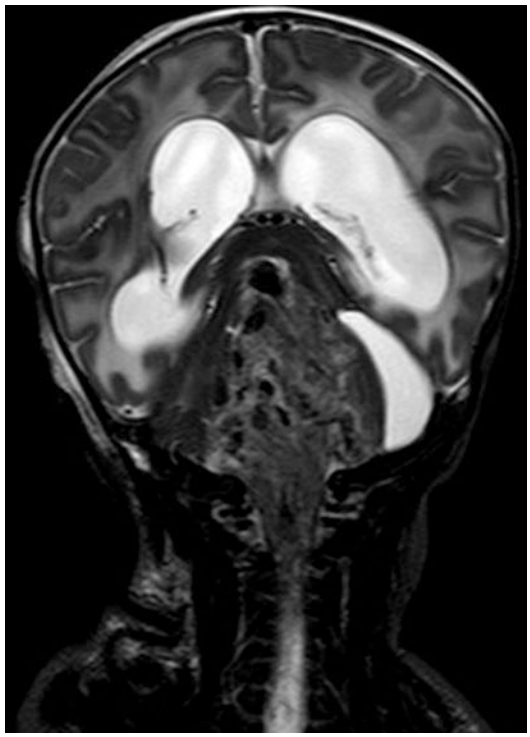
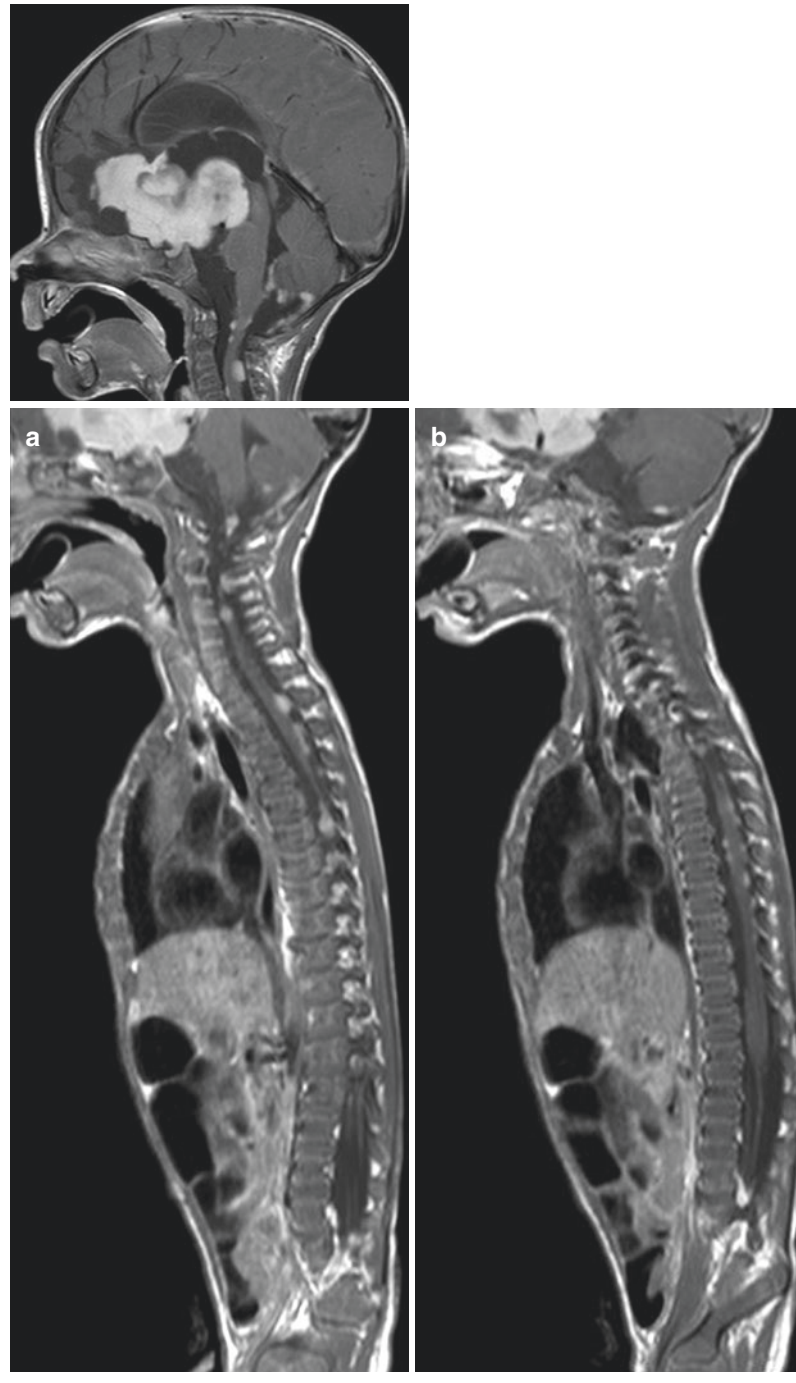


Fig. 49.4 D.P.C., 1-month-old boy, presenting to the emergency department because of a reduced level of consciousness

Hydrocephalus is a frequent problem in these patients, both at diagnosis and later on during their management. It is commonly related to the obstruction of the CFS flow produced by the tumor and can be complicated by cystic components (Figs. 49.5, 49.6, and 49.7). Many patients require more surgical procedures dedicated to the treatment of the hydrocephalus. Buetow et al. describe 21 patients out of 45 at diagnosis had already presented with hydrocephalus [2]. In our series, hydrocephalus was already present at diagnosis in 21 patients (24.4%) out of 86, and in 39 patients (41.4%) out of 94, the first surgical treatment offered consisted of a diversion procedure on CSF or in the cystic components of the tumor.

The increased use of ultrasound and MRI during pregnancy has of course given rise to a number of cases of CNS tumors diagnosed during fetal life [9, 14, 40–45]. Most of the reports discuss lesions observed late during pregnancy [9, 41, 43, 44]. In our series, 3 patients (3.5%) out of 86 received a diagnosis in utero (Fig. 49.8). Many reports describe diagnosis in utero for teratoma [40, 44]. It is less common a diagnosis in utero than for other histologies, such as the craniopharyngioma described by Kageji et al. [9]. In our series, the three cases diagnosed using fetal scans were PNET in two cases and glioneuronal tumor in one.

The increased use of fetal ultrasound can otherwise increase the discussion on how and when congenital tumors develop. In our series, we observed a case of a 2-month-old girl admitted for macrocrania who had undergone serial fetal ultrasound before birth because the mother was followed up at the high-risk pregnancy service owing to a previous miscarriage related to a confirmed genetical disease. The last fetal ultrasound was performed 10 days before birth, and the report described all the normal brain fetal morphology with no evidence of any abnormalities: normal midline structures, normal brain sonography, and



Figs. 49.5 and 49.6 **a**, **b** E.A., 7-month-old boy, presenting with macrocrania and Russell syndrome. On MRI at diagnosis he had an optic chiasmatic tumor with hydrocephalus and multiple spinal metastases. Histology: high-grade glioma

normal anthropometric parameters. The patient was admitted as an emergency and sent by the pediatrician because of macrocrania (increased head circumference of 6 cm in 1 month) and a bulging fontanelle. On admission, the patient presented the lesion shown in Fig. 49.9. She underwent an emergency procedure of CSF diversion but had a respiratory arrest 6 h after admission into hospital. The histology obtained by a biopsy revealed a glioblastoma multiforme.

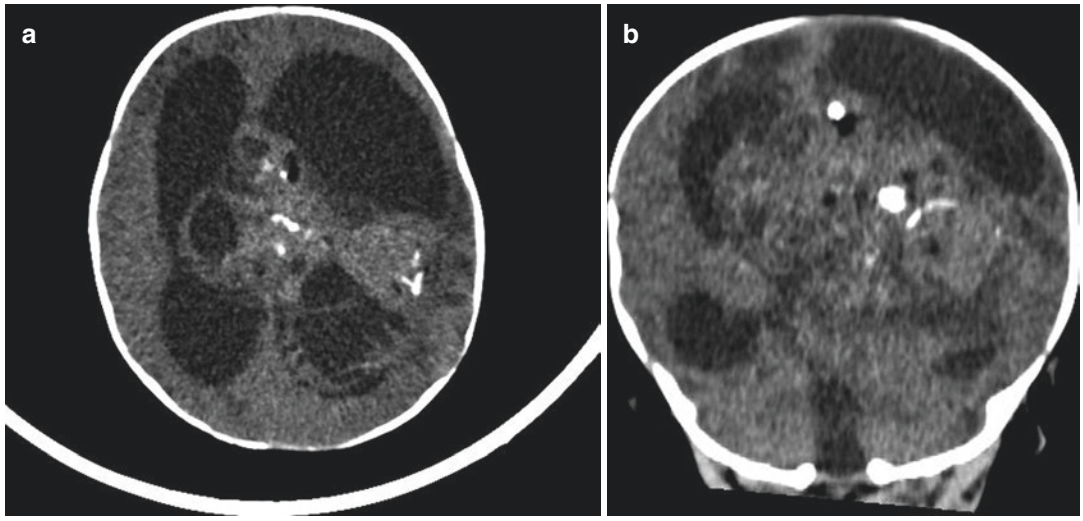


Fig. 49.7 G.F., 2-month-old boy, presenting with macrocrania. CT at presentation discovered a giant supratentorial tumor with solid and cystic components and associated hydrocephalus. Histology: immature teratoma

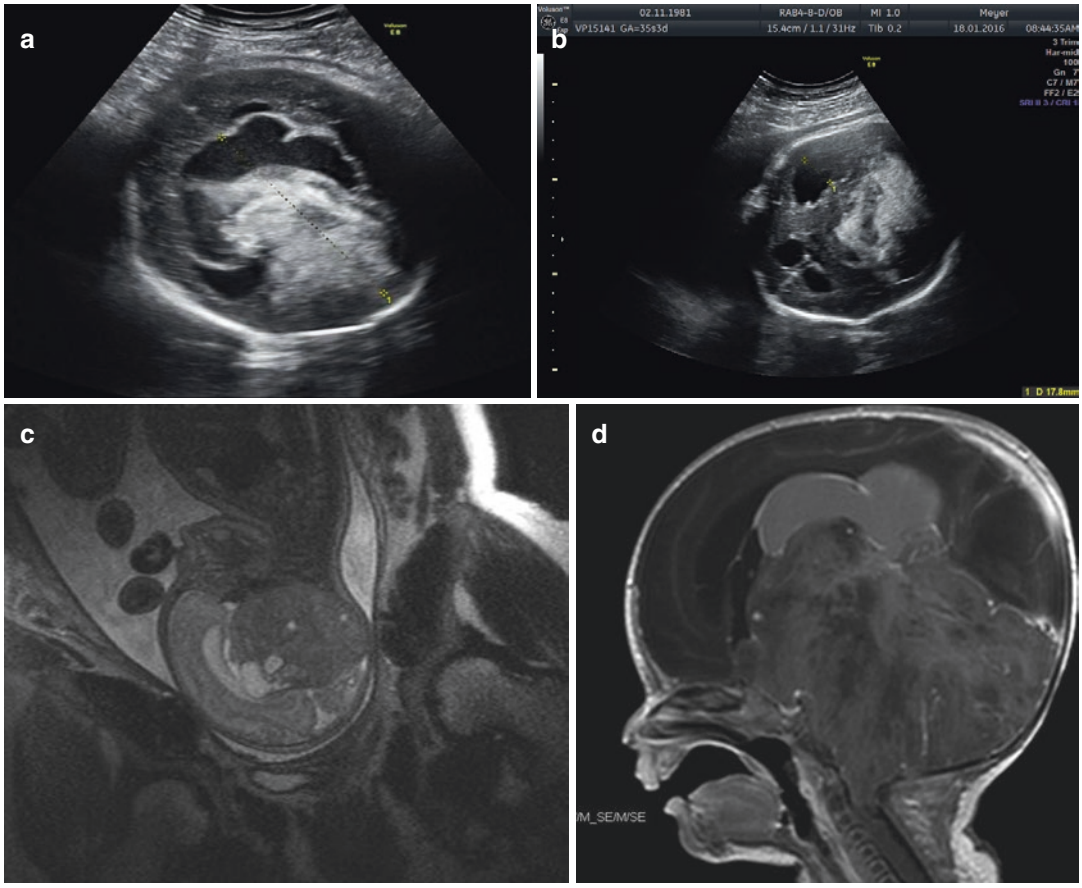


Fig. 49.8 (**a**, **b**) M.F.G., ultrasound at 35 weeks' gestation revealed a huge posterior fossa tumor with associated obstructive hydrocephalus (we thank Dr. Roberto Biagiotti for the ultrasound images). (**c**) Fetal MRI. (**d**) MRI at birth. Histology: primitive neuroectodermal tumor

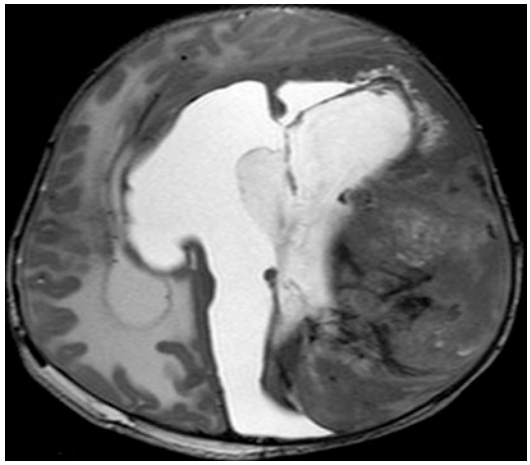


Fig. 49.9 A.T., 2-month-old baby girl. Histology: glioblastoma multiforme; Mib-1: 85%

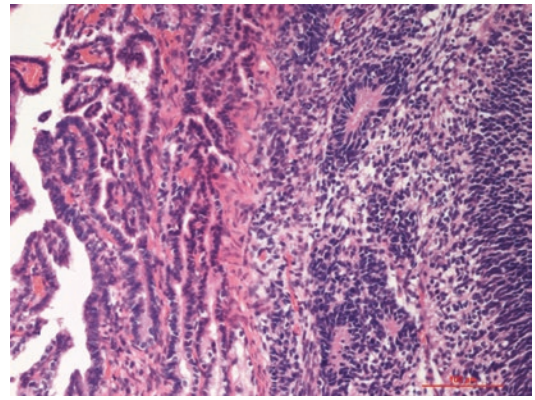


Fig. 49.10 Immature teratoma. Mature (choroid plexus is appreciable on the left) and immature (neural tube-like structures are appreciable on the right) tissues, hematoxylin and eosin (H&E), original magnification ×20

49.4 Histology

The first congenital intracranial tumor was reported by Holt in 1917, who described a gliosarcoma in a 2-week-old infant [46]. Successive reports demonstrated that there is a large variety of histopathological types of congenital brain tumors. The proportion of each histotype varies among different series. Indeed, the literature surrounding this population is mostly composed of case reports or small case series, and only a few recent papers provided a literature review. Larouche et al. published a literature review drawing many series together, including more than 1200 patients, and confirmed the marked histological heterogeneity [47].

The histotypes encountered during the intrauterine life and within the first year of age are remarkably different from those occurring in older children and adults. Teratoma is the most common perinatal congenital brain tumor, representing about 30% of all CNS tumors detected during the fetal and neonatal periods [48]. Other tumor subtypes are astrocytomas (low-grade astrocytoma and high-grade astrocytoma), embryonal tumors, and choroid plexus tumors. Less common histologies include glioneuronal tumors, craniopharyngiomas, and ependymomas [49].

49.4.1 Teratoma

Teratoma is the most common congenital CNS tumor. It typically occurs along the midline of the body from the coccyx, which is the most common site, to the pineal gland. The head and neck are the second most frequent sites. Intracranial lesions typically arise in the pineal region. Teratomas are germ cell tumors composed of tissues derived from the three germ cell layers (ectoderm, endoderm, and mesoderm). Ectodermal components, especially neural tissue, are the dominant feature of fetal cases [49]. Teratomas are histologically classified as mature or immature. Mature teratomas consist exclusively of fully differentiated tissues, i.e., skin and skin appendage, adipose tissue, neural tissue, muscle, cartilage, bone, or glands; whereas immature teratomas also contain incompletely differentiated components similar to fetal tissues. Frequently, immature components are primitive neuroectodermal structures resembling the neural tube (Fig. 49.10) [50].

49.4.2 Astrocytomas

Astrocytomas follow teratomas in frequency, accounting for 20–45% of all congenital brain tumors [51]. They can present various degrees of

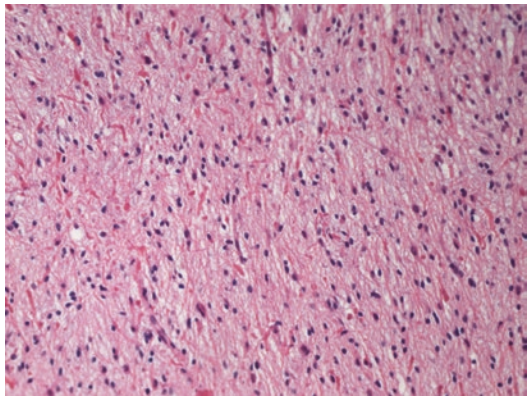


Fig. 49.11 Pilocytic astrocytomas. Small bipolar cells and Rosenthal fibers (elongated eosinophilic structures), H&E, original magnification ×20

differentiation and can range from low-grade tumors to high-grade tumors.

Low-grade gliomas are mostly represented by pilocytic astrocytomas and less frequently by SEGAs, both grade I tumors according to the World Health Organization (WHO) [50]. Commonly, they are well circumscribed and have only a narrow margin of infiltration into the surrounding tissues.

Pilocytic astrocytomas may be sporadic or occur in patients carrying the NF1 mutation. Most pilocytic astrocytomas in NF1 are localized within the optic pathway, and a bilateral growth is characteristic [52]. Pilocytic astrocytomas often have a microscopically biphasic pattern, with compact areas composed of small bipolar and stellate-shaped cells and loose-textured areas composed of multipolar cells with microcysts. Rosenthal fibers and eosinophilic granular bodies are commonly observed, particularly in compact areas (Fig. 49.11). Mitoses are uncommon, but sometimes pilocytic astrocytomas in early childhood may exhibit morphologically aggressive features and be misdiagnosed as high-grade tumors [53, 54].

A variant of pilocytic astrocytoma named pilomyxoid astrocytoma has been described. Its most typical morphological characteristic is an angiocentric astrocytic proliferation embedded in a myxoid background. The first reports indicated that pilomyxoid astrocytomas typically affect infants and young children, arises in the hypothalamic/chiasmatic region, and has a less favorable prognosis [55]. Nevertheless, a number of subsequent studies provided evidence that these tumors may occur later in life, in regions other than the hypothalamic/chiasmatic area, and have a benign behavior [56].

A few cases of SEGAs have been reported in the perinatal period either as sporadic tumors or associated with the tuberous sclerosis complex (TSC) [57, 58]. SEGAs are benign, slowly growing tumors typically arising in the wall of the lateral ventricles. The histogenesis of SEGA is controversial. Older studies suggested an astrocytic nature, whereas a number of recent reports demonstrated a mixed glioneuronal nature. Indeed, SEGAs consist of three types of cells, which can be present in different proportions: small/spindle cells, gemistocytic-like cells, and ganglion-like cells (Fig. 49.12). These three types of cells may show at an immunohistochemical and ultrastructural level glial and/or neuronal features (Fig. 49.12) [59]. Nuclear pleomorphism and increased mitotic activity may be observed in some rare cases [50].

High-grade astrocytomas, anaplastic astrocytomas, and glioblastomas are more common in the fetus and in neonates than in older children [51]. Anaplastic astrocytomas are WHO grade III diffusely infiltrating lesions with nuclear atypia, increased cellularity, and greater proliferative activity. In the current WHO classification of CNS tumors, anaplastic astrocytomas are further subdivided according to the presence or absence of isocytrate dehydrogenase (IDH) 1 or 2 gene mutation: anaplastic astrocytoma IDH-mutant (better prognosis) and anaplastic astrocytoma IDH-wildtype (poorer prognosis) [50]. Pediatric astrocytomas, either low grade or high grade, in most cases, do not harbor these mutations [60]. However, to the best of our knowledge, no published information about the IDH gene mutations in congenital anaplastic astrocytoma have been reported in the English medical literature to date.

Glioblastomas (WHO grade IV tumors) represent about half of all perinatal astrocytomas in Isaacs' series [45]. They are microscopically characterized by hypercellularity, marked

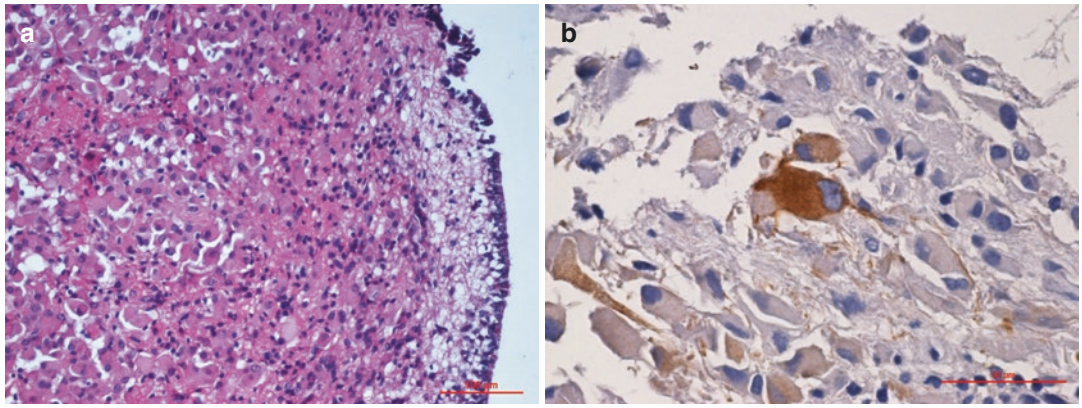


Fig. 49.12 Subependymal giant cell astrocytoma. (**a**) Subependymal proliferation (the thin ependymal lining is appreciable on the right) of predominant gemistocytic-like cells, H&E, original magnification ×20. (**b**) Ganglion-like cells as demonstrated by immunohistochemistry, neurofilaments, original magnification ×60

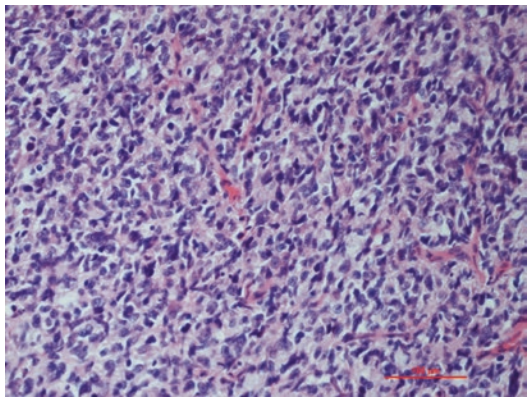


Fig. 49.13 Glioblastoma. Hypercellularity and pleomorphism. H&E, original magnification ×20

pleomorphism, intense mitotic activity, microvascular proliferation, and palisading necrosis [50] (Fig. 49.13). Fetal and neonatal glioblastomas are genetically different from their adult counterparts and show a low frequency of known genetic defects [61].

A new entity of astrocytic tumors called diffuse midline glioma H3 K27M-mutant was introduced in the latest edition of the WHO classification [50]. Diffuse midline glioma H3 K27M-mutant is an infiltrative midline high-grade (WHO IV) brain tumor that predominates in children. This kind of tumor has a poor prognosis despite current therapies (2-year survival rate of <10%) [50]. To the best of our knowledge, no congenital cases have been yet described in the English-language medical literature.

49.4.3 Choroid Plexus Tumors

Choroid plexus tumors comprise papillomas (WHO grade I), atypical papillomas (WHO grade II), and carcinomas (WHO grade III) [50]. They originate from the choroid plexus epithelium and consequently are mostly located within the ventricular system, in particular, the lateral ventricles, where the normal choroid plexus is. Choroid plexus tumors occur sporadically or in rare cases in association with familiar syndromes, in particular, the Aicardi and Li-Fraumeni syndromes [50]. Choroid plexus papillomas account for 2–4% of all brain tumors that occur in children aged <15 years and for 10–20% of those occurring in the first year of life [62]. Those tumors are benign and histologically characterized by a papillary pattern of growth in a single layer of uniform cuboidal-columnar epithelial cells with round-oval basally situated nuclei. The mitotic activity is absent or very low. Atypical choroid plexus papillomas are a rare and newly introduced entity, with intermediate characteristics between papillomas and carcinomas. Their dominant microscopic characteristic is increased mitotic activity (Fig. 49.14), and from a clinical point of view, they carry a higher risk of recurrence. However, there is evidence that a high mitotic count has much prognostic value in adults and children older than 3 years of age, but not in younger children [63]. Choroid plexus carcinomas are frankly malignant epithelial neoplasms,

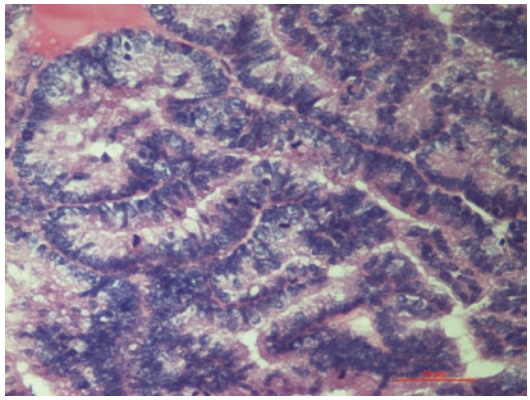


Fig. 49.14 Atypical choroid plexus papilloma. Columnar and mitotically active neoplastic cells with a papillary architecture, H&E, original magnification ×40

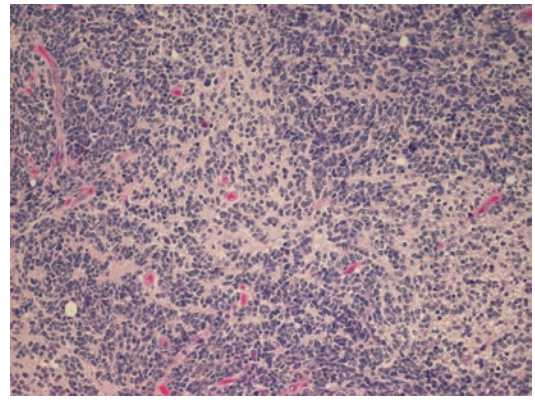


Fig. 49.15 Medulloblastoma. Small round undifferentiated cells, in many areas organized in rosettes (Homer Wright rosettes consisting of a halo of tumor cells surrounding a central region containing neuropil), H&E, original magnification ×20

with frequent mitoses, increased cellular density, nuclear pleomorphism, and necrotic areas. Lesions with these morphological features account for 14% of tumors occurring in the first year of life [50, 62].

49.4.4 Embryonal Tumors

Embryonal tumors are highly malignant [50]. As a group, in most series, they follow teratomas, astrocytomas, and choroid plexus tumors in terms of frequency in the perinatal age [13, 64]. The WHO classifies embryonal tumors as medulloblastoma, embryonal tumor with multilayered rosettes C19MC-altered, medulloepithelioma, CNS neuroblastoma and ganglioneuroblastoma, embryonal tumor not otherwise specified, and atypical teratoid/rhabdoid tumor [50]. In the current WHO classification of CNS tumors, CNS primitive neuroectodermal tumor (PNET) and supratentorial PNET have been removed from the diagnostic lexicon [50]. Indeed, Sturm et al. recently conducted integrated genomic analyses of 323 CNS-PNET patients and demonstrated that among the tumors diagnosed as PNET, there is a proportion of tumors displaying molecular profiles indistinguishable from those of various other well-defined CNS tumor entities and another proportion of tumors with peculiar molecular characteristics. These observations suggest the existence of four new genetically defined entities designated as "CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2)," "CNS Ewing sarcoma family tumor with CIC alteration (CNS EFT-CIC)," "CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1)," and "CNS high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)" [65].

Medulloblastoma is the most common CNS embryonal tumor. Although it constitutes approximately 25% of CNS tumors in children, the congenital form is rare [66]. Microscopically, medulloblastomas are cerebellar tumors composed of small round undifferentiated cells with mild to moderate nuclear pleomorphism and a high mitotic count (Fig. 49.15). Of the four histological variants of medulloblastoma (classic, desmoplastic/nodular, extensive nodularity, and large cell/anaplastic), medulloblastoma with extensive nodularity is, by far, the most common type in children younger than 2 years [67]. The recognition of this entity is important, as the outcome can be excellent [68]. In the last WHO classification, medulloblastomas are classified not only according to their histopathological features but also to their molecular characteristics [50]. The molecular classification distinguishes four principal groups: WNT-activated MB (10%), SHH-activated MB (30%), group 3 MB (20%), and group 4 MB (40%), both non-WNT/non-SHH [50].

Atypical teratoid/rhabdoid tumors were first described in 1987 by Lefkowitz et al. [69]. They constitute 1–2% of all pediatric brain tumors, are highly aggressive, and are usually present in children younger than 2 years and may be congenital. Atypical teratoid/rhabdoid tumors are embryonal tumors composed of poorly differentiated elements, frequently including rhabdoid cells, which are immature, large tumor cells with vesicular nuclei, prominent nucleoli, moderate amounts of cytoplasm, and pale intracytoplasmic rhabdoid inclusions (Fig. 49.16). Mutations of the SMARCB1 gene (or rarely the SMARCA4 gene), resulting in loss of expression of the INI1 protein, are the hallmark of this tumor [50]. Constitutional SMARCB1 mutations define the rhabdoid predisposition syndrome where affected patients are predisposed to renal and extrarenal rhabdoid tumors and exceptionally to a variety of CNS tumors, including choroid plexus carcinomas, PNETs, and a subset of medulloblastomas [50].

49.4.5 Glioneuronal Tumors

49.4.5.1 Ganglioglioma

Gangliogliomas are rare, well-differentiated, and commonly low-grade (WHO I) glioneuronal tumors composed of neoplastic glial cells in combination with dysplastic ganglion cells (Fig. 49.17) [50] . The age at presentation can range from 2 months to 70 years. Diagnosis in newborns is rare, with only few cases reported in the literature [70, 71]. Most are localized in the temporal lobe (70%) but every site of CNS can be involved. The most common genetic alteration in these tumors is BRAF V600E mutation, occurring in about 20–60% of investigated cases [50].

49.4.5.2 Desmoplastic Infantile Astrocytomas/Gangliogliomas

Desmoplastic infantile astrocytomas/gangliogliomas (DIAs/DIGs) are benign neoplasms (WHO I) [50] and are almost exclusively found in infants [72, 73]. Their incidence can only be estimated from institutional series, and it ranges from 0.3 to 15.8% [73, 74]. Macroscopically, the appearance of these tumors is that of a massive, supratentorial, cystic lesion with a solid mural nodule. Multi-lobar involvement is common. Histologically, they are composed of a prominent collagenous stroma with a neuroepithelial population restricted to neoplastic astrocytes (DIAs) or to astrocytes together with a variable mature neuronal component (DIGs) [50].

49.4.5.3 Craniopharyngiomas

Craniopharyngiomas constitute 5–11% of all intracranial tumors in children, but they seldom occur in the perinatal period. Overall, craniopharyngiomas account for 5.6% of all tumors

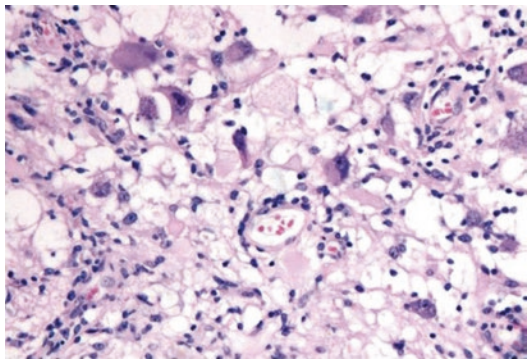


Fig. 49.16 Atypical teratoid/rhabdoid tumors. Large tumor cells with prominent nucleoli and high mitotic activity (a mitosis is appreciable in the center of the figure), H&E, original magnification ×60

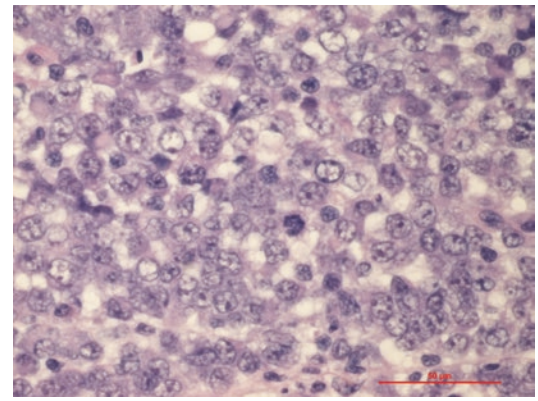


Fig. 49.17 Ganglioglioma. Neoplastic elongated glial cells in combination with neoplastic ganglion cells and lymphocytes, H&E, original magnification ×20

diagnosed in the fetal and neonatal periods [49]. They are benign epithelial tumors (WHO I) of the sellar region, presumably derived from the embryonic remnants of Rathke's pouch epithelium [50]. There are two clinicopathological variants of craniopharyngioma with distinct genotypes and phenotypes [50]. Adamantinomatous craniopharyngiomas show CTNNB1 mutations and aberrant nuclear expression of beta-catenin in about 95% of cases. Papillary craniopharyngiomas occur almost exclusively in adults and harbor BRAFV600E mutations in 80–95% of cases. Adamantinomatous craniopharyngioma is characteristically solid and cystic and composed of well-differentiated epithelium with basal palasading organized in cords, lobules, and nodular whorls. Anucleate nests of squamous ghost cells, keratin pearls, microcystic areas, calcifications, and lymphocytic and giant cell infiltrates are also typical. Piloid gliosis with Rosenthal fibers is commonly observed in the surrounding brain (Fig. 49.18). Papillary craniopharyngioma affects adults almost exclusively, is rarely cystic, and is mostly localized in the area of the third ventricle. Histologically, it is characterized by fibrovascular cores lined with squamous epithelium [50].

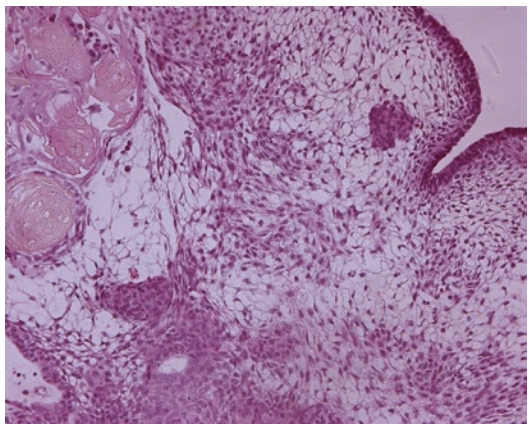


Fig. 49.18 Craniopharyngioma. Well-differentiated epithelium (bottom left, top right), stellate cells, and squamous ghost (top left), H&E, original magnification ×20

49.4.6 Ependymal Tumors

Ependymomas are included among rare congenital brain tumors. Congenital ependymomas may either present in the fetus or manifest in the neonatal period, but are more common during the first year of life [75–77]. Ependymomas are circumscribed WHO grade II or III gliomas composed of monomorphic small cells, in a fibrillary matrix, arranged in ependymal rosettes (true) and pseudorosettes with perivascular enucleate zones. Pseudorosettes can be found in almost all ependymomas, whereas ependymal rosettes are present in only a few cases [50].

49.4.7 Differential Diagnosis

Besides the tumors, other congenital conditions can mimic the clinical presentation of tumors. Tumor-like masses are not uncommon and should be included in the differential diagnosis of congenital brain tumors. The lesions most commonly found are spontaneous intracranial hemorrhage and congenital malformation, in particular, giant subcortical heterotopia. Intracranial hemorrhage can occur in the presence of coagulation factor deficiency or vascular malformations [78, 79]. Giant subcortical heterotopia is part of the so-called neuronal migration disorder, and it presents as a mass-like nodular conglomerate of dysplastic grey matter that may replace a cerebral lobe or even the greater part of a hemisphere [80].

49.5 Treatment

The treatment for congenital brain tumors does not substantially differ in terms of the basic principles from the treatment for brain tumors in older patients, as it consists of surgical and medical treatment. Having said that, it is actually so different compared with the treatment of older children with brain tumors that it is mandatory to consider them separately.

Younger children have specific requirements. There are fewer weapons that can be used than in

older children and adults, because of the detrimental effect that chemotherapy and radiotherapy can have on their development. As a general rule, it is advisable not to use radiotherapy in children younger than 3 years of age [81]. The first consequence is evidently to refer to the surgical treatment: a complete surgical resection is the best chance of survival, but it is often difficult to obtain. Tumors are frequently huge in dimension, and an aggressive surgical approach may not be possible, as it cannot always be tolerated by young children.

In addition, as observed in the previous paragraphs, there is a significant number of different histologies in a relatively small number of series and cases reported in the medical literature. The result is of course that the treatment of these patients is a challenge.

49.5.1 Surgical Treatment

49.5.1.1 Anesthesia and Surgical Position

The first elements to be considered when it comes to surgery are the anesthesia and the position of the head. Children younger than 1 year of age have a significant disproportion in terms of dimension between the head and the body; they present a small amount of blood, which is estimated around 60–80 mL per kg of body weight, and have an immature immunological and endocrine system to cope with the surgical stress.

The body temperature of small children tends to decrease during surgery. During anesthesia, the metabolic activity of the body is reduced, and the body temperature is lower. At the same time, in children, the size of the head compared with the overall dimension of the body is larger than in adults and produces a significant loss of temperature. To start with, it is advisable to operate on infants and very young children in operating rooms where it is possible to increase the temperature of the room, to use a preheated solution for IV infusion, and to use a disposable heated coat and mattress during the surgical procedure.

When it comes to positioning, it is important again to consider that the head is small, but at the same time, in infants and younger children, it constitutes up to two thirds of the body. In infants, it is advisable to avoid some positions, such as the sitting position. Correct positioning of the head is extremely important, as it allows many possible complications to be reduced during the surgical procedure. It is critical, while chasing the "perfect" position, to try to obtain one that allows prevention of cerebral collapse. Cerebral collapse is a complication that can follow almost every resective surgery on the brain of very young babies. The positioning of the head is a challenging and complex moment that requires close cooperation between surgeon and anesthesist to consider and to help to prevent possible complications during surgery. A horseshoe head holder is generally preferred to a pin head holder, owing to the thin skull of infants and the associated risk of fractures of the skull itself with pins. Once the head is positioned to try to optimize the needs of surgeon and anesthesist, it is important to place adequate anti-decubitus material at points of increased body pressure to reduce the risk of pressure sores as the skin of infants is extremely delicate.

49.5.1.2 Risk of Bleeding

It is mandatory to start surgery only if there is an adequate volume of blood, platelets, and plasma for transfusion available in the operating room. Young children with brain tumors are frequently in a situation of increased intracranial pressure, which can be associated with a higher risk of bleeding, even during the very first steps of surgery, when the surgeon deals with skin and bone. For this reason, if the CSF dynamic is perturbated on admission, the first line of treatment has to be CSF diversion (ventriculoperitoneal shunt or external ventricular drainage) or neuroendoscopy. These "minor" surgical procedures allow a rebalancing of the intracranial pressure and help to reduce the pressure and distortion on the normal

brain parenchyma improving life functions and with them the general and neurological condition of the patient. The same considerations are advisable if the tumor presents with a significant cystic component. When a procedure can reduce the dimensions of the cyst and the intracranial pressure, it is advisable again to operate first on the cystic component and, eventually, if still advisable according to the results of cytology/histology and to the general and neurological condition of the patient, to carry out a resective surgery on the rest of the tumor. If these features (intracranial pressure, distortion, and compression of the brain parenchyma) are addressed before the resective surgery, the expected results will be first a reduction of the bleeding and second, but no less important, a more physiological anatomy.

A minor loss of blood in infants can produce a significant change in the main parameters. It is very important that the surgeon reduces the blood loss as much as possible and that the anesthetist allows an adequate and immediate replacement of fluids and blood from the very start of the surgery. The tumors are often massive and, especially when malignant, have a rich vessel texture with a consequent high risk of bleeding. The previous recommendations are even stronger for proceeding with the surgery. If during the resective craniotomy the bleeding is too much and/or the vital functions are too stressed, it is very important to stop the resection immediately and to pursue good hemostasis, replenishing the volume of the cavity left from the tumor removed by using hemostatic material, and if the resection is not considered adequate, reschedule the surgery after a few days when the general condition of the patient has improved. A multistep surgery when dealing with large brain tumors in very young children does often warrant better results in terms of both final tumor resection and morbidity/mortality.

In our series of 94 congenital tumors operated on, there was one infant who weighed 2.5 kg and who died during surgery because of bleeding that could not be controlled. The histology revealed glioblastoma multiforme.

49.5.1.3 Cerebral Collapse

We underlined before that congenital cerebral tumors may have a huge volume, especially if compared with the volume of the normal brain. As a consequence, during and after radical resection, the residual normal brain collapses. This fact may cause neurological deficit even in remote areas. The main reason for neurological problems depends on the abnormal angle that is acquired by neural fibers and tracts following the line of brain collapse. For this reason, it is mandatory to allow a progressive recovery of the normal shape of the brain during the resective procedure, first of all with an adequate support of IV fluid and then with specific maneuvers. It is possible to use transiently various devices that are useful to replace the volume loss left where the tumor was. Instruments such as Fogarty balloons or Foley catheters can be passed through the cerebral cortex into the cavity obtained after the resection of the tumor and kept inflated during the time necessary for the brain to expand as much as possible (Fig. 49.19).

After surgery, particular care must be taken to try to keep the position of the head as neutral as possible, to attempt to reduce the passive motion of the brain into the head.

49.5.1.4 Instrumentation

The standard equipment of neurosurgical operating rooms must of course be warranted, starting with the operative microscope. A neuronavigation system can be useful, but it needs to be a magnetic one, as a nonrigid fixation is generally preferred. It is important from this point of view to consider that, as mentioned above, there can be significant shifting of the brain structures during and after the resection of the tumor, especially if it is large and, consequently, this reduces the appropriateness of the neuronavigation.

The use of intraoperative ultrasound can be of use to reduce this loss of accuracy.

The use of intraoperative monitoring in infants is not as useful as it can be in older children. There are at least two reasons for this. The first is that, as

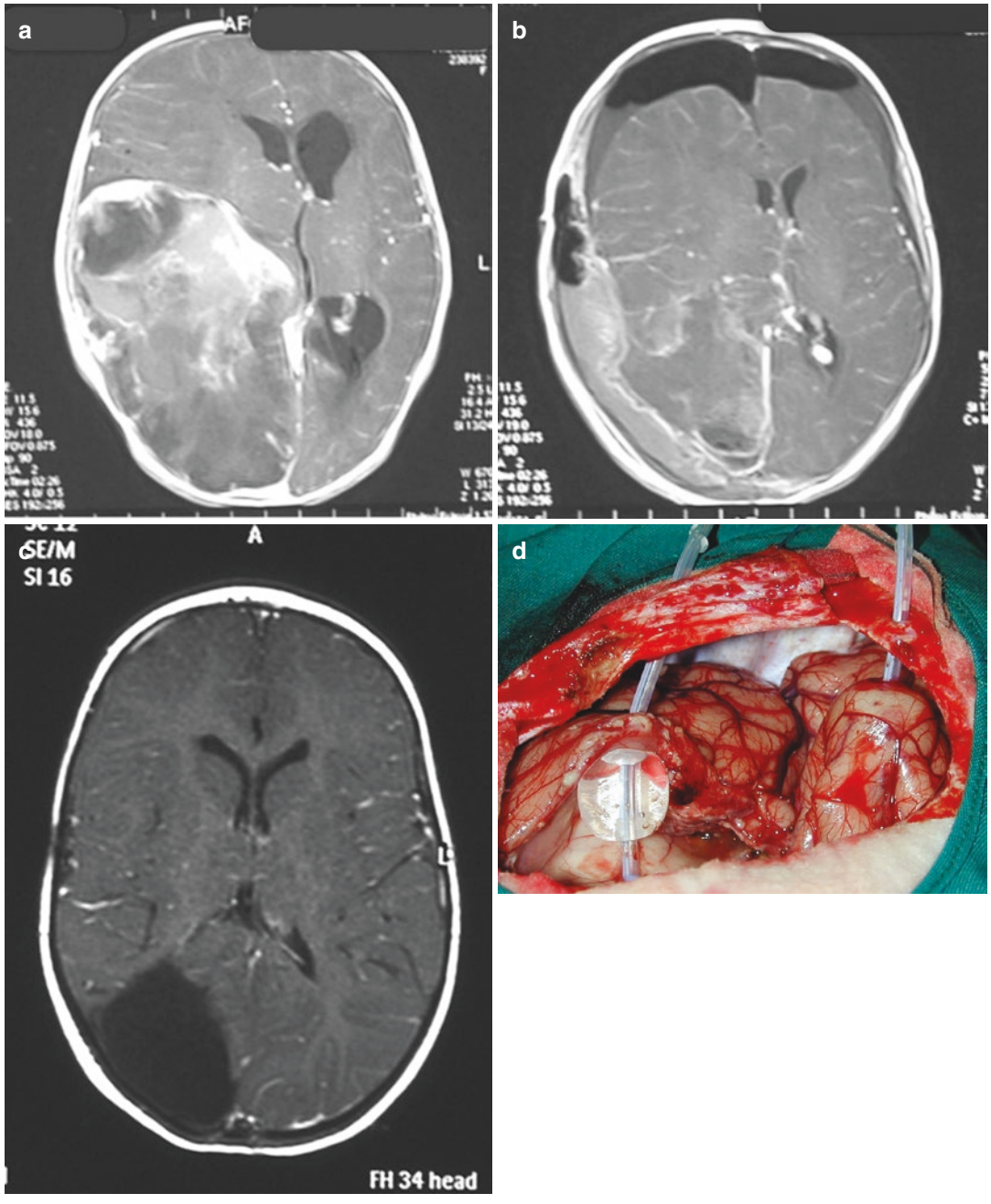


Fig. 49.19 J.B, 2-month-old girl. Presenting with a bulging fontanelle and a reduced level of consciousness. (**a**) MRI at presentation. (**b**) MRI after gross total surgical resection. The cerebral collapse is evident with a prominent subdural collection and a distortion of the midline structures. (**c**) MRI 2 years after surgery. According to the WHO classification at the time of surgery, the tumor was diagnosed as a PNET. (**d**) Intraoperative images of the progressive reduction of cerebral collapse with the use of a Fogarty balloon

said before, in very young children, the maturity of the neurons and white matter is not complete. As a consequence, intraoperative monitoring may not be reliable. The second reason is that sometimes in infants, the tumor is so huge in dimension that it completely deforms the architecture and

anatomy of the brain, thus also rendering intraoperative monitoring unreliable.

49.5.2 Medical Treatment

The most commonly encountered pathological conditions include teratomas, low- and high-grade astrocytomas, craniopharyngiomas, and choroid plexus and embryonal tumors. Less commonly encountered diseases include ependymomas, germinomas, malignant schwannomas, and malignant meningiomas [82, 83].

Beyond the histological type, congenital CNS tumors have a dismal prognosis because of age and the need for neurosurgical support and a newborn intensive care unit. Some malignant histotypes start out as large-scale injuries not diagnosed in the fetal age. For all these reasons and the poor prognosis, many pediatric oncology centers prefer not to treat them.

Being rare diseases, the therapeutic approaches are not standardized, owing to the lack of a clear understanding of the role of genetic patterns and support therapy management in infants with congenital CNS tumors. Therefore, there is still no consolidated treatment through an international consensus for the therapy of congenital malignant brain tumors.

The prognostic factors are residual disease after surgery, histology, and the presence of metastasis.

In children under 12 months, the treatment includes surgery and adjuvant chemotherapy to avoid or to defer radiation therapy. As is well known, the predisposition of the young brain to radiotherapy-induced cognitive deficits and leukoencephalopathy, which increases for a long time after radiotherapy, has set age limitations on the use of radiotherapy in infants. However, the ideal approach for very young children remains postoperative chemotherapy alone, which can lead to a good outcome in half the cases [84–86].

Teratomas and craniopharyngiomas only require a surgical approach, with the aim of obtaining a complete resection of the disease. Teratomas are not only the main intracranial germ cell congenital brain tumor, but is also the most common neonatal brain tumor in several major studies [87, 88]. Teratomas arise from several locations within the CNS, the pineal, the hypothalamic area, the suprasellar region, and the cerebral hemispheres, and they could erode through the skull and extend into the orbit, oral cavity, or into the neck. Intracranial teratomas are typically large cystic tumors with solid areas replacing much of the brain [89]. The prognosis worsens with increasing tumor size and decreasing gestational age at diagnosis. They have one of the lowest survival rates for all patients with perinatal brain tumors, which could be attributed to the presence of advanced disease at the time of diagnosis [51]. Research into markers such as beta-human chorionic gonadotropin (β-HCG) and alpha-fetoprotein (α-FP) in addition to imaging could help to reach a more certain preoperative diagnosis, especially for immature/mature teratomas and germinomas. Generally, children with high levels of β-HCG or α-FP and proven tumor are considered to suffer from a malignant disease [90].

Craniopharyngiomas are the most common tumors in the parasellar region in childhood, but they seldom occur in the perinatal period [91]. They are considered benign tumors, but when occurring in fetuses and neonates they generally have a poor prognosis [50, 92]. Surgery is the main treatment for these tumors, also because postoperative therapy could cause several side effects in these patients [93].

Astrocytomas follow teratomas in frequency, accounting for 18–47% of all congenital lesions, and they present with various degrees of differentiation, from benign to malignant tumors [51].

Fetal astrocytomas differ from those in the pediatric population in terms of their gross and histological features, site of origin, and clinical manifestations; in particular, cerebellar pilocytic astrocytoma is notably absent in the fetal group. Congenital astrocytomas are generally solid masses involving the cerebral hemispheres, thalamus, or optic nerve [49].

Furthermore, there is a high association between optic pathway pilocytic astrocytomas (grade I) and neurofibromatosis type 1 (NF-1), approaching 50% in some series [94]. There is no

correlation between the extent of surgical resection, the presence of residual tumor, irradiation, and the length of survival or degree of residual disability in congenital optic pathway gliomas. Optic pathways astrocytomas are considered benign in nature, because their natural history can evolve with long periods of dormancy and they can occasionally present spontaneous regression; therefore, their treatment should be as conservative as possible. Radiotherapy is not recommended, especially in patients with NF-1 because of the high risk of a second malignant neoplasm [94]. Interestingly, patients with a tuberous sclerosis complex develop low-grade astrocytomas (subependymal giant cell astrocytomas) in the perinatal period [57].

Anaplastic astrocytomas (WHO grade III) may occur in the fetus and newborn. Children with anaplastic astrocytomas have a better outcome than those with glioblastoma, with long-term survivors reported. One-third of all astrocytomas are glioblastomas multiforme (WHO grade IV). In infants, they often arise from the cerebral hemisphere and basal nuclei. Glioblastomas involve a high risk of bleeding and infection. Bleeding (within the tumor) may be the initial imaging finding in the perinatal period [95].

The overall survival rate for newborns with astrocytoma remains discouraging. The meta-analysis of Isaacs reported that overall, only one third (16 out of 47) of the patients survived and six (13%) were stillborn. Infants diagnosed with low-grade astrocytomas showed a higher rate of survival (37%) vs infants with high-grade astrocytoma (anaplastic astrocytoma or glioblastoma multiforme; 14%). Only 2 out of 15 (13%) patients with glioblastoma survived [96]. The low survival could be recognized in a chemotherapy regimen with limited success in infants less than 3 months of age [65] and in the impossibility of using radiation treatment on immature brains because of its injurious effects on growth and development of the brain and skeleton [51].

The term PNET is applied to a group of small-cell malignant tumors of the central and peripheral nervous systems and soft tissues. As previously mentioned, PNETs have been removed from the current WHO classification of CNS tumors [50]. Tumors in the past diagnosed as CNS-PNETs occurred primarily in the pediatric age group and were characterized by the capacity for differentiation along neuronal, astrocytic, muscular ependymal, and melanotic cell lines [51]. One-fourth of all tumors diagnosed as cerebral PNETs occurred before 2 years of age and were highly aggressive, metastasizing widely throughout the CSF pathways and invading the meninges of the brain and spinal cord [83].

Medulloblastoma follows teratomas, and astrocytomas, and choroid plexus tumors in incidence in several perinatal series [51]. At diagnosis, these tumors could have metastatic lesions as the initial manifestation, which is unusual for a brain tumor in this age group [97]. Congenital anomalies in patients with medulloblastoma have been described (e.g., imperforate anus, omphalocele, myelomeningocele, cleft palate, cerebellar agenesis, dural arteriovenous malformations, and acrania) [51].

Patients with Gorlin syndrome are at an increased risk of medulloblastoma, with an incidence of 1–2% [98]. Furthermore, there is a significant association between medulloblastoma and rhabdoid tumor of the kidney [99]. The loss of portions of chromosome 17p has been described in medulloblastoma patients [100].

Medulloblastomas originate from the vermis of the cerebellum and grow into the fourth ventricle and adjacent cerebellar hemispheres. Subsequently, obstructive hydrocephalus and leptomeningeal seeding occur along the cerebrospinal axis [51]. The tumor enters the bloodstream and metastasizes in the CSF and seldom to organs outside the CNS, primarily to the liver, lungs, and bone marrow, and sometimes to the lymph nodes [97, 101]. The treatment of infants with medulloblastoma is problematical because irradiation of the infant brain carries a high risk of intellectual, skeletal, and endocrine sequelae [102].

The prognosis for newborns with medulloblastoma in general remains discouraging.

Infants clearly have a worse prognosis than older children, although the outcome appears to be improved by chemotherapy [103]. Isaacs reported that only 1 out of 19 neonates with medulloblastoma was alive after adjuvant treatment [51]. The highly malignant AT/RT is similar biologically and histologically to the rhabdoid tumors present in the kidney, soft tissues, and other sites [104, 105]. The major site of origin of these aggressive tumors is the posterior fossa, particularly the cerebellum, but the cerebral hemispheres and the brainstem are other primary sites [106]. AT/RT is associated with the monosomy 22 [107]. AT/RT has been often misdiagnosed as PNET or medulloblastoma because 70% of AT/RTs sometimes contain histological characteristics indistinguishable from classic PNET/medulloblastoma [108]. Nonetheless, differentiation between these two entities is important because AT/RT has a dismal prognosis and requires radical and aggressive treatment with surgery and adjuvant therapies such as radiotherapy and high-dose chemotherapy with autologous bone marrow transplant [109].

Choroid plexus carcinomas are diagnosed in the first year of life in about one-third of the cases [110]. Most choroid plexus carcinomas occur in the lateral ventricles. They can disseminate throughout the cerebrospinal subarachnoid space. This feature may already be present at diagnosis, and, in any case, when present, it worsens the prognosis [111]. Choroid plexus tumors have one of the best survival rates of all congenital brain tumors (73% survival rate of the 33 patients) [51].

The main treatment remains a total surgical resection [112], but currently the use of chemotherapy in patients with this malignancy has produced some encouraging results, achieving a better outcome than in older children and adults [51].

Despite the remarkable mortality of congenital brain tumors, each center does not refer to specific guidelines that can help in the treatment of these cancers. Moreover, there are currently no differentiated protocols for each histological subtype.

Generally, both European and American clinical studies demonstrated the efficacy of high-dose chemotherapy (HDCT) and autologous stem cell rescue (ASCR) for most malignant brain tumors in very young patients.

During the last decades, therapeutic approaches have been varied with different survival rates. The report of the Children's Memorial Hospital of Chicago, on 341 infants treated during the period 1967 to 1980, showed that only 18 patients (malignant glioma or medulloblastoma) underwent radiotherapy. Any children treated with a combination of nitrosoureas and vincristine did not achieve remission of the disease. The survival rates at 1, 3, and 5 years were confirmed to be 46%, 30%, and 22% respectively. They concluded that postoperative radiation therapy was recommended for malignant tumors with evidence of disease. However, caution was expressed concerning the use of whole-brain and spinal cord irradiation in infants aged less than 12 months [113]. They obtained better results in terms of overall survival, given the use of radiotherapy (more than 5000 rads of the whole brain). Jooma et al. reported a large series of 100 infants with intracranial tumors symptomatic during the first year of life that were treated with chemotherapy and 39 patients were treated with radiotherapy. The cumulative average survival was 27 months, which increased to 37 months after a good resection. The operative mortality was 30%. The irradiated patients had a 5-year survival rate of 43%. The morbidity was highly irrespective of radiotherapy; however, 60% of patients who survived 12 months showed a moderate or severe disability [75].

Some therapeutic approaches are evaluable through single reports of congenital malignant gliomas. A 2-month-old infant diagnosed with a gliosarcoma underwent a subtotal resection and monthly chemotherapy (including vincristine, carmustine, procarbazine, cytosine arabinoside, cisplatin, and cytoxan) without tumor progression at 11 months of follow-up [114]. Two cases of congenital glioblastomas were subjected to partial removal. One patient was subjected to chemotherapy after surgery consisting of etoposide,

vincristine, cisplatin, and cyclophosphamide. The patient completed chemotherapy and was alive with minimal neurological deficits and no evidence of disease. Interestingly, the second patient omitted adjuvant chemotherapy for religious reasons. Currently, the child is alive with minimal neurological deficit and no evidence of his malignancy 2 years after surgery [86]. A patient with glioblastoma multiforme underwent surgery and adjuvant chemotherapy according to the Children's Cancer Group (CCG) 9921 protocol, consisting of carboplatin, etoposide, ifosfamide, and vincristine. The patient was alive at 23 months of age [115]. A girl with congenital glioblastoma was approached with surgery, adjuvant chemotherapy, and radiation therapy. The MRI scan, 3 years after her surgery, showed no evidence of tumor recurrence [116]. Eventually, a child with a congenital malignant meningioma treated with surgery and chemotherapy according to the CCG protocol for children aged less than 3 years with malignant brain tumors (CCG 9921, Regimen A: cisplatin, etoposide, vincristine, and cyclophosphamide) was alive with no evidence of disease on MRI at 14 months of age [116, 117].

Di Rocco and coworkers reported a meta-analysis on a multicenter international series of 886 children with brain tumor treated during the first year of life. Radiotherapy was administered in only 129 cases, and 119 infants were subjected to chemotherapy (without specifying the type of therapy). 53.4% of these patients were still alive (473 out of 886). They demonstrated that around half of patients with congenital brain tumors can survive with few side effects associated with chemotherapy and infants receiving whole-brain radiation tended to have greater deficits in the long term [38].

A study described a statistical analysis of 307 infantile brain tumors collected from different countries. 51.1% of the patients were subjected only to surgery treatment. A total of 110 infants received radiotherapy and only 37 received chemotherapy. The 3-year overall survival was only 35.5% and 26.1% after 5 years [21].

The Italian experience for children younger than 3 years, independently of tumor histology, proposes four courses in the induction phase that included methotrexate 250 mg/kg plus vincristine 0.04 mg/kg, etoposide 80 mg/kg, cyclophosphamide 135 mg/kg plus vincristine 0.04 mg/kg, and carboplatin 25 mg/kg. Peripheral blood stem cells have to be collected for rescue therapy. Intensification and consolidation phases include two high-dose chemotherapy regimens: thiotepa at myeloablative doses (10 mg/kg/day for 3 days) followed by ASCR. The second conditioning regimen also includes carboplatin (16 mg/kg/day for 2 days) with thiotepa [118, 119].

Tumors such as AT/RT and choroid plexus carcinoma could receive intrathecal chemotherapy with methotrexate coupled with systemic chemotherapy [119].

After the induction phase (four cycles of chemotherapy and before HDCT plus ASCR), brain and spine MRI are performed to evaluate the presence of macroscopic solid or leptomeningeal metastasis. Bone marrow examination and cerebrospinal fluid (CSF) cytology are part of the initial evaluation looking for metastatic disease made before beginning the therapy. It is required for most embryonal tumors such as medulloblastomas and AT/RT [84–86, 120].

In conclusion, chemotherapy remains a much accepted and well-tolerated adjuvant therapy for this age group. It has been proven beneficial as an adjuvant therapy in many tumors once the mass is resected incompletely or in cases with malignant pathology in spite of complete resection. Only patients with malignant unresectable CNS tumors or poor responders to chemotherapy could be subjected to radiotherapy or neoadjuvant chemotherapy [121].

It is noteworthy from clinical observations and experimental in vivo data that the immature brain is much more susceptible to radiation. An intellectual or growth retardation, delayed hypopituitarism, occlusive neurovascular complications, and risks of a second malignant neoplasm in the treatment field have been reported [122]. Actually, to avoid these intolerable side effects for pediatric patients, proton therapy probably offers the greatest margin of benefit [123]. Several small series on proton treatment for low-grade gliomas, sarcomas, or other pediatric tumors are available, all reporting excellent

tolerability and comparable outcomes with photons [124].

Our knowledge of congenital brain tumors is still limited, and a standard, effective, and well-accepted treatment protocol for optimal management of neonatal brain tumors is yet to be defined.

The goals to be achieved are an improvement of management and prognosis of these cancers through a better knowledge of the clinical behavior and genetic characteristics.

Some epidemiological studies of congenital brain tumors have documented several causes. However, the search for causative factors for developing brain tumors continues. Certainly, the associations between primary brain tumors and several genetic syndromes have been recognized [116]. In these tumor predisposition syndromes, individuals inherit a germline mutation in a tumor suppressor gene. Tumors arise when the remaining copy of the tumor suppressor is mutated or silenced, giving rise to cells with a growth advantage. Because tumorigenesis requires the accumulation of multiple mutations in cells, these individuals are at an increased tumor risk because all cells carry an initial mutation [125]. In addition, these syndromes could be caused by de novo mutations ("primary"). Therefore, it is crucial to clarify the clinical and molecular mechanisms at the basis of these tumors [126].

49.6 Clinical Series

A retrospective evaluation was performed with the use of a query that investigated the electronic database where all the patients are recorded in our Unit of Neurosurgery. The query asked to look for patients with the word "tumor" in the diagnosis and that had a maximum "365" days of life when first recorded and/or diagnosed in our center. During the past 20 years, under the care of the senior author (Lorenzo Genitori), 94 patients younger than 1 year of age were admitted for a CNS tumor diagnosed when they were younger than 365 days. Of these, we considered 83 patients, because 11 were admitted for spine tumors. Among them, 25 (30.1%) were properly defined as congenital (diagnosed before 2 months of age); 58 (69.9%) were between 2 and 12 months of age at diagnosis. Thirteen patients were excluded because of a lack of data (1 in the group of patients younger than 2 months, 12 in the group of patients older than 2 months). When considered all together, the 70 patients consisted of 47 boys vs 23 girls (M/F 2:1) and presented a supratentorial tumor in 52 cases (74.2%). An intraventricular tumor was observed in 15 of them (21.4%; 3 in the group of patients younger than 2 months and 12 in the group of patients older than 2 months at diagnosis).

Clinical signs/symptoms related to increased intracranial pressure were the most common at presentation and were indicated as the reason for seeking for medical advice in 31 patients (44.2%). Hydrocephalus and macrocrania were reported in 17 patients (24.3%) each. It is relevant that 5 patients (7.1%) on admission already had a reduced level of consciousness.

In our series of 94 patients, the predominant histotypes were astrocytomas (37%), embryonal tumors (24%), mixed neuronal-glial tumors (18%), and choroid plexus tumor (16%). Teratomas, ependymomas, and pineoblastomas were less common (4%, 1%, and 1% respectively), which is not in line with most of the relevant medical literature on congenital CNS tumors, where teratomas are generally referred to as the most common histology.

The discrepancies in the histotype incidence may depend on many factors, e.g., the number of cases, the age range considered, and the year of publication of the study. The scant medical literature on congenital tumors is insufficient to evaluate the exact frequency of each histotype. Moreover, the frequency of some histotypes is age-related. In particular, intracranial teratomas are more often diagnosed during intrauterine development and in newborns; thus, studies that consider this age range could report a higher incidence of these tumors [127]. Furthermore, older studies did not consider tumors that have been described in more recent years (i.e., AT/RT and atypical choroid plexus papilloma). On the other

hand, some histologies are no longer included in the current WHO classification of CNS tumors and therefore will disappear from the medical literature to come, but are of course mentioned in the studies published in the past (i.e., PNET).

In our experience, low-grade and high-grade lesions are equally distributed among astrocytomas. The most frequent low-grade astrocytoma is pilocytic astrocytoma, whereas the most frequent high-grade astrocytoma is glioblastoma. Embryonal tumors are the second most frequent diagnosis in our series. We diagnosed PNETs (PNET has been now removed from the diagnostic lexicon) and AT/RTs with equal frequency and then medulloblastomas. Mixed neuronal-glial tumors in most cases were gangliogliomas. Our series also includes two desmoplastic infantile gangliogliomas, one with areas of melanotic differentiation and one with an unusually high mitotic index. In the group of choroid plexus tumors, the most frequently encountered lesions were choroid plexus papillomas, followed by atypical choroid plexus papilloma and carcinoma (one case). We observed congenital teratomas in a small number of cases, probably as a consequence of the age range considered. All our teratomas affected infants less than 2 months of age at diagnosis. Ependymomas and pineoblastomas were the rarest congenital tumors diagnosed in our series.

Surgical treatment was offered to all the patients to obtain a diagnosis, to reduce/remove the mass, and to control the hydrocephalus. In the series of 70 patients analyzed, the first surgical approach in 33 cases consisted of a procedure aiming to deal with hydrocephalus and/or cystic components of the tumor and/or to obtain a biopsy of the tumor (11 patients). A craniotomy was offered directly to 37 patients. Several patients were treated surgically using a multistep approach, aiming to control the intracranial pressure first and then to remove the tumor. If necessary, patients were offered multistep surgery to remove the tumor.

With this surgical strategy, 31 patients were operated for tumor resection more than once. Four patients, 2 diagnosed when younger than 2 months of age and 2 diagnosed when older than 2 months of age, were operated four times for craniotomy and resection of the tumor.

One patient diagnosed at birth died during surgery. The patient had a massive bleeding followed by cardiac arrest and on scans presented a right-sided hemispheric lesion that on testing turned out to be a glioblastoma multiforme.

Mean follow-up was 53 months (minimum 1 month and maximum 18 years). At the last follow-up, 20 patients (28.6%) had died (11 in the group diagnosed when younger than 2 months of age [44%], 9 in the group diagnosed when older than 2 months of age [20%]), 22 (31.4%) were alive with evidence of disease (6 in the group diagnosed when younger than 2 months of age [24%], 16 in the group diagnosed when older than 2 months of age [35.6%]), and 28 (40%) were alive with no evidence of disease on brain and spine MRI (8 in the group diagnosed when younger than 2 months of age [32%], 20 in the group diagnosed when older than 2 months of age [44.4%]). Relevant clinical data referring to the 70 patients included in the analysis are summarized in Tables 49.2 and 49.3.

49.7 Conclusions

Children younger than 12 months with CNS tumors are still burdened with a high mortality. It appears from our experience that there is a cutoff of different mortality between strictly congenital (diagnosis before 2 months of age) and children diagnosed when older than 2 months of age. Treatment is challenging because of the higher risk associated with surgery, especially of bleeding, and because adjuvant treatments are limited as they are associated with unacceptable side effects. Multistep surgery to control intracranial hypertension and to gradually resect the tumor

Table 49.2 Summary of essential clinical elements of 25 patients diagnosed with brain tumors when younger than 2 months in our series

	AT/RT	Choroid plexus tumors	Glioneuronal	HGG	LGG	Medulloblastomas	PNET	Mature teratomas	Immature teratomas	Others	Total
Male	2	1	2	2		1		1	3	3	15
Female	1		1	2			3		1	2	10
Supratentorial		1	3	4		1	2		3	3	17
Subtentorial	3							1	1	2	7
Supra-subtentorial							1				1
Increased IIC	2		2	2		1	1		2	1	11
Seizures											
AWD			2						1	3	6
NED			1	1			2	1	2	1	8
DOD	3	1		3		1	1		1	1	11
Total	3	1	3	4	–	1	3	1	4	5	25

Table 49.3 Summary of essential clinical elements of 45 patients diagnosed with brain tumors when older than 2 months in our series

	AT/RT	Choroid plexus tumors	Glioneuronal	HGG	LGG	Medulloblastomas	PNET	Mature teratomas	Immature teratomas	Others	Total
Male	1	5	3	4	12	1	2			4	32
Female		2	3	1	3	1				3	13
Supratentorial	1	7	4	5	11		1			6	35
Subtentorial			1		3	2				1	7
Supra-subtentorial			1		1		1				3
Increased IIC	1	5	1	2	6	2	2			1	20
AWD			2	2	7	1				4	16
NED		6	4		6	1	1			2	20
DOD	1	1		3	2		1			1	9
Total	1	7	6	5	15	2	2			7	45

can postpone the treatment and increase survival. It appears that the improvement observed in terms of mortality is probably related to the better surgical understanding of these tumors and to the improvement in terms of surgical instruments. The role of chemotherapy is still under investigation in most cases, but in some small series, it seems to increase overall survival and reduce mortality.

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Part X

Miscellaneous

Vascular Anomalies in Children

50

Oumama El Ezzi and Anthony de Buys Roessingh

50.1 Introduction

Vascular anomalies are rare but frequently encountered in the pediatric population. It is fundamental to distinguish between vascular tumors and vascular malformations.

Vascular tumors are proliferative lesions due to an accelerated turnover of endothelial cells. Vascular malformations are structural anomalies due to innate errors in the embryonic development of blood vessels. They are generally classified according to their dominant abnormal vessel: venous (70%), lymphatic (15%), capillary (10%), arteriovenous (5%), or combined malformations. We also commonly divide them into low- or high-flow malformation.

Thanks to the work of Mulliken and Glowacki in 1982 [1] and the classification of the International society for the study of vascular anomalies (ISSVA) in 1996, [2] the understanding of vascular anomalies has been considerably structured. The ISSVA classification was updated at the April 2014 General Assembly in Melbourne, Australia [3].

The diagnosis is often determined by the medical history and the clinical findings. In case of uncertainty, or when treatment is considered, ultrasonography, Doppler flow imaging, and magnetic resonance imaging (MRI) may be indicated, under sedation or anesthesia. They allow the identification of the nature and extent of the lesion. When the diagnosis remains uncertain, biopsy and histopathological examination are necessary.

Most of these vascular anomalies do not require treatment. But when treatment is needed, it is complicated and requires a multidisciplinary approach. A proper diagnosis is the starting point for an optimal treatment.

50.2 Vascular Tumors

The majority of vascular tumors are benign, and 95% are infantile hemangioma.

50.2.1 Hemangiomas

Hemangiomas are principally divided into two groups: infantile hemangiomas and congenital hemangiomas. Other types are much less frequent. They are proliferative vascular lesions due to an accelerated turnover of endothelial cells.

50.2.1.1 Infantile Hemangioma (IH)

IHs are the most common benign tumors in infancy, present in 10% of children under the age of 1 year [1]. A high incidence has been reported in premature infants and girls [4].

Sixty percent are located in the cervicofacial region, while the others arise on the trunk and the extremities. They generally appear within a few

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weeks after birth and then rapidly grow during early infancy, up to the age of 1 year. This phase is followed by a stable period of a few months and then a spontaneous involution over several years [5]. The involution may be complete or partial, and the residual skin may be atrophic and telangiectatic (Fig. 50.1). Eighty percent are solitary lesions. However, multiple (more than five) hemangiomas can be present and are likely to be associated with visceral lesions, most often hepatic and gastrointestinal. An abdominal ultrasound is then recommended in this case [6].

A more extensive medical evaluation is indicated in certain circumstances, namely, depending on the location of the IH. Several locations need particular attention. Infants who have large hemangiomas of the face or scalp are at risk of PHACES syndrome: posterior fossa anomalies, hemangioma, arterial lesions, cardiac anomalies/aortic coarctation, abnormalities of the eye and sternal clefting and/or supraumbilical raphe [7] (Fig. 50.2). They need to undergo imaging of the head, neck, and chest and ophthalmological and skin examinations [8].

IHs located in the lumbosacral, perineal, or lower extremities may be part of the LUMBAR syndrome: lower body IH and other skin defects, urogenital anomalies and ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies. They also require further investigation [9] (Fig. 50.3).

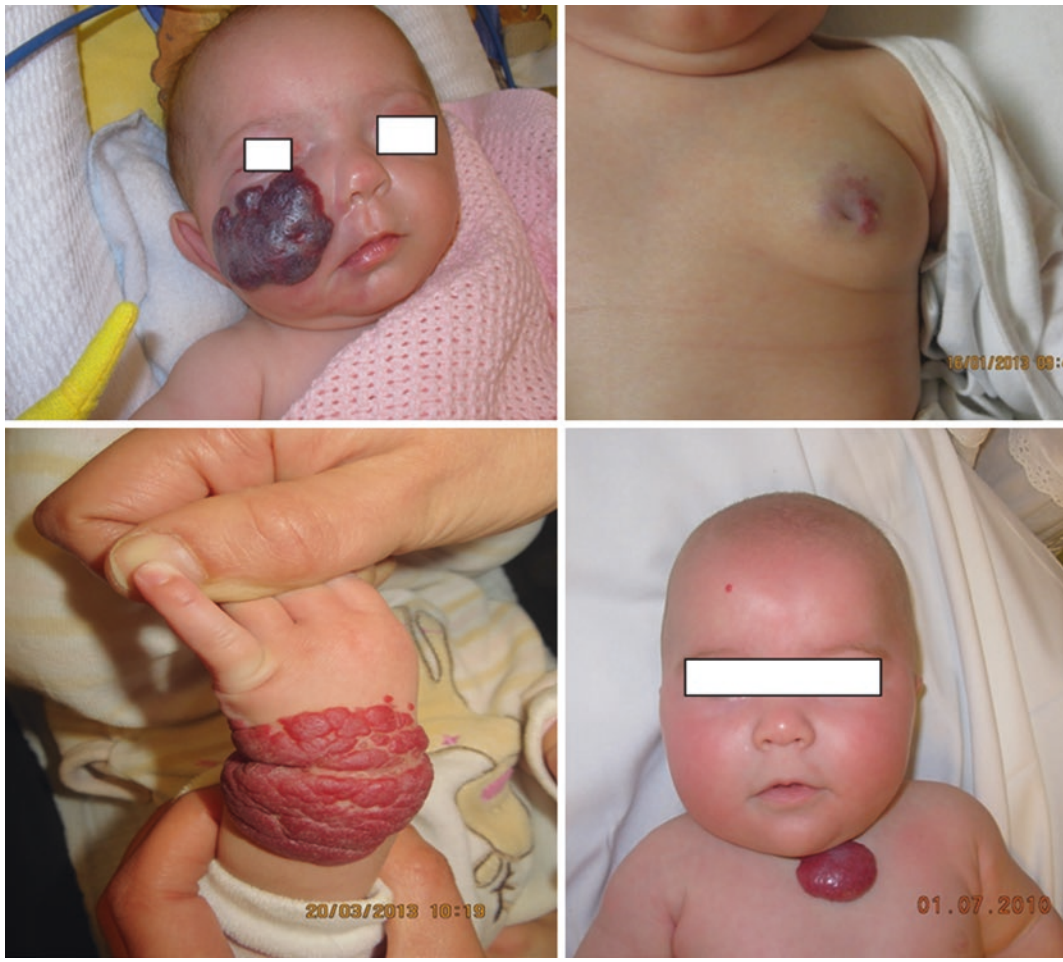

Fig. 50.1 Infantile hemangioma: cutaneous, subcutaneous, Mixed

Periorbital hemangiomas may cause visual impairment with amblyopia or anisometropia. An MRI is necessary to evaluate the extent of this kind of hemangioma [10] (Fig. 50.4).

Anal and vulvar hemangiomas may develop ulceration by irritation. In this case, alginate or hydrocolloids dressings with Eosin® 2% can be used for local treatment in addition to systemic treatment.

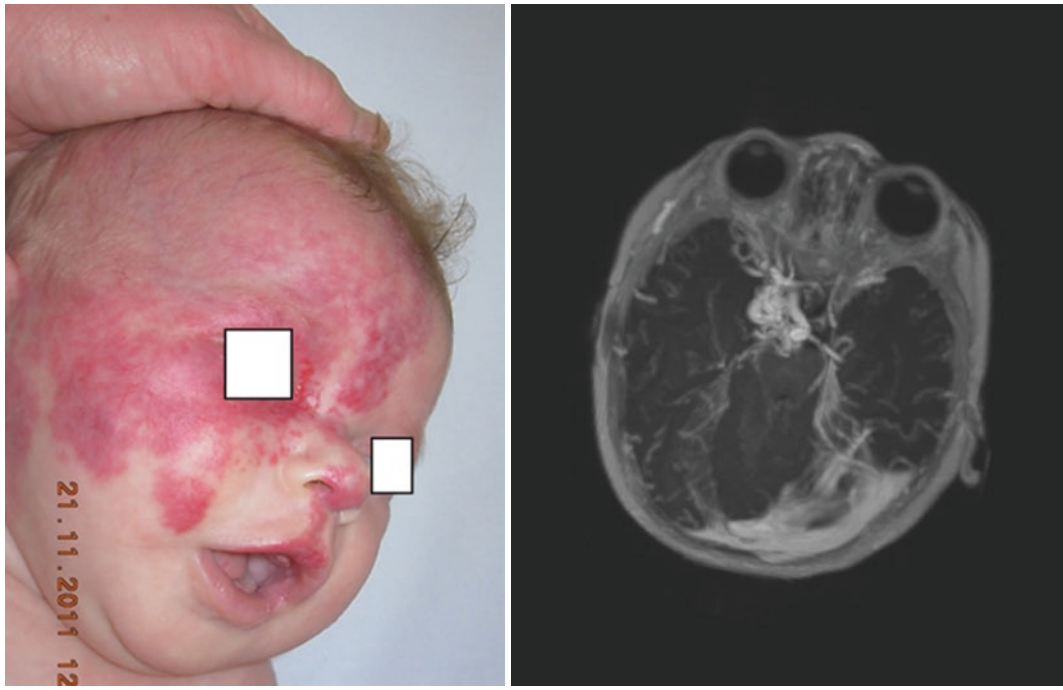

Fig. 50.2 PHACE syndrome, frontal pachygyria and complex malformation of the willis circle

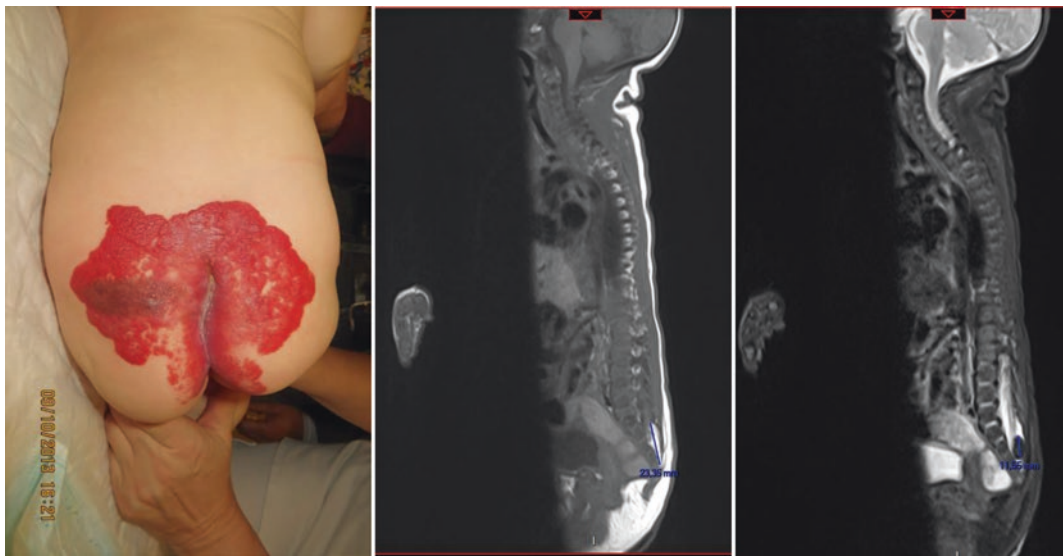

Fig. 50.3 LUMBAR syndrome: Sacral hemangioma, intradural lipoma, and marrow fixed in S2

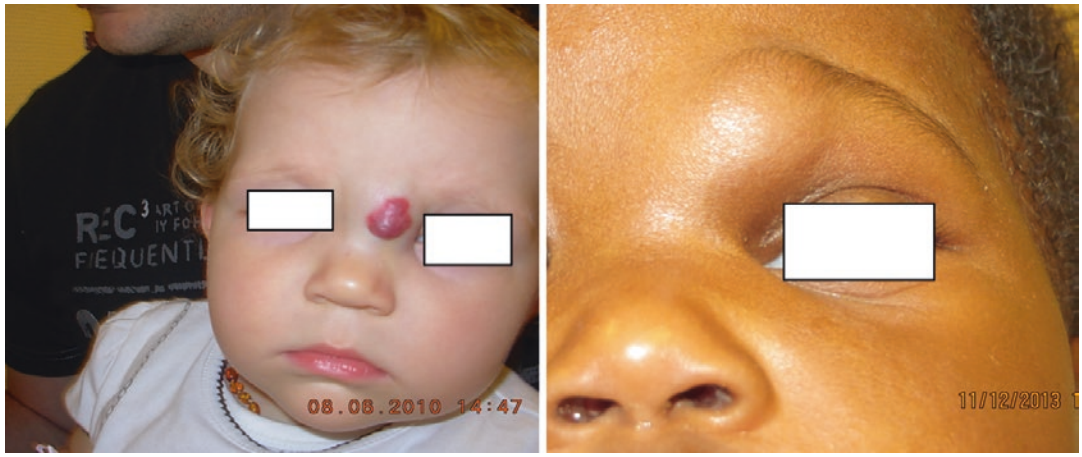

Fig. 50.4 Periorbital hemangioma

Hemangioma of the nasal tip, also called "Cyrano hemangioma," may be very large. It can cause significant esthetic and functional impairment such as ulceration, nasal obstruction, and disturbance of visual field. This lesion can also interfere with the development of the nose [11]. Their treatment is still controversial, but late surgery is always necessary to remove the remaining scar tissue and repair the nasal tip.

The vast majority of IHs do not require treatment. Management during the proliferation phase is reserved for hemangiomas which may cause airway obstruction, functional or psychological problems, bleeding, and ulceration; this is the case in approximately 10% of IHs [12].

Propranolol, a nonselective β-blocker, is the first-line treatment [13]. Its mechanism of action includes vasoconstriction, angiogenesis inhibition, and endothelial cell apoptosis [14]. The most common dosage of propranolol is 1–3 mg/kg/day, given in 2–3 doses up to the age of 1 year. In our practice, before the initiation of propranolol treatment, blood glucose levels and renal function were first monitored, and a cardiac ultrasound and electrocardiogram (ECG) were performed by pediatric cardiologists. Blood pressure and cardiac rhythm were checked every 30 min for 4 h after the first dose. The treatment is initiated with 1 mg/kg/day in the first 24 h and then 2 mg/kg/day from the second day onward on an outpatient setting. Heart malformations and respiratory problems such as bronchiolitis or asthma were contraindications to commencing treatment.

Clinical condition, weight, heart rate, and blood pressure are checked at each visit and the dosage of propranolol adapted according to body weight every 8 weeks [12].

This treatment has proved to be safe and effective, with very few side effects. The feared effects of propranolol are bradycardia, hypotension, bronchospasm, and hypoglycemia [15].

There are nowadays far fewer indications for surgical treatment. It is reserved for some facial lesions and essentially for the sequelae of the involuted hemangiomas. Pulsed dye laser may reduce superficial discoloration of residual telangiectasia and better control ulcerated hemangiomas [16].

50.2.1.2 Congenital Hemangioma (CH)

Congenital hemangiomas are distinct from the infantile hemangiomas that appear after birth, in that they are fully developed at birth. Depending on their evolution, they are divided into two categories: rapidly involuting congenital hemangiomas (RICHs) and non-involuting congenital hemangiomas (NICHs). RICHs involute completely by the age of 14 months, whereas NICHs do not regress but rather continue to grow progressively [17, 18]. RICHs present as a voluminous, pink or purplish, infiltrating mass surrounded by a white halo. NICHs are usually smaller [19, 20] (Fig. 50.5). RICHs can

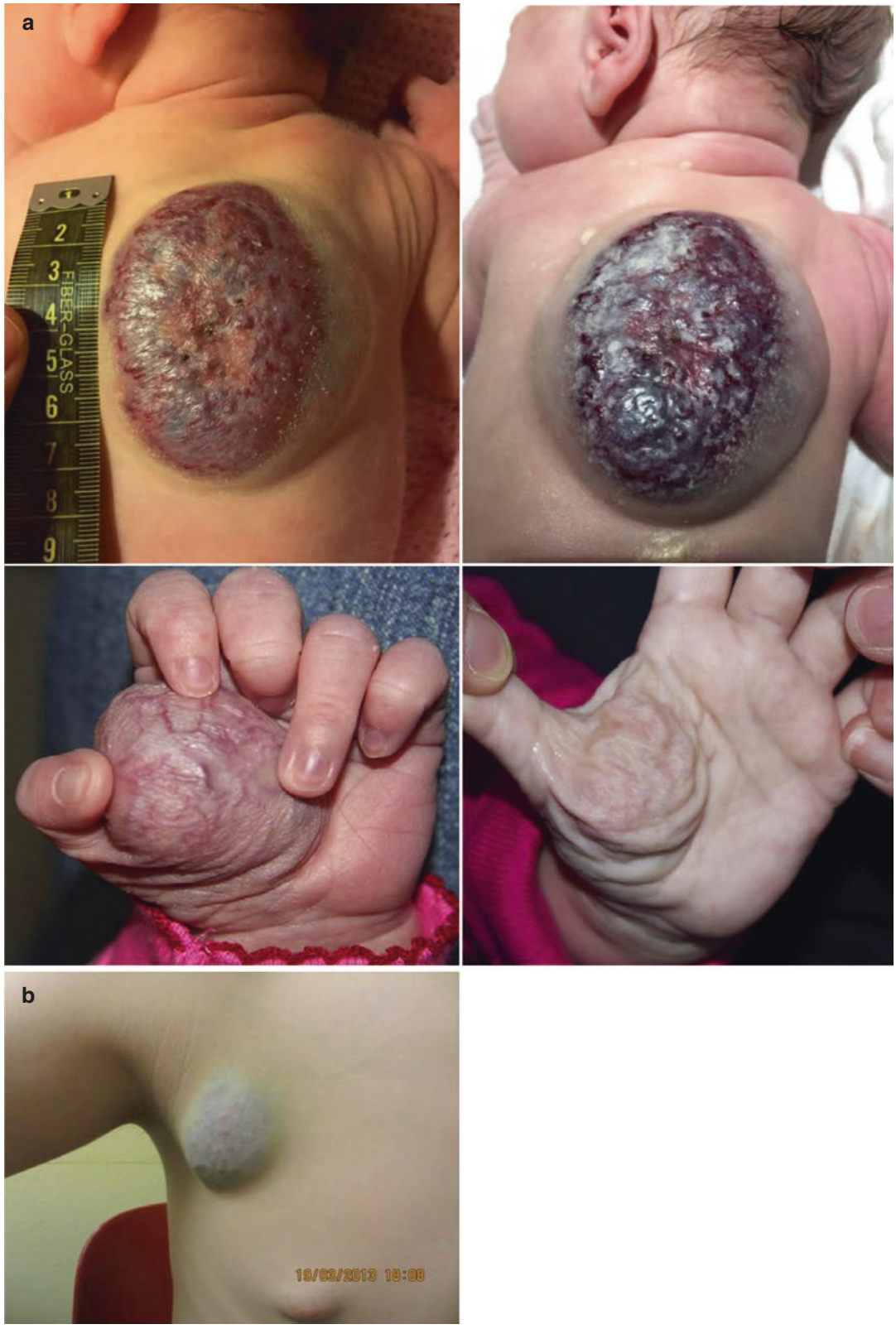

Fig. 50.5 Congenital hemangioma: RICH (**a**) and NICH (**b**)

sometimes be associated with a moderate and transient coagulopathy. When associated with acute cardiac failure, they may require emergency embolization to reduce arteriovenous shunting [20].

Unlike IHs, neither RICHs nor NICHs expressed glucose transporter-1 protein (GLUT-1), a protein involved in glucose transport [21].

50.2.2 Tufted Angioma/Kaposiform Hemangioendothelioma

These seem to be two different expressions for the same tumor spectrum. They present as a rapidly progressing tumor located in the skin or soft tissue of the extremities and trunk. They derive from vascular endothelial cells, are locally aggressive, and have a great capacity of proliferation. They can be associated with the Kasabach-Merritt phenomenon characterized by important thrombocytopenia, hemolytic anemia, and disseminated intravascular coagulation that may result in life-threatening hemorrhage [22, 23] (Fig. 50.6).

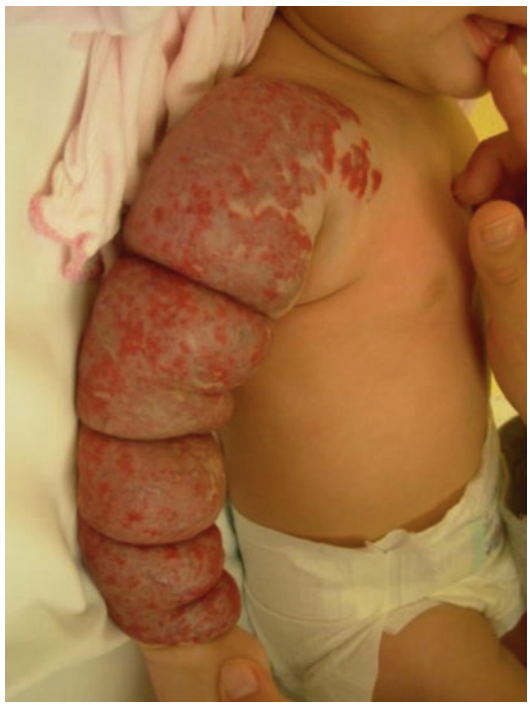

Fig. 50.6 Kaposiform hemangioendothelioma

50.3 Vascular Malformations

Vascular malformations affect 0.5% of the population. They result from errors in the embryonic development of blood vessels and are characterized by the lack of smooth muscle with mature endothelial channels [24]. Malformations present at birth may not be clinically evident. They grow proportionally to body growth with no spontaneous involution. They are subclassified according to the vessels involved and the rate of flow. Slow-flow lesions include capillary, venous, and lymphatic malformations. Fast-flow lesions are mainly represented by arteriovenous malformations. Combined anomalies may be present.

50.3.1 Low-Flow Malformations

50.3.1.1 Capillary Malformations

CMs are congenital vascular malformations of the skin characterized by ectatic capillaries and postcapillary venules in the dermis. Also called port-wine stains (PWS), they are present in 0.4% of newborns, with no difference between sexes. In 83% of cases, the lesion is present on the head and neck [24]. They are caused by the dilation of capillaries whose diameter ranges from 10 to 150 μm. They are present at birth, and their diameter remains stable throughout life. Their color, however, gradually changes from red to deep purple. Over time, they can lead to hypertrophy or nodule formation as they invade and deform mucous membranes, the lips in particular.

Depending on their localization, PWS may reveal the presence of certain syndromes, principally the Sturge-Weber syndrome (SWS). SWS is characterized by cerebral nervous system and ocular anomalies associated to a PWS in the area of the ophthalmic (V1) and maxillary (V2) trigeminal nerve. It originates from a failure of regression of a vascular plexus around the cephalic portion of the neural tube which is destined to become facial skin. This results in residual vascular tissue which forms angiomas of the leptomeninges, face, and ipsilateral eye [25] (Fig. 50.7).

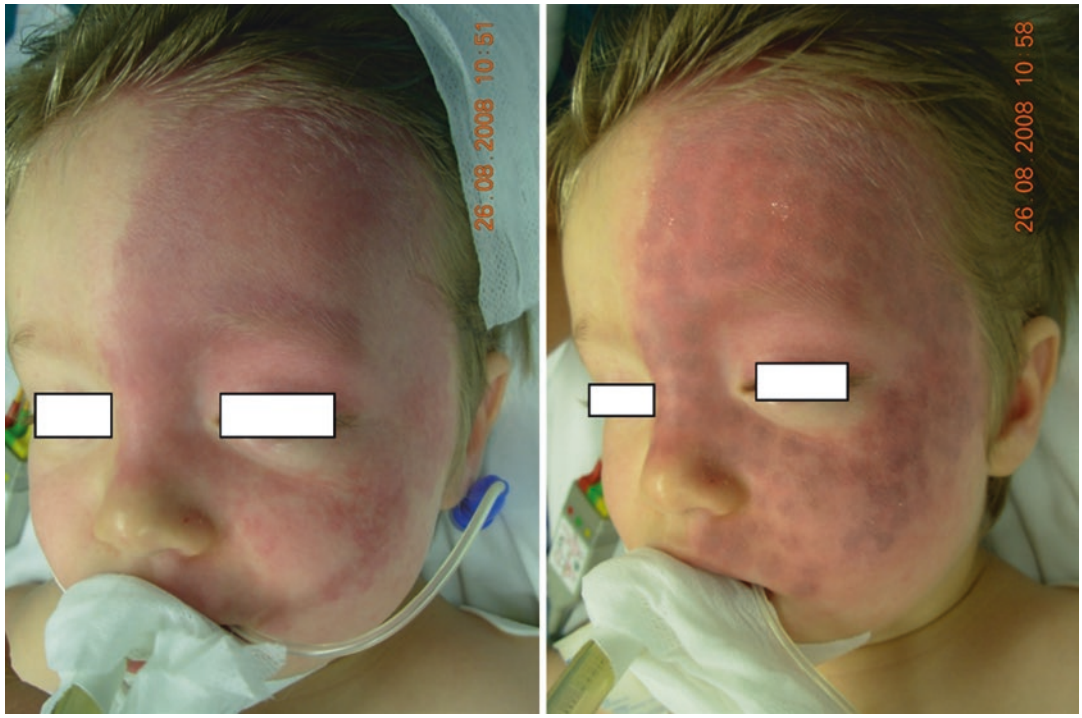

Fig. 50.7 Sturge-Weber Syndrome, PWS before and after Laser treatment

In some cases, the patient may develop neurological problems such as epilepsy, cognitive deficits, and mental retardation. Seizures first occur during the first year of life in 75% of patients and before the second year in 90%. MRI is the imaging technique of choice for diagnosis of SWS, showing the leptomeningeal vascular malformation that confirms the diagnosis. It is generally recommended to realize this exam by the age of 1 year, as structural changes are more evident at that time. Early diagnosis and management can minimize subsequent seizure. Glaucoma is one of the serious ocular manifestations in SWS, affecting approximately 30–70% of patients. It is not always present at birth. Patient should then be assessed by an ophthalmologist every 3 months for the first years of life and annually thereafter. Choroidal hemangioma is present in 40–50% of patients with SWS [26].

Capillary malformations of the forehead, eyelids, nose, and nuchal region are very common. They are usually defined as nevus simplex, salmon patch, and angel kiss or stork's bite. They often discolor spontaneously within the first 1 or 2 years of life. They do not need to be investigated for underlying malformations [27].

The standard treatment for capillary malformation is the pulsed dye laser (PDL) that produces selective photothermolysis on vessels at a chosen wavelength of 595 nm. This effect will shut the microcirculation in small blood vessels, thus toning down the color of the angioma and making it less visible.

In standard clinical practice, laser treatment must be repeated several times, with an interval of 6–8 weeks between each session, in order to be effective and to cover the entire affected surface. The procedure may take place under general anesthesia, and metal lenses must be worn to avoid the risk of retinal lesions. Several parameters can be modified, such as the fluence (J/cm^2) of the laser beam, the diameter (mm) of the light bundle, the duration (ms) of the pulse, the cooling of the skin, and the time interval between each session [27].

Prognosis is thought to be improved if treatment is started by 6 months of age [20].

In hypertrophic forms, generally affecting the lips and eyelid, debulking surgery, skin grafting of facial esthetic units, and reconstructive flaps are sometimes indicated as the patient grows.

Capillary telangiectasia is a less frequent anomaly affecting capillaries. It consists in permanent dilation of superficial dermal capillaries. It can be congenital, generally related to hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome, an autosomal dominant vascular anomaly associating multiple mucocutaneous and visceral vascular lesions. Telangiectasia looks the same as spider-like, red maculopapule, usually of 1–4 mm in diameter. When acquired, they can reveal a hepatocellular insufficiency.

Finally, angiokeratomas are solitary hyperkeratotic papules or plaques with a verrucous surface, ranging in color from deep red to blue-black. PDL therapy is the treatment of choice. The Nd:YAG laser has been used successfully [28] (Fig. 50.8).

50.3.1.2 Lymphatic Malformations

Lymphatic malformations (LMs) are benign, slow-flow vascular anomalies composed of dilated lymphatic channels and cysts that affect 1/200–4000 live births, without significant difference between sexes. LMs may involve any part of the body, but the majority (48–75%) is found in the cervicofacial region. 20–42% are found on the extremities [29]. LMs can be revealed as a sudden mass with a bluish discoloration that signs a bleeding event. They can infiltrate the viscera, bone, and soft tissues. Their imaging assessment is essentially based on ultrasound and MRI.

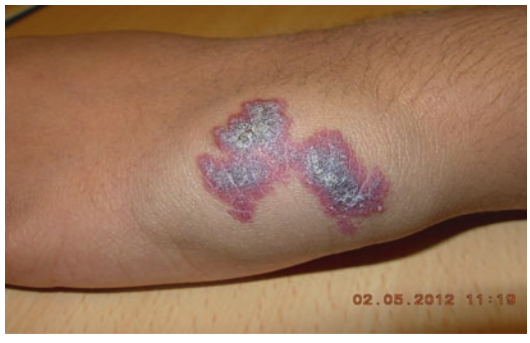

Fig. 50.8 Angiokeratoma of the wrist

LMs are classified according to their size as microcystic (less than 2 cm) or macrocystic (greater than 2 cm), but they can also be mixed (Fig. 50.9). On physical examination, macrocystic lesions are solitary soft subcutaneous masses with normal overlying skin. They are compressible, anechoic cysts with specific thin septations without Doppler flow. Microcystic lesions usually appear as vesicles filled with lymphatic fluid. They present as tiny cavities with a hyperechoic and solid appearance [24] (Fig. 50.10).

The indication for treatment is based on the age of the patient, the site, size and type of the lesion, and functional symptoms such as swelling, bleeding, recurrent infection, dysphagia, respiratory distress, or cosmetic deformity. Severe forms may require treatment based on sclerotherapy or surgical resection.

Percutaneous sclerotherapy is considered as the first-line treatment of LMs and has a greater success with macrocystic LMs. Many agents are used, for instance, doxycycline, bleomycin, absolute ethanol, Betadine, OK-432 (lyophilized *Streptococcus*), and alcoholic zein solution. Under imaging guidance, the sclerosant agent is injected by direct approach after decompression of the cyst. The aim is to induce an inflammatory reaction in lymph-vessel endothelium, resulting in size reduction. These procedures are generally performed under general anesthesia. Complications include local extravasation, skin necrosis, cellulitis, and compression of nearby structures such as airways and nerves [30, 31]. Sclerotherapy probably carries less risk than surgery. A complete excision is challenging because of the proximity to vital structures.

Laser therapy and radiofrequency ablation can be considered as other therapeutic modalities, particularly in microcystic forms of LM.

50.3.1.3 Venous Malformations

Venous malformations (VMs) are the most common congenital, dysplastic vascular malformations [32]. Histologically, they are characterized by ectatic and tortuous venous

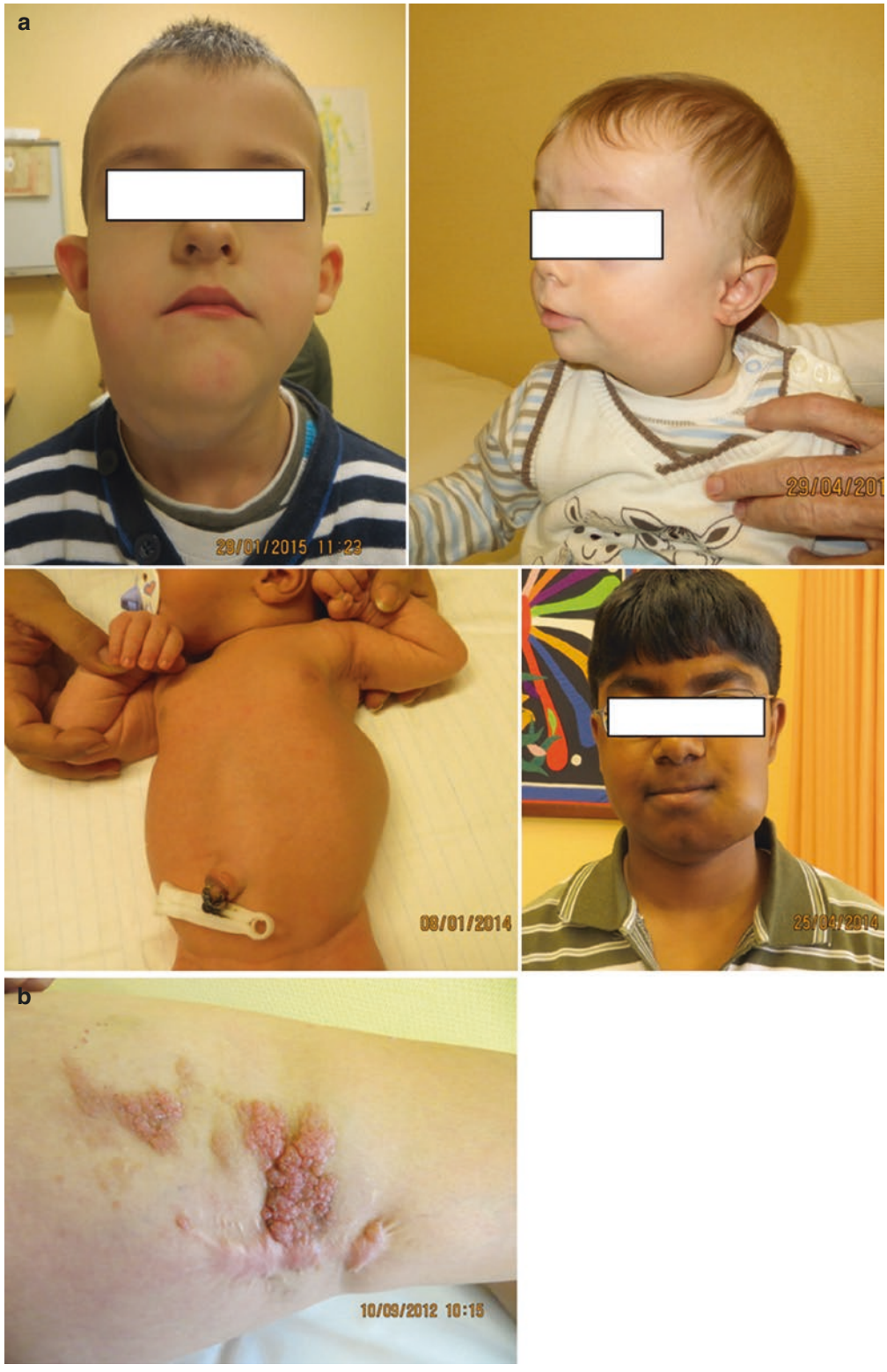

Fig. 50.9 Lymphatic malformation: macrocystic (**a**) and microcystic (**b**)

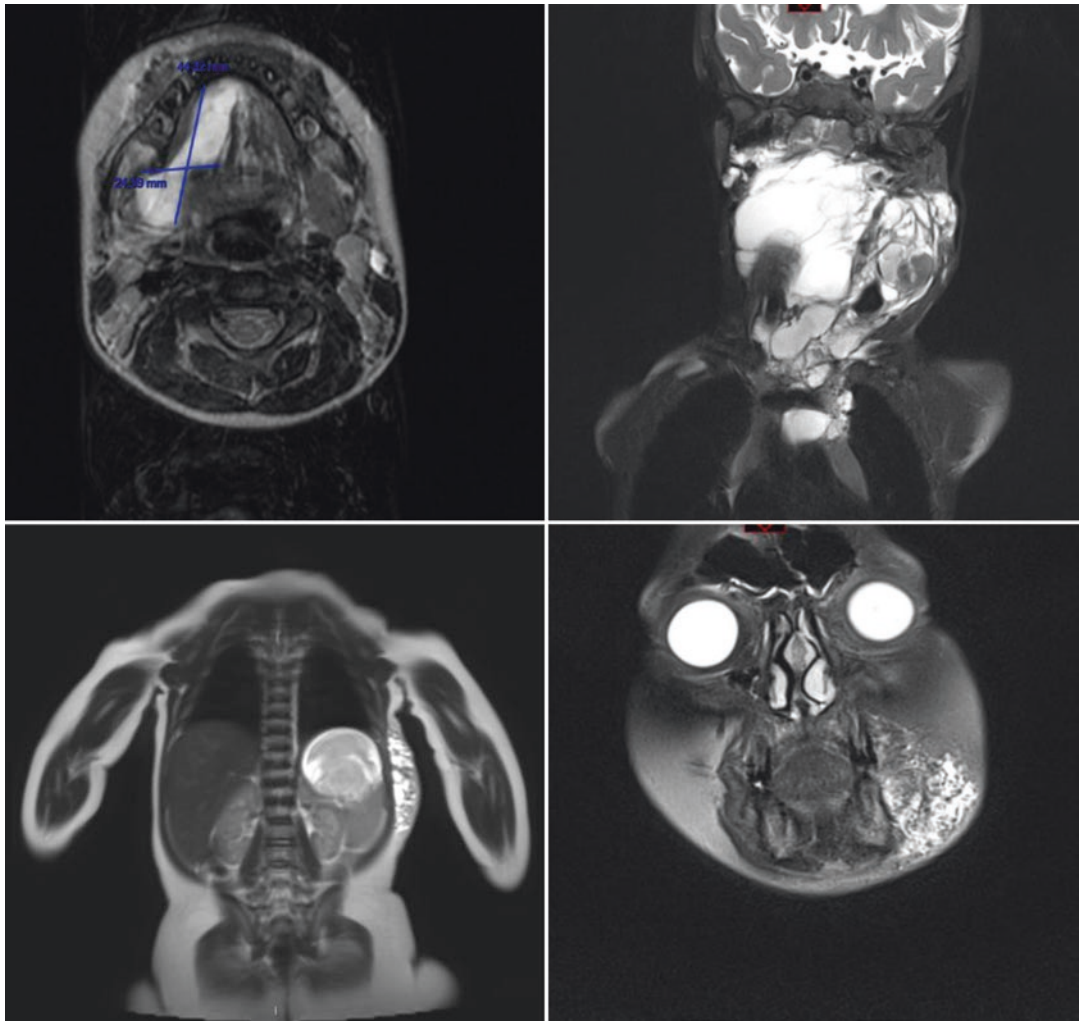

Fig. 50.10 Lymphatic malformation, MRI aspect

channels delimited by normal endothelium with decreased perivascular cell coverage [33].

The gene TIE2 has been implicated in VMs and cutaneomucosal venous malformations [34].

Their prevalence is about 1% with an incidence of 1 in 10,000. More than 40% of lesions are found on the head and neck, 40% on the extremities, and 20% on the trunk [35].

Sometimes present at birth, MVs usually grow discreetly during childhood and may expand rapidly with puberty under the influence of hormones. Clinically, they appear as bluish, soft, depressible tumors. They refill during Valsalva manoeuvers or depending on the position of the patient. They do not have a palpable pulse or thrill. Like LMs, venous malformations can be well circumscribed in the cutaneous or subcutaneous tissue or diffuse and infiltrating muscles, bones, and intra-articular cavities, resulting in functional impairment and cosmetic disturbance (Fig. 50.11).

Although VMs are generally asymptomatic, complications such as pain, inflammation, localized intravascular coagulopathy, and recurrent thrombotic episodes may occur.

Temporo-masseterian MVs may have extension to the jaw, the buccal floor, and the

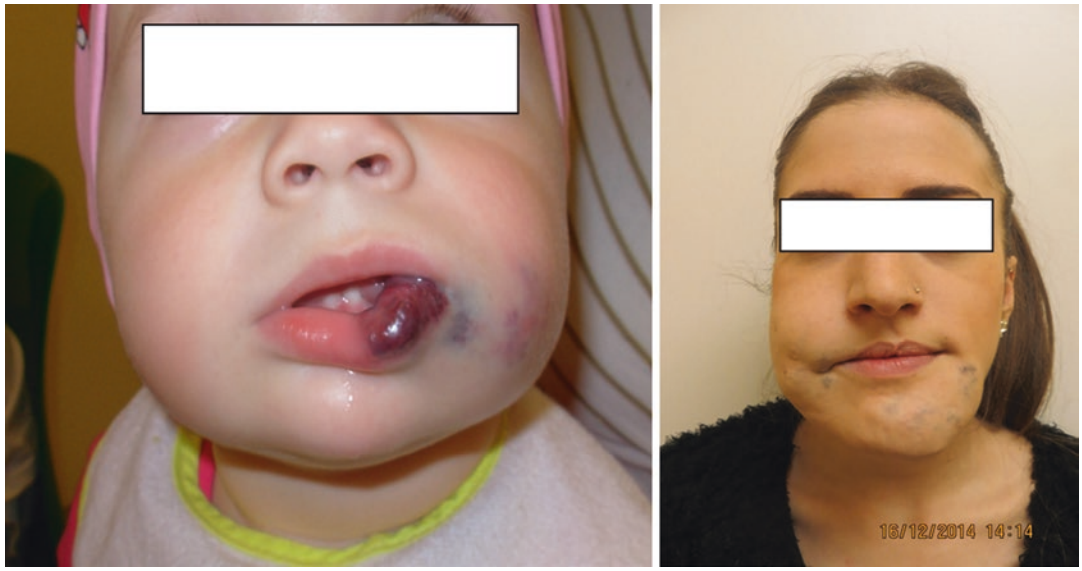

Fig. 50.11 Venous malformation

pharyngo-laryngeal region leading to respiratory or swallowing disorders. Labial and jugal MVs can be responsible of disorder of the dental articulation.

The imaging investigation of choice is US Doppler that shows slow-flow compressible lesion without flow voids and occasionally thrombus or phlebolith [36, 37].

Treatment options include compression and pain management. Compression garments can help to decrease pain and swelling especially in extremities [20].

For most lesions, no further intervention is indicated. However, if necessary, percutaneous sclerotherapy or surgery can be performed. As in LMs, sclerotherapy consists in puncturing the malformation and injecting the sclerosing agent into the cavities under radiographic control. Sclerotherapy is commonly used as primary therapy or to shrink VMs before surgery. The surgical approach is designed to treat well-defined lesions of small dimension and, at a lower level of effectiveness, to debulk diffuse ones and minimize aesthetic sequelae.

Upper aerodigestive tract venous malformations can be treated by 980-nm diode endovascular laser that greatly reduces dysphagia and sleep apnea symptoms [38].

MVs can be isolated or be part of syndromes such as the Blue rubber bleb naevus (BRBN) syndrome, characterized by the presence of multiple cutaneous and visceral venous malformations, particularly in the digestive tract. The cutaneous lesions appear as bluish, protruding masses, disseminated all over the teguments especially on the palm and sole and increasing with age. Gastrointestinal tract malformations are a source of chronic bleeding and hemorrhage, thus dominating the prognosis. Surgical treatment of these lesions by endoscopic fulguration or intestinal resection may be required in some cases.

Management is often multidisciplinary and can include medical, interventional radiological, and surgical treatment [39, 40].

Rarely, venous malformations present as glomangiomas: dark and tender venous nodules characterized histologically by the presence of smooth muscle-like glomus cells.

Finally, although it is not a venous malformation in the true sense of the term, Sinus pericranii (SP) is an entity that must be known. SP is a rare congenital or acquired disorder characterized by a communication between an extracranial vein and an intracranial venous sinus, through diploic veins. It presents as a subcutaneous mass which

changes with the head's position or a blue or red macular discoloration or alopecia localized on the scalp close to the midline. MRI is the imaging technique of choice; it shows dilated vascular structures communicating through the cranial vault. SP may have potentially serious complications, including thrombosis and massive hemorrhage. Treatment is proposed for cosmetic or prophylactic reasons. Conventional surgery, endovascular therapy, and percutaneous injection have been described [41].

50.3.2 Fast-Flow Malformations

50.3.2.1 Arteriovenous Malformations (AVMs)

AVMs are congenital malformations and result from an abnormal and direct connection between arteries and veins, bypassing capillary beds. Vessels become dilated, veins become arterialized, and pressure remains high. AVMs are characterized by a nidus and a complex network of feeding arteries and draining veins [42]. They occur in 0.1% of the general population. Clinically, they present as warm cutaneous or subcutaneous tumors that may resemble capillary malformations with a possible palpable thrill. They may cause pain, ulceration, or hemorrhage.

AVMs are present at birth, remain dormant during childhood, and may become symptomatic at puberty or after a direct traumatism that stimulates their expansion [43]. They are progressive, invasive, and destructive. Their clinical progression is illustrated by the Schobinger classification [44] (Table 50.1).

The diagnosis is confirmed by Doppler ultrasound, MRI, and arteriography. They show a high-flow malformation with AV shunting and arterialized veins [45].

Table 50.1 Schobinger classification of arteriovenous malformation

	Stage	Features
I	Quiescence	Skin discoloration, pink/blue and warm
II	Expansion	Audible pulsation, bruit, thrill
III	Destruction	Ulceration, bleeding, infection
IV	Compensation	Congestive cardiac failure

AVMs are the most challenging lesions to manage and have high rates of morbidity and recurrence. No single modality of treatment is effective, and multimodal therapy is often necessary. The aim of the treatment is to obliterate the nidus. The present management of AVMs is based on superselective embolization of the feeding arteries and nidus, followed, if necessary, by a surgical excision of the AVM. Embolization alone may not be sufficient and may lead to an early revascularization, making the vascular supply more complex by stimulating angiogenesis and collateralization. It is often reserved for nonoperable AVMs in order to palliate symptoms (Fig. 50.12). But it may also be used preoperatively to delineate the lesion in order to reduce intraoperative bleeding [46, 47]. The surgical approach entails the risk of life-threatening bleeding and leads to a high probability of recurrence if partial. It is reserved for very well-defined lesions.

50.3.3 Combined Malformations

There are several patients who present a mixed vessel-type malformation. These patients often have significant morbidity, and their management is obviously more complicated.

50.3.3.1 Klippel-Trenaunay Syndrome (KTS)

KTS is characterized by the presence of a capillary malformation associated with bone and/or soft tissue overgrowth and superficial or deep venous system anomalies of the affected limb. Bleeding angiokeratomas can appear on the skin area affected by the capillary malformation. An intrapelvic extension with the presence of submucosal venous varicosities leading to rectal bleeding is extremely rare [25] (Fig. 50.13).

50.3.3.2 Parkes Weber Syndrome (PWS)

PWS associates large cutaneous capillary malformation, underlying arteriovenous shunting, and bony and soft tissues hypertrophy. It is caused by mutations in RASA1, mapped to

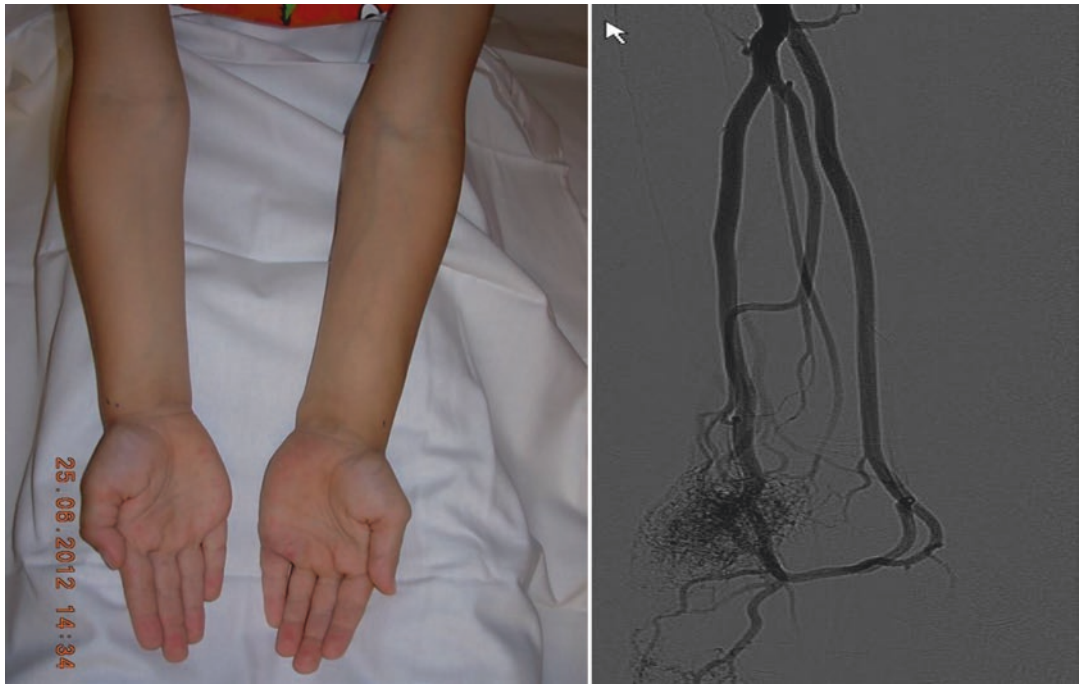

Fig. 50.12 Arteriovenous malformation, nidus on arteriography

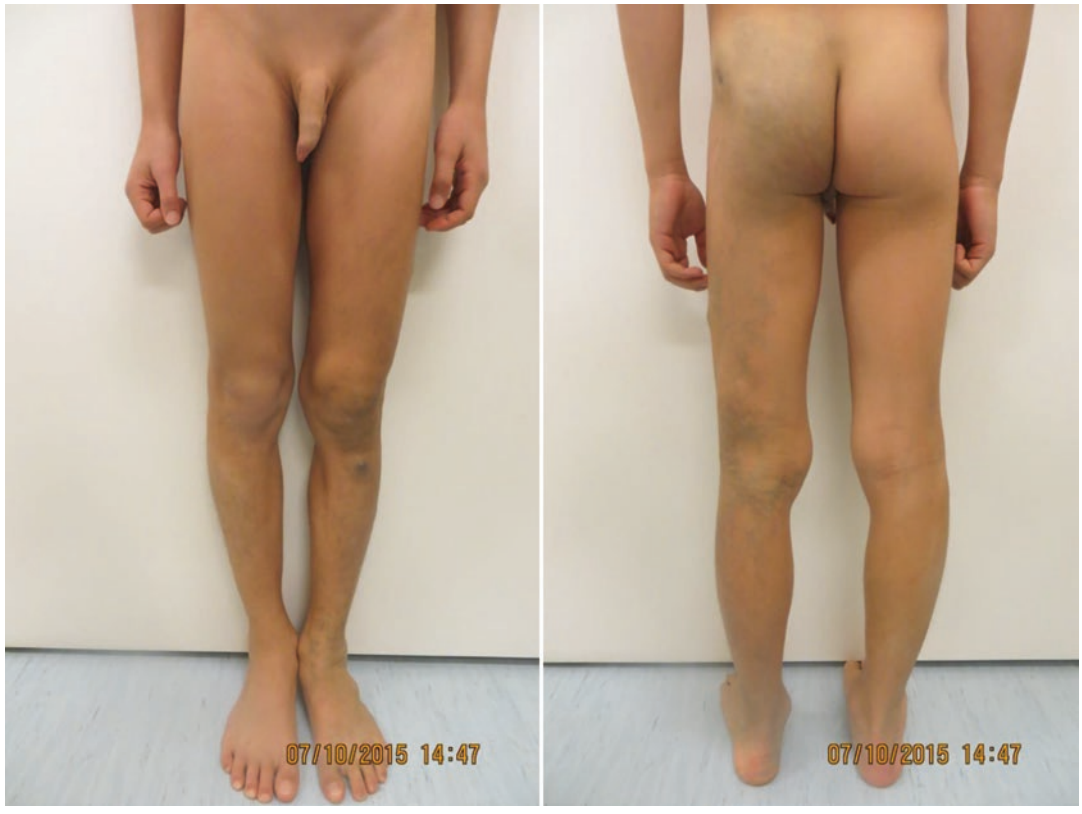

Fig. 50.13 Klippel-Trenaunay Syndrome

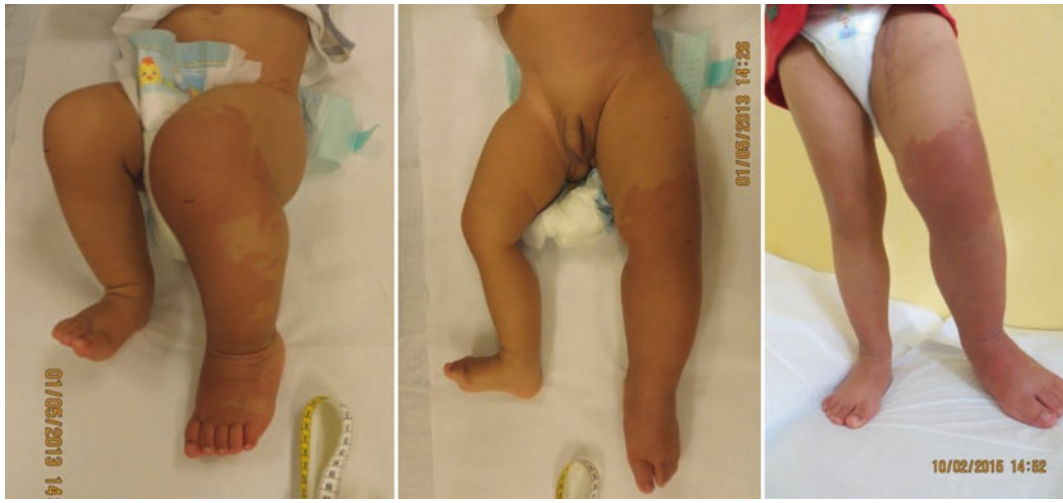

Fig. 50.14 Parkes Weber Syndrome

5q14.3 [48, 49] (Fig. 50.14). Limb enlargement may be significant and lead to an early asymmetry. Orthopedic follow-up is recommended.

50.3.3.3 Wyburn Mason Syndrome (Syndrome de Bonnet Dechaume Blanc)

It is a rare condition characterized by arteriovenous malformations in the central nervous system and the retina and an upper facial port-wine stain.

The syndrome can cause seizures, subarachnoid hemorrhage, and focal neurologic deficits. Present at birth, it generally worsens with time. Treatment is symptomatic and supportive [28].

50.3.3.4 Cobb Syndrome

Cobb syndrome is a rare metameric disorder, characterized by a spinal vascular abnormality in association with vascular skin lesion of the same metamer.

Patients can remain asymptomatic for a long time, but the evolutive risk is essentially neurological secondary to an acute medullary bleeding.

Radiological exploration, especially medullary MRI, must be realized each time a metameric angioma of the trunk is diagnosed. Current treatment is based on embolization and/or surgery [50].

Table 50.2 Simplified ISSVA classification of vascular anomalies

Vascular tumors
Infantile hemangioma
Congenital hemangioma
Rapidly involuting congenital hemangiomas
Non-involuting congenital hemangiomas
Kaposiform hemangioendothelioma
Others
Vascular malformations
Slow-flow vascular malformations
Venous malformations
Lymphatic malformations
Capillary malformations
Fast-flow vascular malformation
Arteriovenous malformations/fistulas
Combined complex vascular malformations

ISSVA International Society for the Study of Vascular Anomalies

50.4 Conclusion

Vascular anomalies are a rare disease that presents with a large spectrum of clinical symptoms and a different biological behavior. They can lead to serious functional disorders and cosmetic impairment.

It is essential to distinguish between vascular tumors and malformations.

The ISSVA classification is a valuable tool that offers a better understanding of this pathology and allows the practice of a common scientific language (Table 50.2).

The keystone of a good management of vascular anomalies is a precise diagnosis, adequate investigation, and appropriate treatment.

Treatment options include conservative management as long as the patients are asymptomatic; but interventional radiology, laser therapy and open surgery may prove necessary. Multimodal treatment is often required and should only be designed by a multidisciplinary team.

The mammalian target of rapamycin (MTOR) pathway, responsible of cell growth and survival, and its inhibition by sirolimus, an MTOR inhibitor, appear to be promising for complex vascular malformations [51].

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