CHAPTER 16

Fetal Therapy

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 treatment of fetal anemia and thrombocytopenia is reviewed in Chapter 15, and the treatment of some fetal infections is discussed in Chapters 64 and 65.

MEDICAL THERAPY

Fetal pharmacotherapy, administered to the mother and transported transplacentally, can be used to treat an array of serious conditions. Two well-described examples are *fetal tachyarrhythmia* treatment with medications such as digoxin, and corticosteroid therapy to prevent virilization of female fetuses with *congenital adrenal hyperplasia.* More recently, a course of corticosteroid therapy—the same used to promote lung maturity before preterm birth—has been used to stabilize the growth of large fetal lung masses and avoid fetal surgery.

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. Fetal M-mode sonography (p. 322) should be performed to determine the atrial and ventricular rate to clarify the relationship between atrial and ventricular beats, thereby diagnosing the rhythm disturbance type.

Premature Atrial Contractions

This is by far the most common arrhythmia. Premature atrial contractions are identified in 1 to 2 percent of pregnancies and are generally a benign finding (Hahurij, 2011; Strasburger, 2010). They represent immaturity of the cardiac conduction system and typically resolve either with advancing gestation or in the neonatal period. Although they may be conducted, they are more commonly blocked, and with handheld Doppler or fetoscope, they sound like a dropped beat. Premature atrial contractions are not associated with major structural cardiac abnormalities, but they sometimes occur with an atrial septal aneurysm. As shown in Figure 10-24 (p. 212), 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 beats per minute. Unlike other causes of bradycardia, this carries a benign prognosis and does not require treatment (Strasburger, 2010).

Approximately 2 percent of fetuses with premature atrial contractions are later identified to develop *supraventricular tachycardia (SVT)* and require urgent treatment to prevent development of hydrops (Copel, 2000; Srinivasan, 2008). Given the importance of identifying such tachycardia, the fetus with premature atrial contractions is often monitored with heart rate assessment every 1 to 2 weeks until ectopy resolution.

Tachyarrhythmias

The two most common are *supraventricular tachycardia* 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—300 to 500 bpm. There are varying degrees of atrioventricular block, such that the ventricular rate 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 slightly above normal. There is often a readily discernible cause such as maternal fever or hyperthyroidism, or rarely, fetal anemia or infection.

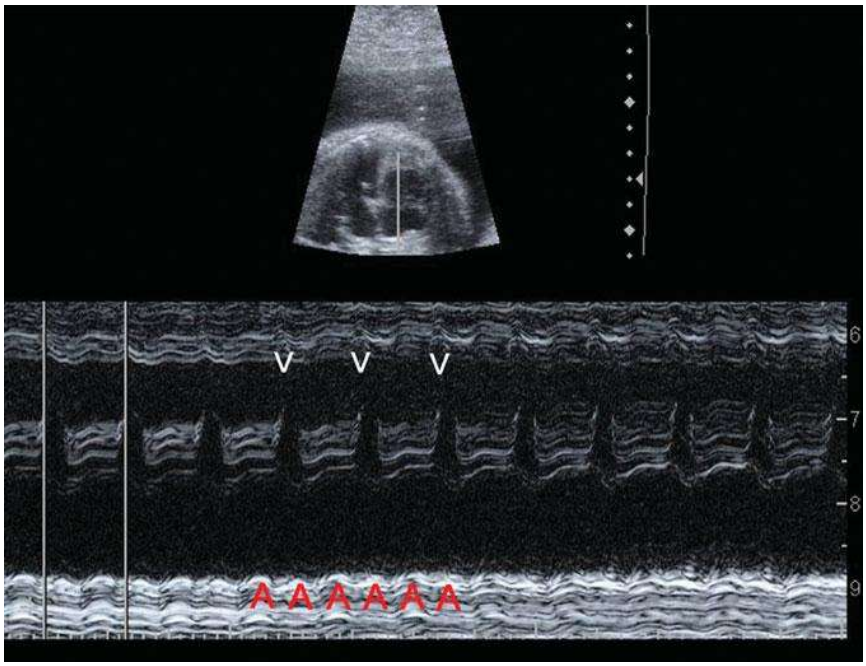

FIGURE 16-1 Atrial flutter. In this M-mode image at 28 weeks, calipers mark the ventricular rate, which is approximately 225 bpm. There are two atrial beats (*A*) for each ventricular beat (*V*), such that the atrial rate is approximately 450 bpm with 2:1 atrioventricular block.

If a 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). Nonsustained 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 such a degree that the risk of 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. A maternal electrocardiogram should be performed before and during therapy. If the fetus has become hydropic, the drug may need to be administered directly via the umbilical vein (Mangione, 1999; Simpson, 2006).

Various antiarrhythmic medications have been used, most commonly 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. Digoxin is usually the first-line agent. Amiodarone (Cordarone) has been associated with fetal and neonatal hypothyroidism, which may be severe (Niinikoski, 2007; Simpson, 2006).

In a review of 485 cases of fetal tachyarrhythmia, hydrops was reported in approximately 40 percent of those with either SVT or atrial flutter (Krapp, 2003). Digoxin was the first-line agent selected in two thirds with either tachyarrhythmia. Treatment was more effective in nonhydropic fetuses than in those in whom hydrops had already developed. With therapy, the neonatal survival rate with either arrhythmia exceeded 90 percent (Krapp, 2003).

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 *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 cases of atrioventricular block 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 another connective-tissue disease (Chap. 59, p. 1172). The risk of third-degree heart block with these antibodies is only 2 to 5 percent, but it may be up to 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).

Research efforts have focused on maternal corticosteroid therapy to 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 sonography was used to monitor for fetal heart block. If identified, maternal treatment was dexamethasone 4 mg orally daily. There were several important findings. First-degree block was

rare and did not generally precede to more advanced block; progression from second- to third-degree block was not prevented with maternal dexamethasone therapy; and third-degree atrioventricular block was *irreversible* (Friedman, 2008, 2009). In rare cases, there was a potential benefit in reversing first-degree atrioventricular block. However, the authors cautioned that there was a need to weigh this potential benefit against the risks of chronic antepartum corticosteroid treatment, including impaired fetal growth (Friedman, 2009).

Maternal terbutaline has also been administered to increase the fetal heart rate in cases with sustained bradycardia of any cause in which the fetal heart rate is ≤ 55 bpm. Cuneo and associates (2007) reported reversal of hydrops with this therapy in a few cases. However, outcomes in those with structural abnormalities remained poor.

Congenital Adrenal Hyperplasia

Several autosomal recessive enzyme deficiencies cause impaired fetal synthesis of cortisol from cholesterol by the adrenal cortex, resulting in congenital adrenal hyperplasia (CAH). This is the most common etiology of androgen excess in females with pseudohermaphroditism (Chap. 7, p. 148). 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, development of a urogenital sinus, or even creation of a penile urethra and scrotal sac (Fig. 7-18, p. 149).

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 is approximately 1:15,000 overall and is higher in selected populations. For example, it develops 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. The remaining 25 percent with classic CAH have the *simple virilizing type* and require glucocorticoid supplementation. Without prompt recognition and treatment, infants with the salt-wasting form can develop hyponatremia, dehydration, hypotension, and cardiovascular collapse. As discussed in Chapter 32 (p. 631), 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 nearly 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, which may involve vaginoplasty, clitoroplasty, and labioplasty (Braga, 2009).

If treatment is elected, the typical 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. To prevent virilization, treatment 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 comprise 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 for common mutations and deletions of the *CYP21A2* gene, which encodes the 21-hydroxylase enzyme. It is informative in 80 to 98 percent of cases, and for the remainder, gene sequencing may detect rarer alleles (Nimkarn, 2010). Women who elect treatment do so with a plan to undergo prenatal diagnosis and stop therapy if the fetus is male or an unaffected female. Prenatal diagnosis with molecular genetic testing may be performed on chorionic villi—at 10 to 12 weeks' gestation—or on amniocytes after 15 weeks. Ideally, the goal is to limit dexamethasone exposure in males and in unaffected females.

Recently, maternal treatment with dexamethasone has become a topic of significant controversy. The Endocrine Society has recommended that treatment be given only in the context of research protocols (Miller, 2013; Speiser, 2010). If therapy is initiated shortly before 9 weeks, the dosage of dexamethasone used is not considered to have significant teratogenic potential because organogenesis of major organs has already taken place (McCullough, 2010). There are ongoing concerns, however, about 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.

Development of cell-free fetal DNA testing of maternal serum has potential to replace invasive tests such as chorionic villus sampling and amniocentesis for CAH (Chap. 13, p. 279). Determination of fetal gender using cell-free fetal DNA is reported to have at least 95-percent sensitivity when performed at or beyond 7 weeks' gestation (Devaney, 2011). Although not yet clinically available in 2013, DNA analysis of the *CYP21A2* gene has also been reported using cell-free fetal DNA testing.

Congenital Cystic Adenomatoid Malformation

Also called congenital pulmonary airway malformation (CPAM), this lung mass is a hamartomatous overgrowth of terminal bronchioles. Sonographically, congenital cystic adenomatoid malformation (CCAM) is a well-circumscribed mass that may appear solid and echogenic or may have one or multiple variably sized cysts (Fig. 10-18, p. 207). Lesions with cysts 5 mm or larger are generally termed macrocystic, whereas microcystic lesions have smaller cysts or appear solid (Adzick, 1985). Therapy for macrocystic CCAM is discussed on page 330.

Infrequently, a microcystic CCAM may demonstrate rapid growth between 18 and 26 weeks' gestation. The mass may become so large that it causes mediastinal shift, compromised cardiac output and venous return, and resultant hydrops (Cavoretto, 2008). A CCAM-volume ratio (CVR) has been used to quantify size and risk for hydrops in these severe cases (Crombleholme, 2002). The CVR is an estimate of the CCAM volume—length × width × height × 0.52—divided by the head circumference. In the absence of a dominant cyst, a

CVR exceeding 1.6 has been associated with a hydrops risk of approximately 75 percent, whereas the risk is < 5 percent with a smaller CVR.

If the CVR exceeds 1.4 or 1.6 or if signs of hydrops develop, corticosteroid treatment has been advocated 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. In some reports, hydrops has resolved in nearly 80 percent of cases, and approximately 85 percent of these treated cases survived (Curran, 2010; Loh, 2012; Peranteau, 2007). However, others found that high-risk CCAMs displayed a variable response to corticosteroid treatment, and perinatal mortality rates were > 40 percent (Morris, 2009c).

Thyroid Disease

Identification of fetal thyroid disease is rare and usually prompted by sonographic detection of a fetal goiter. There are several possibilities to consider. If a woman has previously been treated for Graves disease with either thyroid ablation or surgical resection, she may continue to produce IgG thyroid-stimulating immunoglobulins. These cross the placenta to cause *fetal thyrotoxicosis*. In a woman receiving medication for Graves disease, transplacental passage of propylthiouracil or methimazole usually prevents this, as discussed in Chapter 58 (p. 1149). Occasionally, maternal treatment—or overtreatment—for thyrotoxicosis may cause *fetal hypothyroidism* (Bliddal, 2011a). Other potential causes of fetal hypothyroidism resulting in goiter include transplacental passage of thyroid peroxidase antibodies and fetal thyroid dyshormonogenesis (Agrawal, 2002).

If a goiter is identified, it is important to determine whether the fetus is hyper- or hypothyroid. Thyroid hormone levels may be measured in amnionic fluid, but *fetal blood sampling,* discussed in Chapter 14 (p. 300), is preferred for guiding treatment (Abuhamad, 1995; Ribault, 2009). A primary purpose of therapy—in addition to correcting the physiological abnormality—is to decrease goiter size. The goiter may compress the trachea and esophagus to such a degree that the fetus may develop severe hydramnios and the neonate may develop airway compromise. Hyperextension of the fetal neck by a goiter may result in 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 Graves disease with transplacental passage of thyroid-stimulating immunoglobulins. Most recommend fetal blood sampling to confirm the diagnosis (Duncombe, 2001; Heckel, 1997; Srisupundit, 2008). Confirmed fetal thyrotoxicosis is followed by maternal antithyroid treatment, and if the mother develops hypothyroidism, she is given supplemental levothyroxine (Hui, 2011).

Fetal Hypothyroidism

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 (Bliddal, 2011a; Ribault, 2009). There have been numerous case reports of intraamnionic levothyroxine treatment. However, optimal dosage and frequency have not been established, and reported dosages range from 50 to 800 mg every 1 to 4 weeks (Abuhamad, 1995; Bliddal, 2011b; Ribault, 2009).

Fetal Stem-Cell Transplantation

In theory, stem-cell transplantation could be used to treat various hematological, metabolic, and immunological diseases. It could also serve as a delivery vehicle for gene transfer to treat other genetic conditions. The fetal period is ideal for this because in the first and early second trimesters, the fetus lacks an adaptive immune response to foreign antigens—described as *preimmune* (Tiblad, 2008). Also, pretreatment chemotherapy or radiation is not necessary before transplantation, and graft-versus-host disease is less likely.

Fetal stem-cell transplantation has been most successful in the treatment of immunodeficiency syndromes. Engraftment has been achieved in fetuses with severe combined immunodeficiency and bare lymphocyte syndrome (Tiblad, 2008). Treatment of red blood cell and metabolic disorders, however, has not been successful (Mummery, 2011). Stem-cell transplantation has been attempted to treat hemoglobinopathies without success. Some children with α- and β-thalassemia have remained transfusion dependent despite achieving engraftment (Tiblad, 2008; Westgren, 1996). One fetus with osteogenesis imperfecta, type II, was transplanted with fetal mesenchymal stem cells and developed both engraftment and chimerism (Le Blanc, 2005; Mummery, 2011). Although long-term outcomes of such cases remain uncertain, the technology holds great promise.

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 (Walsh, 2011). Open fetal surgery is a highly specialized, multidisciplinary intervention performed at relatively few centers in the United States and for only a few fetal conditions. It was pioneered more than three decades ago by Harrison and coworkers (1982) at the University of California, San Francisco. 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 lacking. The Agency for Healthcare Research and Quality has stressed that when considering fetal surgery, the overriding concern must be maternal and fetal safety. Accomplishing the fetal goals of the procedure are secondary (Walsh, 2011).

Some abnormalities amenable to fetal surgical treatment, antepartum or intrapartum, are shown in Table 16-2. Information regarding the procedures, their indications, and complications is provided to assist patient evaluation and

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 is an animal model for the defect and procedure

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

counseling. It is beyond the scope of this text to provide technical information necessary to perform these procedures or address individual circumstances in which their benefits may outweigh potential risks.

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(ies) of 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 a highly-skilled multidisciplinary team and extensive preoperative counseling. The mother must undergo general endotracheal anesthesia to suppress both uterine contractions and fetal responses. Using sonographic guidance to avoid the placental edge, a 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 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 will be needed later in gestation and for all future deliveries.

Risks

Morbidities associated with fetal surgery have been well characterized. In a review of 87 open procedures from the University of California, San Francisco, Golombeck and colleagues (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) from Children's Hospital of Philadelphia reviewed subsequent pregnancy outcomes following open fetal surgery and reported that 14 percent 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.

Myelomeningocele Surgery

As depicted and described in Chapters 10 (p. 202) and 14 (p. 287), spina bifida, that is, a congenital open vertebral defect, may be associated with herniation of meninges alone (meningocele) or of meninges and spinal cord nerve roots (myelomeningocele). Despite postnatal repair, affected individuals may have varying degrees of paralysis, bladder and bowel

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
Score derived from Bayley Mental Development Index and difference between functional and anatomical level of lesion (30 months)[a]	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.
Data from Adzick, 2011.

dysfunction, developmental delays, and brainstem dysfunction from the Arnold-Chiari II malformation. Evidence from animal and human studies supports a two-hit hypothesis. Spinal cord damage results from both failure of neurulation during embryonic development and ongoing exposure throughout gestation of the neural elements to amniotic fluid (Adzick, 2010; Meuli, 1995, 1997).

Spina bifida is the first nonlethal birth defect for which fetal surgery has been offered. It meets all of the criteria listed in Table 16-1. Preliminary reports demonstrated that compared with historical controls, infants who had undergone fetal myelomeningocele surgery had reversal of the Arnold-Chiari II malformation and were less likely to require ventriculoperitoneal shunt placement (Bruner, 1999; Sutton, 1999).

Based on this evidence, the National Institutes of Health sponsored a randomized multicenter trial of prenatal versus postnatal myelomeningocele repair—the *Management of Myelomeningocele Study—MOMS* (Adzick, 2011). Criteria for participation in the MOMS trial included: (1) singleton fetus at 19.0 to 25.9 weeks' gestation; (2) upper myelomeningocele boundary between T1 and S1 as confirmed by fetal magnetic resonance (MR) imaging; (3) evidence of hindbrain herniation; and (4) 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. Using these criteria and following comprehensive multidisciplinary counseling, only 15 percent of screened patients underwent the procedure.

The MOMS trial demonstrated improved infant outcomes in the prenatal surgery cohort (see Table 16-3). Infants 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 outcome was also significantly better in the prenatal surgery group.

When counseling prospective families, however, it is essential to place these results into context. 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 ≤ 34 weeks, which significantly increased the risk for respiratory distress syndrome (Adzick, 2011). Long-term data from this trial are pending.

Since publication of the MOMS trial, fetal myelomeningocele has become the most common indication for open fetal surgery at the University of California, San Francisco (Vrecenak, 2013). This is not unexpected, as myelomeningocele is more common than other defects for which open fetal surgery is offered. Also, with other abnormalities, surgery is offered only in the most severe cases—usually prompted by development of hydrops. Rapid expansion of centers offering fetal myelomeningocele surgery has raised concerns about the importance of training and ongoing experience, adherence to the MOMS trial criteria, and need for a registry to ensure that future cases achieve the same success as in the MOMS trial (Cohen, 2014; Vrecenak, 2013).

Thoracic Masses

In the past, if hydrops developed in a fetus with a large extralobar pulmonary sequestration or cystic adenomatoid malformation without a dominant cyst, open fetal surgery with lobectomy was the only treatment available other than preterm delivery (Chap. 10, p. 207). Because most thoracic masses are small and have a benign prognosis, fetal surgery is rarely necessary for fetuses with such masses. Also, larger masses are generally treated with a trial of corticosteroids, and open fetal surgery is reserved for those cases prior to 32 weeks in which hydrops is developing. In fetuses with early hydrops and minimal placentomegaly, 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 is discussed on page 331.

Sacrococcygeal Teratoma

This germ cell tumor has a birth prevalence of about 1 per 28,000 (Derikx, 2006; Swamy, 2008). Sonographically, a sacrococcygeal teratoma (SCT) is a solid and/or cystic mass that arises from the anterior sacrum (Fig. 16-2). It may grow rapidly, usually extending inferiorly and externally (Fig. 10-12, p. 204). 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, p. 318). Fetal MR imaging may be helpful in evaluating the extent of the internal tumor component.

In 30 pregnancies with a prenatal diagnosis of SCT, the perinatal mortality rate exceeded 40 percent (Hedrick, 2004). Fetal loss approaches 100 percent if hydrops or placentomegaly develop (Vrecenak, 2013). The group at the Children's Hospital of Philadelphia has recommended 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). As shown in Figure 16-2, hysterotomy is performed and the external component resected. The coccyx and any deep tumor are left in place for postnatal removal. Because tumor debulking interrupts the vascular steal, normal fetal physiology may be restored.

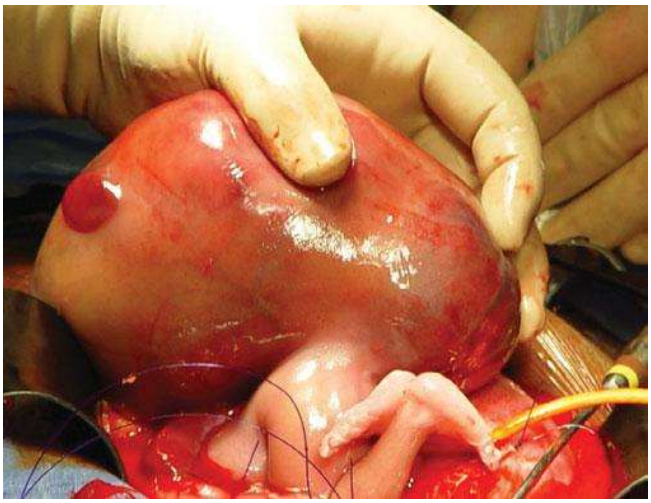

FIGURE 16-2 Photograph of open fetal surgery for resection of a sacrococcygeal teratoma. Hysterotomy has been completed, and the caudal portion of the fetus has been delivered onto the surgical field. The tumor is held by the surgeon's hand. (Photograph contributed by Dr. Timothy M. Crombleholme.)

Fetoscopic Surgery

These procedures use fiberoptic endoscopes only 1 to 2 mm in diameter to cross the maternal abdominal wall, the uterine wall, and membranes. Instruments such as lasers fit through 3- to 5-mm cannulae that surround the endoscope. Thus, fetoscopic surgeries are usually performed at highly specialized centers, and many are considered investigational. 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

As discussed in Chapter 45 (p. 907), fetoscopic laser ablation of placental anastomoses has become the preferred management for many cases of 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 (Quintero, 1999; Society for Maternal-Fetal Medicine, 2013). In this country, pregnancies with stage I TTTS are not routinely offered laser ablation. However, following a consensus conference held by the North American Fetal Therapy Network (NAFTNet), as of 2013, a randomized trial that includes laser therapy for stage I TTTS is underway (Stamilio, 2010).

Technique. The procedure is typically performed under epidural analgesia with intravenous sedation. A fetoscope is used to view the vascular equator that separates the placental cotyledons supplying each twin to permit selective laser photocoagulation of arteriovenous anastomoses that cross this equator (Fig. 16-3).

The randomized trial of TTTS conducted in the United States and reported by Crombleholme and associates (2007) used the following methodology. First, a small skin incision

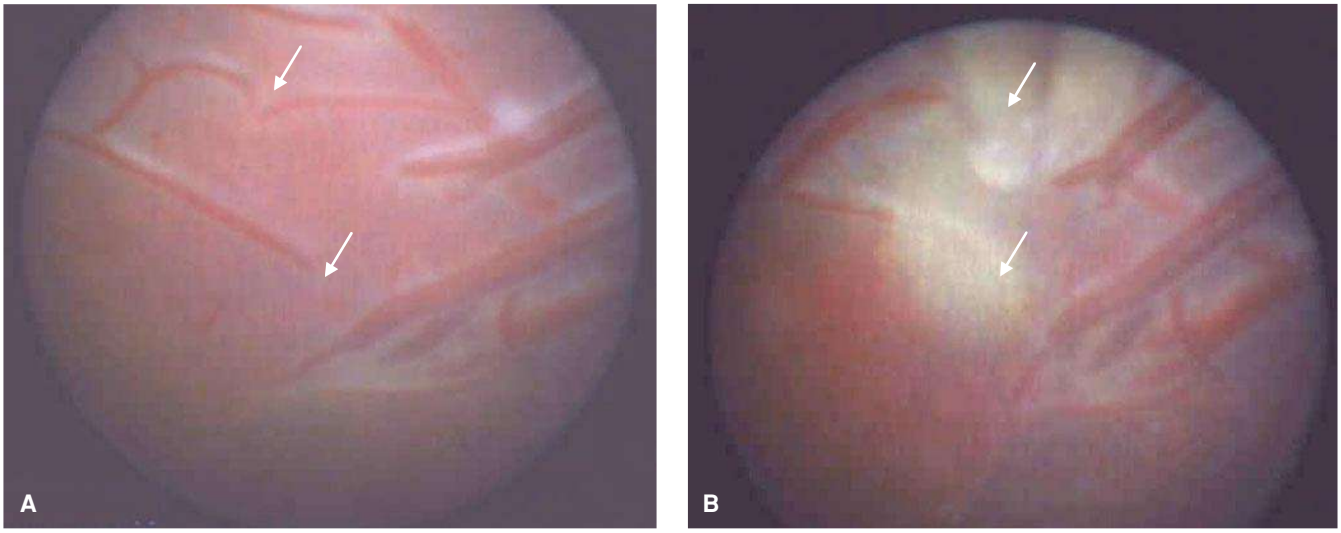

FIGURE 16-3 Laser therapy for twin-twin transfusion syndrome (TTTS). Fetoscopic photograph of the fetal surface of the placenta. **A.** Vascular anastomoses (*arrows*) are shown before selective laser ablation. **B.** Sites of ablation are seen as blanched yellow-white areas (*arrows*). (Photographs contributed by Dr. Timothy M. Crombleholme.)

allows ultrasound-guided placement of a 3.3-mm fetoscope containing separate ports for the lens, the laser, and rapid infusion of saline as needed. More recently, fetoscopes as small as 1.2 mm have been used (Chalouhi, 2011). Next, the chorionic plate of the placenta is mapped three times: first to identify all anastomoses at the vascular equator, then to mark and record the location of each connecting vessel, and after photocoagulation, to verify that no connecting vessels were missed or had recanalized. Vessels are photocoagulated with 60 watts of power using a 600-µm diameter diode laser with the endostat placed 1 cm from the vessel surface. A 400-µm neodymium:yttrium-aluminum-garnet (Nd:YAG) laser also may be used. At the end of the procedure, amnioreduction is performed to decrease the single deepest pocket of amnionic fluid to below 5 cm, and antibiotics are injected into the amnionic cavity.

If cardiomyopathy has been identified in the recipient twin, nifedipine, 20 mg every 6 hours, may be given to the mother 24 to 48 hours before photocoagulation and continued following the procedure, in an effort to improve recipient twin survival (Crombleholme, 2010).

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 (Society for Maternal-Fetal Medicine, 2013). 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 twin-anemia polycythemia sequence in 2 to 12 percent (Habli, 2009; Robyr, 2006). Finally, almost 85 percent of laser-treated TTTS pregnancies deliver before 34 weeks (Habli, 2009).

Twin anemia polycythemia sequence (TAPS) is a type of chronic fetofetal transfusion. It is characterized by large differences in hemoglobin concentrations between the twins of a monochorionic pair in the absence of amnionic fluid volume differences. It may occur spontaneously in 3 to 5 percent of monochorionic twins, although it has been recognized more frequently as a complication of laser-treated TTTS. Differences in middle cerebral artery peak systolic velocity, described in Chapter 10 (p. 221), between the twins may assist in identifying this complication (Robyr, 2006; Slaghekke, 2010).

Congenital Diaphragmatic Hernia

Fetal therapy for this anomaly is more controversial than for others. 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 (Chap. 10, p. 206). Associated anomalies occur in 40 percent of cases and confer a considerably lower survival rate. With isolated CDH, the major causes of mortality are pulmonary hypoplasia and pulmonary hypertension. 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).

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. Cases with associated anomalies are typically excluded, as are those without liver herniation. Prediction is further hampered because of improvements in neonatal care for infants with CDH. These include permissive hypercapnia, "gentle ventilation" to avoid barotrauma, and delayed surgery.

Lung-to-Head Ratio. This sonographic ratio was developed by investigators from the University of California, San Francisco

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 (Fig. 10-20, p. 209), divided by the head circumference. Investigators found that the survival rate was 100 percent if the LHR was above 1.35, and there were no survivors if it was below 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 was about 60 percent (Metkus, 1996).

Jani and coworkers (2006) evaluated the LHR in 184 cases from an international registry of isolated CDH between 22 and 28 weeks' gestation. The survival rate was 15 percent if the LHR was 0.8 to 1.0, 65 percent with LHRs 1.0 to 1.5, and 80 percent with LHRs 1.6 or more. There were no survivors with LHRs below 0.8. As of 2013, trials underway in the United States and Europe have selected a threshold LHR of 1.0 or lower for inclusion.

Magnetic Resonance Imaging. This has been used to estimate the volume of lung tissue ipsilateral and contralateral to the diaphragmatic hernia, which may then be compared with a gestational age-matched reference. Mayer and colleagues (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. 10-44, p. 225). Two reasons underlie the rationale for assessing liver volume. The first is that 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. In preliminary reports, MR assessment of the degree of liver herniation has been found to correlate with postnatal survival rates and may even be more useful as a predictor than lung volume (Cannie, 2008; Walsh, 2000; Worley, 2009).

Tracheal Occlusion. Early attempts to treat severe diaphragmatic herniation used open fetal surgery. Unfortunately, repositioning of the liver into the abdomen resulted in kinking of the umbilical vein with subsequent fetal demise (Harrison, 1993).

Knowledge that fetal lungs normally produce fluid and that fetuses with upper airway obstruction develop hyperplastic lungs formed the rationale for tracheal occlusion (Hedrick, 1994). Initially, the trachea was occluded with an external clip (Harrison, 1993). Currently, a detachable silicone balloon is placed within the trachea endoscopically, using a 3-mm operating sheath and fetoscopes as small as 1 mm (Deprest, 2011; Ruano, 2012). The ex-utero intrapartum treatment procedure (p. 331) was developed in tandem with these procedures, and it is used at delivery during reversal of the tracheal occlusion.

A randomized trial of the *fetal endoscopic tracheal occlusion (FETO)* technique was conducted in pregnancies with isolated CDH, liver herniation, and LHR below 1.4 (Harrison, 2003). Pregnancies included had a predicted survival rate < 40 percent with conventional postnatal therapy based on historical data. The trial was stopped after only 24 women had been enrolled because no benefit was identified. Survival rates 90 days after birth were unexpectedly high in both groups and approximated 75 percent. Potential benefits of FETO may have been offset by the high rate of early preterm birth. The mean age at delivery was just older than 30 weeks, and fetuses were delivered an average of 6 weeks after the procedure. This left less time for catch-up growth (Wenstrom, 2003).

Following this study, there has been continued enthusiasm for the technique, particularly outside the United States. Using a lower lung-to-head ratio threshold of 1.0 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).

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. Percutaneous shunts are used to drain fluid in cases of selected urinary and thoracic abnormalities. Radiofrequency ablation has become increasingly available for selected indications such as twin-reversed arterial perfusion sequence. Fetal cardiac catheterization procedures hold promise for pregnancies with severe hypoplastic left heart syndrome but currently remain investigational.

Thoracic Shunts

A shunt placed from the fetal pleural cavity into the amniotic cavity may be used to drain pleural fluid. 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 be secondary to congenital viral infection or aneuploidy, or they may be associated with a malformation such as *extralobar 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 under 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 (Fig. 16-4). 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

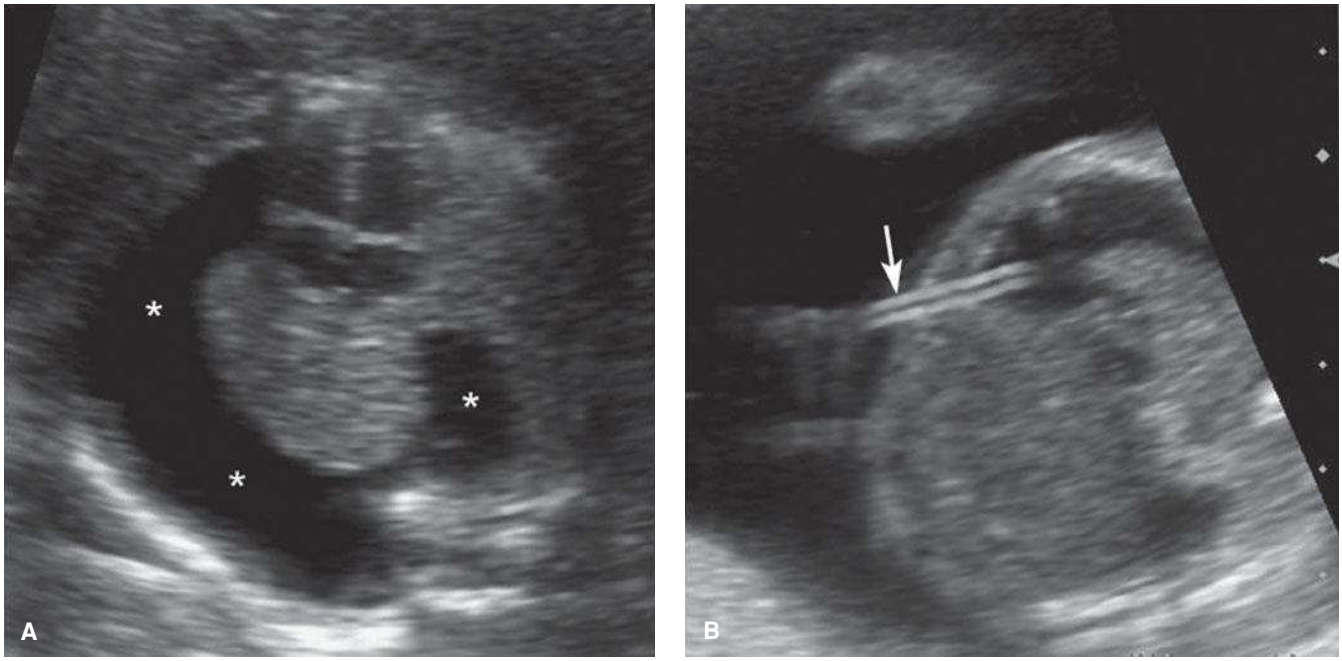

FIGURE 16-4 Thoraco-amnionic shunt placement. **A.** A large, right-sided fetal pleural effusion (*asterisks*) and ascites were identified at 18 weeks' gestation. The effusion was drained but rapidly reaccumulated. The xanthochromic fluid contained 95-percent lymphocytes, consistent with chylothorax. **B.** A double-pigtail shunt (*arrow*) was inserted under ultrasound guidance. Following shunt placement, the effusion and ascites resolved.

normal position (Mann, 2010). The overall survival rate is reported to be 70 percent, and that of hydropic fetuses approximates 50 percent (Mann, 2010; Yinon, 2010). Shunt displacement into the amnionic cavity is not uncommon. If the shunt remains in place, it must be clamped immediately upon delivery of the infant to avoid pneumothorax.

Shunts have also been used to drain a dominant cyst in fetuses with macrocystic *congenital cystic adenomatoid malformation*. Fortunately, cysts rarely are large enough to pose a risk for hydrops or pulmonary hypoplasia. Shunt placement may reduce the volume of the CCAM by as much as 70 percent and may reverse hydrops and improve survival rates (Knox, 2006; Mann, 2010). Survival rates following shunt placement for CCAM approximate 70 percent (Wilson, 2004).

Urinary Shunts

Vesicoamnionic shunts are used in fetuses with bladder-outlet obstruction that would otherwise have a grim prognosis. Distal obstruction of the urinary tract occurs more often in male fetuses, and the most common etiology is *posterior urethral valves,* followed by *urethral atresia* and by *prune belly syndrome*, which is also called *Eagle-Barrett syndrome*. Diagnosis is discussed in Chapter 10 (p. 216). Sonographic findings include dilatation of the bladder and proximal urethra, termed the "keyhole" sign, along with bladder wall thickening (Fig. 10-33, p. 217). Oligohydramnios before midpregnancy leads to pulmonary hypoplasia. Unfortunately, the outcome may be poor even when amnionic fluid volume is normal. Evaluation includes a careful search for associated 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; Manning, 1986).

Shunt placement allows urine to drain from the bladder into the amnionic cavity. This attempts to preserve renal function and improve oligohydramnios to prevent pulmonary hypoplasia. Potential candidates are fetuses without other severe anomalies or aneuploidy 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 type of anomaly tends to be even more severe. Serial bladder drainage—vesicocentesis—is performed at 24- to 48-hour intervals under sonographic guidance to determine the urine electrolyte and protein content. This permits classification of the renal prognosis as good or poor (Table 16-4).

Amnioinfusion is usually performed before shunting to aid placement of the distant end of the catheter into the amnionic

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.

cavity. Amnioinfusion also assists sonographic fetal anatomical survey to ensure than no other abnormalities are present. 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, with the distal end within the fetal bladder and the proximal end within the amnionic cavity.

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 infant survival rates have ranged from 50 to 90 percent (Biard, 2005; Walsh, 2011). It is not known whether vesicoamnionic shunt placement confers a benefit in terms of long-term renal function (Holmes, 2001). A third of surviving children have required dialysis or renal transplantation, and almost half have respiratory problems (Biard, 2005).

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 the treatment of *twin-reversed arterial perfusion (TRAP) sequence,* also known as *acardiac twin* (Chap. 45, p. 908). Without treatment, the mortality rate for the normal or pump twin in TRAP sequence exceeds 50 percent. The procedure is also used for selective termination with other monochorionic twin complications (Bebbington, 2012).

The procedure is performed under sonographic guidance, and a 17- or 19-gauge RFA needle is placed into the base of the umbilical cord of the acardiac twin and into its abdomen. After a 2-cm area of coagulation is achieved, color Doppler sonography is used to verify absent flow into this twin. Several centers have reported a significantly improved rate of survival for the normal twin following RFA for TRAP sequence (Lee, 2007; Livingston, 2007). RFA was performed at approximately 20 weeks in 98 pregnancies with TRAP sequence reported by the North American Fetal Therapy Network (Lee, 2013). 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—12 percent were delivered at about 26 weeks.

RFA has generally been offered to TRAP sequence pregnancies 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 recommended if the estimated weight of the acardius is < 50 percent of the pump twin (Jelin, 2010).

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, but intervention may permit muscle growth and preserve ventricular function (Walsh, 2011). Possible fetal 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. There is a registry for these cases—the International Fetal Cardiac Intervention Registry (www.ifcir.org).

Of these, fetal aortic valvuloplasty is the most commonly performed. 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 development of hypoplastic left heart and permit postnatal biventricular repair (McElhinney, 2010). Under sonographic guidance, an 18-gauge needle is inserted into the left ventricle with the tip positioned in front of the stenotic aortic valve. A 2.5- to 4.5-mm balloon catheter is then guided into the aortic annulus and inflated several times. Arzt and Tulzer (2011) reviewed the collective experience of two major centers that perform fetal cardiac procedures—one in Boston and the other in Linz, Austria. Technical procedural success was achieved in 75 percent of cases, and there was a 9-percent fetal loss rate. All required postnatal aortic valvuloplasty, two thirds needed early aortic valve replacement, and less than half achieved the goal of postnatal biventricular repair.

Fetal atrial septostomy, also using a percutaneous balloon catheter, has been offered in selected cases of hypoplastic left heart with an intact or highly restrictive interatrial septum. This condition has a postnatal mortality rate of approximately 80 percent (Glantz, 2007). In one report of 21 cases, the procedure-related loss was about 10 percent, and the short-term neonatal survival rate was 58 percent (Marshall, 2008).

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

Ex-Utero Intrapartum Treatment

This procedure is designed to allow the fetus to remain perfused by the placental circulation after being partially delivered, so that life-saving 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). It was refined when tracheal occlusion was developed to treat congenital diaphragmatic hernia, because it was necessary to reestablish an airway after the trachea had been "plugged" or "clipped" (Mychaliska, 1997). Components of the procedure are shown in Table 16-5.

Some indications for the ex-utero intrapartum treatment (EXIT) procedure are listed in Table 16-2. It is the procedure of choice for intrapartum management of giant neck masses such as the one shown in Figure 16-5. Also, it is frequently used to remove the endotracheal balloon following fetal surgery for congenital diaphragmatic hernia (Laje, 2012; Ruano, 2012). Less common indications include treatment of *congenital high airway obstruction sequence (CHAOS)* and selected cases of severe fetal *micrognathia*, both discussed in Chapter 10 (Figs. 10-14 and 10-19, p. 205). Morris and coworkers (2009b) have proposed that in addition to a fetal jaw measurement below the 5th percentile, cases to be

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

Adapted from Moldenhauer, 2013.

considered for EXIT procedures are those with indirect evidence of obstruction, including hydramnios, an absent stomach bubble, or glossoptosis. Fetal MR imaging may be helpful in this setting (Chap. 10, p. 226).

This procedure can also be used as a bridge to other procedures. For example, during an EXIT procedure, resection of large thoracic masses may be accomplished by fetal thoracotomy performed with the placental circulation intact. 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 undergoing *EXIT-to-resection* survived. In contrast, there were no survivors with urgent postnatal surgery done alone. Similarly, Moldenhauer (2013) reported that 20 of 22 infants 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; Stoffan, 2012).

An 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 nursing personnel from many of these specialties. Counseling should include procedure-related risks such as hemorrhage from placental abruption or uterine atony, need for cesarean delivery in future pregnancies, increased 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 also associated with a longer operating time—approximately 40 minutes longer depending on the procedure, increased blood loss, and a higher incidence of wound complications (Noah, 2002).

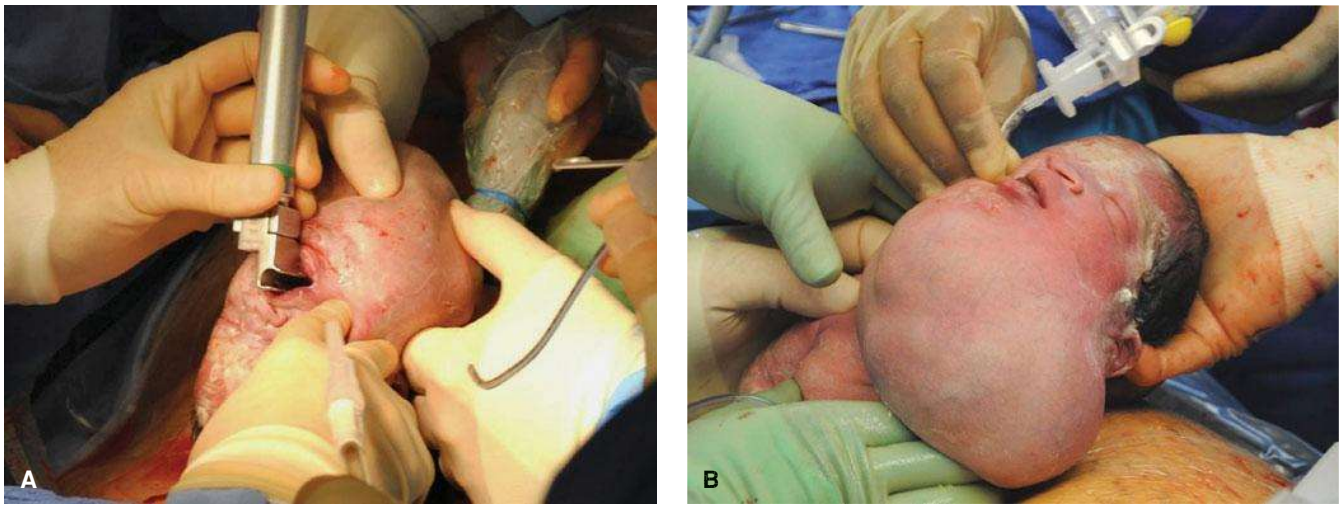

FIGURE 16-5 Ex-utero intrapartum treatment—EXIT procedure. **A.** This fetus was diagnosed prenatally with a large venolymphatic abnormality involving the face and neck. Involvement of the floor of the mouth, proximity to the anterior trachea, and mediastinal extension were evident on magnetic resonance imaging. 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. (Photographs contributed by Drs. Stacey Thomas and Patricia Santiago-Muñoz.)

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