CHAPTER 16: Fetal Therapy

Minor grades of hydramnios rarely require active treatment. On the other hand, when the abdomen is immensely distended and respiration is seriously hampered, the termination of pregnancy is urgently indicated. In such cases, the symptoms can be promptly relieved by perforating the membranes through the cervix, after which the amniotic fluid drains off and labour pains set in.

—J. Whitridge Williams (1903)

INTRODUCTION

The concept of fetal therapy—even amniocentesis—was not considered by Williams in his first edition. Aside from a few destructive procedures to aid vaginal delivery, any type of fetal treatment is not mentioned as even a remote possibility. Again, fast forward to this 25th edition, when interventions developed during the past three decades have dramatically altered the course of selected fetal anomalies and conditions. Reviewed in this chapter are fetal disorders amenable to treatment with either maternal medication or surgical procedures. The management of fetal anemia and thrombocytopenia is reviewed in Chapter 15, and treatment of some fetal infections is discussed in Chapters 64 and 65.

MEDICAL THERAPY

Fetal pharmacotherapy uses medications administered to the mother and then transported transplacentally to the fetus. As described here, it can be used to treat an array of serious conditions.

Arrhythmias

Fetal cardiac rhythm disturbances may be broadly categorized as *tachyarrhythmias,* heart rates >180 beats per minute (bpm); *bradyarrhythmia,* heart rate <110 bpm; and ectopy, typically premature atrial contractions. If these are identified, fetal M-mode sonography is performed to measure the atrial and ventricular rates and to clarify the relationship between atrial and ventricular beats, thereby diagnosing the type of rhythm disturbance.

Premature Atrial Contractions

This is by far the most common arrhythmia and is identified in 1 to 2 percent of pregnancies (Hahurij, 2011; Strasburger, 2010). Generally a benign finding, premature atrial contractions represent immaturity of the cardiac conduction system, and they typically resolve later in gestation or in the neonatal period. If the premature atrial contraction is conducted, it sounds like an extra beat when auscultated with handheld Doppler or fetoscope. However, premature atrial contractions are more commonly blocked and sound like dropped beats.

In general, premature atrial contractions are not associated with major structural cardiac abnormalities, although they sometimes occur with an atrial septal aneurysm. As shown in Figure 10-34, M-mode evaluation demonstrates that the dropped beat is a compensatory pause following the premature atrial contraction. They may occur as frequently as every other beat, known as *blocked atrial bigeminy*. This results in an auscultated fetal ventricular rate as low as 60 to 80 bpm. Unlike other causes of bradycardia, atrial bigeminy is benign and does not require treatment (Strasburger, 2010).

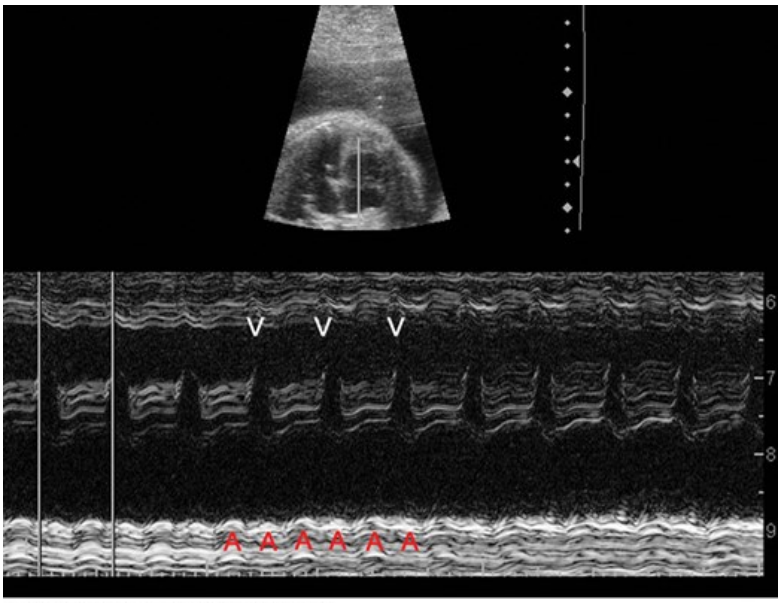
Approximately 2 percent of fetuses with premature atrial contractions are later found to have a *supraventricular tachycardia* (Copel, 2000; Srinivasan, 2008). Given the importance of identifying and treating supraventricular tachyarrhythmias, a fetus with premature atrial contractions is often monitored with heart rate assessment every 1 to 2 weeks until the ectopy resolves. This requires neither sonography nor fetal echocardiography, as the rate and rhythm may be easily ascertained with handheld Doppler.

Tachyarrhythmias

The two most common tachyarrhythmias are *supraventricular tachycardia* (SVT) and *atrial flutter.* SVT is characterized by an abrupt increase in the fetal heart rate to 180 to 300 bpm with 1:1 atrioventricular concordance. The typical range is 200 to 240 bpm. SVT may develop secondary to an ectopic focus or to an accessory atrioventricular pathway leading to a reentrant tachycardia. Atrial flutter is characterized by a much higher atrial rate, generally 300 to 500 bpm, with varying degrees of atrioventricular block. As a result, the ventricular rate in a fetus with atrial flutter may range from below normal to approximately 250 bpm (Fig. 16-1). In contrast, fetal *sinus tachycardia* typically presents with a gradual heart rate rise to a rate that is only slightly above normal. With this, readily discernible causes may be maternal fever or hyperthyroidism, or rarely, fetal anemia or infection.

FIGURE 16-1

Atrial flutter. In this M-mode image at 28 weeks' gestation, calipers mark the ventricular rate, which is approximately 225 bpm. There are two atrial beats (*A*) for each ventricular beat (*V*), such that the atrial rate is approximately 450 bpm with 2:1 atrioventricular block.



If a fetal tachyarrhythmia is identified, it is important to determine whether it is *sustained*—defined as present for at least 50 percent of the time. It may be necessary to monitor the fetal heart rate for 12 to 24 hours upon initial detection, and then periodically to reassess (Srinivasan, 2008). Unsustained or intermittent tachyarrhythmias generally do not require treatment, provided that fetal surveillance is reassuring.

Sustained fetal tachyarrhythmia with ventricular rates exceeding 200 bpm impairs ventricular filling to a degree that the risk for hydrops is significant. With atrial flutter, lack of coordinated atrioventricular contractions may further compound this risk. Maternal administration of antiarrhythmic agents that cross the placenta may convert the rhythm to normal or lower the baseline heart rate to forestall heart failure. Therapy may require dosages at the upper end of the therapeutic adult range. Thus, a maternal electrocardiogram is obtained before and during therapy.

Antiarrhythmic medications most commonly used include digoxin, sotalol (Betapace), flecainide (Tambocor), and procainamide (Pronestyl). Their selection depends on the type of tachyarrhythmia as well as provider familiarity and experience with the drug. Traditionally, digoxin has been the initial preferred treatment, although it may poorly transfer to the fetus after hydrops has developed. Many centers now use flecainide or sotalol as first-line therapy (Jaeggi, 2011; Shah, 2012). In many cases, additional agents are needed, particularly if hydrops has developed. SVT is generally more likely than atrial flutter to convert to a normal rhythm. With either arrhythmia, however, the overall neonatal survival rate now exceeds 90 percent (Ekman-Joelsson, 2015; Jaeggi, 2011; van der Heijden, 2013).

Bradyarrhythmia

The most common etiology of pronounced fetal bradycardia is *congenital heart block*. Approximately 50 percent of cases occur in the setting of a structural cardiac abnormality involving the conduction system. These include *heterotaxy*, in particular *left-atrial isomerism*; *endocardial cushion defect*; and less commonly *corrected transposition of the great vessels* (Srinivasan, 2008). The prognosis of heart block secondary to a structural

cardiac anomaly is extremely poor, and fetal loss rates exceed 80 percent (Glatz, 2008; Strasburger, 2010).

In a structurally normal heart, 85 percent of atrioventricular block cases develop secondary to transplacental passage of maternal anti-SSA/Ro or anti-SSB/La antibodies (Buyon, 2009). Many of these women have, or subsequently develop, systemic lupus erythematosus or other connective tissue disease (Chap. 59, Perinatal Mortality and Morbidity). The risk of third-degree heart block with these antibodies is small—only about 2 percent. But, the risk may reach 20 percent if a prior infant has been affected. Immune-mediated congenital heart block confers a mortality rate of 20 to 30 percent, requires permanent pacing in two thirds of surviving children, and also poses a risk for cardiomyopathy (Buyon, 2009). If associated with effusions, bradyarrhythmias, or endocardial fibroelastosis, neonatal status may progressively worsen after birth (Cuneo, 2007).

Initial research efforts focused on maternal corticosteroid therapy to potentially reverse fetal heart block or forestall it. Friedman and colleagues (2008, 2009) conducted a prospective multicenter trial of pregnancies with anti-SSA/Ro antibodies—the PR Interval and Dexamethasone (PRIDE) study. Weekly sonographic surveillance was performed, and heart block was treated with maternal oral dexamethasone 4 mg daily. Unfortunately, progression from second- to third-degree block was not prevented with maternal dexamethasone therapy, and third-degree atrioventricular block was *irreversible*. In rare cases, there was a potential benefit in reversing first-degree atrioventricular block. However, first-degree block did not generally progress even without treatment. In a subsequent review of 156 pregnancies with isolated second- or third-degree fetal heart block, dexamethasone therapy similarly did not affect disease progression, need for pacemaker in the neonatal period, or overall survival rates (Izmirly, 2016). Thus, dexamethasone use cannot be recommended for this indication.

More recent efforts have turned to potential therapy with hydroxychloroquine (Plaquenil), a mainstay of treatment for systemic lupus erythematosus (Chap. 59, Perinatal Mortality and Morbidity). In a multicenter review of more than 250 pregnancies in women whose prior pregnancies had been complicated by neonatal lupus, recurrence of congenital heart block was significantly lower if the woman had been treated with hydroxychloroquine during pregnancy (Izmirly, 2012). Research in this area is ongoing.

Maternal terbutaline has also been given to increase the fetal heart rate in cases with sustained bradycardia of any cause in which the fetal heart rate is below 55 bpm. Reversal of hydrops with this therapy has been reported (Cuneo, 2007, 2010).

Congenital Adrenal Hyperplasia

Several autosomal recessive enzyme deficiencies cause impaired fetal synthesis of cortisol from cholesterol by the adrenal cortex. This results in congenital adrenal hyperplasia (CAH). CAH is the most common etiology of androgen excess in females with 46,XX disorders of sex development, formerly female pseudohermaphroditism (Chap. 3, Bladder and Perineal Abnormalities). Lack of cortisol stimulates adrenocorticotrophic hormone (ACTH) secretion by the anterior pituitary, and the resulting androstenedione and testosterone overproduction leads to virilization of female fetuses. Sequelae may include formation of labioscrotal folds, persistence of a urogenital sinus, or even creation of a penile urethra and scrotal sac.

More than 90 percent of CAH cases are caused by 21-hydroxylase deficiency, which is found in classic and nonclassic forms. The incidence of classic CAH approximates 1:15000 births overall and is higher in selected populations. For example, it has been reported in approximately 1:300 Yupik Eskimos (Nimkarn, 2010). Among those with classic CAH, 75 percent are at risk for *salt-wasting adrenal crises* and require postnatal treatment with mineralocorticoids and glucocorticoids to prevent hyponatremia, dehydration, hypotension, and cardiovascular collapse. The remaining 25 percent with classic CAH have the *simple virilizing type* and also require glucocorticoid supplementation. As discussed in Chapter 32 (Routine Newborn Care), all states mandate newborn screening for CAH.

The efficacy of maternal dexamethasone treatment to suppress fetal androgen overproduction and either obviate or ameliorate virilization of female fetuses has been recognized for more than 30 years (David, 1984; New, 2012). Prenatal corticosteroid therapy is considered successful in 80 to 85 percent of cases (Miller, 2013; Speiser, 2010). The alternative is consideration of postnatal genitoplasty, a complex and somewhat controversial surgical procedure (Braga, 2009).

The typical preventive regimen is oral dexamethasone given to the mother at a dosage of 20 µg/kg/d—up to 1.5 mg per day, divided in three doses. The critical period for external genitalia development is 7 to 12 weeks' gestation, and treatment to prevent virilization should be initiated by 9 weeks —*before it is known whether the fetus is at risk*. Because this is an autosomal recessive condition, affected females make up only 1 in 8 at-risk conceptions.

Typically, carrier parents are identified after the birth of an affected child. Molecular genetic testing is clinically available, initially using sequence

analysis of the *CYP21A2* gene, which encodes the 21-hydroxylase enzyme (Nimkarn, 2016). If this is uninformative, gene-targeted deletion/duplication analysis is performed, and additional testing such as whole exome sequencing may be considered (Chap. 13, Whole Genome Sequencing and Whole Exome Sequencing).

A goal of prenatal diagnosis is to limit dexamethasone exposure in males and in unaffected females. Prenatal diagnosis with molecular genetic testing may be performed on chorionic villi—at 10 to 12 weeks' gestation—or on amniocytes after 15 weeks. Cell-free DNA testing of maternal serum has potential to replace invasive tests such as chorionic villus sampling and amniocentesis for CAH (Chap. 13, Fetal DNA in the Maternal Circulation). Determination of fetal gender using cell-free fetal DNA has at least 95-percent sensitivity when performed at or beyond 7 weeks' gestation (Devaney, 2011). In the research setting, cell-free DNA testing using hybridization probes flanking the *CYP21A2* gene can be effective as early as $5^{6/7}$ weeks' gestation (New, 2014).

Maternal treatment with dexamethasone has become a topic of significant controversy. The Endocrine Society recommends that treatment be given only in the context of research protocols (Miller, 2013; Speiser, 2010). It should be noted that if therapy is initiated shortly before 9 weeks, the dose of dexamethasone used is not considered to have significant teratogenic potential because organogenesis of major organs has already taken place (McCullough, 2010). Ongoing concerns, however, focus on the potential effects of either excess *endogenous* androgens or excess *exogenous* dexamethasone on the developing brain. Although maternal dexamethasone has been used for many years to prevent virilization of female fetuses with CAH, long-term safety data are relatively limited.

Congenital Cystic Adenomatoid Malformation

Sonographically, this malformation is a well-circumscribed lung mass that may appear solid and echogenic or may have one or multiple variably sized cysts (Fig. 10-24). Lesions with cysts ≥5 mm are termed macrocystic, whereas microcystic lesions have smaller cysts or appear solid (Adzick, 1985). Also called congenital pulmonary airway malformation (CPAM), it represents a hamartomatous overgrowth of terminal bronchioles. Therapy for macrocystic congenital cystic adenomatoid malformation (CCAM) is discussed later (Percutaneous Procedures).

Occasionally, a microcystic CCAM may demonstrate rapid growth, generally between 18 and 26 weeks' gestation. The mass may become so large that it causes mediastinal shift, which may compromise cardiac output and venous return, resulting in hydrops (Cavoretto, 2008). A CCAM-volume ratio (CVR) has been used to quantify size and risk for hydrops in these severe cases (Crombleholme, 2002). This ratio is an estimate of the CCAM volume (length × width × height × 0.52) divided by the head circumference. In a series of 40 pregnancies with microcystic CCAM, the mean CVR was 0.5 at 20 weeks' gestation, peaking in size at 1.0 at 26 weeks, followed by a pronounced decline prior to delivery (Macardle, 2016). A third of fetuses had no increase in mass size. In the absence of a dominant cyst, a CVR exceeding 1.6 is associated with a hydrops risk as high as 60 percent. However, CCAM growth resulting in hydrops develops in fewer than 2 percent of cases if the initial CVR is below 1.6 (Ehrenberg-Buchner, 2013; Peranteau, 2016). Importantly, a CVR in the range of 1.6 indicates that the mass essentially fills the thorax, and thus it is not unexpected that ascites or hydrops may develop.

If the CVR exceeds 1.6 or if signs of hydrops develop, corticosteroid treatment has been used in an effort to improve outcome. Regimens include dexamethasone—6.25 mg every 12 hours for four doses, or betamethasone—12.5 mg intramuscularly every 24 hours for two doses. Following a single course of corticosteroids, hydrops resolved in approximately 80 percent of cases, and 90 percent of treated fetuses survived (Loh, 2012; Peranteau, 2016). Recently, multiple courses of steroids—generally two—have been advocated for fetuses with large CCAM lesions and with persistent or worsening hydrops or ascites despite a single course of medication (Derderian, 2015; Peranteau, 2016).

Thyroid Disease

Identification of fetal thyroid disease is rare and usually prompted by sonographic detection of a fetal goiter. If a goiter is found, determination of fetal hyper- or hypothyroidism is essential, and thyroid hormone levels may be measured in amnionic fluid or fetal blood. Traditionally, fetal blood sampling, described in Chapter 14 (Fetal Blood Sampling), is preferred to amniocentesis for guiding treatment, although data are limited (Abuhamad, 1995; Ribault, 2009). Goals of therapy are correction of the physiological abnormality and diminished goiter size. The goiter may compress the trachea and esophagus to such a degree that severe hydramnios or neonatal airway compromise may develop. Hyperextension of the fetal neck by a goiter can create labor dystocia.

Fetal Thyrotoxicosis

Untreated fetal thyrotoxicosis may present with goiter, tachycardia, growth restriction, hydramnios, accelerated bone maturation, and even heart

failure and hydrops (Huel, 2009; Peleg, 2002). The cause is usually maternal Graves disease with transplacental passage of IgG thyroid-stimulating immunoglobulins. Fetal blood sampling may confirm the diagnosis (Duncombe, 2001; Heckel, 1997; Srisupundit, 2008). Confirmed fetal thyrotoxicosis is followed by maternal antithyroid treatment. During this, if the mother develops hypothyroidism, she is given supplemental levothyroxine (Hui, 2011).

Fetal Hypothyroidism

In a woman receiving medication for Graves disease, transplacental passage of methimazole or propylthiouracil may cause *fetal hypothyroidism* (Bliddal, 2011a). Other potential causes of fetal hypothyroidism resulting in goiter include transplacental passage of thyroid peroxidase antibodies, fetal thyroid dyshormonogenesis, and maternal overconsumption of iodine supplements (Agrawal, 2002; Overcash, 2016).

Goitrous hypothyroidism may lead to hydramnios, neck hyperextension, and delayed bone maturation. If the mother is receiving antithyroid medication, discontinuation is generally recommended, along with intraamnionic levothyroxine injection. Numerous case reports describe intraamnionic levothyroxine treatment. However, optimal dosage and frequency have not been established, and reported dosages range from 50 to 800 µg every 1 to 4 weeks (Abuhamad, 1995; Bliddal, 2011b; Ribault, 2009).

SURGICAL THERAPY

Also called *maternal-fetal surgery*, these procedures are offered for selected congenital abnormalities in which the likelihood of fetal deterioration is so great that delaying treatment until after delivery would risk fetal death or substantially greater postnatal morbidity. Open fetal surgery is a highly specialized intervention performed at relatively few centers in the United States and for only a few fetal conditions. Criteria for consideration of fetal surgery are listed in Table 16-1. In many cases, data regarding the safety and efficacy of these procedures are limited. The Agency for Healthcare Research and Quality stresses that when considering fetal surgery, the overriding concern must be maternal and fetal safety. Accomplishing the fetal goals of the procedure is secondary (Walsh, 2011).

TABLE 16-1

Guiding Principles for Fetal Surgical Procedures

Accurate prenatal diagnosis for the defect is available, with staging if applicable
The defect appears isolated, with no evidence of other abnormality or underlying genetic syndrome that would significantly worsen survival or quality of life
The defect results in a high likelihood of death or irreversible organ destruction, and postnatal therapy is inadequate
The procedure is technically feasible, and a multidisciplinary team is in agreement regarding the treatment plan
Maternal risks from the procedure are well documented and considered acceptable
There is comprehensive parental counseling
It is recommended that there be an animal model for the defect and procedure

Modified from Deprest, 2010; Harrison, 1982; Vrecenak, 2013; Walsh, 2011.

Some abnormalities amenable to fetal surgical treatment, antepartum or intrapartum, are shown in Table 16-2. An overview of these procedures, their indications, and complications is provided here to assist with initial patient evaluation and counseling. Additional content is also found in *Cunningham and Gilstrap's Operative Obstetrics*, 3rd edition.

TABLE 16-2

Selected Fetal Abnormalities Amenable to Fetal Surgery

Open Fetal Surgery Myelomeningocele Congenital cystic adenomatoid malformation (CCAM) Extralobar pulmonary sequestration Sacrococcygeal teratoma
Fetoscopic Surgery Twin-twin transfusion: laser of placental anastomoses Diaphragmatic hernia: fetal endoscopic tracheal occlusion (FETO) Posterior urethral valves: cystoscopic laser Congenital high airway obstruction: vocal cord laser Amnionic band release
Percutaneous Procedures Shunt therapy Posterior-urethral valves/bladder outlet obstruction Pleural effusion: chylothorax or sequestration Dominant cyst in CCAM Radiofrequency ablation Twin-reversed arterial perfusion (TRAP) sequence Monochorionic twins with severe anomaly in 1 twin Chorioangioma Fetal intracardiac catheter procedures Aortic or pulmonic valvuloplasty for stenosis Atrial septostomy for hypoplastic left heart with restrictive atrial septum
Ex-Utero Intrapartum Treatment (EXIT) Procedures Congenital diaphragmatic hernia after FETO Congenital high airway obstruction sequence (CHAOS) Severe micrognathia Tumors involving neck or airway EXIT-to-resection: resection of fetal thoracic or mediastinal mass EXIT-to-extracorporeal membrane oxygenation (ECMO): congenital diaphragmatic hernia

Open Fetal Surgery

These procedures require extensive preoperative counseling and multidisciplinary care. The mother must undergo general endotracheal anesthesia to suppress both uterine contractions and fetal responses. Using intraoperative sonographic guidance to avoid the placental edge, a low-transverse hysterotomy incision is made with a stapling device that seals the edges for hemostasis. To replace amnionic fluid losses, warmed fluid is continuously

infused into the uterus thorough a rapid infusion device. The fetus is gently manipulated to permit pulse oximetry monitoring and to establish venous access, in case fluids or blood are emergently needed. The surgical procedure is then performed. After completion, the hysterotomy is closed and tocolysis begun. Tocolysis typically includes intravenous magnesium sulfate for 24 hours, oral indomethacin for 48 hours, and, at some centers, oral nifedipine until delivery (Wu, 2009). Prophylactic antibiotics are also administered and generally continued for 24 hours following the procedure. Cesarean delivery is needed later in gestation and for all future deliveries.

Risks

Morbidities associated with fetal surgery are well characterized. In a review of 87 open procedures, Golombeck and coworkers (2006) reported the following morbidities: pulmonary edema—28 percent, placental abruption—9 percent, blood transfusion—13 percent, premature rupture of membranes—52 percent, and preterm delivery—33 percent. Wilson and associates (2010) reviewed subsequent pregnancy outcomes following open fetal surgery and reported that 14 percent of women experienced uterine rupture and 14 percent had uterine dehiscence. Morbidities identified in the recent *Management of Myelomeningocele Study (MOMS)* are shown in Table 16-3 (Adzick, 2011). Other potential risks include maternal sepsis and fetal death during or following the procedure, particularly if hydrops is present.

TABLE 16-3

Benefits and Risks of Fetal Myelomeningocele Surgery versus Postnatal Repair

	Fetal Surgery (n = 78)	Postnatal Surgery (n = 80)	*p* value
Benefits (Primary Outcomes)			
Perinatal death or shunt by 12 months[a]	68%	98%	<0.001
Shunt placement by 12 months	40%	82%	<0.001
Composite developmental score[a,b]	149 ± 58	123 ± 57	0.007
Hindbrain herniation (any)	64%	96%	<0.001
Brainstem kinking (any)	20%	48%	<0.001
Independent walking (30 months)	42%	21%	0.01
Risks			
Maternal pulmonary edema	6%	0	0.03
Placental abruption	6%	0	0.03
Maternal transfusion at delivery	9%	1%	0.03
Oligohydramnios	21%	4%	0.001
Gestational age at delivery	34 ± 3	37 ± 1	<0.001
Preterm birth			
<37 weeks	79%	15%	<0.001
<35 weeks	46%	5%	
<30 weeks	13%	0	

[a]Each primary outcome had two components. The perinatal death components of the primary outcomes as well as the Bayley Mental Development Index at 30 months did not differ between the two study cohorts.

[b]Score derived from Bayley Mental Development Index and difference between functional and anatomical level of lesion (30 months).

Data from Adzick, 2011.

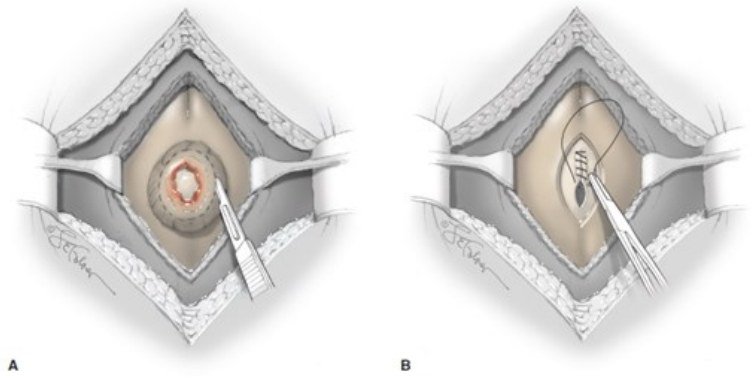
Myelomeningocele Surgery

Even with postnatal repair, children with myelomeningocele generally have varying degrees of paralysis, bladder and bowel dysfunction, developmental delays, and brainstem dysfunction from the Arnold-Chiari II malformation (Chap. 10, Ventriculomegaly). Damage is postulated to result

from abnormal embryonic neurulation and from ongoing exposure of neural elements to amnionic fluid (Adzick, 2010; Meuli, 1995, 1997). Fetal myelomeningocele meets the criteria listed in Table 16-1 and is the first nonlethal birth defect for which fetal surgery has been offered (Fig. 16-2).

FIGURE 16-2

Fetal myelomeningocele surgery. **A.** With the edges of both the laparotomy and hysterotomy incisions retracted, the skin around the defect is incised. Subsequently, the neural placode is sharply dissected from the arachnoid membrane. **B.** The dural membrane is reflected to the midline to cover the neural placode and is reapproximated using suture. In some cases a patch is needed (not shown). The fetal skin incision is subsequently sutured. Last, hysterotomy and laparotomy are then closed. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



In preliminary reports, infants following antepartum defect repair were more likely to have reversal of the Arnold-Chiari II malformation and were less likely to require ventriculoperitoneal shunt placement (Bruner, 1999; Sutton, 1999). Spurred by this, the randomized, multicenter MOMS trial was conducted (Adzick, 2011). Criteria for trial participation included: (1) a singleton fetus at 19.0 to 25.9 weeks' gestation; (2) an upper myelomeningocele boundary between T1 and S1 confirmed by fetal magnetic resonance (MR) imaging; (3) evidence of hindbrain herniation; and (4) a normal karyotype and no evidence of a fetal anomaly unrelated to the myelomeningocele. Women at risk for preterm birth or placental abruption, those with a contraindication to fetal surgery, and women with body mass index >35 kg/m^2 were excluded.

The MOMS findings demonstrated improved early childhood outcomes in the prenatal surgery cohort (see Table 16-3). Children who had undergone prenatal surgery were twice as likely to walk independently by 30 months. They had significantly less hindbrain herniation and were only half as likely to undergo ventriculoperitoneal shunting by the age of 1 year. A primary outcome was a composite score that was derived from the Bayley Mental Development Index and from the difference between the functional and anatomical level of the lesion at 30 months. This primary outcome was also significantly better in the prenatal surgery group.

When counseling prospective families, however, results are placed in perspective. For example, despite improvements in the proportion with independent ambulation, *most* children who received fetal surgery were not able to ambulate independently, and nearly 30 percent were not able to ambulate at all. Prenatal surgery did not confer improvements in fetal or neonatal death rates or in the Bayley Mental Development Index score at age 30 months. And, as shown in Table 16-3, surgery was associated with a small but significant risk for placental abruption and maternal pulmonary edema. Moreover, nearly half were delivered before 34 weeks, which significantly increased the risk for respiratory distress syndrome (Adzick, 2011). Long-term surveillance data have only recently become available for children who underwent fetal myelomeningocele repair prior to the MOMS trial. At a median follow-up of 10 years, these children have higher rates of behavioral problems and adverse executive functioning compared with population norms (Danzer, 2016).

Since publication of the MOMS findings, fetal myelomeningocele surgery rates have grown. Expansion of centers offering this procedure has raised concerns about the importance of training and ongoing experience, adherence to the MOMS research criteria, and need for a registry to ensure that future efforts have similar success rates (Cohen, 2014; Vrecenak, 2013).

Thoracic Masses

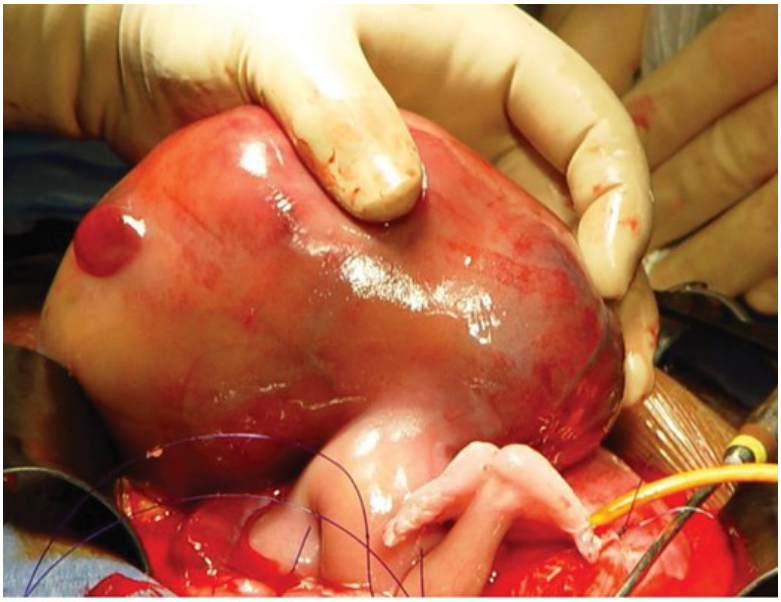
In the past, if hydrops developed in a fetus with a large pulmonary sequestration or cystic adenomatoid malformation without a dominant cyst, open fetal surgery with lobectomy was the only treatment available other than preterm delivery. Most thoracic masses are small and have a benign prognosis, and larger masses are generally treated with corticosteroids (Surgical Therapy). Fetal surgery is generally reserved for cases prior to 32 weeks in which hydrops is developing, and in selected cases, the survival rate following open lobectomy approximates 60 percent (Vrecenak, 2013). Use of the ex-utero intrapartum treatment procedure in the treatment of fetal lung masses at delivery is discussed later in Ex-Utero Intrapartum Treatment.

Sacrococcygeal Teratoma

This germ cell tumor has a prevalence of approximately 1 per 28,000 births (Derikx, 2006; Swamy, 2008). Sonographically, a sacrococcygeal teratoma (SCT) is a solid and/or cystic mass that arises from the anterior sacrum (Fig. 16-3). Fetal MR imaging can aid evaluation of the extent of the internal tumor component. The mass may grow rapidly, usually extending inferiorly and externally (Fig. 10-18). Hydramnios is common, and hydrops may develop from high-output cardiac failure, either as a consequence of tumor vascularity or secondary to bleeding within the tumor and resultant anemia. *Mirror syndrome*—maternal preeclampsia developing along with fetal hydrops—may occur in this setting (Chap. 15, Mirror Syndrome).

FIGURE 16-3

Fetal surgery for sacrococcygeal teratoma resection. Following laparotomy and hysterotomy, the caudal portion of the fetus has been delivered onto the surgical field. The tumor is held by the surgeon's hand. (Used with permission from Dr. Timothy M. Crombleholme.)



The perinatal mortality rate for cases of SCT diagnosed prenatally approximates 40 percent (Hedrick, 2004; Shue, 2013). Poor prognostic factors include a solid component comprising more than 50 percent of the tumor mass and a tumor volume-to-fetal weight ratio (tumor volume divided by estimated fetal weight) exceeding 12 percent prior to 24 weeks' gestation (Akinkuotu, 2015). Fetal loss rates approach 100 percent if hydrops or placentomegaly develop (Vrecenak, 2013). The group at the Children's Hospital of Philadelphia recommends consideration of open fetal surgery for SCT only in cases in which the tumor is completely external (Type I) and in which high cardiac output with early hydrops has developed in the second trimester (Vrecenak, 2013). For excision, hysterotomy is performed, and the external component is resected. The coccyx and any deep tumor are left in place for postnatal removal. Because tumor debulking interrupts the pathological vascular steal, normal fetal physiology may be restored.

Fetoscopic Surgery

As with open fetal surgeries, these procedures are performed at highly specialized centers, and some are considered investigational. To accomplish them, fiberoptic endoscopes only 1 to 2 mm in diameter are used to penetrate the maternal abdominal wall, the uterine wall, and membranes. Instruments such as lasers fit through 3- to 5-mm cannulas that surround the endoscope. Morbidities are generally lower than with open fetal surgery, but they still may be formidable, particularly if maternal laparotomy is required for access (Golombeck, 2006). Examples of some conditions treated by

fetoscopy are listed in Table 16-2.

Twin-Twin Transfusion Syndrome

Indications and Technique

As discussed in Chapter 45 (Diagnosis), fetoscopic laser ablation of placental anastomoses is the preferred management for severe twin-twin transfusion syndrome (TTTS). It is generally performed between 16 and 26 weeks' gestation for monochorionic-diamnionic twin pregnancies with stage II to stage IV TTTS. These categories of the Quintero Staging System are described in Chapter 45 (Diagnosis) (Quintero, 1999; Society for Maternal-Fetal Medicine, 2013).

For the procedure, a fetoscope is used to view the vascular equator that separates the placental cotyledons supplying each twin (Fig. 16-4). Arteriovenous anastomoses along the placental surface of the vascular equator are photocoagulated using a 600-µm diameter diode laser or a 400-µm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser (Fig. 16-5). The procedure is typically performed under epidural or local analgesia. At the end, amnioreduction is performed to decrease the single deepest pocket of amnionic fluid to below 5 cm, and antibiotics are injected into the amnionic cavity.

FIGURE 16-4

Selective laser photocoagulation for twin-twin transfusion syndrome. The fetoscope is inserted into the recipient-twin sac and positioned over the vascular equator, which lies in between the two placental cord insertion sites. Arteriovenous anastomoses along the placental surface are individually photocoagulated using the laser. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)

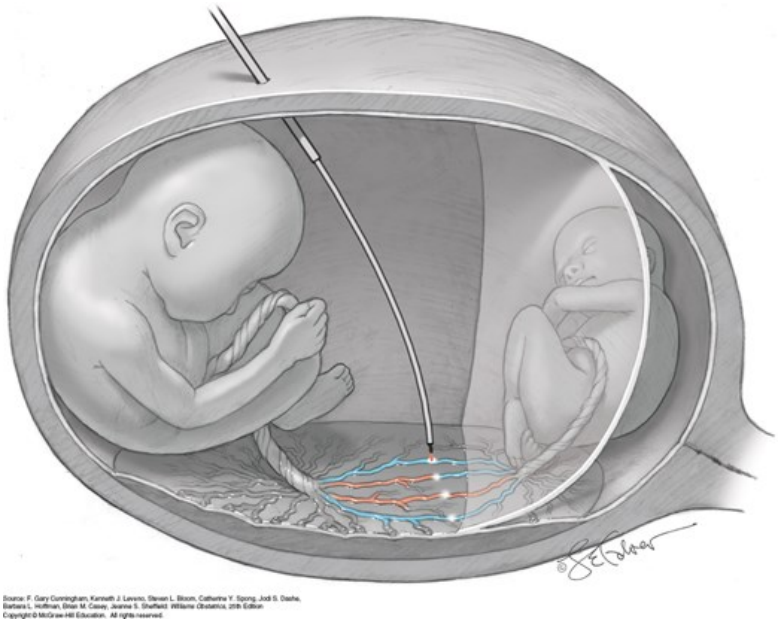
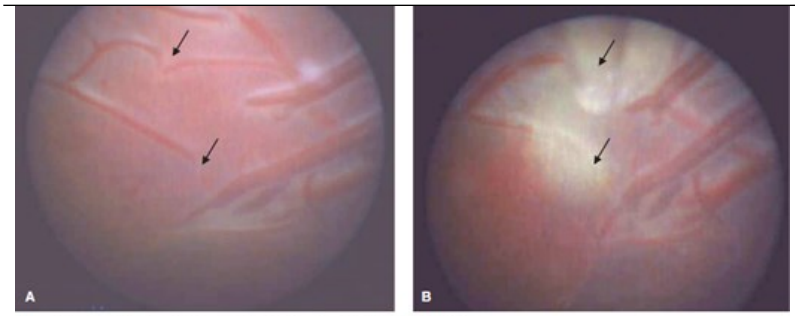


FIGURE 16-5

Fetoscopic photograph of laser photocoagulation for twin-twin transfusion syndrome. **A.** Vascular anastomoses (*arrows*) are shown before photocoagulation is performed. **B.** The ablation sites appear as blanched yellow-white areas (*arrows*). (Used with permission from Dr. Timothy M. Crombleholme.)



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With *selective laser photocoagulation,* anastomoses crossing between the twins along the vascular equator are individually coagulated (Ville, 1995). Unfortunately, residual anastomoses remain in up to a third of cases and may lead to TTTS recurrence or to the development of twin-anemia polycythemia sequence (TAPS). The latter is a feto-fetal transfusion characterized by large differences in hemoglobin concentrations between a pair of monochorionic twins. To address these complications, the *Solomon technique* was developed. With this, after selective photocoagulation, the laser is used to coagulate the entire vascular equator, from one edge of the placenta to the other (Slaghekke, 2014a). The Solomon technique lowers the proportion of pregnancies with recurrent TTTS and TAPS in multiple trials. Also, placental dye-injection studies confirm a significant reduction in the number of residual anastomoses (Ruano, 2013; Slaghekke, 2014b).

Complications

Families should have reasonable expectations of procedural success and potential complications. Without treatment, the perinatal mortality rate for severe TTTS is 70 to 100 percent. Following laser therapy, the anticipated perinatal mortality rate approximates 30 to 50 percent, with a 5- to 20-percent risk for long-term neurological handicap (Society for Maternal-Fetal Medicine, 2013). Cystic periventricular leukomalacia and grade III to IV interventricular hemorrhage are identified neonatally in up to 10 percent of laser-treated cases (Lopriore, 2006).

Procedure-related complications include preterm prematurely ruptured membranes in up to 25 percent, placental abruption in 8 percent, vascular laceration in 3 percent, amnionic band syndrome resulting from laser laceration of the membranes in 3 percent, and TAPS in 16 percent with photocoagulation and 3 percent with the Solomon modification (Habli, 2009; Robyr, 2006; Slaghekke, 2014b). Finally, most laser-treated TTTS pregnancies deliver before 34 weeks.

Congenital Diaphragmatic Hernia

The prevalence of congenital diaphragmatic hernia (CDH) is approximately 1 in 3000 to 4000 births, and the overall survival rate is 50 to 60 percent. Associated anomalies occur in 40 percent of cases and confer a considerably lower survival rate. The main causes of mortality among those with isolated CDH are pulmonary hypoplasia and pulmonary hypertension. And, the major risk factor is liver herniation, which complicates at least half of cases and is associated with a 30-percent reduction in the survival rate (Mullassery, 2010, Oluyomi-Obi, 2017).

Because of maternal and fetal risks associated with fetal surgical intervention, efforts have focused on identifying those least likely to survive with postnatal therapy alone. Fetuses with associated anomalies are typically excluded, as are those without liver herniation. Prediction is further hampered because of improvements in neonatal care for newborns with CDH. These include permissive hypercapnia, “gentle ventilation” to avoid barotrauma, and delayed surgery.

Lung-to-Head Ratio

This sonographic ratio was developed to improve prediction of survival in fetuses with isolated left-sided CDH diagnosed before 25 weeks’ gestation (Metkus, 1996). The lung-to-head ratio (LHR) is a measurement of the right lung area, taken at the level of the four-chamber view of the heart, divided by the head circumference (Fig. 10-23). Investigators found that the survival rate was 100 percent if the LHR was >1.35, and there were no survivors if it was <0.6. Nearly three fourths of pregnancies had values between 0.6 and 1.35, and prediction was difficult in this large group because the overall survival rate approximated 60 percent (Metkus, 1996).

As of 2017, trials underway have selected a threshold LHR of <1.0 or an observed-to-expected LHR <25 percent for study inclusion. An observed LHR is

obtained sonographically from the affected fetus, whereas the expected LHR is an established reference value from normal fetuses (Peralta, 2005). In a recent metaanalysis, the odds ratio for survival with an LHR <1.0 was only 0.14 (Oluyomi-Obi, 2017). Similarly, with an observed-to-expected LHR <25 percent, survival rates ranged from 13 to 30 percent. In contrast, an observed-to-expected LHR >35 percent was associated with survival rates ranging from 65 to 88 percent.

Magnetic Resonance Imaging

This has been used to estimate the total volume of lung tissue, both ipsilateral and contralateral to the diaphragmatic hernia, which may then be compared with a gestational age-matched reference. Mayer and coworkers (2011) performed a metaanalysis of 19 studies involving more than 600 pregnancies in which isolated CDH was evaluated with fetal MR imaging. Factors significantly associated with neonatal survival included the side of the defect, total fetal lung volume, observed-to-expected lung volume, and fetal liver position.

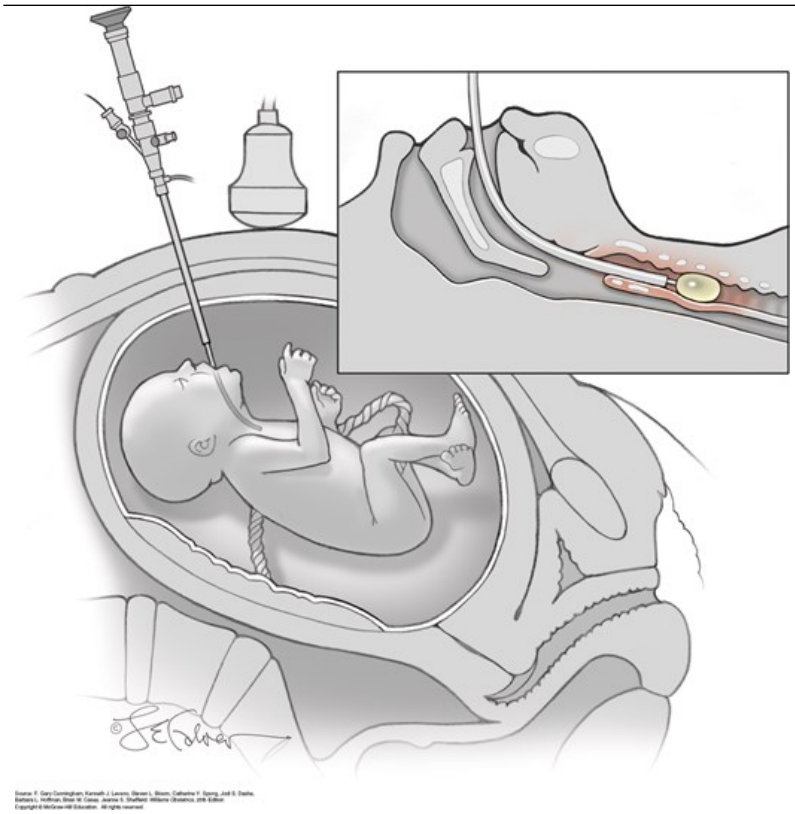
Fetal MR imaging has also been used to quantify the volume of herniated liver (Fig. 10-57). Two reasons underlie the rationale for assessing liver volume. First, liver herniation is perhaps the strongest predictor of outcome in fetuses with isolated CDH. Second, liver volume might be a more reliable predictor because lungs are inherently more compressible than liver. Indeed, these MR parameters—lung volumes and degree of liver herniation—correlate well with postnatal survival rates and may be more useful predictors than sonographic parameters (Bebbington, 2014; Ruano, 2014; Worley, 2009).

Tracheal Occlusion

Early attempts to treat severe diaphragmatic herniation used open fetal surgery to reposition the liver into the abdomen, which unfortunately kinked the umbilical vein and led to fetal demise (Harrison, 1993). Knowledge that lungs normally produce fluid and that fetuses with upper airway obstruction develop hyperplastic lungs formed the rationale for tracheal occlusion. The idea was to “plug the lung until it grows” (Hedrick, 1994). Initial efforts focused on occluding the trachea with an external clip (Harrison, 1993). Subsequently, a detachable silicone balloon was placed within the trachea endoscopically (Fig. 16-6).

FIGURE 16-6

Fetoscopic tracheal occlusion (FETO). The endoscope enters the fetal oropharynx and advances down the trachea. Inset: The balloon is inflated to occlude the trachea, and then the endoscope is removed. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap’s Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



The balloon technique—termed *fetal endoscopic tracheal occlusion (FETO)*—uses a 3-mm operating sheath and fetoscopes as small as 1 mm (Deprest, 2011; Ruano, 2012). The procedure is generally performed between 27 and 30 weeks' gestation, with the goal of removing the balloon at approximately 34 weeks, either through a second fetoscopic procedure or by ultrasound-guided puncture (Jiménez, 2017). If these are unsuccessful, the balloon is removed during an ex-utero intrapartum treatment procedure at delivery (Ex-Utero Intrapartum Treatment).

In 2003, a randomized trial of the FETO procedure in pregnancies with isolated CDH, liver herniation, and LHR <1.4 did not identify a benefit from fetal therapy (Harrison, 2003). Survival rates 90 days after birth were unexpectedly high in both groups and approximated 75 percent. Following this study, however, enthusiasm for the technique continued, particularly outside the United States. Using a lower LHR threshold of 1.0 in addition to liver herniation as prerequisites for inclusion, significantly higher postnatal survival rates have been reported. Rates improved from <25 percent with postnatal therapy to approximately 50 percent with FETO (Jani, 2009; Ruano, 2012). In a recent metaanalysis of five trials that included 211 pregnancies, those treated with FETO were 13 times more likely to survive (Al-Maary, 2016). At present, FETO is available in the United States only in research trials.

Endoscopic Myelomeningocele Repair

After publication of the MOMS findings, research efforts focused on whether maternal morbidities associated with open fetal myelomeningocele repair might be mitigated if the procedure was accomplished endoscopically. Araujo Junior and associates (2016) conducted a systematic review that included 456 open cases and 84 endoscopic surgeries. The endoscopic procedures were generally performed by inserting instruments through the maternal abdominal wall and then through the uterine wall, with partial carbon dioxide insufflation of the uterus. The rate of maternal myometrial dehiscence or attenuation was only 1 percent following endoscopy compared with 26 percent following open procedures. However, endoscopy was associated with significantly increased rates of preterm delivery before 34 weeks—80 versus 45 percent, and of perinatal mortality—14 versus 5 percent.

Belfort and colleagues (2017) recently described their outcomes in 22 pregnancies with fetal myelomeningocele using a technique in which the maternal abdomen was opened, the uterus exteriorized, and the procedure then performed endoscopically using warmed carbon dioxide insufflation. In contrast with earlier endoscopic reports, most treated pregnancies were delivered at term, with no perinatal losses. Further, the proportion of infants requiring hydrocephalus treatment prior to 1 year of age—approximately 40 percent—was similar to that with open fetal surgery in the MOMS trial (Adzick, 2011; Belfort, 2017). Research efforts in this area will undoubtedly continue.

Percutaneous Procedures

Sonographic guidance can be used to permit therapy with a shunt, radiofrequency ablation needle, or angioplasty catheter. With these procedures, desired instruments cross the maternal abdominal wall, uterine wall, and membranes to reach the amniotic cavity and fetus. Risks include maternal infection, preterm labor or prematurely ruptured membranes, and fetal injury or loss.

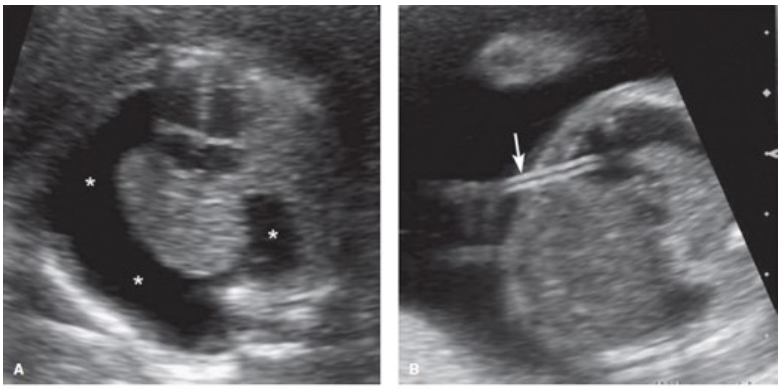
Thoracic Shunts

A shunt placed from the fetal pleural cavity into the amniotic cavity may be used to drain pleural fluid (Fig. 16-7). A large effusion may cause a significant mediastinal shift, resulting in pulmonary hypoplasia or in heart failure and hydrops. The most common etiology of a primary effusion is *chylothorax*—caused by lymphatic obstruction. Pleural effusions may also form secondary to congenital viral infection or aneuploidy, or they may be associated with a malformation such as *pulmonary sequestration.* Yinon and associates (2010) reported aneuploidy in approximately 5 percent and associated anomalies in 10 percent of cases.

Typically, the effusion is first drained using a 22-gauge needle with sonographic guidance. Tests for aneuploidy and infection are performed, as well as a cell count. A pleural-fluid cell count with greater than 80-percent lymphocytes, in the absence of infection, is diagnostic of chylothorax. If the fluid reaccumulates, a trocar and cannula may be inserted through the fetal chest wall, and a double-pigtail shunt may be placed to drain the effusion. If the effusion is right-sided, the shunt is placed in the lower third of the chest to permit maximum expansion of the lung. If left-sided, the shunt is placed along the upper axillary line to allow the heart to return to normal position (Mann, 2010). The overall survival rate is 70 percent, and that for hydropic fetuses approximates 50 percent (Mann, 2010; Yinon, 2010). Shunt displacement into the amniotic cavity is not uncommon. If the shunt remains in place, it must be clamped immediately upon delivery of the newborn to avoid pneumothorax.

FIGURE 16-7

Thoracoamnionic shunt placement. **A.** A large, right-sided fetal pleural effusion (*asterisks*) and ascites were identified at 18 weeks' gestation. The effusion was drained but rapidly reaccumulated. The xanthochromic fluid contained 95-percent lymphocytes, consistent with chylothorax. **B.** A double-pigtail shunt (*arrow*) was inserted under ultrasound guidance. Following shunt placement, the effusion and ascites resolved.



Shunts can also drain a dominant cyst in fetuses with macrocystic *congenital cystic adenomatoid malformation*. However, cysts rarely are large enough to pose a risk for hydrops or pulmonary hypoplasia. Shunt placement may improve survival to 90 percent in the absence of hydrops and to more than 75 percent with hydrops (Litwinska, 2017).

Urinary Shunts

Vesicoamnionic shunts are used in selected fetuses with severe bladder-outlet obstruction in which diminished amniotic fluid portends a grim prognosis (Fig. 16-8). Distal obstruction of the urinary tract occurs more often in male fetuses. The most common etiology is *posterior urethral valves,* followed by *urethral atresia* and by *prune belly syndrome*, which is also called *Eagle-Barrett syndrome.* Sonographic findings include dilation of the bladder and proximal urethra, termed the "keyhole" sign, along with bladder wall thickening (Fig. 10-45). Associated oligohydramnios before

midpregnancy leads to pulmonary hypoplasia. Unfortunately, postnatal renal function may be poor even when amnionic fluid volume is normal.

Evaluation includes a careful search for concurrent anomalies, which may coexist in 40 percent of cases, and for aneuploidy, which has been reported in 5 to 8 percent of cases (Hayden, 1988; Hobbins, 1984; Mann, 2010). Fetal urine sampled at vesicocentesis may be used to perform genetic studies. As with other structural fetal abnormalities, chromosomal microarray analysis is recommended. Because visualization may be limited due to lack of amnionic fluid, counseling should include the increased likelihood that associated anomalies may be missed sonographically.

Potential candidates are fetuses without other severe anomalies or genetic syndromes and without sonographic features that confer poor prognosis, for example, renal cortical cysts. Therapy is generally offered only if the fetus is male, because in females, the underlying anomaly tends to be even more severe. Serial bladder drainage—vesicocentesis—performed under sonographic guidance at approximately 48-hour intervals is used to evaluate fetal urine electrolyte and protein content. Fetal urine is normally hypotonic due to tubular resorption of sodium and chloride, whereas isotonic urine in the setting of obstruction suggests renal tubular damage. Serial assessment permits classification of the renal prognosis as good or poor and helps guide candidate selection (Table 16-4).

TABLE 16-4

Fetal Urinary Analyte Values with Bladder Outlet Obstruction

Analyte	Good Prognosis	Poor Prognosis
Sodium	<90 mmol/L	>100 mmol/L
Chloride	<80 mmol/L	>90 mmol/L
Calcium	<7 mg/dL	>8 mg/dL
Osmolality	<180 mmol/L	>200 mmol/L
β_2-Microglobulin	<6 mg/L	>10 mg/L
Total protein	<20 mg/dL	>40 mg/dL

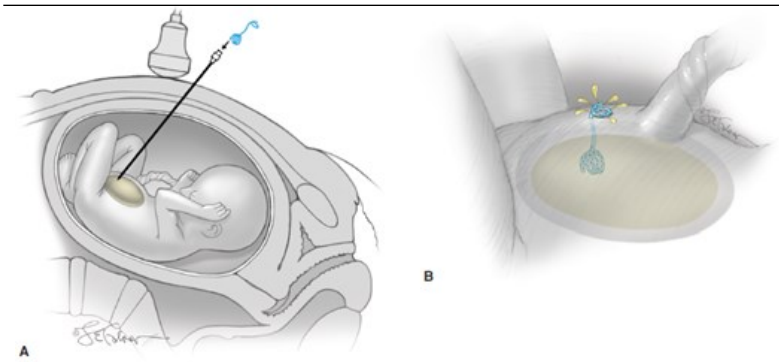
Good or poor prognosis is based on values from serial vesicocentesis performed between 18 and 22 weeks' gestation, using the last specimen obtained.

Data from Mann, 2010.

Shunt placement allows urine to drain from the bladder into the amnionic cavity. When successful, this often prevents pulmonary hypoplasia, however, renal function is not reliably preserved. Before shunting, amnioinfusion of warmed lactated Ringer solution is generally performed to aid catheter placement. Amnioinfusion also aids sonographic evaluation of fetal anatomy. A small trocar and cannula are then inserted into the fetal bladder under sonographic guidance. The shunt is placed as low as possible within the bladder to avoid dislodgement after bladder decompression. A double-pigtail catheter is used. The distal end lies within the fetal bladder, and the proximal end drains into the amnionic cavity.

FIGURE 16-8

Vesicoamnionic shunt placement. **A.** After amnioinfusion is performed, a trocar is inserted into the distended fetal bladder under sonographic guidance. The pigtail catheter is threaded into the trocar. **B.** The double-pigtail shunt has been deployed down the trocar, and the trocar has been removed. The distal end of the shunt is coiled within the fetal bladder, and the proximal end is draining into the amnionic cavity. (Reproduced with permission from Shamshirsaz AA, Ramin, SM, Belfort MA: Fetal therapy. In Yeomans ER, Hoffman BL, Gilstrap LC III, et al: Cunningham and Gilstrap's Operative Obstetrics, 3rd ed. New York, McGraw-Hill Education, 2017.)



Complications include displacement of the shunt out of the fetal bladder in up to 40 percent of cases, urinary ascites in about 20 percent, and development of gastroschisis in 10 percent (Freedman, 2000; Mann, 2010). Preterm delivery is common, and neonatal survival rates range from 50 to 90 percent (Biard, 2005; Walsh, 2011). A third of surviving children have required dialysis or renal transplantation, and almost half have respiratory problems (Biard, 2005). In one randomized trial, vesicoamnionic shunt placement was compared with conservative management in 31 cases (Morris, 2013). Those receiving shunts had higher survival rates. However, only two children had normal renal function at age 2 years.

Radiofrequency Ablation

With this procedure, high-frequency alternating current is used to coagulate and desiccate tissue. Radiofrequency ablation (RFA) has become a favored modality for treatment of *twin-reversed arterial perfusion (TRAP) sequence,* also known as *acardiac twin* (Chap. 45, Twin Anemia–Polycythemia Sequence). Without treatment, the mortality rate for the normal or pump twin in severe TRAP sequence exceeds 50 percent. The procedure is also used for selective termination with other monochorionic twin complications (Bebbington, 2012).

Under sonographic guidance, a 17- to 19-gauge RFA needle is directed into the base of the umbilical cord of the acardiac twin and inserted into its abdomen. After a 2-cm area of coagulation is achieved, color Doppler sonography is applied to verify absent flow into the acardius. In several centers, survival rates for the normal twin following RFA have significantly improved (Lee, 2007; Livingston, 2007). RFA was performed at approximately 20 weeks' gestation in 98 pregnancies with TRAP sequence reported by the North American Fetal Therapy Network (NAFTNet). The median gestational age at delivery was 37 weeks, and the neonatal survival rate was 80 percent. The major complication was prematurely ruptured membranes and preterm birth. Twelve percent were delivered at approximately 26 weeks (Lee, 2013).

RFA has generally been offered for TRAP sequence when the volume of the acardiac twin is large. In the NAFTNet series cited above, the median size of the acardius relative to the pump twin was 90 percent (Lee, 2013). Considering procedure-related risks, expectant management with close fetal surveillance is instead considered if the estimated weight of the acardius is below 50 percent of the pump twin (Jelin, 2010). Finally, acardiac twins are more likely to complicate monoamnionic gestations. In one recent series, pump twin survival following RFA was 88 percent in monochorionic diamnionic pregnancies but only 67 percent in monoamnionic pregnancies (Sugibayashi, 2016).

Fetal Intracardiac Catheter Procedures

Selected fetal cardiac lesions may worsen during gestation, further complicating or even obviating options for postnatal repair. Severe narrowing of a cardiac outflow tract may result in progressive myocardial damage in utero, and a goal of fetal intervention is to permit muscle growth and preserve ventricular function (Walsh, 2011). These innovative procedures include *aortic valvuloplasty* for critical aortic stenosis; *atrial septostomy* for hypoplastic left heart syndrome with intact interatrial septum; and *pulmonary valvuloplasty* for pulmonary atresia with intact interventricular septum.

Fetal aortic valvuloplasty is the most commonly performed cardiac procedure, accounting for 75 percent of cases reported by the International Fetal Cardiac Intervention Registry (Moon-Grady, 2015). It is offered for selected cases of critical aortic stenosis in which the left ventricle is either normal sized or dilated. The goal is to prevent progression to hypoplastic left heart and to permit postnatal biventricular repair (McElhinney, 2009). Under sonographic guidance, an 18-gauge cannula is inserted through uterus and fetal chest wall and into the left ventricle. Although the procedure is ideally performed percutaneously—through the maternal abdominal wall—laparotomy may be needed if the fetal position is unfavorable. The cannula tip is positioned in front of the stenotic aortic valve, and a 2.5- to 4.5-mm balloon catheter is then guided into the aortic annulus and inflated. Fetal bradycardia requiring treatment complicates a third of cases, and hemopericardium requiring drainage affects approximately 20 percent (Moon-

Grady, 2015).

From the first 100 cases at Boston Children's Hospital, 85 children survived, 38 of whom achieved biventricular circulation (Freud, 2014). Despite these successes, the mortality rate and risk for neurodevelopmental impairment in childhood appear to be similar to cases treated with postnatal repair (Laraja, 2017; Moon-Grady, 2015).

Fetal atrial septostomy, also using a percutaneous balloon catheter, is offered in select cases of hypoplastic left heart with an intact or highly restrictive interatrial septum. This condition has a postnatal mortality rate of nearly 80 percent (Glantz, 2007). In an effort to ensure patency, atrial septal stent placement has also been performed. Of 37 cases of atrial septostomy, survival to hospital discharge was almost 50 percent (Moon-Grady, 2015).

Fetal pulmonary valvuloplasty has been offered in cases of pulmonary atresia with intact interventricular septum to prevent development of hypoplastic right heart syndrome. Although success is achieved in approximately two thirds of cases, it is not yet clear whether outcomes are improved compared with standard postnatal repair (Arzt, 2011; McElhinney, 2010).

Ex-Utero Intrapartum Treatment

This procedure allows the fetus to remain perfused by the placenta after being partially delivered, so that lifesaving treatment can be performed before completing the delivery. The technique was first developed to obtain an airway with fetal tumors involving the oropharynx and neck (Catalano, 1992; Kelly, 1990; Langer, 1992). An ex-utero intrapartum treatment (EXIT) procedure is performed by a multidisciplinary team, which may include an obstetrician, maternal-fetal medicine specialist, pediatric surgeon(s), pediatric otolaryngologist, pediatric cardiologist, anesthesiologists for the mother and fetus, and neonatologists, as well as specially trained nursing personnel. Components of the procedure are shown in Table 16-5.

TABLE 16-5

Components of the Ex-Utero Intrapartum Treatment (EXIT) Procedure

Comprehensive preoperative evaluation: specialized sonography, fetal echocardiography, magnetic resonance imaging, fetal karyotype if possible
Uterine relaxation with deep general anesthesia and tocolysis
Intraoperative sonography to confirm placental margin and fetal position and to visualize vessels at uterine entry
Placement of stay-sutures followed by use of uterine stapling device to decrease uterine entry bleeding
Maintenance of uterine volume during the procedure via continuous amnioinfusion of warmed physiological solution to help prevent placental separation
Delivery of the fetal head, neck, and upper torso to permit access as needed
Fetal injection of intramuscular vecuronium, fentanyl, and atropine
Fetal peripheral intravenous access, pulse oximeter, and cardiac ultrasound
Following procedure, umbilical lines placed prior to cord clamping
Uterotonic agents administered as needed

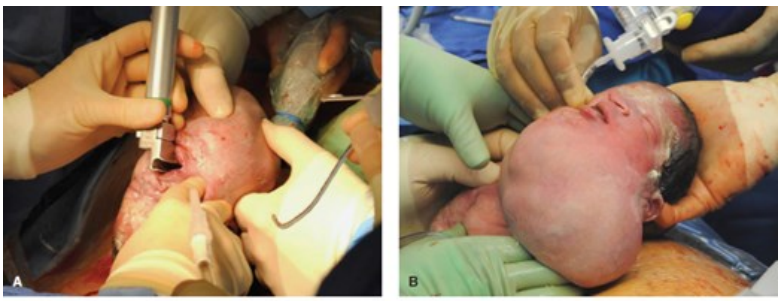
Data from Moldenhauer, 2013.

Selected indications are listed in Table 16-2. EXIT is the preferred procedure for intrapartum management of large venolymphatic malformations of the neck such as the one shown in Figure 16-9. At the Children's Hospital of Philadelphia, criteria for EXIT with a cervical venolymphatic malformation include compression, deviation, or obstruction of the airway by the mass, and also involvement of the floor of the mouth (Laje, 2015). In a review of 112 pregnancies with fetal cervical venolymphatic malformations, only about 10 percent met these criteria. Other indications for EXIT include severe *micrognathia* and *congenital high airway obstruction sequence (CHAOS)*, which are discussed in Chapter 10 (Figs. 10-20 and 10-26). Criteria for an EXIT procedure for micrognathia include a fetal jaw measurement below the 5th percentile along with indirect evidence of obstruction, such as hydramnios, an absent stomach bubble, or glossoptosis (Morris, 2009b). Case selection for EXIT procedures is generally based on fetal MR imaging findings (Chap. 10, Adjunct to Fetal Therapy).

FIGURE 16-9

Ex-utero intrapartum treatment (EXIT) procedure for a venolymphatic malformation. **A.** Upon delivery of the head, placental circulation was

maintained and an airway was established over the course of 20 minutes by a team of pediatric subspecialists that included a surgeon, anesthesiologist, and otolaryngologist. **B.** Following a controlled intubation, the fetus was ready for delivery and transfer to the neonatal intensive care unit team. (Used with permission from Drs. Stacey Thomas and Patricia Santiago-Muñoz.)



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In some cases, an EXIT procedure has been used as a bridge to other procedures. For example, resection of large thoracic masses may be accomplished by fetal thoracotomy performed with intact placental circulation. In a series of 16 fetuses with CCAM volume ratios >1.6 or hydrops, all of whom had mediastinal compression, Cass and colleagues (2013) reported that nine infants undergoing *EXIT-to-resection* survived. In contrast, there were no survivors with urgent postnatal surgery alone. Similarly, Moldenhauer (2013) reported that 20 of 22 newborns treated with EXIT-to-resection for lung masses survived. The EXIT procedure has also been used as a bridge to extracorporeal membrane oxygenation—*EXIT-to-ECMO*—in pregnancies with severe congenital diaphragmatic hernia. However, it has not been found to clearly confer survival benefit in such cases (Morris, 2009a; Shieh, 2017; Stoffan, 2012).

Counseling prior to an EXIT procedure includes procedure-related risks such as hemorrhage from placental abruption or uterine atony, need for cesarean delivery in future pregnancies, higher risk for subsequent uterine rupture or dehiscence, possible need for hysterectomy, and fetal death or permanent neonatal disability. Compared with cesarean delivery, the EXIT procedure is associated with greater blood loss, a higher incidence of wound complications, and a longer operating time—approximately 40 minutes longer depending on the procedure (Noah, 2002).

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