Prenatal Diagnosis and Fetal Therapy

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Contents

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125.1 Introduction [1]

Prenatal diagnosis and fetal therapy have had a major impact in pediatric surgery in the last three decades. Although prenatal diagnosis is rare in many African countries, as prenatal ultrasound becomes available, pediatric surgeons have to be aware that the natural history of malformations seen in utero is the same as its postnatal counterpart.

Expertise in surgical correction of congenital malformations may favourably influence the perinatal management of prenatally diagnosed anomalies, by changing the site of delivery for immediate postnatal treatment; altering the mode of delivery to prevent obstructed labour or haemorrhage; early delivery to prevent ongoing fetal organ damage; or treatment in utero to prevent, minimise or reverse fetal organ injury as a result of a structural defect. The referral base for a pediatric surgeon now includes the fetal and perinatal period.

The diagnosis and management of complex fetal anomalies require a team effort by obstetricians, neonatologists, geneticists, pediatricians and pediatric surgeons to deal with all the maternal and fetal complexities of diagnosis of a structural defect. This team should be able to provide information to prospective parents on fetal outcomes, possible interventions, appropriate setting, time and route of delivery and expected postnatal outcomes. The role of the surgical consultant, in this team, is to present information regarding the prenatal and postnatal natural history of an anomaly, its surgical management and the long-term outcome.

125.2 Congenital Malformation

Congenital malformations are significant causes of perinatal mortality and morbidity. Single major birth defects affect 3% of newborns, and 0.7% of babies have multiple defects. The prenatal hidden mortality is higher since the majority abort spontaneously. Despite improvements in perinatal care, serious birth defects still account for 20% of all deaths in the newborn period and an even greater percentage of serious morbidity later in infancy and childhood. The major causes of congenital malformation are chromosomal abnormalities, mutant genes, multifactorial disorders and teratogenic agents.

125.3 Prenatal Diagnosis [2–4]

Prenatal diagnosis has remarkably improved our understanding of surgically correctable congenital malformations. It has allowed us to influence the delivery of a baby, offer prenatal surgical management and discuss the options of termination of pregnancy for seriously handicapping or lethal conditions. Screening for trisomy 21 may now be offered in the first trimester (e.g., nuchal scan combined test) (Fig. 125.1) or second trimester (e.g., triple blood test). Better resolution and increased experience with ultrasound scans have led to the recognition of ultrasound 'soft markers', which have increased the detection rate of fetal anomalies, though at the expense of higher false positive rates.

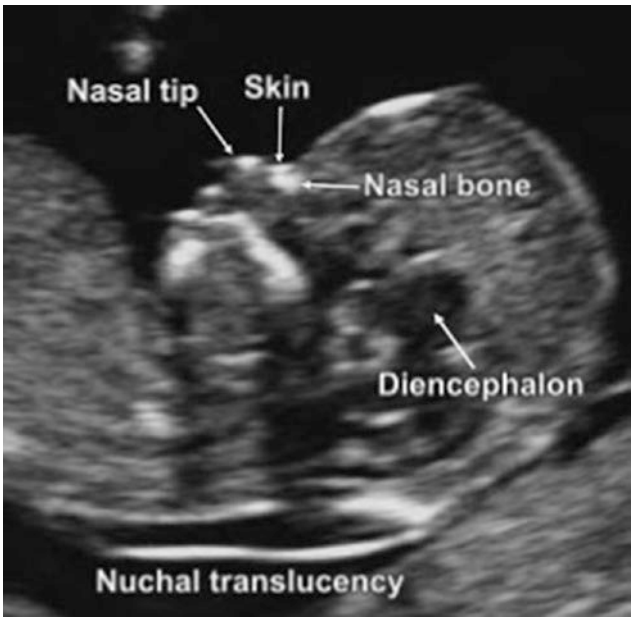

Fig. 125.1 Nuchal thickening on scan

Routine ultrasound screening identifies anomalies and places these pregnancies in the high-risk categories with maternal diabetes, hypertension, genetic disorders, raised alpha-fetoprotein, etc. High-risk pregnancies may be offered further invasive diagnostic investigations such as amniocentesis or chorionic villous sampling. Structural abnormalities difficult to define on ultrasound such as hindbrain lesions or in the presence of oligohydramnios are better imaged on ultrafast magnetic resonance imaging (MRI). With the increasing range of options and sophistication of diagnostic methods (Fig. 125.2), parents today are faced with more information, choice and decisions than ever before, which can create as well as help to solve dilemmas.

125.4 Specific Surgical Conditions [5–7]

125.4.1 Congenital Diaphragmatic Hernia (CDH) (Fig. 125.3a, b)

CDH accounts for 1 in 3000 live births and challenges the neonatologist and pediatric surgeons in the management of this high-risk condition. Mortality remains high (over 60%) when the 'hidden' mortality of in utero

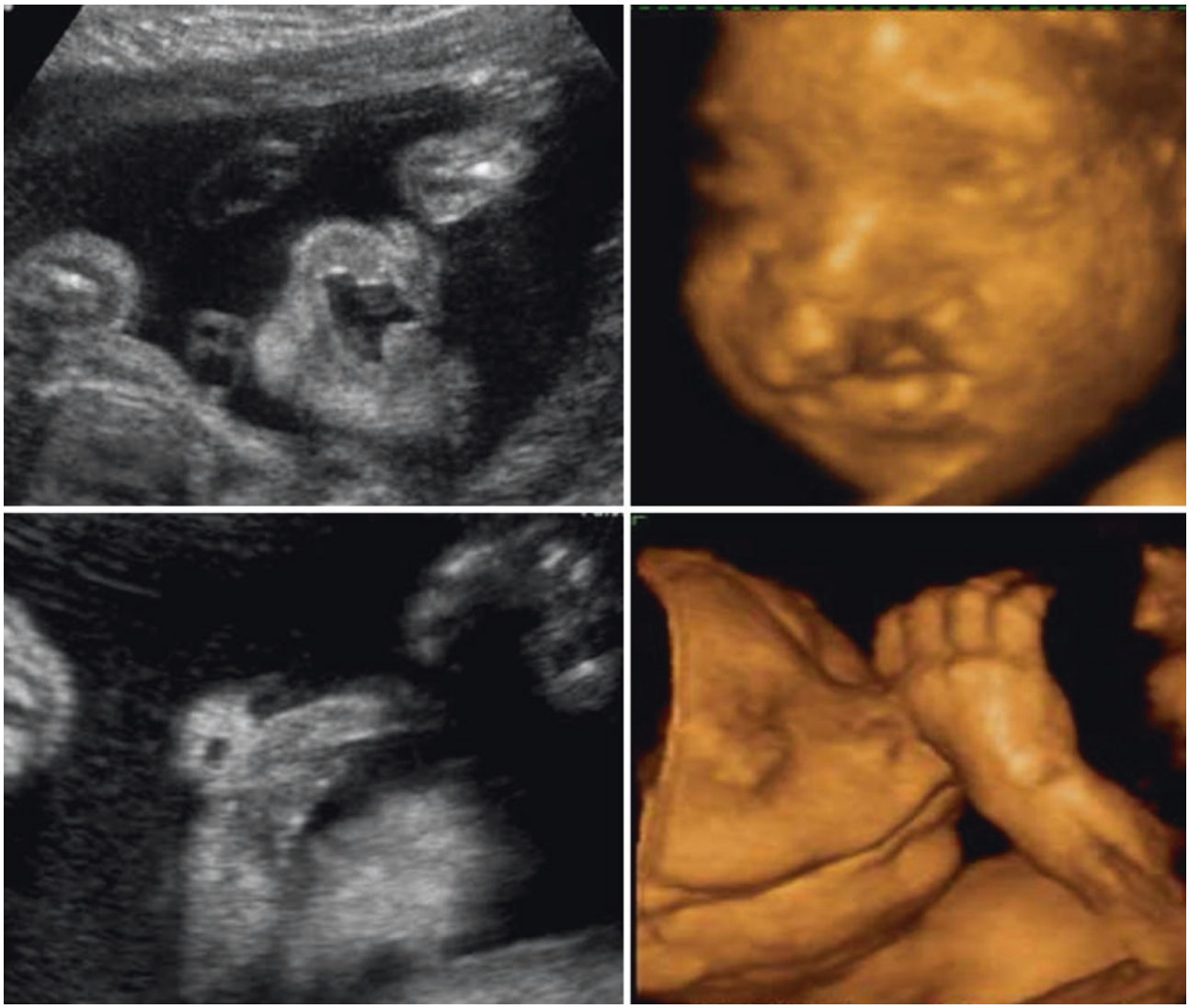

Fig. 125.2 2-D and 3-D scan of facial banding

death and termination of pregnancy are taken into account and around 25–30% in liveborn babies with isolated CDH despite all the tools available in high-income countries. Lung hypoplasia and pulmonary hypertension account for most deaths in isolated CDH newborns. Associated anomalies (30–40%) signify a grave prognosis with a survival rate of less than 10%.

In the UK, most CDH are diagnosed at the 20-week anomaly scan with a detection rate approaching 60%. Magnetic resonance imaging (MRI) has a useful role in accurately differentiating CDH from cystic lung lesions and may be useful in measuring fetal lung volumes as a predictor of outcome. Cardiac anomalies (20%), chromosomal anomalies (trisomy 13 and 18) (20%) and urinary, gastrointestinal and neurological (33%) anomalies can co-exist with CDH. In isolated cases, early CDH detection, presence of the liver in the chest and fetal lung-to-head ratio (LHR) of less than 1 (or observed/expected LHR < 25%) are implicated as poor predictors of outcome [ref?]. In these patients with poor prognostic signs, fetal surgery for CDH over the last two decades has been disappointing; however, benefit from fetal intervention with tracheal occlusion (FETO) awaits randomised studies. Antenatal steroids have not been shown to improve outcomes in the clinical setting. Elective delivery at a specialised centre is recommended, with no benefit from caesarean section.

125.4.2 Congenital Lung Lesions (Fig. 125.4)

Congenital pulmonary airway malformations (CPAM, previously called congenital cystic adenomatoid malformations or CCAM), bronchopulmonary sequestrations (BPS) or 'hybrid' lesions containing features of both are

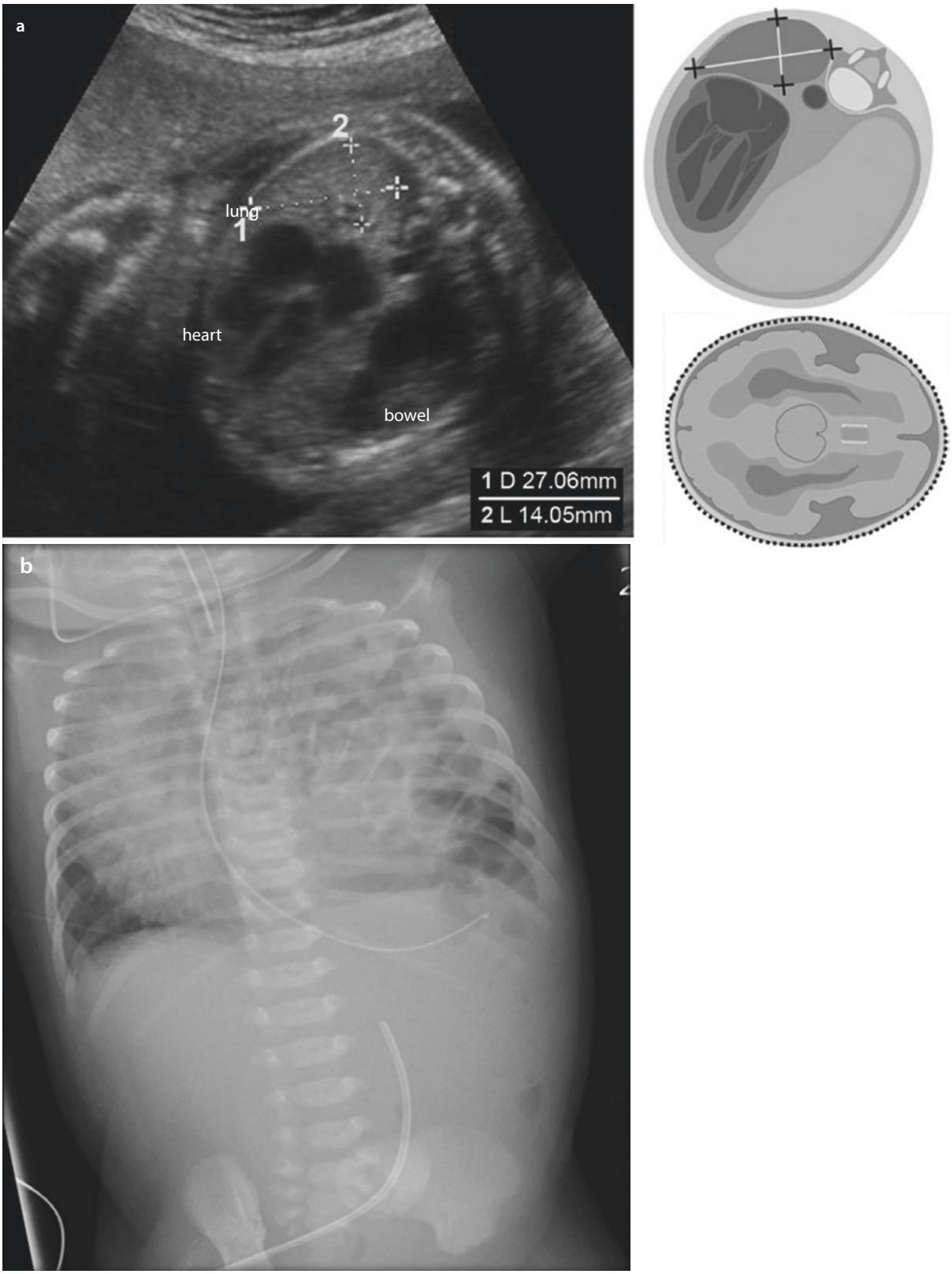

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Fig. 125.3 **a**, **b** Diaphragmatic hernia

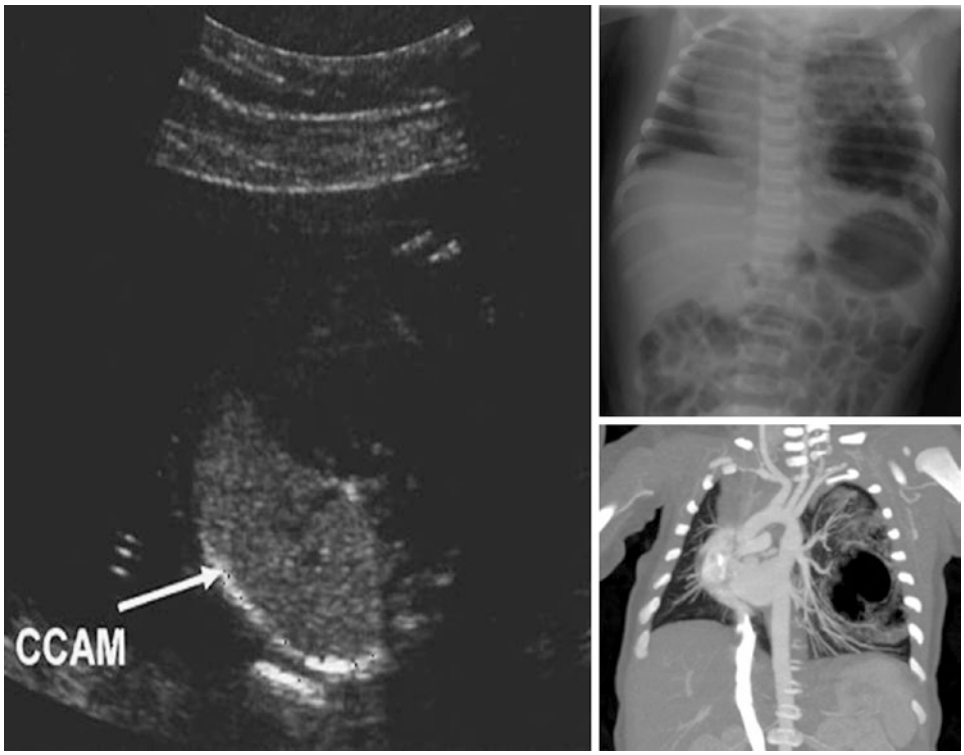

Fig. 125.4 Congenital lung cyst

common lung lesions noted on prenatal scan. Less common lung anomalies include bronchogenic cysts, congenital lobar emphysema and bronchial atresia. Congenital lung lesions are rare anomalies with an incidence of 1 in 10,000 to 1 in 35,000.

Prenatal detection rate of congenital lung cysts at the routine 18–20-week scan is almost 100% and may be the commonest mode of actual presentation. They are generally described as microcystic (hyperechoic on ultrasound), macrocystic or mixed. Most of these lesions are easily distinguished from congenital diaphragmatic hernia; however, sonographic features of CPAM or BPS are not sufficiently accurate and correlate poorly with histology. The finding of a systemic arterial supply to the lesion confirms the diagnosis of BPS; however, the differentiation between extralobar and intralobar cannot be confirmed until postnatal imaging. Magnetic resonance imaging (MRI), though not routinely used, may provide better definition for congenital lung lesions; however, inaccuracies were still reported in 11% of cases [ref?].

Bilateral disease and hydrops foetalis are indicators of poor outcome, whilst mediastinal shift, polyhydramnios and early detection do not correlate with outcome. The CPAM volume ratio (CVR) has been a useful tool to predict the development of hydrops. When diagnosed in the second trimester, these lesions should be followed closely (weekly or biweekly initially) as they may grow and lead to hydrops. Observation and reassurance are warranted for lesions with a CVR < 1.4 as many will start regressing after 26 weeks of gestation with a generally favourable outcome. For microcystic lesions with a CVR > 1.4 or associated with hydrops, maternal betamethasone administration often reduces the size of the lesion and alleviates the mass effect, probably by reducing lung fluid production. This simple treatment has nearly rendered obsolete the open fetal surgeries for lobectomy that were performed in a few centres. Macrocystic lesions do not respond as well to steroid administration, but needle decompression, often followed by placement of a fetal thoraco-amniotic shunt, has led to the reversal of hydrops and a good outcome in many reports. In some instances of large BPS associated with pleural effusion and hydrops, drainage of the pleural fluid has led to the reversal of the hydrops. Laser ablation of the systemic arterial vessel feeding the malformation has also been reported.

Overall, in only 10% of cases the need for fetal intervention arises. In the absence of termination of pregnancy, the natural fetal demise rate of antenatally diagnosed cystic lung disease is 28% in major fetal centres. In the absence of hydrops, the prognosis is excellent with the majority of babies being asymptomatic at birth. In fact, ill-advised termination of pregnancy is probably the most common cause of mortality. It is well documented that spontaneous involution of lung lesions can

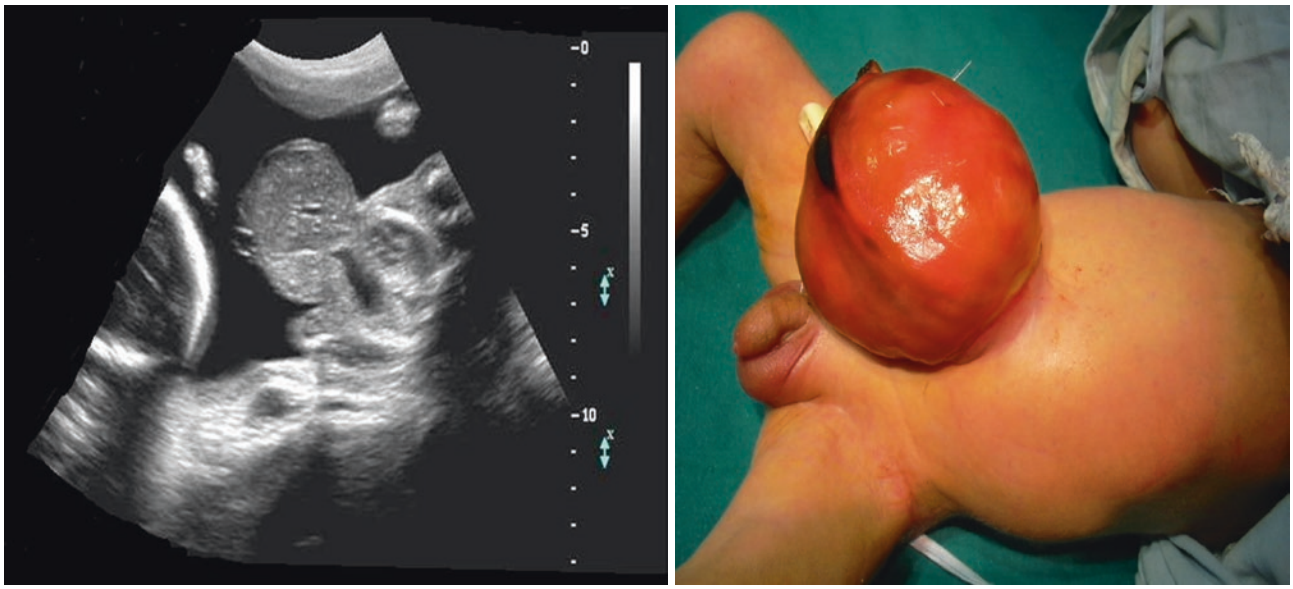

Fig. 125.5 Exomphalos

occur in utero, but apparent spontaneous 'disappearance' of antenatally diagnosed lesions should be interpreted with care, as nearly half of these cases subsequently still require surgery. Apparently, normal plain radiographs after birth are generally followed by chest CT scan at 2–4 months of age.

Normal vaginal delivery is recommended unless maternal condition indicates otherwise. Large lesions that persist throughout the third trimester are predicted to become symptomatic shortly after birth; thus delivery at a specialised centre would be appropriate. However, smaller lesions are less likely to be symptomatic at birth and could be delivered at the referring institution with follow-up in a pediatric surgery clinic.

125.4.3 Abdominal Wall Defects

Exomphalos and gastroschisis are both common but distinct abdominal wall defects with an unclear aetiology and a controversial prognosis. Attention may be drawn to their presence during the second trimester because of raised maternal serum alpha-fetoprotein level or abnormal ultrasounds scan.

125.4.4 Exomphalos (Fig. 125.5)

Exomphalos (or omphalocele) is characteristically a midline defect, usually near the insertion point of the umbilical cord, with a viable sac composed of amnion and peritoneum containing herniated abdominal contents. Incidence is known to be 1 in 4000 live births. Associated major abnormalities which include trisomy 13,18 and 21, Beckwith-Wiedemann syndrome (macroglossia, gigantism, exomphalos), pentalogy of Cantrell (sternal, pericardial, cardiac, abdominal wall and diaphragmatic defect) and cardiac, gastrointestinal and renal abnormalities are noted in 60–70% of cases; thus karyotyping, in addition to detailed sonographic review and fetal echocardiogram, is essential for complete prenatal screening. Fetal intervention is not indicated in this condition. If termination is not considered, normal vaginal delivery at a centre with neonatal surgical expertise is recommended, and delivery by caesarean section is only reserved for large exomphalos with exteriorised liver to prevent liver rupture with haemorrhage. Pulmonary hypoplasia is frequently associated with large exomphalos, as well as premature labour and delivery. Management of the abdominal wall defect should be conservative initially in any neonate who requires respiratory support.

125.4.5 Gastroschisis (Fig. 125.6)

Gastroschisis is an isolated lesion that usually occurs on the right side of the normally inserted umbilical cord with evisceration of the abdominal contents directly into the amniotic cavity. The incidence is increasing from 1.66 per 10,000 births to 4.6 per 10,000 births affecting mainly young mothers typically less than 20 years old. Associated anomalies are noted in only 5–24% of cases, with most being secondary to the gastroschisis. Bowel atresia is the most common co-existing abnormality, followed by undescended testes. Arthrogryposis is also associated but uncommon. On prenatal scan with a detection rate of 100%, the bowel appears to be free floating, and the loops may appear to be thickened due

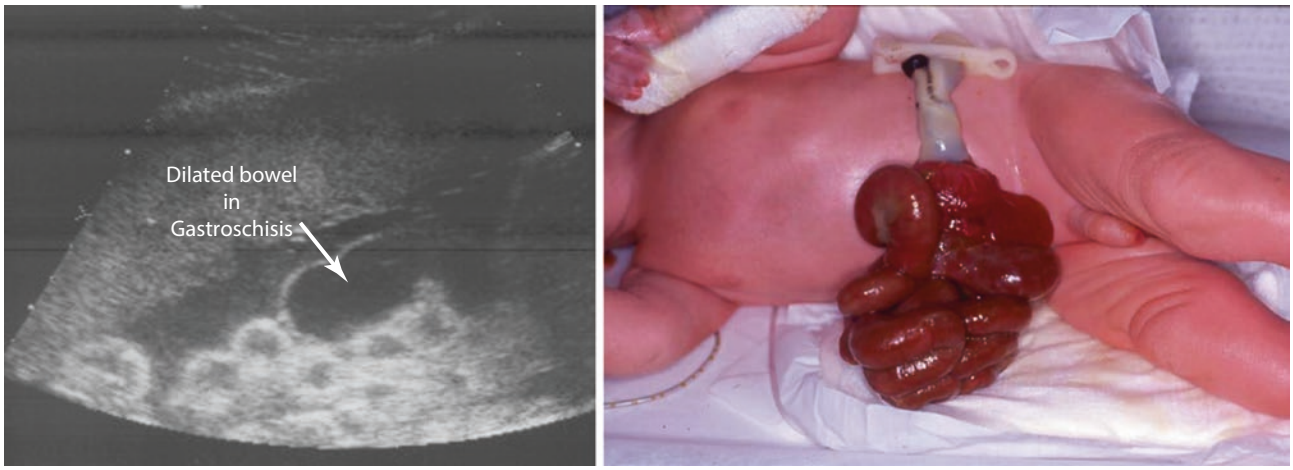

Fig. 125.6 Gastroschisis

to damage by amniotic fluid exposure (and/or a relative pinching at the level of the defect) causing a 'peel' formation. Dilated loops of bowel may be seen from obstruction secondary to protrusion from a narrow defect or atresia due to intestinal ischaemia.

Predicting outcome in foetuses with gastroschisis based on prenatal ultrasound finding remains a challenge. There is some evidence that maximum small bowel diameter may be predictive; however, thickened matted bowel and Doppler measurements of the superior mesenteric artery are not accurate predictors of outcome. To reduce the rate of third-trimester fetal loss, serial ultrasounds are performed to monitor the development of bowel obstruction and vaginal delivery around 37 weeks recommended at a centre with neonatal surgical expertise. Spontaneous fetal demise is less than 5–10%, and prognosis of liveborn babies is excellent in high-income countries with 95% survival. In Africa, survival rates is much lower, even close to 0 in some countries, due in large part to the limited availability of neonatal intensive care units and especially parenteral nutrition, which is required for 2–3 weeks or more before adequate bowel function returns. Gradual reduction using a silastic silo allows complete reduction and a sutureless closure, avoiding general anaesthesia and intubation in many cases; this technique has led to significant improvements in survival in some African countries.

125.4.6 Oesophageal Atresia (OA) with or Without Tracheo-oesophageal Fistula (TOF)

Repair of OA/TOF is a condition which measures the skill of a pediatric surgeon from trainee to independent surgeon. The incidence is estimated at 1 in 3000 births. Prenatally, the condition may be suspected from maternal polyhydramnios and absence of a fetal stomach bubble at the 20-week anomaly scan or later in gestation. Prenatal scan diagnosis of OA/TOF is estimated to be less than 42% sensitive with a positive predicted value of 56%. Pure OA is more likely to be diagnosed prenatally since no fluid can make it to the stomach, but this represents only 10% of cases. Additional diagnostic clues are provided by associated anomalies such as trisomy 13,18 and 21, VACTERL sequence (vertebral, anorectal, cardiac, tracheo-oesophageal, renal, limbs) and CHARGE association (coloboma, heart defects, atresia choanae, retarded development, genital hypoplasia, ear abnormality). These associated anomalies are present in more than 50% of cases and worsen the prognosis; thus, prenatal karyotyping is essential. Duodenal atresia may co-exist with OA/TOF. The risk of recurrence in subsequent pregnancies for isolated OA/TOF is less than 1%. Delivery is advised to be at specialised centre with neonatal surgical input.

125.4.7 Gastrointestinal Lesions (Fig. 125.7)

The presence of dilated loops of bowel (>15 mm in length and 7 mm in diameter) on prenatal ultrasound scan is indicative of bowel obstruction.

Duodenal atresia (Fig. 125.7) has a characteristic 'double bubble' appearance on prenatal scan, resulting from the simultaneous dilatation of the stomach and proximal duodenum. Detection rate on the second trimester anomaly scan is almost 100% in the presence of polyhydramnios and the 'double bubble' sign. Associated anomalies are present in approximately 50% of cases with most notably trisomy 21 in 30% of cases, cardiac anomalies in 20% and the presence of the VACTERL association (vertebral, anorectal, cardiac, tracheo-oesophageal, renal and limbs).

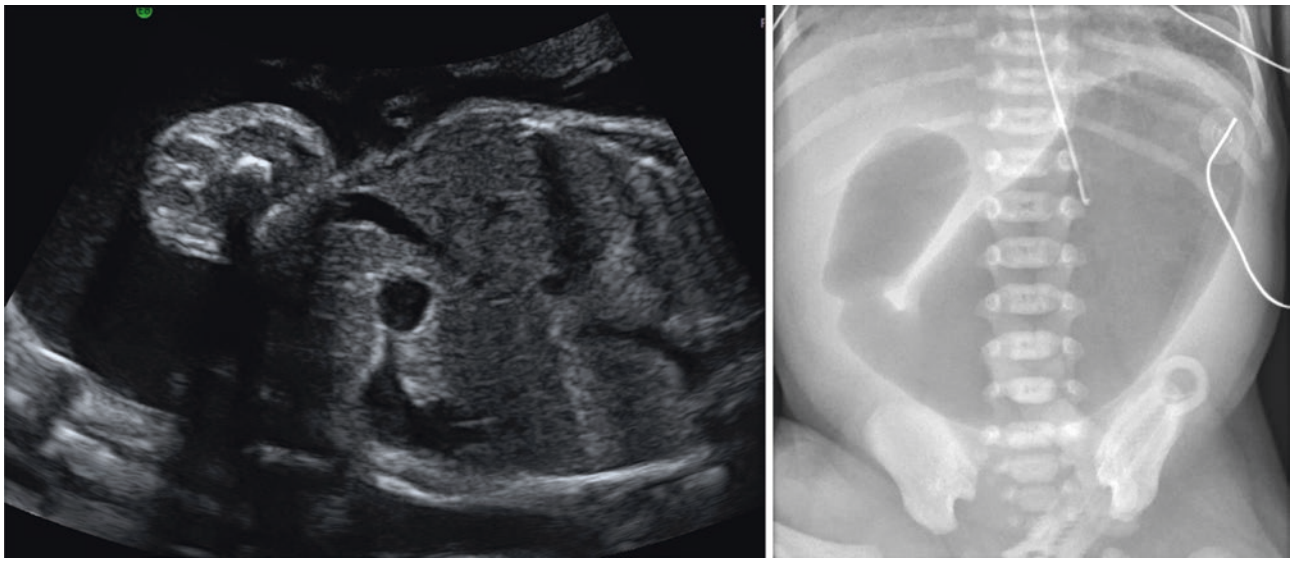

Fig. 125.7 Duodenal obstruction

The incidence of duodenal atresia is 1 in 5000 live birth. The postnatal survival rate is >95% with associated anomalies, low birth weight and prematurity contributing to the <5% mortality. Temporary delay in enteral feeding occurs due to the dysmotility in the dilated stomach and duodenum. Duodenal tapering may allow earlier return of function, and the use of a transanastomotic feeding tube helps in avoiding the need for parenteral nutrition.

There are many bowel abnormalities which may be noted on prenatal scanning (dilated bowel, ascites, cystic masses, hyperperistalsis, polyhydramnios and echogenic bowel); however, none is absolutely predictive of postnatal outcome. Patients with obstruction frequently have findings (especially in the third trimester) of bowel dilatation, polyhydramnios and hyperperistalsis, but ultrasound is much less sensitive in diagnosing large bowel anomalies than those in small bowel. Since the large bowel is mostly a reservoir, with no physiologic function in utero, defects in this region such as anorectal malformations or Hirschsprung's disease, are very difficult to detect. Bowel dilatation and echogenic bowel may be associated with cystic fibrosis; therefore, all such foetuses should undergo postnatal evaluation for this disease. Prenatally diagnosed small bowel atresia does not select for a group with a worse prognosis, and survival rates are 95–100%.

125.4.8 Sacrococcygeal Teratoma (Fig. 125.8)

Sacrococcygeal teratoma (SCT) is the commonest neonatal tumour accounting for 1 in 35,000 to 40,000 births. Four types have been defined by Altman in the 1970s:

- Type 1 external tumour with a small presacral component
- Type 2 external tumours with a large presacral component
- Type 3 predominantly presacral with a small external component
- Type 4 entirely presacral

In the era before prenatal diagnosis, the latter carried the worst prognosis due to delay in diagnosis and malignant presentation. Prenatally this classification has no prognostic value, but tumour characteristics such as solid vs cystic, vascularity, size at diagnosis and rate of growth are most important, as well as premature labour and delivery. Doppler ultrasound is the most important diagnostic and prognostic tool and may be supplemented with fetal echocardiogram and fetal MRI to provide better definition of the intrapelvic component. SCT is often a highly vascular tumour, and the foetus may develop high cardiac output failure, anaemia from bleeding within the tumour and ultimately hydrops with a mortality of almost 100% once this occurs. Fetal treatment of tumour resection or ablation of feeding vessel has been attempted in hydropic patients or when high cardiac output and other tumour characteristics predict its development. The maternal mirror syndrome is a pre-eclampsia-type picture that develops in severe cases; once this occurs, it is too late for fetal intervention, and delivery is mandatory to save the mother. Early delivery after 26 weeks with ligation or embolisation of the feeding vessels has been reported. A staged approach with initial tumour debulking and delayed complete resection has also been employed. Caesarean section should be offered to patients with large tumours to avoid the risks

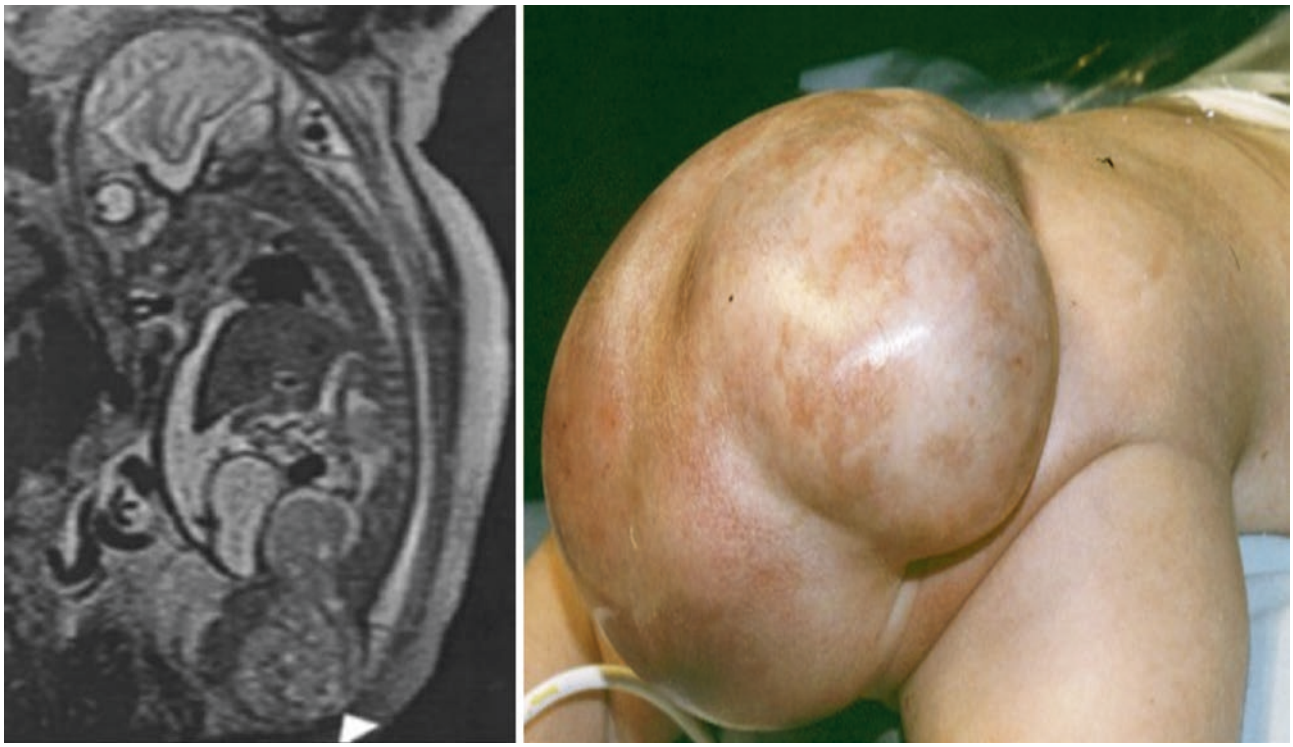

Fig. 125.8 Sacrococcygeal teratoma (MRI)

of dystocia and bleeding during delivery. Postnatal outcomes following surgery in type 1 and 2 lesions are favourable; however, type 3 and 4 tumours may present with urological problems and less favourable outcomes. Long-term follow-up with alpha-fetoprotein and serial rectal examinations +/– pelvic ultrasounds is mandatory to exclude recurrence of the disease.

125.4.9 Renal Anomalies

Urogenital abnormalities are among the commonest disorders seen in the perinatal period and account for almost 20% of all prenatally diagnosed anomalies. The routine use of antenatal ultrasound scans has resulted in the early detection of these conditions and in selected cases has led to the development of management strategies including fetal intervention aimed at preservation of renal function. Two major issues are the indications for intervention in bladder outlet obstruction and early pyeloplasty in infancy in cases with hydronephrosis.

Prenatal evaluation of a dilated urinary tract is based on serial ultrasound scans as well as measurement of urinary electrolytes in severe bilateral cases. Ultrasonography provides measurements of the renal pelvis, assessment of the renal parenchyma as well as the detection of cysts in the cortex. In severe disease, lack of amniotic fluid may make ultrasound assessment of the renal tract difficult, and MRI may be helpful. Oligohydramnios is indicative of poor renal function and poor prognosis owing to the associated pulmonary hypoplasia. Urogenital anomalies co-exist with many other congenital abnormalities, and amniocentesis should be offered in appropriate cases. It is estimated that 3% of infants will have an abnormality of the urogenital system, and half of these will require some form of surgical intervention.

125.4.10 Upper Urinary Tract Obstruction

Antenatal hydronephrosis accounts for 0.6–0.65% pregnancies. The most common cause of prenatal hydronephrosis is pelviureteric junction obstruction (PUJ), others being transient hydronephrosis, physiological hydronephrosis, multicystic kidney, posterior urethral valves, ureterocoele, ectopic ureter, etc. The prognosis of antenatally diagnosed hydronephrosis in unilateral disease and in renal pelvic diameter of <10 mm is excellent. Spontaneous resolution is noted in 20% of patients at birth and 80% at 3 years of age. Only 17% of prenatally diagnosed hydronephrosis need surgical intervention.

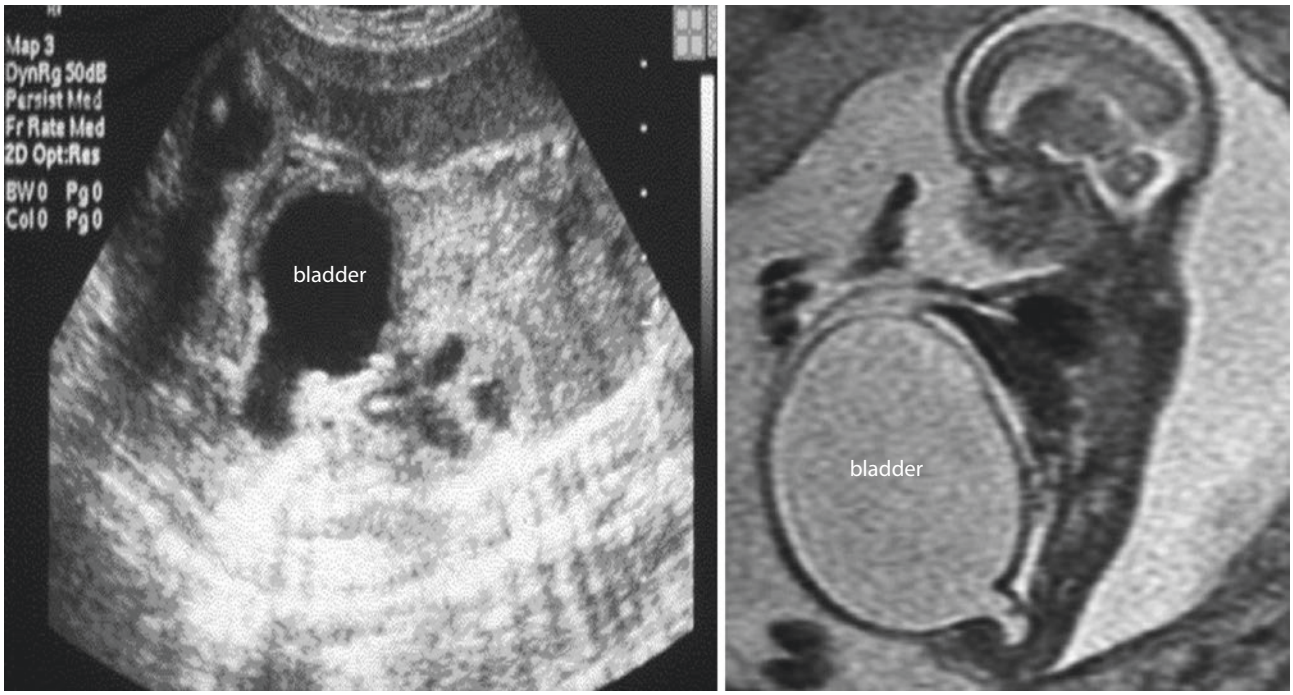

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Fig. 125.9 Scan and MRI of posterior urethral valves

125.4.11 Lower Urinary Tract Obstruction (Fig. 125.9)

Posterior urethral valves (PUV) are the most common cause of lower urinary tract obstruction in boys with an incidence of 1 in 2000 to 4000 lives male births. The diagnosis of PUV is suspected on the prenatal ultrasound finding of bilateral hydronephrosis associated with a thickened bladder and decreased amniotic fluid volume in a male foetus. Serial fetal urine analysis may provide prognostic information on renal function. Prenatal diagnosis for patients with PUV is a poor prognostic sign with 64% incidence of renal failure and transient pulmonary failure, compared to 33% in the postnatally diagnosed patients. Pulmonary hypoplasia secondary to oligohydramnios largely contributes to the morbidity and mortality from fetal urethral obstruction. Outcomes of fetal intervention with vesicoamniotic shunting or fetal cystoscopic ablation of the urethral valve are still under review and await a multicentre trial.

125.5 Conclusion

Prenatal diagnosis allows improved perinatal management for foetuses with surgically correctable malformations. The mode of delivery, timing and location may be altered to allow proper postnatal management with improved outcomes even in resource-limited settings. fetal intervention is seldom indicated. Diagnosis of lethal malformations may lead to pregnancy termination, but even in settings where this is not possible, better preparation of the family is a benefit of fetal diagnosis. During prenatal counselling, the pediatric surgeon should be aware that the natural history of prenatally diagnosed malformations is very different from the postnatally diagnosed ones.

125.6 Evidence-Based Research

Title	Factors Affecting Improved Prenatal Screening: A Narrative Review
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Reference	Glob J Health Sci. 2015 Se 28;8(5):50903. doi: ► https://doi.org/10.5539/gjhs.v8n5p160
Problem	Prenatal screening deals with the detection of structural and functional abnormalities in the foetus. Health-care providers can minimise unintended pregnancy outcomes by providing proper counselling and performing prenatal screening. The purpose of the present review study is to investigate factors affecting improved prenatal screening
Intervention	The present study is a narrative review searching public databases such as Google Scholar and specialised databases such as PubMed, Magiran, Scientific Information Database, Elsevier, Ovid and Science Direct as well. Using the keywords 'prenatal screening', 'fetus health' and 'prenatal counseling', 70 relevant articles published from 1994 to 2014 were selected. After reviewing the abstracts, the full data from 26 articles were ultimately used for writing the present review study
Comparison/control	Three general themes emerged from reviewing the studies, health-care providers' skills, clients' characteristics and ethical considerations, which were the main factors affecting improved prenatal screening
Outcome/effect	Prenatal screening can be successful if performed by a trained and experienced expert through techniques suitable for the mother's age. Also simultaneously providing proper counselling and giving a full description of the risks and benefits of the procedures for clients are recommended

Key Summary Points

1. The boundaries of pediatric surgical practice have been extended by prenatal diagnosis.
2. The care of patients with surgically correctable defects can now be planned prenatally with the collaborative effort of obstetricians, geneticists, neonatologists and pediatric surgeons.
3. The understanding of the specific surgical condition's prenatal natural history is essential.
4. Prenatal diagnosis has its limitations.
5. Associated anomalies need detecting.
6. Understanding the risks and indications of fetal intervention programmes and postnatal outcomes are essential.
7. Prenatal counselling is an essential component of pediatric surgical practice and should be ensured in the training programme for future pediatric surgeons.
8. More fetal lives are saved by appropriate prenatal counselling than by fetal surgery.

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