Chapter 22

Management of Pregnancy and Delivery in Prenatally Diagnosed Congenital Anomalies

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Additional information is available at the end of the chapter

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Abstract

Prenatal diagnosis of congenital anomalies provides valuable information and allows proper management of pregnancy and delivery. The common congenital anomalies are cardiovascular anomalies, congenital anomalies of the central nervous system, fetal thoracic anomalies, abdominal wall defects, kidney and urinary tract defects, and esophageal, gastrointestinal, and anorectal abnormalities. Different defects require particular assessment, evaluation and care. Pregnancy management mainly includes detection of the malformations, genetic assessment, ultrasound follow-ups and evaluation of fetal well-being as well as performing various invasive or non-invasive procedures. Managing delivery is also highly important and fetal anomaly specific. The main aspects of delivery management discussed in this chapter are delivery place, timing, route and delivery room care.

Keywords: congenital anomalies, management, pregnancy, delivery

1. Introduction

Prenatal diagnosis of congenital anomalies provides parents an opportunity to obtain prognostic information prior to birth, learn about treatment options before and after delivery, reach decisions concerning the management approach that is best for their family (e.g., whether to terminate pregnancy or undergo in utero intervention, if available; nonintervention), and plan for specific needs at birth [1].

2. Cardiovascular anomalies

Identification and management of fetal cardiac abnormalities are important because congenital anomalies are the leading cause of infant death and congenital heart disease accounts for 30–50% of these deaths [1]. The best time for evaluating the fetal heart anatomy is 18–22 weeks of gestation, because the fetal cardiac anatomy can be visualized well at this stage of pregnancy, a complete fetal anatomic survey can be performed, and there is time for further evaluation (e.g., echocardiogram, chromosomal microarray), if indicated, while the fetus is still periviable [2]. After 30 weeks of gestation, it can be difficult to obtain good images as the fetus becomes more crowded within the amniotic cavity. Fetal arrhythmias, myocarditis, cardiomyopathy, heart failure, valvular insufficiency or obstruction and cardiac tumors have variable onset. Fetal echocardiography should be performed in fetuses at a higher risk of congenital heart disease (**Table 1**).

Indications with higher risk profile (estimated >2% absolute risk)	**Indications with lower risk profile (estimated >1 and <2% absolute risk)**
- Maternal pregestational diabetes mellitus or diabetes mellitus diagnosed in the first trimester	- Maternal medications (anticonvulsants, lithium, vitamin A, paroxetine, NSAIDs in first/second trimester)
- Maternal phenylketonuria (uncontrolled)	- Congenital heart disease in second-degree relative of fetus.
- Maternal autoantibodies (SSA/SSB), especially if a previous child had SSA/SSB-related heart disease	- Fetal abnormality of the umbilical cord or placenta (e.g., single umbilical artery, agenesis of the ductus venosus)
- Maternal cardiac teratogens (e.g., thalidomide, angiotensin-converting enzyme [ACE] inhibitor, retinoic acid, nonsteroidal anti-inflammatory drugs [NSAIDs] in the third trimester)	- Fetal intra-abdominal venous anomaly
- Maternal first trimester rubella infection	
- Maternal infection with suspicion of fetal myocarditis because of poor contractility or effusions on standard four-chamber cardiac examination (e.g., coxsackie virus, adenovirus, cytomegalovirus)	
- Pregnancy conceived by assisted reproduction technology (ART)	
- Congenital heart disease in first-degree relative of fetus (maternal, paternal or sibling)	
- Disorder of first- or second-degree relative with Mendelian inheritance with congenital heart disease association (e.g., Noonan, tuberous sclerosis, Holt-Oram, velocardiofacial [DiGeorge] syndrome/22q11 deletion, Alagille syndrome, Williams syndrome)	
- Fetal cardiac abnormality (structural, functional, arrhythmia) suspected on obstetrical ultrasound	
- Fetal noncardiac abnormality suspected on obstetrical ultrasound	
- Fetal chromosome testing reveals a genetic mutation, deletion, rearrangement, or aneuploidy	
- Fetal tachycardia or bradycardia or frequent or persistent irregular heart rhythm	
- Fetal increased nuchal translucency >95 percentile (≥3 mm) on first trimester ultrasound	
- Monochorionic twinning	
- Fetal hydrops or effusions	

Table 1. Indications for fetal echocardiography [2].

2.1. Pregnancy management

When a fetal cardiac abnormality is detected, additional evaluation and follow-up are indicated.

- Assessment for extracardiac anomalies. The extracardiac abnormalities are detected in 20–40% of all fetal cardiac anomalies [1, 3]; the cardiac anomalies are part of numerous fetal syndromes [4]. A systematic review and meta-analysis of studies of prenatal ultrasound and magnetic resonance imaging (MRI) found that brain abnormalities, delay in head growth, and brain-sparing were observed in subgroups of fetuses with congenital heart disease [5] However, the prognostic significance of these findings was unclear.

- Genetic assessment. Fetal genetic assessment is indicated because chromosome abnormalities are common in fetuses with cardiac defects, even when isolated [6]. Forty-one percent of fetuses with prenatally diagnosed structural cardiac defects had an abnormal karyotype [7]. The incidence in infants of congenital heart disease about 15% [6], it is higher because of in utero mortality in many cases, such as the lethal autosomal trisomies (e.g., trisomy 9 or 16). The risk of fetal aneuploidy varies depending on the malformation. For example (risk percent, [2]): atrioventricular septal defect (46–73%), truncus arteriosus (19–78%), double-outlet right ventricle/conotruncal malformations (6–43%), coarctation/arch interruption (5–37%), tricuspid valve dysplasia (including Ebstein malformation, 4–16%), tetralogy of Fallot (7–39 percent), hypoplastic left heart syndrome (HLHS, 4–9%), pulmonic stenosis/atresia with intact septum (1–12%), and transposition of great arteries (0%).

- Ultrasound follow-up. The necessity, timing, and frequency of serial assessment should be guided by the nature and severity of the lesion, presence of heart failure, anticipated timing and mechanism of progression, and the options available for prenatal and postpartum intervention [2]. At least one follow-up examination early in the third trimester is reasonable in order to look for abnormalities that progressed in severity or may not have been detectable earlier in gestation and have peripartum clinical implications. Some causes of progressive fetal cardiac dysfunction include worsening valvular insufficiency or obstruction, increasing obstruction to blood flow in the great arteries, and development or worsening of myocarditis or cardiomyopathy, arrhythmias, or cardiac tumors [2]. Intrauterine fetal growth restriction is more prevalent in these fetuses with congenital heart disease [8].

- Referral to a pediatric cardiologist. The purpose is to educate the patient about the suspected diagnosis and discuss management options before and after delivery, including the preferred site for delivery [1].

- Evaluation of fetal well-being. Fetuses with cardiac structural anomalies, functional disorders, or arrhythmias that have the potential to compromise tissue oxygen delivery are generally followed with antepartum testing, with intervention if results are abnormal. In one retrospective cohort study, fetuses with a genetic syndrome, extracardiac anomaly, or severe valvular regurgitation were at increased risk for fetal demise: 15/197 (7.6%) fetuses with one or more of these risk factors died in utero versus 3/270 (1%) fetuses without any of these risk factors [9]. Six of the 22 fetal deaths occurred at 20–23 weeks and 16 occurred

at 26–41 weeks (including three deaths at 37, 39, and 41 weeks). However, there is no strong evidence of the value of this practice and antepartum fetal testing with the nonstress test, biophysical profile, or fetal movement count has not been tested specifically in this clinical setting. The type of test depends on the underlying abnormality; for example, the biophysical profile is particularly useful in fetuses with arrhythmias and provides an opportunity to monitor for development or progression of hydrops in any fetus with severely altered hemodynamics.

- Fetal therapy. Transplacental medical therapy can improve the prognosis of some fetal arrhythmias [1]. Invasive in utero cardiac intervention (aortic or pulmonary balloon valvuloplasty, atrial needle septoplasty) may improve the prognosis of some lesions, such as HLHS or severe valvular abnormalities (severe mitral regurgitation, aortic stenosis, pulmonary atresia). Current evidence on the effectiveness of prenatal intervention for CHD derives mostly from case reports and a few larger series; although the results of the meta-analysis are encouraging in terms of perinatal survival, they should be interpreted with caution when comparing with procedures performed after delivery [10].

2.2. Delivery management

- Delivery place. Delivery should be planned at a facility with the appropriate level of care for the mother and neonate. Neonates with ductal-dependent lesions and most with critical cardiac lesions should be delivered at a facility with a level III NICU and pediatric cardiology expertise. If this is not feasible, transport arrangements should be established in advance of delivery [1].

Specialized delivery room care is recommended for fetuses with:	- d-transposition of the great arteries - sustained or uncontrolled tachyarrhythmias with heart failure or hydrops fetalis
Specialized delivery room care planning is reasonable for fetuses with:	- hypoplastic left heart syndrome (HLHS) with restrictive or intact atrial septum and abnormal pulmonary vein flow (pulmonary vein forward/reversed flow ratio < 3) or abnormal hyperoxia test in the third trimester - complete heart block and low ventricular rate, cardiac dysfunction, or hydrops fetalis
Specialized delivery room care planning may be considered in fetuses with:	- tetralogy of Fallot with absent pulmonary valve - Ebstein anomaly with hydrops fetalis - total anomalous pulmonary venous return, obstructed
Specialized delivery room care is not needed for fetuses with:	- mild tetralogy of Fallot, ventricular septal defect, atrioventricular septal defect - shunt lesions - most ductal-dependent lesions, but initiation of prostaglandin E1 may be indicated in neonatal intensive care unit - controlled arrhythmias

Table 2. Need for specialized delivery room care in specific anomalies.

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- Timing and route. Cesarean delivery is performed for standard obstetrical indications, as there is no evidence that route of delivery of fetuses with congenital heart disease affects outcome [11]. Based on observational data, induction of labor or scheduled cesarean before 39 weeks of gestation is not recommended in the absence of standard maternal or fetal concerns about well-being, as even early term delivery has been associated with worse outcomes after neonatal cardiac surgery [2, 12]. One exception may be single ventricle defects, where earlier delivery may be beneficial [13].
- Delivery room care. Risk assessment for anticipated compromise in the delivery room or during the first few days of life is disease-specific (**Table 2**, [2]).

3. Congenital anomalies of the central nervous system (CNS)

Malformations of the central nervous system (CNS) are among the most common types of major congenital anomalies. Ultrasound examination is an effective modality for prenatal diagnosis of these anomalies. Poor timing of the examination, rather than poor sensitivity, can be an important factor in failing to detect a CNS abnormality [14]. Ideally, pregnancies at increased risk of fetal CNS anomalies and those with suspicious findings on a basic examination should undergo fetal neurosonography performed by clinicians with expertise in this area. Magnetic resonance imaging (MRI) is an option for further evaluation in cases of diagnostic uncertainty when additional information will influence subsequent management of the pregnancy [15].

3.1. Holoprosencephaly

Holoprosencephaly is a fetal anomaly that cannot be altered or treated. Elective termination of pregnancy is recommended if the diagnosis is made early (till 22–24 weeks of gestation under the pregnancy termination law in different countries). Because approximately 30–50% of fetuses with this anomaly have chromosomal abnormalities, prenatal karyotype is recommended. A family history (the familial recurrences have been reported), the history of current pregnancy (exposure to ethanol, salicylates) should be obtained, the evaluation for cytomegalovirus should be done. If the parents choose the conservative management, there is no fetal intervention for this condition and the cesarean delivery should be considered only for maternal indications [16].

3.2. Agenesis of the corpus callosum

During routine screening for fetal anomalies at 20–22 weeks of gestation, the two most important clues that the corpus callosum needs further assessment to exclude a callosal abnormality are (1) non-visualization of the cavum septi pellucidi and (2) ventriculomegaly (lateral ventricles measuring >10 mm). The cause of this anomaly may be genetic, infectious (TORCH infections and Zika virus), vascular, or toxic (alcohol—fetal alcohol syndrome). Callosal dysgenesis

was isolated in only 24% of the fetuses, and isolated callosal abnormalities are associated with normal neurodevelopmental outcome in approximately two-thirds of fetuses [17].

3.2.1. Pregnancy management

- Genetic assessment. Genetic factors are most common. Among the genetic causes, "syndromic" diagnosis is made in 30–45% of cases and a monogenic cause can be identified in 20–35%. Over 200 genetic syndromes, many of which may have variable phenotype, include disorder of the corpus callosum as a feature.
- Magnetic resonance imaging (MRI) is most helpful after the 20th week of gestation, since about 20% of apparently isolated cases diagnosed by ultrasound have associated CNS anomalies on MRI [18].
- Evaluation of fetal well-being. If an isolated agenesis of corpus callosum is detected and the chromosomes are normal, the usual standard pregnancy management should be recommended.

3.2.2. Delivery management

Vaginal delivery is recommended unless is significant hydrocephalus with macrocephaly. Delivery prior to term is not advisable [16].

3.3. Dandy-Walker malformation

'Isolated' Dandy-Walker malformation (DWM) in the light of recent literature, which has demonstrated a potential good clinical and intellectual outcome of fetuses presenting with DWM characterized by partial vermian agenesis and absence of associated anatomical anomalies [19].

3.3.1. Pregnancy management

- Assessment for associated CNS and extra-CNS anomalies. The presence of the additional anomalies adversely affects survival and prognosis for the infant and child with DWM. The risk of associated intracranial anomalies appears to be 20–60%, and in this situation, the mental retardation and perinatal mortality are increased [16].
- Genetic assessment. In the syndromic form of DWM, malformations of the heart, face, limbs, or gastrointestinal or genitourinary system may be present. DWM may occur as part of a Mendelian disorder (e.g., Meckel syndrome), a chromosomal aneuploidy (e.g., 45X, triploidy), environmental exposures (e.g., rubella, alcohol), a multifactorial etiology (e.g., congenital heart defect, neural tube defects), or as a sporadic defect (e.g., holoprosencephaly).
- Evaluation of fetal well-being. The option for elective termination of pregnancy is offered for parents if the diagnosis of DWM with associated CNS anomalies is made early. If the diagnosis is made in the third trimester, conservative management is recommended. In

most cases, the cyst, ventricular dilatation, and cisterna magna enlargement occur slowly, rarely severe or rapidly increasing ventriculomegaly needs for obstetrical intervention [16]. There is no fetal intervention for DWM.

3.3.2. Delivery management

The cesarean delivery should be considered only for maternal indications.

3.4. Anencephaly

3.4.1. Pregnancy management

Anencephaly is the most common neural tube defect (NTD) [20]. The anencephalic fetus can be definitively identified by the 12th postmenstrual week by TVS; although in some cases, this diagnosis has been made as early as 9–10 postmenstrual weeks [21]. Early diagnosis can be made if the cranium is examined carefully at the time of nuchal translucency measurement [22].

Up to 75% of anencephalic infants are stillborn. Liveborn infants generally die within hours but occasionally survive for a few days or weeks. There are no neurosurgical management options. In most developed countries where abortion is legal, these pregnancies are interrupted earlier [23]. Because of their poor prognosis, anencephalic infants have been considered as potential organ donors for transplantation. The clinical cases reported that anencephalic infants are not good candidates for organ donation because they do not generally meet criteria for brain death until their clinical condition has declined to the point where the solid organs are damaged [24]. Polyhydramnios develops in up to 50% of the cases during the second and third trimester due to decreased fetal swallowing, but is not present during the first trimester [20].

Prevention is the most important aspect of management of anencephaly. Periconceptional folic acid supplementation is recommended for all women who are pregnant or who may become pregnant. Higher doses of folic acid supplements are usually recommended for women who are taking anticonvulsant drugs or who have had a previous pregnancy affected by a NTD.

3.4.2. Management of labor

Because polyhydramnios is often associated with this condition, the rate of premature labor is increasing. Labor and delivery are frequently associated with an unstable fetal position, dystocia of labor, placental abruption, and postpartum hemorrhage. The cesarean delivery should be considered only for maternal indications.

3.5. Exencephaly

Exencephaly has been detected as early as the 10th postmenstrual week. In the second trimester, the usual appearance of the cranium encasing the brain is lost. The exposed brain has

a heterogeneous appearance and is not covered by the cranium. Although the cranial vault is absent, the fetal facial bones can be clearly visualized. Maternal serum alpha-fetoprotein levels are highly elevated.

3.5.1. Pregnancy management

Exencephaly is a lethal condition, the termination of pregnancy should be recommended for parents. Typically, exencephaly is not associated with chromosomal abnormalities, but, because of the severity of the defect, a chromosome analysis should be performed to permit accurate genetic counseling [16].

3.5.2. Delivery management

The cesarean delivery should be considered only for maternal indications. There are no indications for resuscitation of the newborn.

3.6. Encephalocele

3.6.1. Pregnancy management

Encephalocele can be diagnosed at 11–14 weeks during sonographic screening for aneuploidy.

- Genetic assessment. Cephalocele usually occurs as an isolated lesion, but may be a part of a syndrome such as Meckel (or Meckel-Gruber) or Walker-Warburg syndrome in a small percentage of cases. Both syndromes are autosomal recessive.
- Assessment for associated anomalies. Detailed sonography or MRI should be performed to verify the diagnosis and to search for associated anomalies.

Obstetrical management depends on the size of defect, the gestational age at diagnosis, and the presence or absence of associated anomalies. Prognosis depends on (1) the presence and amount of brain in the herniated sac (this is the most important consideration) and (2) the presence or absence of hydrocephalus, microcephaly, and other anomalies. If the encephalocele is diagnosed at less than 22–24 weeks of gestation, the termination of the pregnancy can be offered to the parents. If the pregnancy is not terminated, the consultations of neurosurgeon, neonatologist, and medical genetics are recommended [16].

Fetuses with neural tube defects or central nervous system abnormalities typically remain active; however, the quality of fetal movement is often different from that in normal fetuses [20]. The fetus with an encephalocele did not respond to repeated vibroacoustic stimulation (VAS) with a movement or fetal heart rate (FHR) acceleration [25].

3.6.2. Delivery management

When diagnosed prenatally, vaginal delivery may be safe if the lesion is relatively small. Large encephaloceles require cesarean section. Neonates with encephalocele should be delivered at

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a facility with a level III NICU. Surgical treatment is appropriate in most cases unless the encephalocele is massive and there is severe microcephaly or other lethal anomalies. The procedure basically consists of removing the overlying sac and closing the defect including the dural defect [26]. In patients with basal encephaloceles or cerebrospinal fluid (CSF) leakage, prompt closure is important to reduce the risk of infection. Patients with hydrocephalus usually undergo ventriculoperitoneal shunt placement prior to encephalocele repair to prevent postoperative CSF leaks.

3.7. Iniencephaly

3.7.1. Pregnancy management

Iniencephaly is a rare, lethal developmental anomaly. Associated malformations occur in up to 84% of cases and include hydrocephaly, microcephaly, ventricular atresia, holoprosencephaly, polymicrogyria, agenesis of the cerebellar vermis, occipital encephalocele, diaphragmatic hernia, thoracic cage deformities, urinary tract anomalies, cleft lip and palate, omphalocele, and polyhydramnios [20]. The sonographic diagnosis has been made as early as 12.5–13 postmenstrual weeks. Detailed sonography or MRI should be performed to verify the diagnosis and to search for associated anomalies. If the iniencephaly is diagnosed at less than 22–24 weeks of gestation, the termination of the pregnancy can be offered to the parents.

3.7.2. Delivery management

The presence of the hyperextended fetal head might cause dystocia. There is no indication for aggressive resuscitation of neonates [16].

3.8. Spinal dysraphism and the Arnold-Chiari malformation

3.8.1. Pregnancy management

Assessment for other abnormalities should be performed by the detailed sonography. Associated brain abnormalities include hydrocephaly, relative microcephaly, agenesis of the corpus callosum, and diastematomyelia. Non-CNS anomalies consist of congenital scoliosis or kyphosis and hip deformities [20]. There is a high prevalence of genetic abnormalities among fetuses with NTDs, especially in the presence of other congenital anomalies so microarray should be offered. The diagnostic sensitivity of prenatal sonography for detection of myelomeningocele in a high risk population is about 97–98% with 100% specificity [27]. Determining the site and extent of the spinal lesion is important because these features correlate with neurologic outcome; more severe neurologic dysfunction is associated with higher and larger lesions. Sonographic diagnosis of open spina bifida typically occurs during the second trimester of the pregnancy.

When the diagnosis of NTD is confirmed, the parents should be offered the opportunity to discuss the long-term prognosis for a child with multidisciplinary team (neonatologist,

medical geneticist, pediatric neurologist, pediatric neurosurgeon, pediatric urologist, pediatric orthopedic surgeon). Long-term prognosis is related to the location of the NTD—the lower the defect, the better the prognosis [16]. In fetuses with myelomeningoceles, higher and larger lesions on MRI were significantly associated with full-time wheelchair use. High lesion level was associated with dysphagia. The absence of a covering membrane was associated with scoliosis and high-risk bladder dysfunction [28]. If the diagnosis is at less than 22–24 weeks of gestation, the opportunity of pregnancy termination can be offered to the parents. During prenatal counseling, discussion with the parents includes the natural history of myelomeningocele and the prenatal management decisions, including termination of the pregnancy, pursuit of additional prenatal testing, choice of delivery setting, and, when applicable, the possibility of fetal surgery. The postnatal management choices are also discussed, including surgical closure of the defect and possible need for ventriculoperitoneal shunt placement. Longitudinal follow-up after prenatal diagnosis of myelomeningocele suggests that approximately 60–70% of pregnancies end in termination or fetal demise [29, 30].

- Fetal intervention. Fetal surgery for myelomeningocele can arrest leakage of spinal fluid from the back and might therefore prevent or reverse herniation of the hindbrain (Chiari II malformation) and hydrocephalus [31]. Prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks [32]. These benefits occurred despite a higher risk of preterm delivery and pulmonary complications among infants undergoing fetal surgery and of obstetrical complications, including placental abruption, dehiscence of the hysterotomy site, and maternal transfusion at delivery [32, 33]. Because fetal surgery is associated with risks of fetal and maternal complications, the family should be informed about the option of prenatal surgery, including the uncertainty regarding whether the risks of the procedure are outweighed by the potential benefits, particularly since long-term outcomes are not clearly known. Women with pregnancies complicated by fetal myelomeningocele who meet established criteria for in utero repair should be counseled in a nondirective fashion regarding all management options, including the possibility of open maternal-fetal surgery. Maternal-fetal surgery for myelomeningocele repair should be offered only to carefully selected patients at facilities with an appropriate level of personnel and resources [34].

3.8.2. Delivery management

For infants with a prenatal diagnosis of myelomeningocele who do not undergo fetal intervention, delivery should occur at a center with a level III NICU, pediatric neurosurgery services, and other personnel experienced in the neonatal management of these infants. Latex-free gloves and equipment should be used during delivery and subsequent care of the infant because patients with myelomeningocele are at risk for developing life-threatening latex allergy.

Term delivery is preferable, but increasing ventriculomegaly with macrocephaly on prenatal ultrasound may necessitate preterm delivery. Fetuses presenting in the breech position are

typically delivered by cesarean section. The optimal route of delivery of a fetus presenting in the vertex position is controversial. Vaginal delivery is reasonable if the head is normal size, the meningocele is unlikely to cause dystocia, and there are no obstetrical indications for cesarean [35].

3.9. Fetal cerebral ventriculomegaly

3.9.1. Pregnancy management

Fetal cerebral ventriculomegaly is a relatively common finding on second trimester obstetrical ultrasound examination. Many cases are associated with other abnormal findings, but in some fetuses, ventriculomegaly is the only abnormality [36]. Most children with isolated, mild ventriculomegaly have a normal outcome. The risk of abnormal outcome increases with the severity of ventriculomegaly, progression of ventriculomegaly, and presence of other anomalies. After ventriculomegaly is identified, further management involves identifying whether additional abnormalities (CNS and non-CNS) are present, diagnostic evaluation for the most common causes of ventriculomegaly, and counseling patients about the prognosis and potential pregnancy interventions. If the etiology of ventriculomegaly has been determined (e.g., trisomy, CMV) or associated malformations are identified, the parents can be given more specific information. Before viability, pregnancy termination is an option and should be offered.

- Assessment for associated CNS and extra-CNS anomalies. Associated abnormalities have been reported in 10–76% of cases [36, 37]. Identification of these abnormalities helps in determining the cause of ventriculomegaly and the prognosis. Fetal MRI can be used to identify underlying CNS abnormalities not detected by sonography. Because CNS infection can result in ventriculomegaly, it is important to look for characteristic sonographic findings of fetal infection, such as intracerebral and periventricular calcifications, hepatic calcifications, hepatosplenomegaly, ascites, and polyhydramnios.
- Evaluation for infection. Tests for CMV infection, toxoplasmosis, Zika virus infection, and lymphocytic choriomeningitis virus infection should be recommended. Sporadic cases of ventriculomegaly associated with other viruses have also been reported (mumps enterovirus 71 (EV71), parainfluenza virus type 3, parvovirus B19) [36]. PCR for CMV and toxoplasmosis should also be obtained when amniocentesis is performed. If the patient declines amniocentesis or karyotyping has been done previously, maternal serology is used to identify an infectious etiology. However, serology is neither as sensitive nor as specific as PCR on amniotic fluid, thus amniotic fluid PCR is the preferred method of evaluation for infection [36].
- Genetic assessment. Fetuses with apparently isolated mild ventriculomegaly in 4.7% were found to have an abnormal karyotype [38]. The risk is higher with severe ventriculomegaly or associated abnormalities.
- Follow-up evaluation. Follow-up ultrasound examinations are obtained to look for regression or progression of ventriculomegaly and to re-evaluate for anomalies. Early isolated

mild ventriculomegaly may resolve by the third trimester; progression occurs in 16% of cases and has been associated with a worse outcome [36, 39]. Follow-up ultrasounds have detected fetal abnormalities not detected on the initial scan in 13% of cases [36]. Therefore, at least one additional detailed ultrasound examination should be performed between 28 and 34 weeks of gestation to look for CNS and non-CNS abnormalities and regression or progression of dilatation. Antepartum fetal testing has no proven benefit in pregnancies with isolated fetal ventriculomegaly in the absence of other findings, such as intrauterine growth restriction or oligohydramnios.

- Fetal intervention. Intrauterine treatment with ventriculoamniotic shunting was performed in the 1980s. The expert consensus at that time was that these results did not represent an improvement in outcome over expectant management, which led to a de facto moratorium on such procedures [40]. At present, however, such procedures are investigational [36].

3.9.2. Delivery management

Ventriculomegaly may or may not be accompanied by macrocephaly. Most infants with ventriculomegaly have a normal head circumference (HC), there is no increased risk of cephalopelvic disproportion, and cesarean delivery is not required except for standard obstetric complications. When the HC exceeds 40 cm, abdominal delivery should be considered.

Cephalocentesis, which almost always results in fetal death, is rarely used to decompress the head, allow vaginal delivery, and avoid maternal morbidity from cesarean delivery, in cases in which the neurological prognosis is so dismal (trisomy 13 or 18 or lethal co-existent anomalies) [41].

4. Fetal thoracic anomalies

4.1. Congenital diaphragmatic hernia

4.1.1. Pregnancy management

Over the past 20 years, prenatal detection of congenital diaphragmatic hernia (CDH) has improved worldwide, reaching up to 60% in Europe. Pulmonary hypoplasia and persistent pulmonary hypertension are the two main determinants of neonatal mortality and morbidity, so new tools have been focused on their evaluation. Fetal surgery for severe cases requires proper evaluation of the prognosis of fetuses with CDH [42]. After CDH is identified, further management involves referral to a tertiary center for confirmation of the diagnosis, assessment of severity and associated anatomic and genetic abnormalities, multidisciplinary counseling about options and prognosis, and planning further management. Management may be expectant with prenatal referral to a center with expertise in caring for these infants, termination of pregnancy, or fetal intervention [43]. The mean gestational age at diagnosis is about 24 weeks. Polyhydramnios may be present due to esophageal compression. Hydrops fetalis can occur from mediastinal shift and compression of the great vessels.

- Assessment for associated anomalies. Ultrafast fetal MRI to look for associated abnormalities and liver herniation and to estimate lung volumes and fetal echocardiography should be performed.

CDH can be an isolated anomaly, part of a syndrome, or nonsyndromic but associated with other abnormalities. Approximately 50–70% of cases of CDH are isolated. Pulmonary hypoplasia, intestinal malrotation, and cardiac dextroposition are due to the hemodynamic or mechanical consequences of CDH; thus, they are usually considered part of the CDH sequence and do not negate the designation 'isolated CDH.' The other 30–50% of cases are called 'complex', 'nonisolated', or 'syndromic' CDH (CDH+) because they are associated with additional abnormalities, including major structural malformations, chromosomal abnormalities, and/or single gene disorders. Malformations occur in all major organ systems, with no specific pattern [43]. An underlying syndrome is present in approximately 10% of CDH cases occurring with associated anomalies [43]. CDH is a prominent finding in the Fryns phenotype; facial dysmorphology, distal digital hypoplasia, and cardiac/renal/brain anomalies can also occur. CDH and diaphragmatic eventration are also an occasional component of many other syndromes, including Apert, Killian/Teschler-Nicola (Pallister-Killian), CHARGE, Coffin-Siris, Goltz, Perlman, Swyer, Brachmann-Cornelia De Lange, Goldenhar sequence, Beckwith Wiedemann, Simpson-Golabi-Behmel, Donnai-Barrow, Mathew-Wood, Jarcho-Levin, Fraser, Stickler, Pierre Robin, and others [43, 44].

Associated anomalies are most common with bilateral CDH and in stillborn infants with CDH, where the prevalence is as high as 95% [43]. Anomalies in stillborn infants with CDH primarily consist of neural tube defects (anencephaly, myelomeningocele, hydrocephalus, and encephaloceles) and cardiac defects (ventriculoseptal defects, vascular rings, and coarctation of the aorta) [45].

- Genetic assessment. Chromosomal anomalies are identified in 10–20% of prenatally identified cases; the most common diagnoses include trisomies 18, 13, and 21 [43, 46]. Other karyotype abnormalities, such as monosomy X, tetrasomy 12 p (isochromosome 12p), partial trisomy 5, partial trisomy 20, and polyploidies, have also been reported [43, 47].
- Evaluation of prognostic factors for survival. Prognosis is worse in the setting of an abnormal chromosomal microarray, severe associated anomalies, right-sided defect, liver herniation, and lower fetal lung volume [43, 48]. The lung area to head circumference ratio (LHR) is more predictive of morbidity than mortality. A large defect is more likely to result in pulmonary hypoplasia and death than a small defect. The size of the defect is not measurable prenatally, so the presence of liver herniation and fetal lung volume measurements serves as a proxy for defect size [43]. Several other clinical findings for survival have not been confirmed (early gestational age at diagnosis, severe mediastinal shift, polyhydramnios, a small lung-thorax transverse area ratio, left ventricle/right ventricle index, left heart hypoplasia, and the stomach in the chest) [43].

Liver herniation is the most reliable prenatal predictor of postnatal survival. A systematic review of studies that used ultrasound or MRI to evaluate outcome of fetuses with liver herniation included 710 fetuses and reported significantly higher survival rate in fetuses without

herniation (74% versus 45% with herniation) [49]. Ultrafast fetal MRI using rapid HASTE technique is the most powerful tool to accurately demonstrate liver herniation [50]. Ultrasound can be useful; in particular, color flow Doppler can visualize bowing of the ductus venosus to the left of the midline or coursing of the portal branches or hepatic veins to the lateral segment of the left lobe above the diaphragm; however, ultrasound has not always accurately demonstrated liver herniation in the fetus with left-sided CDH [43, 50].

Absolute or relative fetal lung volume appears to be useful for predicting survival, but the optimum equation has not been determined [43, 51]. Several small studies have suggested that postnatal survival is poor when fetal lung volume measured by MRI is less than about 30% of expected lung volume for gestational age and especially when <15% [43]. Lung volume can also be assessed using 3D sonography, but MRI may be more reliable.

Right- versus left-sided lesion. Right-sided CDH have a poorer outcome than that reported for fetuses with left-sided CDH with similar lung size before birth [52].

Lung area to head circumference ratio (LHR) is an estimate of contralateral lung size and mediastinal shift at the level of the atria on transverse scan of the fetal thorax. Although there is a significant correlation between LHR and survival, the lower limit of LHR compatible with survival is dropping, so the test is less predictive than in the past [43, 53]. LHR is now more indicative of morbidity than mortality [43]. In left CDH, the LHR is calculated using a two-dimensional perpendicular linear measurement of right lung area (in square millimeters) divided by the head circumference (in millimeters) to minimize lung size differences owing to gestational age [43]. Measurement of fetal lung volume is much more useful than LHR in fetuses without liver herniation [54]. Because lung growth is four times greater than head growth during pregnancy [55], some experts suggest that the LHR should be expressed as a function of gestational age (observed [O]/expected [E] LHR). The O/E LHR can be calculated using a formula specifically developed for this measuring technique and has been validated in fetuses with unilateral isolated CDH in terms of both mortality and morbidity [53]. An online calculator is available (www.totaltrial.eu). O/E LHR is considered extreme if <15%, severe at 15–25%, moderate at 26–35%, and mild if 36–45% [44].

- Fetal interventions. Fetal endoscopic tracheal occlusion (FETO) is an investigational procedure for treatment of isolated severe congenital diaphragmatic hernia to prevent or reverse pulmonary hypoplasia and restore adequate lung growth for neonatal survival. The rationale for this approach is that the dynamics of fetal lung fluid can dramatically affect lung growth [43]. Under normal circumstances, the lungs are net producers of amniotic fluid with lung liquid volume and intratracheal pressure maintained at constant values by fetal laryngeal mechanisms [43]. Prenatal tracheal occlusion (TO) obstructs the normal egress of lung fluid during pulmonary development, increasing transpulmonic pressure and resulting in large fluid-filled lungs. Lack of lung expansion 2 and 7 days after TO is a poor prognostic sign and may indicate that the occlusion is inadequate [56]. Techniques to achieve minimally invasive fetoscopic reversible fetal TO have been developed to decrease the risks of preterm labor and restore surfactant deficiency [43]. A percutaneous

procedure under local anesthesia, with fetal pain relief and immobilization, is possible [57]. Fetal TO in severe CDH is associated with a high incidence of PPROM and preterm delivery but a substantial improvement in survival. Smaller and fewer trocars were utilized in another study, resulting in a lower rate of preterm rupture of membranes and preterm delivery [58].

Important factors in offering prenatal therapy continue to be, first and foremost, determining which fetuses have a poor prognosis. The optimal timing, duration, and release of occlusion in humans are not known. The Eurofetus group has had early success with fetal TO [59]. The insertion of the balloon at 26–28 weeks for severe cases and 30–32 weeks for moderate cases is recommended. Ideally, the occlusion is reversed before delivery at 34 weeks, usually by fetoscopy or ultrasound-guided puncture.

The FETO Consortium subsequently reported the outcome of 210 consecutive procedures [57]. Compared with the outcome of expectantly managed cases enrolled in their registry, FETO increased survival in severe cases with left CDH from 24–49% and right CDH from 0–35% ($p < 0.001$) [57]. However, at least 10 deaths attributed to difficulty with balloon removal before or at the time of emergent delivery have been reported [60]. The Eurofetus consortium also noted that preterm delivery, usually due to premature rupture of membranes, is a common complication and occurred in 17% of cases within 3 weeks of the procedure [43]. FETO has resulted in few clinical side effects on the developing trachea, except in very early occlusions and complications arising at the time of removal [43]. Neonates have tracheomegaly, which does not seem to have a clinical impact other than a barking cough on effort. The Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trial is ongoing in Europe and feasibility studies for FETO are ongoing at several North American fetal centers [43].

- Follow-up assessment. There are no data from well-designed studies on which to base recommendations for antepartum obstetrical management. The intrauterine risk of fetal demise is 2–8%, but higher when other anomalies are present [43]. Twice-weekly nonstress testing or biophysical profile testing at 33–34 weeks should be offered [43]. Ultrasound examinations at 28, 30, 32, and 34–35 weeks of gestation to assess fetal growth and amniotic fluid volume. Polyhydramnios may develop at 28–32 weeks if fetal swallowing is impaired, and oligohydramnios may develop if the fetus is compromised later in gestation. Signs of secondary complications, such as particulate meconium in fluid, dilated stomach in chest, effusions, or ascites, may lead us to deliver the fetus preterm. Fetal growth restriction or oligohydramnios may also lead us to deliver the fetus early. Antenatal glucocorticoids are given, if appropriate, to decrease morbidity from preterm delivery as for standard indication [43].

4.1.2. Delivery management

The optimal mode and gestational age for delivery of an infant diagnosed prenatally with CDH is uncertain [43]. A planned induction of labor between 38 and 39 weeks of gestation is suggested so that the fetus is monitored from the earliest stage of labor and so pediatric

surgery and neonatology services are prepared to care for the infant. The fetal lung maturity prior to delivery should not be assessed [43]. Up to 50% of cases require extracorporeal membrane oxygenation (ECMO); therefore, the delivery at a tertiary center with ECMO capability is recommended [43]. Cesarean delivery is performed for standard obstetrical indications [43].

4.2. Congenital pulmonary airway malformation

4.2.1. Pregnancy management

Prenatal diagnosis of congenital pulmonary airway malformation (CPAM) has increased with widespread use of prenatal ultrasonography and magnetic resonance (MR) imaging. When CPAM is diagnosed, the quantitative evaluation helps predict the prenatal course of the disease and should include the following [61]:

1. Congenital pulmonary airway malformation volume ratio (CVR)—Obtained by calculating the volume of the lung mass using the formula for the volume of an oval and normalizing it by gestational age. To normalize by gestational age, the lung mass volume should be divided by the head circumference. CVR = height x anteroposterior diameter x transverse diameter x 0.52 (constant)/head circumference.
2. Mass-to-thorax ratio (MTR)—The ratio between the transverse diameter of the mass and the transverse diameter of the thorax. It is measured on an axial image of the chest, where the four-chamber view of the heart is present.
3. Observed to expected lung-to-head ratio (o/e LHR)—Initially described as a predictor of outcome in congenital diaphragmatic hernia.

The prenatal course depends on the gestational age, size of the mass, amount of mediastinal shift, fetal hemodynamics, and associated anomalies, more than the type of lesion [61]. About 50% of masses persist to delivery [62]. Fifteen percent of these masses decrease in size during the late second and the third trimesters; the majority have a relative decrease in size due to normal fetal thoracic growth, but a few increase in size [61]. It is difficult to predict at the time of the initial ultrasound whether lesions will regress, stabilize, or continue to grow and lead to significant problems, including hydrops, need for surgical intervention or postnatal respiratory assistance, or death. The use of CVR, MTR, and, to a lesser degree, o/e LHR helps better identify patients at risk [61, 63]. A CVR >1.6 is predictive of risk for hydrops, respiratory distress at birth, and probable need for early surgery [61], whereas a CVR <0.91 at presentation predicts a favorable outcome so follow-up examinations can be less frequent [61, 63]. A MTR <0.51 suggests the fetus is at low risk for developing complications [61, 63]. In the absence of hydrops, the prognosis is good with reported live birth rates ≥95% [61].

- Assessment for associated anomalies. A comprehensive fetal survey, including fetal echocardiography, should be performed as 10–20% of fetuses with CPAM have associated congenital abnormalities, such as esophageal atresia with tracheoesophageal fistula, bilateral

renal agenesis or dysgenesis, intestinal atresia, other pulmonary malformations, and diaphragmatic, cardiac, central nervous system, and bony anomalies [61]. Fetal echocardiography is recommended in all patients at time of diagnosis to rule out congenital cardiac anomalies.

- Follow-up assessment. All patients should have serial prenatal follow-up examinations every 1 to 4 weeks to assess change in size of the lung mass, change in CVR, and development of polyhydramnios and hydrops [61]. The frequency depends on the gestational age and CVR. Closer follow-up should be performed in those patients at high risk of developing hydrops (CVR ≥1.6, age < 26 weeks), whereas the interval between examinations can be lengthened if the CPAM is very small, CVR is <0.91 [63]. The presence of hydrops is a sign for impending fetal demise and thus it is an indication for fetal intervention [61]. The recommendation of proceeding with fetal intervention is based on results from small case series showing good survival (>90%) if hydrops resolves [61].

For fetuses greater than 32–34 weeks of age, early delivery with immediate postnatal resection is a reasonable option [61]. Ex utero intrapartum therapy (EXIT) has been used to stabilize fetuses with large lesions expected to have difficulty breathing at delivery [64].

For gestations between 20 and 32 weeks, several interventions with the goal of improving fetal hemodynamics and preventing lung hypoplasia have been described and appear to improve survival [61]. Drainage procedures are used for CPAMS with dominant cysts, while solid masses are treated by resection or ablation. Karyotype analysis is recommended prior to initiating fetal therapy [61]. All of the following interventions should be considered investigational.

Antenatal corticosteroids are the only medical treatment of CPAM. They are used primarily for treatment of microcystic CPAM, since these masses cannot be managed by minimally invasive procedures, but have been used for macrocystic disease, as well [61]. In uncontrolled studies, maternal steroid administration appeared to reverse hydrops and improve outcome [61]. Multiple courses of antenatal betamethasone for high-risk fetal CPAMs often result in favorable short-term outcomes without the need for open fetal resection. The fetuses who did not respond to a first course of steroids stabilized or improved (e.g., reduction in lesion size, resolving hydrops) after receiving two to four courses of therapy [65]. The median interval between the first and second courses of steroids was about 2 weeks (range 1–6 weeks) [61].

- Fetal intervention. Successful fetal surgery depends on surgical experience, optimal maternal anesthesia, uterine relaxation, hysterotomy, fetal exposure, and intraoperative fetal monitoring.

4.2.2. Drainage procedures

- Thoracentesis—For fetuses with large pleural effusions, thoracentesis to prevent pulmonary hypoplasia is possible, but rapid reaccumulation of fluid limits its usefulness [61]. The fluid should be sent for cell count to exclude an infectious etiology [61].

- Cyst aspiration should decompress a large macrocyst and reverse the mediastinal shift. Although fluid reaccumulation is common and limits its usefulness [61].
- Thoracoamniotic shunt provides a therapeutic option for select fetuses with large macrocystic lung lesions or pleural effusion at risk for hydrops and/or pulmonary hypoplasia. Survival following shunting depends on gestational age at birth, reduction in mass size, and hydrops resolution [66]. Complications include displacement or malfunction of the catheter, thrombus occlusion of the catheter, fatal fetal hemorrhage, procedure-related abruptio placentae, premature rupture of membranes, and preterm labor [61].

4.2.3. Surgical resection

For solid or mixed solid/cystic CPAM with a large solid component, in-utero open resection has been successfully performed. Following resection, hydrops resolves over 1 to 2 weeks with reversal of the mediastinal shift over 3 weeks [61]. Maternal-fetal surgery requiring hysterotomy appears to be associated with an increased risk of premature labor, premature rupture of membranes, and subsequent pregnancy (uterine dehiscence or rupture) [61]. Percutaneous laser ablation of solid CPAM has been reported in only a few case reports and further research is warranted [61].

4.2.4. Sclerotherapy

A single study described fetal sclerotherapy in three patients under 26 weeks with CPAM and hydrops, severe mediastinal shift, and polyhydramnios [67]. Sclerotherapy was performed with percutaneous injection of Ethamolin (ethanolamine oleate) or Polidocanol (aethoxysklerol) into the mass under ultrasound guidance using a 22-gauge needle [61]. Resolution of hydrops and of the mass effect was observed in all cases. The patients were delivered at term without complications. Further studies are indicated to assess the risks and benefits of this innovative technique [67].

4.2.5. Delivery management

If the lung mass has resolved or is small with no mediastinal shift or hydrops, CPAM itself is not an indication for early delivery or cesarean delivery [61]. Neonatal respiratory problems would be unlikely, but the delivery should be recommended in a tertiary care center. For fetuses with large masses that cause mediastinal shift and/or hydrops, delivery should be planned for a tertiary care center with an intensive care nursery capable of resuscitation of a neonate with respiratory difficulties, including capability of extracorporeal membrane oxygenation (ECMO), and with pediatric surgeons experienced in care of these infants [61]. If hydrops develops after 32 weeks of gestation, early delivery is recommended, possibly with the use of EXIT [61]. In EXIT, the fetus is partially delivered and intubated without clamping the umbilical cord. Uteroplacental blood flow and gas exchange are maintained by using inhalational agents to provide uterine relaxation and amnioinfusion to maintain uterine volume. This provides time for resection of the lung mass prior to complete delivery of the infant

in rare instances or, more often, cannulation for extracorporeal membrane circulation, thus creating a controlled situation for delayed removal of the CPAM. Overall fetal survival of 90% has been reported [61].

4.3. Bronchopulmonary sequestration

4.3.1. Pregnancy management

Bronchopulmonary sequestration (BPS) is usually a small lesion and decreases in size in late gestation in about 75% of cases [68].

- Assessment of additional anomalies and genetic evaluation. When a lung mass is first identified, thorough assessment for additional anomalies is necessary. Intralobar sequestration is not associated with an increased risk of additional anomalies [68]. Extralobar BPS is associated with anomalies in up to two-thirds of cases [68]. These anomalies include chest wall and vertebral anomalies hindgut duplications, diaphragmatic hernia, congenital heart disease, and renal and intracranial abnormalities [68]. The incidence of chromosomal abnormalities is not increased above baseline in fetuses with BPS alone [68]. Karyotype analysis is recommended prior to initiating fetal therapy.

Parents should be counseled about the possible course of the BPS during pregnancy. At initial presentation in the early midtrimester, it is difficult to accurately predict what the outcome will be for an individual fetus, but some predictions are possible, e.g., a large BPS with hydrops in the second trimester is likely to do poorly [68].

- Follow-up assessment. All patients should have serial prenatal follow-up examinations to assess change in size of the lung mass and development of hydrops [68]. The frequency depends on the size of the lesion. The larger lesions should be followed more closely. The presence of hydrops is a sign of impending fetal demise and an indication for fetal intervention [68]. This recommendation is based on results from small case series showing higher survival rates if hydrops resolves [68]. Because hydrops is uncommon, fetal intervention is rarely required and is warranted only in cases where the fetus is severely compromised and remote from term. For fetuses greater than 32–34 weeks of age, early delivery with immediate postnatal resection is a reasonable option [68].

For gestations between 20 and 32 weeks, several interventions with the goal of improving fetal hemodynamics and preventing lung hypoplasia have been described and appear to improve survival [69]. These interventions should only be undertaken at centers experienced in fetal surgery. Prenatal intervention requires extensive counseling to the parents on the potential risks versus benefits of surgery.

- Fetal intervention. If the BPS is solid with a large pleural effusion, thoracentesis to prevent pulmonary hypoplasia is possible, but rapid reaccumulation of fluid limits its usefulness. It can be used as a temporizing maneuver to provide prognostic information about the possible result from placement of a thoracoamniotic shunt [68]. The fluid should be sent for cell

count to exclude an infectious etiology [68]. Complications of shunts include displacement or malfunction of the catheter, thrombus occlusion of the catheter, fatal fetal hemorrhage, procedure-related abruptio placentae, premature rupture of membranes, and preterm labor [68]. There is also a risk of trauma to the fetal chest wall, especially if the procedure is performed before 20 weeks [68].

- In-utero open resection, percutaneous laser ablation of the feeding vessel has been successfully performed in several small studies [68]. Percutaneous ultrasound-guided fetal sclerotherapy has also been described [68]. Sometimes two procedures were necessary.

4.3.2. Delivery management

If the lung mass has resolved or is small with no mediastinal shift or hydrops, BPS itself is not an indication for early delivery or cesarean delivery [68]. Neonatal respiratory problems would be unlikely. For fetuses with large masses that cause mediastinal shift and/or hydrops, delivery should be planned for a tertiary care center with an intensive care nursery capable of resuscitation of a neonate with respiratory difficulties, including capability of extracorporeal membrane oxygenation (ECMO), and with pediatric surgeons experienced in care of these infants [68]. If hydrops develops after 32 weeks of gestation, early delivery is recommended, possibly with the use of EXIT. In EXIT, the fetus is partially delivered and intubated without clamping the umbilical cord. Uteroplacental blood flow and gas exchange are maintained by using inhalational agents to provide uterine relaxation and amnioinfusion to maintain uterine volume. This provides time for initiating extracorporeal membrane circulation to stabilize the infant, thus creating a controlled situation before resection of BPS in another operating room [68].

4.4. Congenital lobar emphysema

Congenital lobar emphysema (CLE) is a rare congenital malformation and sometimes is detected by prenatal ultrasonography. Lung lesions have increased echogenicity and/or a cystic appearance and usually can be differentiated from other congenital lung lesions [70]. A chest mass may even disappear on prenatal ultrasound and become apparent again on postnatal evaluation [70]. Predictors of severe respiratory distress or mortality include polyhydramnios, fetal hydrops, and lung to thorax transverse area ratio (L/T value) of less than 0.25 [70]. Approximately 25% of cases present at birth, 50% by 1 month of age, and nearly all by 6 months of age. Infants typically have tachypnea and increased work of breathing and often have cyanosis. Recurrent pneumonia or poor feeding with failure to thrive are less frequent presentations that may occur in milder forms [70].

4.5. Pulmonary agenesis

Any fetus with suspected bilateral pulmonary agenesis should have a detailed sonographic assessment to confirm the diagnosis. If the diagnosis is made till periviable pregnancy, the pregnancy termination is an option. If the diagnosis is made at a later gestational age, the delivery should be planned without monitoring for fetal distress [16].

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5. Congenital abdominal wall defects

5.1. Gastroschisis

5.1.1. Pregnancy management

There is wide variability in the antenatal management of gastroschisis due to a lack of high-quality evidence to guide clinical practice [71].

- Assessment of associated anomalies. Associated gastrointestinal anomalies and problems (e.g., malrotation, atresia, stenosis, perforation, necrosis, volvulus) occur in up to 25% of cases [72] and may be related to vascular disruption caused by herniated bowel. Disruption of the superior mesenteric artery, for example, may lead to volvulus or to "apple peel" jejunal-ileal lesions. Meckel's diverticulum and gallbladder atresia also occur, but are less common. Bladder herniation has been reported in 6% of cases, with bowel or urinary tract dilation [73]. Most cases have no extraintestinal abnormalities, approximately 10% of gastroschisis cases were associated with major unrelated defects, approximately 2% of cases were part of a recognized syndrome, and cardiac anomalies were detected in 2–3% of cases [74]. Oligohydramnios is the most common amniotic fluid abnormality, but polyhydramnios may occur, particularly in fetuses with reduced bowel motility or obstruction [73].
- Genetic assessment. The prevalence of chromosomal abnormalities in fetuses with isolated gastroschisis is not increased above the baseline population risk, so invasive fetal genetic testing is not routinely offered. The fetal genetic evaluation is suggested if nongastrointestinal structural abnormalities are identified on ultrasound examination. Chromosome abnormalities were detected in 1.2% of the total cases, which included isolated and nonisolated, and the most frequent abnormalities were trisomy 18, trisomy 13, sex chromosome anomalies, and trisomy 21 [73].
- Follow-up assessment. The most common pregnancy complications associated with gastroschisis include development of growth restriction (30–60% of cases), intrauterine fetal demise (3–6%), spontaneous preterm birth (30%), and bowel dilation and wall thickening (common, frequency depends on diagnostic criteria) [73]. The mechanisms causing these adverse outcomes in gastroschisis are unclear. Therefore, pregnancy monitoring is empiric and typically includes serial ultrasound examinations for assessment of fetal growth and fetal bowel abnormality and standard tests for antepartum fetal surveillance [73].
- Assessment of fetal growth and amniotic fluid volume—serial ultrasound examinations every 3 weeks for assessment of fetal growth and amniotic fluid volume (AFV). If growth arrest or oligohydramnios is diagnosed, umbilical artery Doppler flow is evaluated [73]. A systematic error of birth weight underestimation when using the Hadlock formulas in fetuses affected with gastroschisis was found [75]. Siemer and colleagues developed a specific formula for estimating fetal weight in fetuses with abdominal wall defects using

the biparietal diameter, occipitofrontal diameter, and femur length measurements [76]. Oligohydramnios may be related to fetal growth restriction and is a risk factor for cord compression and its sequelae. Polyhydramnios is less common, but an important finding because it is often caused by dysfunction of the gastrointestinal tract due to bowel atresia [73].

- Assessment of fetal bowel. Gastric dilatation, bowel dilatation, and bowel wall thickening have been considered poor prognostic signs by several investigators [73]. If these significant changes are observed prior to 34 weeks, a course of glucocorticoids is suggested for fetal maturation [73].
- Antepartum fetal surveillance. Fetal growth restriction and amniotic fluid abnormalities are commonly accepted indications for increased antepartum fetal surveillance. The precise timing and frequency of testing is arbitrary [73].

5.1.2. Delivery management

Gastroschisis increases the risk of preterm delivery; delivery should occur in a facility with appropriate resources for caring for these neonates. Gastroschisis alone is not an indication for preterm intervention or cesarean delivery [73].

The decision on timing of delivery is based on a combination of factors, including gestational age, ultrasound findings (fetal growth profile, AFV, appearance of fetal bowel), and fetal testing results (NST, BPP, umbilical cord Doppler if fetal growth restriction is present). In the absence of standard obstetric indications for abdominal delivery, a trial of labor rather than scheduled cesarean birth for most patients is suggested. Cesarean delivery is reasonable if the liver is significantly herniated because of the theoretic risk of dystocia and trauma. Delivery of pregnancies complicated by fetal gastroschisis at 37 or 38 weeks of gestation is suggested to minimize neonatal morbidity and mortality and avoid the possibility of term (39–40 weeks) stillbirth; however, there is no consensus on the optimum timing of delivery of these pregnancies [73].

5.2. Omphalocele

5.2.1. Pregnancy management

Omphalocele and gastroschisis are the most common fetal abdominal wall defects. By the end of the first trimester (11–14 weeks), almost all omphaloceles can be detected by prenatal ultrasound examination [77].

- Genetic assessment. Multiple chromosomal abnormalities have been reported among fetuses with omphalocele. As many as 60% of omphaloceles not containing liver are associated with fetal aneuploidy, particularly trisomy 18 or 13 [77, 78]. Fetal genetic studies should be offered if omphalocele or related body wall defects are identified prenatally, because of the high risk of aneuploidy. It is reasonable to offer amniocentesis for genetic testing for Beckwith-Wiedemann syndrome, but this testing is complicated and should be discussed

with a geneticist [77]. There is a 10–20% risk of Beckwith-Wiedemann syndrome in fetuses with apparently isolated omphalocele on ultrasound.

- Assessment of associated anomalies. Associated abnormalities that occur with increased frequency in these fetuses include additional gastrointestinal abnormalities, cardiac defects (up to 50% of cases), genitourinary anomalies, orofacial clefts, neural tube defects, defects of the diaphragm, polyhydramnios, and growth restriction. Associated syndromes are best categorized by upper, middle, and lower midline omphalocele defects. Omphalocele has been associated with several syndromes, including Pentalogy of Cantrell (upper midline defect), amniotic band sequence, schisis association (at least two of the following defects: neural tube defect, oral cleft, omphalocele, diaphragmatic hernia); lower midline defects are associated with OEIS syndrome (omphalocele, exstrophy of the bladder, imperforate anus, spinal defects), Shprintzen syndrome, Carpenter syndrome, Goltz syndrome, Marshall-Smith syndrome, Meckel-Gruber syndrome, otopalatodigital type II syndrome, CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality) syndrome, and Beckwith-Wiedemann syndrome (hallmark features: macroglossia, gigantism, omphalocele) [77].
- Follow-up obstetrical care. The serial ultrasound examination every 3–4 weeks to evaluate fetal growth is recommended. When growth is appropriate and amniotic fluid volume is normal, weekly nonstress testing or biophysical profile monitoring at 32 weeks of gestation to assess fetal well-being are recommended, as these pregnancies appear to be at increased risk of late fetal death [79]. Fetal growth restriction and preterm delivery are not uncommon in pregnancies complicated by an omphalocele, particularly with associated abnormalities [77]. Nonreassuring fetal testing and/or cessation of fetal growth at or near term is an indication for early delivery. A systematic error of birth weight underestimation in fetuses affected with omphalocele was found, the same situation as discussed in fetuses with gastroschisis. Intrauterine growth restriction in fetuses with abdominal wall defects is predictive of an increased risk of adverse neonatal outcome [77].

5.2.2. Delivery management

Delivery should be planning at a tertiary care center. In the absence of standard indications for early delivery, it is reasonable to await spontaneous labor or achieve 39 weeks of gestation. Preterm birth offers no advantage to affected neonates and is associated with increased morbidity and mortality. There is no evidence that cesarean delivery improves outcome in uncomplicated omphalocele; surgery should be reserved for usual obstetric indications [77]. However, some pediatric surgeons have recommended cesarean delivery for fetuses with giant omphaloceles (defined as an omphalocele containing >75% of the liver and defect greater than 5 cm) in an attempt to avoid dystocia, rupture, infection, and hemorrhage [80]. Visceral trauma has also been reported after cesarean delivery [77].

5.3. Bladder exstrophy

Often the diagnosis of bladder exstrophy is made by prenatal ultrasound and, in some cases, may be confirmed by MRI. In the event that a prenatal diagnosis is not made, the diagnosis

should be clinically apparent and recognizable at birth in the delivery room [81]. If a prenatal diagnosis is not made, the diagnosis of bladder exstrophy should be clinically recognizable at delivery. A careful physical examination will differentiate bladder exstrophy from other congenital anomalies that involve abdominal wall defects, such as omphalocele, gastroschisis, and cloacal exstrophy.

Following the prenatal diagnosis of bladder exstrophy, prenatal care includes the following [16, 81]:

1. Education and counseling of the parents, touring the neonatal intensive care unit, meeting the pediatric urologic care team, and allowing the expectant parent(s) the opportunity to interact with other families with a child with bladder exstrophy.

2. Preparation for delivery. In many tertiary centers, one option for planning initial surgical management is an induced vaginal delivery that is scheduled in late gestation with coordination with an on-site pediatric urology service. This approach facilitates bladder closure within 72 hours of life.

The cesarean delivery should be reserved for obstetrical complications.

5.4. Body stalk anomaly and cloacal exstrophy

- Body stalk anomaly (also called limb-body wall complex) is a massively disfiguring and generally lethal malformation of the thorax and/or abdomen, often associated with limb defects. The intrathoracic and abdominal organs lie outside the abdominal cavity and are contained within a sac composed of amnioperitoneal membrane attached directly to the placenta. The umbilical cord may be totally absent or extremely shortened. Severe kyphoscoliosis is often present. Termination of pregnancy is usually offered since the abnormality is generally considered lethal [82]. However, repair has been performed in rare cases [82]. If the pregnancy is continued, vaginal delivery is recommended given the highly lethal nature of this disease, assuming there are no maternal contraindications to vaginal delivery. In this setting, the patient should be extensively counseled on the likelihood of neonatal demise, as well as the severe morbidity associated with a successful repair [82, 83].
- Cloacal exstrophy. The accuracy of sonographic diagnosis appears to be less than 25% due to the rarity of the disorder and the wide spectrum of anatomic variants, which depend upon the degree of cloacal septation completed. Fetal genetic studies during the initial evaluation can be useful, although cloacal exstrophy has not been reported to be associated with specific aneuploidies. The chromosomal findings, which will include gender, may influence the decision to terminate the pregnancy, perform a cesarean delivery for fetal indications, or initiate a series of corrective operations in the newborn period [41]. Although there are no studies of the optimum route of delivery for this rare disorder, cesarean delivery is generally reserved for standard obstetric indications. The umbilical cord should be clamped or ligated carefully to avoid injury to proximate structures. At delivery,

saline-soaked sterile dressings should be applied over the exposed bladder and bowel mucosa and covered with plastic wrap to minimize insensible fluid and heat loss. Survival rates of 80–100% have been reported, but quality of life (e.g., bowel, urinary, and sexual function) is a concern [82].

6. Congenital anomalies of the kidney and urinary tract

6.1. Pregnancy management

Congenital anomalies of the kidney and urinary tract (CAKUT) constitute approximately 20–30% of all anomalies identified in the prenatal period [84]. Defects can be bilateral or unilateral, and different defects often coexist in an individual child. In general, the optimal timing recommended for a screening antenatal ultrasound is between 16 and 20 weeks of gestation because of the following factors at this gestational age. Counseling of families with fetuses with CAKUT should be universally available. If the fetal prognosis is poor, as determined by severe bilateral disease, bilateral RA, oligohydramnios, or unfavorable amniotic fluid analysis, legal termination, if possible, can be offered. In all other cases, continued counseling throughout the pregnancy including discussion of postnatal management is required. In particular, discussion with parents regarding their wishes on the level of support given to offspring with severe oligohydramnios, who are at risk for lung hypoplasia that may be incompatible with life, is helpful in establishing guidelines for initial postnatal care [84].

- Assessment of amniotic fluid volume and analysis of biochemical markers are used to evaluate fetal renal function. By 20 weeks of gestation, fetal urine accounts for more than 90% of the amniotic fluid volume. Thus, a decrease in amniotic fluid volume (oligohydramnios) at or beyond the 20th week of gestation is an excellent predictor of abnormal fetal renal function and CAKUT [84]. Severe oligohydramnios due to CAKUT either involves both kidneys or occurs in a solitary kidney in the fetus. Bilateral renal agenesis (RA) or severe dysgenesis, bilateral ureteric obstruction, or obstruction of the bladder outlet or urethra can result in severe oligohydramnios as early as 18 weeks of gestation. Because an adequate amniotic fluid volume is critical for lung development, severe oligohydramnios due to abnormal fetal renal function in the second trimester can result in lung hypoplasia, a potentially fatal disorder.
- Assessment for additional anomalies. Potter's syndrome consists of a typical facial appearance characterized by pseudoepicanthus, recessed chin, posteriorly rotated, flattened ears and flattened nose, decreased fetal movement, musculoskeletal features including clubfoot and clubhand, hip dislocation and joint contractures, and pulmonary hypoplasia.
- Analysis of amniotic fluid. Although oligohydramnios is the most reliable predictor of abnormal fetal renal function, its absence does not assure normal fetal renal function.

Because amniotic fluid is predominantly composed of fetal urine, measurement of biochemical markers contained in amniotic fluid (fetal urine) can be used to assess fetal renal function [84].

- Follow-up assessment. Repeat antenatal ultrasound examinations are performed to help guide management decisions. The timing is dependent on findings on the initial examination. Fetuses with second trimester hydronephrosis (RPD >4 mm) should undergo repeat testing in the third trimester to assess progression and select those who will benefit most from postnatal testing. A repeat examination 2–3 weeks later in fetuses with bilateral involvement (or an affected solitary kidney) and at 32–34 weeks of gestation in those with unilateral involvement is recommended [85].
- In utero intervention. Although there have been case series of antenatal surgery in fetuses with severe hydronephrosis and oligohydramnios, this intervention has not been shown to improve renal outcome. These procedures may increase the amount of amniotic fluid, thus potentially improving lung development and survival rate. In these rare cases, the procedure should only be performed in select centers with expertise and in infants with severe bilateral hydronephrosis, absent of severe renal parenchymal or cystic disease, favorable urinary electrolyte levels and osmolality, and normal karyotype [84]. Data are limited on whether percutaneous vesicoamniotic shunting compared with conservative observation in fetuses with lower urinary tract obstruction improves survival and renal outcome. The percutaneous vesicoamniotic shunting should not be routinely performed in fetuses with lower urinary tract obstruction [85].

6.2. Delivery management

Cesarean delivery should be reserved for obstetrical indications. The time of delivery depends on the fetal well-being and amniotic fluid volume.

7. Esophageal, gastrointestinal, and anorectal atresia

7.1. Pregnancy management

Prenatal sonographic diagnosis of gastrointestinal atresia is challenging since obstruction may not become evident sonographically until the late second trimester, after the typical time of a fetal anatomic survey (18–20 weeks of gestation). It can also be difficult to differentiate dilated small bowel loops from colon or megaureters sonographically [86]. It is unclear whether prenatal diagnosis of esophageal, gastrointestinal, or anorectal atresia improves the prognosis. However, early prenatal diagnosis provides an opportunity for parental counseling and preparation, screening for associated anomalies, and the option for pregnancy termination or delivery at a setting with appropriate personnel and facilities for newborn care [86].

- Indications for magnetic resonance imaging. MRI may be used to confirm or clarify suspected gastrointestinal abnormalities on ultrasound examination if this information is important for managing the pregnancy. Fetal bowel is well visualized by MRI and easily differentiated from adjacent liver, spleen, kidneys, bladder, and gallbladder. Meconium is also well visualized [87]. The normal esophagus, stomach, and duodenum should always be filled with T2 hyperintense fluid (amniotic fluid).
- Assessment of additional anomalies and follow-up assessment. Many of these pregnancies are complicated by polyhydramnios. After diagnosis, the performance of periodic ultrasound examinations to look for any change in the appearance of the atresia or associated anomalies and to assess interval fetal growth and amniotic fluid volume is recommended. Nonstress tests or biophysical profiles are indicated in pregnancies in which the risk of antepartum fetal demise is increased, such as a fetal anomaly associated with growth restriction [86].

7.2. Delivery management

Atresia alone is not an indication for cesarean delivery in the absence of a standard obstetric indication. However, if the abdominal circumference is much larger than the head circumference, cesarean delivery should be considered due to the risk of fetal abdominal dystocia. Delivery should be planned at a center that has an appropriate level of neonatal support.

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