Fetal Surgery for Lung Lesions, Congenital Diaphragmatic Hernia, and Sacrococcygeal Teratoma

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After more than 2 decades of experimental and clinical work, fetal surgery is an accepted treatment option for highly selected fetuses with life-threatening anomalies. Fetal lung masses associated with hydrops are nearly 100% fatal. These lesions can be resected in utero if they are predominantly solid or multicystic. Thoracoamniotic shunt placement may be effective in the setting of a single large cyst. Fetuses diagnosed with left congenital diaphragmatic hernia before 26 weeks’ gestation with associated liver herniation and a low right lung to head circumference ratio have a relatively poor prognosis with conventional therapy after birth, but in utero therapeutic approaches have yet to show a comparative survival benefit. A prospective randomized trial is required to critically evaluate the efficacy of fetal tracheal occlusion for severe diaphragmatic hernia. Fetal sacrococcygeal teratoma complicated with progressive high output cardiac failure may benefit from in utero resection of the tumor.

WITH THE ADVENT of prenatal diagnosis, pediatric surgeons and neonatologists were challenged with a new patient population—the subset of fetuses with life-threatening malformations who had not survived in the past without prenatal diagnosis, maternal transport, and planned delivery. Although prenatal diagnosis improved perinatal care, improvement in overall morbidity and mortality did not readily follow because some fetuses detected by prenatal diagnosis were already too sick to treat successfully after birth. This frustrating situation led to the development of fetal surgery.

In the 1980s the natural history of several potentially correctable lesions was determined by serial sonographic observation and postnatal follow-up of human fetuses, and selection criteria for intervention were developed. The pathophysiology of these lesions was delineated in animal models, and anesthetic, tocolytic, and surgical techniques for hysterotomy and fetal surgery were refined. Based on this investment in basic and clinical research, open fetal surgery now is being offered to highly selected circumstances when the fetal prognosis is otherwise extremely poor.1 In this article, we summarize the current status of open fetal surgery for fetuses with life-threatening anomalies and give specific recommendations for their prenatal and perinatal management. Specifically, the natural history, pathophysiology, prenatal diagnosis, surgical management, and related experimental studies for congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration (BPS), congenital diaphragmatic hernia (CDH), and sacrococcygeal teratoma (SCT) are discussed after a general description of open fetal surgery and perioperative management.

PERIOPERATIVE MANAGEMENT OF FETAL SURGERY PATIENTS

Preoperative Evaluation and Care

As is the case with any other invasive treatment, the risks and benefits of fetal surgery must be weighed for each patient. For the fetus with a life-threatening malformation, the risk of the procedure is small when compared with the potential benefit of salvage. The risks and benefits for the mother are more difficult to assess. Although fetal malformations associated with hydrops can cause the maternal mirror syndrome (discussed later), which is a threat to maternal health, the mother must bear significant potential risk and discomfort from the fetal surgical procedure. Maternal safety is the paramount issue. Fortunately, there have been no maternal deaths after open fetal surgery and few maternal complications. Risks to the mother must be weighed against the risk of fetal loss or the burden of raising a child with a severe malformation.

Patients referred to a fetal treatment center for possible fetal surgery are evaluated by a multidisciplinary team. The evaluation includes: (1) detailed ultrasonography to confirm the diagnosis and detect any other anatomic abnormalities, (2) ultrafast fetal magnetic resonance imaging for additional anatomic information, (3) a fetal echocardiogram to rule out congenital heart defects and assess fetal cardiac function, and (4) amniocentesis or umbilical blood sampling for fetal karyotyping. In general, the following conditions are contraindications for open fetal surgery: chromosomal abnormality, multiple gestation, other significant anatomic abnormalities, a history of heavy cigarette smoking or other maternal medical risk factors, and the presence of maternal mirror syndrome.

After completion of the evaluation and patient selection, a team meeting that includes fetal/pediatric sur-
geons, obstetricians, anesthesiologists, a nurse coordinator, nurse practitioners, operating room nurses, and a social worker is held to discuss with the family each step of the proposed surgery and postnatal care, as well as the risks, benefits, and alternatives to fetal intervention. The potential risks associated with this intervention including (but not limited to) operative complications are preterm labor, chorioamnionitis, rupture of uterine membranes, uterine rupture, side effects of tocolytics, risk of fetal demise, and the need for cesarean section for all subsequent pregnancies. These risks are outlined clearly and discussed before obtaining consent for treatment. This forum provides the family an opportunity to ask questions and make decisions carefully and knowledgeably.

**Intraoperative Management**

Fetal surgery is a team effort requiring a variety of input from the different team members. Fetal surgical techniques have been described previously in detail and were largely developed at the Fetal Treatment Center of the University of California, San Francisco (UCSF). The operative team usually consists of 2 pediatric surgeons, a perinatologist, a sonographer/echocardiographer, and a scrub nurse. The operative steps are performed by the pediatric surgeon with the assistance of the others.

Patients are admitted immediately before the operation for obstetric monitoring and initiation of tocolysis. Indomethacin and antibiotics are given preoperatively. Maternal general and epidural anesthesia provides anesthesia for the mother and the fetus and ensures good uterine relaxation. The mother is positioned supine with towels placed under her left side to lift her uterus off of the inferior cava to avoid compromise of venous return. Maternal perioperative monitoring includes a radial arterial catheter, blood pressure cuff, large bore intravenous catheters, bladder catheter, electrocardiogram leads, leg compression boots, and a transcutaneous pulse oximeter.

The uterus is exposed through a low transverse abdominal incision. If a posterior placenta is present, suction is used to mobilize the placenta from the posterior wall of the uterus. A subcutaneous uterine ring retractor is utilized to maintain exposure. Sterile intraoperative ultrasound scan is used to delineate the fetal position and placental location. The edge of the placenta is marked under sonographic guidance using the electrocautery. The position and orientation of the hysterotomy is planned to stay parallel to and at least 6 cm from the placental edge and still allow exposure of the appropriate part of the fetus. Manual version of the fetus may be required to optimize fetal operative position.

The hysterotomy is facilitated by the placement of two 0 PDS sutures (Ethicon, Somerville, NJ) under sonographic guidance parallel to the intended incision site and through the full-thickness uterine wall. A uterine stapler (US Surgical Corporation, Norwalk, CT) with absorbable Lactomer staples is then introduced directly through this point of fixation and into the amniotic cavity using a piercing attachment on the lower limb of the stapler. The stapler then is fired, thereby anchoring the amniotic membranes to the uterine wall and creating a hemostatic hysterotomy. For the fetal portion of the procedure, a surgical headlamp and 3.5x optical loupe magnification are helpful. The fetus is positioned with the appropriate fetal anatomy visible through the uterine incision. Continuous intraoperative fetal echocardiography is performed to monitor fetal heart rate and ventricular function. Intraoperative fetal monitoring is provided also by a miniaturized pulse oximeter that is wrapped around the fetal palm or foot and protected with aluminum foil and Tegaderm (3M Company, St Paul, MN) to minimize light exposure. The fetus is kept warm and buoyant in the uterus by the continuous administration of 38° to 40°C Ringer’s lactate solution via a level I rapid infusion device. After the fetal procedure, a water-tight 2-layer uterine closure is performed with double-armed full-thickness 0 PDS interrupted stay sutures followed by a running 2-0 PDS suture. Approximately 400 mL of warmed Ringer’s lactate containing 500 mg of oxacillin is instilled into the amniotic cavity via the level I warming device just before completing the running layer and is continued until sonography shows an adequate amniotic fluid volume. The stay sutures then are tied, an omental flap is mobilized and secured over the hysterotomy site, and the maternal laparotomy incision is closed in layers. It is important to use a subcuticular maternal skin closure covered with a transparent Tegaderm dressing so that monitoring devices can be placed on the maternal abdomen postoperatively.

**Postoperative Management**

Achievement of good uterine relaxation during surgery is achieved by deep inhalational anesthesia and is facilitated postoperatively by adequate analgesia via an epidural catheter. During closure of the hysterotomy, the patient is given a 6-g intravenous loading dose of magnesium sulfate followed by a continuous infusion at 2 to 4 g/h depending on the degree of uterine irritability. The magnesium sulfate infusion is maintained for about 18 to 24 hours postoperatively while monitoring serum magnesium levels and observing for clinical signs of magne-
sium toxicity. The tocolytic regimen also includes indomethacin rectal suppositories (50 mg) preoperatively and every 6 hours postoperatively for 48 hours. Daily fetal echocardiography is performed to detect adverse fetal effects of indomethacin including ductal constriction, tricuspid regurgitation, and oligohydramnios. Patients are converted to a tocolytic regimen of oral nifedipine (10 to 20 mg every 6 hours) by postoperative day 2, which they continue after hospital discharge until the time of delivery.

Fetal heart rate and uterine activity are recorded externally by tocodynamometer, and daily ultrasound scan is taken during the hospitalization (usually 4 days). Fetal movement (an indirect assessment of fetal well-being), anatomic evaluation, amniotic membrane, and amniotic fluid volume status is carefully evaluated by an experienced sonographer. The resolution of hydrops, if present before surgery, will be observed over the next 1 to 3 weeks.

The postoperative outpatient regimen at the nearby Ronald McDonald house involves bedrest (without bathroom and mealtimes), and twice weekly ultrasound scans and obstetric assessments to evaluate the mother and the fetus. Because the midgestation hysterotomy is not in the lower uterine segment, all patients require a cesarean delivery for all future deliveries to avoid uterine rupture during labor. At 36 weeks, an amniocentesis is performed to confirm lung maturity and, if mature, the fetus is delivered by cesarean section.

Complications Specific to Open Fetal Surgery

We recommend these procedures be performed only in tertiary medical centers experienced with open fetal surgery and management of the potential postoperative complications such as amniotic fluid leakage, fetal membrane separation, and preterm labor. The current tocolytic regimen cannot uniformly prevent preterm labor after fetal surgery. For the first 85 cases of open fetal surgery at the Children’s Hospital of Philadelphia (CHOP), the mean duration from surgery to delivery was about 10 weeks, and the mean gestational age at delivery was 34 weeks. Preterm labor remains the “Achilles heel” of fetal surgery and can obscure its benefits.

Noncardiogenic interstitial pulmonary edema is a serious potential complication in mothers who undergo fetal surgery. This complication developed in 15 (23%) of 65 fetal surgery patients at UCSF. In addition to known risk factors such as tocolytic agents (magnesium sulfate and terbutaline) and generous intravenous hydration, it is speculated that disruption of the myometrium and membranes provokes the release of various vasoactive agents (such as prostaglandins and thromboplastins) resulting in increased maternal vascular permeability and pulmonary “capillary leak.” Because accumulation of interstitial fluid is determined by the balance between osmotic and hydrostatic pressure in the capillary bed and interstitium, we have serially measured colloid osmotic pressure after open fetal surgery. We found that maternal colloid osmotic pressure decreases significantly after open fetal surgery and reaches its nadir early on postoperative day 2, corresponding with the risk period for maternal pulmonary edema. Although the decrease in maternal colloid osmotic pressure lowers the threshold for pulmonary edema, aggressive fluid restriction can compromise the maternal-placental-fetal circulation and induce preterm labor. We use a regimen of judicious postoperative intravenous fluid administration and empirical furosemide diuresis if needed, which has dramatically reduced the incidence of this complication.

Amniotic fluid leak can develop either from the hysterotomy site in the abdomen (rare) or via the vagina owing to membrane rupture. In the former case, surgical repair is required, but we have not experienced this complication for several years with our current hysterotomy closure technique. Chorioamniotic separation is a recently recognized complication that can lead to amniotic band formation and membrane rupture. The UCSF group described 5 cases of this complication out of more than 40 cases of open fetal surgery. Three of these fetuses had umbilical cord compromise by a band of amniotic membrane leading to one fetal death. Awareness of this potentially lethal complication and its evaluation by serial ultrasound scan and fetal monitoring is recommended because emergent delivery may be required when this situation develops. Careful sonographic postoperative assessment of our last 54 fetal surgery cases showed that 34% had some evidence (usually minor) of chorioamniotic separation, and this finding was more common in those cases operated on before 23 weeks’ gestation.

FETAL LUNG LESIONS

Congenital cystic adenomatoid malformation (CCAM) is a benign cystic lung mass that is usually restricted to one lobe of the lung. Bilateral lung involvement is rare. Grossly, a CCAM is a discrete, intrapulmonary mass that contains cysts ranging in diameter from less than 1 mm to over 10 cm. Most CCAMs derive their blood supply from the pulmonary circulation. CCAM is characterized histologically by an overgrowth of terminal respiratory bronchioles that form cysts of various sizes and by a lack of normal alveoli. Many pathologists consider CCAM a hamartoma, a developmental abnormality with excess of one or several tissue components. Although the tissue within these malformations does not function in normal gas exchange, there are connections with the tracheobronchial tree as evidenced by air trapping that can develop during postnatal resuscitative efforts.
Bronchopulmonary sequestration (BPS) is a nonfunctioning lung mass that arises as an aberrant outpouching from the developing foregut with systemic vascular supply. BPS lesions are classified into extralobar and intralobar forms. The extralobar form consists of pulmonary tissue that is enveloped in its own pleura, without communication with the normal tracheobronchial tree. It may occur above or below the diaphragm. The intralobar form is found within the normal lung tissue with or without communications with the normal bronchial tree.

**Natural History**

The natural history and clinical spectrum of prenatally diagnosed lung lesions is quite variable and appears to depend on the size and secondary physiologic derangements caused by these tumors. Approximately 15 to 20% of fetal CCAM lesions decrease in size, and two thirds of BPS lesions shrink dramatically before birth. Initial impressions concerning the prognosis of a large lung mass with mediastinal shift should be tempered with the understanding that it can shrink in size or even “disappear” by ultrasound scan. Winters reported on 7 children with prenatally diagnosed CCAM that disappeared during prenatal sonographic follow-up. Postnatal chest computed tomography (CT) scans showed persistent abnormalities in all cases emphasizing the importance of postnatal imaging studies in these patients.

In the face of the variable natural history of these lesions, how can we select the fetuses who would benefit from fetal intervention? Currently, the development of fetal hydrops is considered the only criteria because it is nearly always a predictor of fetal death. In a review by Adzick et al., all 25 fetuses who had large CCAMs associated with hydrops died before or shortly after birth when they were followed expectantly. Although the resolution of fetal hydrops associated with a large CCAM has been reported, this is a very rare circumstance.

**Pathophysiology**

Huge fetal lung lesions have reproducible pathophysiologic effects on the developing fetus. Polyhydramnios is a common obstetric indication for ultrasonography, so a prenatal diagnostic marker exists for many large fetal lung tumors. Polyhydramnios results from esophageal compression by the thoracic mass and decreased fetal swallowing of amniotic fluid. This concept is supported by the frequent absence of fluid in the stomach of fetuses with large thoracic tumors and marked mediastinal shift and the reappearance of stomach fluid and the restoration of normal amniotic fluid volume after effective fetal treatment. Hydrops is secondary to obstruction of the great vessels and cardiac compression from large tumors causing an extreme mediastinal shift. Fetal BPS also can cause fetal hydrops, either directly from the mass effect or from a tension hydrothorax that is the result of fluid or lymphatic secretion from the mass. Although there is some association of both polyhydramnios and hydrops with fetal lung lesions, our experience indicates that either can occur independently of the other.

Much of our knowledge concerning the pathophysiology of a huge chest mass stems from work in laboratory animals. We have developed experimental models that simulate an enlarging intrathoracic mass and result in pulmonary hypoplasia and death at term owing to respiratory insufficiency. Gradual enlargement of an intrathoracic implanted balloon led to a dramatic increase in central venous pressure followed by the development of hydrops in fetal sheep. When the balloon was deflated to simulate resection of the mass, central venous pressure decreased to normal values, and hydrops resolved. We have shown also that fetal pulmonary resection is straightforward. Finally, experiments in nonhuman primates led to the development of the necessary surgical, anesthetic, and tocolytic techniques before clinical use and have shown that fetal intervention is safe for the mother and her future reproductive potential.

The development of fetal hydrops and placental edema associated with large lung masses can lead to the maternal “mirror syndrome,” a potentially devastating maternal illness in which the mother’s condition begins to mirror that of the sick fetus. She develops progressive symptoms of pre-eclampsia including vomiting, hypertension, peripheral edema, proteinuria, and pulmonary edema. The pathophysiology of this condition is unclear, but it may result from the release of vasoactive factors from the edematous placenta. We have learned that this syndrome can develop quickly and that its reversal cannot be accomplished by treatment of the fetal anomaly alone. Therefore, the presence of placental edema and the maternal mirror syndrome is considered a contraindication to open fetal surgery. Earlier fetal intervention is recommended before the related maternal preeclamptic state develops.

Investigations in our laboratory have helped define the biologic characteristics of fetal CCAMs that show rapid growth resulting in fetal hydrops. Liechty et al. reported that large CCAM specimens requiring fetal resection showed increased cell proliferation, decreased apoptosis, and increased mesenchymal platelet-derived growth factor-B gene expression and protein production compared with either normal fetal lung tissue or much smaller CCAMs that were resected after birth.

**Prenatal Diagnosis**

The prenatal diagnosis of CCAM and BPS is made primarily by ultrasound scan. CCAM lesions may be solid or cystic. Adzick et al. have classified prenatally diagnosed CCAM into 2 categories based on gross anat-
omy and ultrasound findings. Macrocystic CCAM lesions contain single or multiple cysts that are 5 mm in diameter or larger and appear cystic on prenatal ultrasound scan. Microcystic lesions are more solid, contain cysts smaller than 5 mm in diameter, and appear echogenic on prenatal ultrasound scan. We have learned that the overall prognosis depends primarily on the size of the CCAM rather than on the lesion type, and the underlying growth characteristics are likely to be important.

On prenatal ultrasonography, BPS lesions usually appear as a well-defined echodense, homogeneous mass. A systemic arterial supply from the aorta detected by Doppler ultrasound scan is the pathognomonic feature for BPS. However, if this Doppler finding is not detected, then an echodense microcystic CCAM and a BPS can have the same sonographic characteristics. Ultrafast fetal magnetic resonance imaging (MRI) may help differentiate CCAM from BPS.23 The ability to differentiate intralobar and extralobar sequestration before birth is limited unless an extralobar sequestration is highlighted by a pleural effusion or is located in the abdomen. There are no diagnostic hallmarks for the specific prenatal diagnosis of an intralobar sequestration. Furthermore, we have described “hybrid” cystic lung lesions that display clinicopathologic features of both CCAM and BPS, which suggests a shared embryonic basis for some of these lung lesions.24,25

In search for a better parameter to predict which fetuses are at risk for the development of hydrops, we are evaluating sonographically determined CCAM volume. We have determined CCAM volume by sonographic measurement using the formula for a prolate ellipse (length$\times$height$\times$width$\times$0.52). A cystic adenomatoid malformation volume ratio (CVR) was obtained by dividing the CCAM volume by head circumference to correct for differences in fetal size. We found that a CVR greater than 1.6 is predictive of increased risk of hydrops with hydrops developing 80% of these CCAM fetuses. The CVR may be useful in selecting fetuses at risk for hydrops and thus need close ultrasound observation and possible fetal intervention.26 By performing serial CVR measurements, we have learned that CCAM growth usually reaches a plateau by 28 weeks’ gestation. For fetuses less than 28 weeks, we recommend twice weekly ultrasound surveillance if the CVR is greater than 1.6 and initial weekly surveillance for fetuses with smaller CVR values.

Although sonographic prenatal diagnosis is becoming increasingly sophisticated, diagnostic errors are possible. Diaphragmatic hernia can be distinguished by careful sonographic assessment, an amniogram with or without a CT scan, or by ultrafast MRI.23 We and others have experience with other fetal thoracic masses including bronchogenic and enteric cysts, mediastinal cystic teratomatoma, congenital lobar emphysema, hemangioma, and bronchial atresia.27,28 We also have described 2 cases of intrathoracic gastric duplication cyst associated with hydrops that were treated with placement of a thoracoamniotic shunt.29 Finally, it is important also to distinguish exceedingly rare bilateral lung lesions from congenital high airway obstruction syndrome (CHAOS) that presents with bilateral large echodense lungs, the absence of mediastinal shift, and hydrops.30

**Surgical Management**

In 1998, we reported a series of more than 175 prenatally diagnosed cases of fetal lung lesions from the Children’s Hospital of Philadelphia and the University of California, San Francisco, and our clinical experience over the past 7 years at the Center for Fetal Diagnosis and Treatment at the Children’s Hospital of Philadelphia now extends to 350 cases. Fetuses without hydrops usually survive intrauterine life and can be treated postnatally in the setting of maternal transport, planned delivery, and immediate postnatal evaluation and treatment at a facility with extracorporeal membrane oxygenation (ECMO) capability. These smaller thoracic lesions can cause respiratory distress in the newborn period, and the smallest masses may be asymptomatic until later in childhood when infection, pneumothorax, or malignant degeneration may occur. In asymptomatic neonates with a cystic lung lesion, we believe that elective resection is warranted because of the risks of infection and occult malignant transformation.31-35 Malignancies consist mainly of pleuropulmonary blastoma in infants and young children, and bronchioloalveolar carcinoma in older children and adults. After confirmation of CCAM location by postnatal chest CT scan with intravenous contrast, we recommend elective resection at one month of age or older. This age has been chosen because anesthetic risk in babies decreases after 4 weeks of age. An experienced pediatric surgeon can perform a lobectomy safely in infants with minimal morbidity. Early resection also maximizes compensatory lung growth. In contrast, we usually have followed up patients with a tiny, asymptomatic, noncystic extralobar BPS if we are confident of the diagnosis based on postnatal imaging studies.

If the fetus is hydropic at presentation or if hydrops develops during serial follow-up, then management depends on the gestational age (Fig 1). For those hydropic fetuses greater than 32 weeks’ gestation, early delivery should be considered so that the lesion can be resected ex utero, but the neonatal outcome is poor. However, we have managed several such cases using an ex utero intrapartum therapy (EXIT) strategy with resection of the mass during the EXIT procedure,36 and this experience is reviewed in detail by Hedrick in this issue of Seminars in Pediatric Surgery.
For those hydropic fetuses less than 32 weeks’ gestation, there is now a new therapeutic option, which is to treat the lesion before birth. The presence or evolution of hydrodrops in association with isolated CCAM before lung maturity should prompt consideration of fetal surgery. Fetal thoracentesis is limited by the rapid reaccumulation of cyst fluid and does not appear to alter the long-term outlook of these fetuses. Thoracoamniotic shunting is effective in cases of a large predominant cyst as long as there is not a large solid component to the CCAM.8,13 This approach is reviewed by Wilson and Johnson in this issue of Seminars in Pediatric Surgery. Multicystic or predominantly solid CCAM lesions do not lend themselves to catheter decompression and require resection. Fetal lobectomy is a reasonable therapeutic choice for those cases. Ipsilateral hypoplastic lung tissue should be saved whenever possible, because we have learned that significant compensatory lung growth can occur.

For fetal surgery candidates, each family undergoes extensive discussion of the risks and benefits of fetal therapy for a lung tumor associated with hydrodrops. Fetal surgery candidates have a normal karyotype by amniocentesis or percutaneous umbilical blood sampling, and no other anatomic abnormalities are present on detailed sonographic and echocardiographic survey.8 The fetal chest is entered by a fifth intercostal space thoracotomy. Invariably, the lesion readily decompresses out through the thoracotomy wound consistent with increased intrathoracic pressure from the mass. Using techniques developed in experimental animals, the appropriate pulmonary lobe(s) containing the lesion is resected.17 The fetal thoracotomy is closed, the fetus is returned to the uterus, warmed Ringer’s lactate containing antibiotics is instilled into the amniotic cavity, and the uterine and abdominal incisions are closed in layers.

The knowledge that hydrodrops is highly predictive of fetal or neonatal demise led to fetal surgical resection of a massive multicystic or predominantly solid CCAM (fetal lobectomy) in 22 cases at 21 to 31 weeks’ gestation with 11 healthy survivors at 1 to 12 years’ follow-up. Resections involved a single lobectomy in 16 cases, right middle and lower lobectomies in 4 cases, extralobar BPS resection in 1 case, and left pneumonectomy for CCAM in 1 case. All cases had histologic confirmation of the diagnosis. In one multicystic case, a thoracoamniotic shunt failed to adequately decompress the mass effect before open fetal surgery. In the 11 fetuses that survived, fetal CCAM resection led to hydrodrops resolution in 1 to 2 weeks, return of the mediastinum to the midline within 3 weeks, and impressive in utero lung growth. Follow-up developmental testing results have been normal in all 11 survivors.

There were 11 fetal deaths in the fetal surgery resection cases. In the first case, the mother had already developed the maternal “mirror” syndrome. The fetal operation was successful, the hydrodrops improved, but the placentomegaly and maternal hyperdynamic state remained, and the fetus was delivered 1 week later. We learned in this case that the maternal hyperdynamic state referred to as the “mirror syndrome” cannot be reversed solely by treatment of the underlying fetal condition. This preeclamptic state is associated with molar pregnancies and fetal conditions that cause placentomegaly and may be caused by a factor released by poorly perfused placental tissue that leads to endothelial cell injury. Until the pathophysiology of the maternal mirror syndrome is understood, earlier intervention before the onset of placentomegaly and the related maternal preeclamptic state may be the only approach to salvage these doomed fetuses. A subsequent case showed that placentomegaly can regress after fetal surgical CCAM resection if clinical signs of the maternal “mirror syndrome” are not present preoperatively.

In cases 6 and 16, 21-week-gestation fetuses became bradycardic and died 8 and 12 hours postoperatively respectively, and postmortem report did not elucidate the cause of death in either case. In case 7, fetal death was caused by uncontrolled intraoperative uterine contractions, which hallmarks this limitation of fetal surgery. In case 18, chorioamnionitis 10 days postoperatively led to early delivery and neonatal death. Finally, in 6 other cases, massive hydrodrops was present at 21 to 24 weeks’ gestation, and all fetuses died intraoperatively, usually after profound bradycardia once the mass was delivered from the fetal chest. We believe that mass delivery and abrupt removal of cardiac compression resulted in pathophysiology similar to abrupt relief of pericardial tamponade with fetal hemodynamic collapse and reactive bradycardia. As such, we have modified our approach before beginning the fetal operation. Before the fetal thoracotomy, we now obtain fetal intravenous access,
check a fetal blood gas and hematocrit level, and pretreat with intravenous atropine and fluid volume (usually warm, fresh blood). We also use fetal echocardiography on a routine basis for all fetal surgery cases regardless of lesion type to monitor fetal myocardial performance, particularly because maternal-fetal general anesthesia is a fetal myocardial depressant.

In the future, minimally invasive approaches to fetal lung lesions associated with hydrops may be possible. Laser therapy to fulgurate a fetal CCAM has been reported, but we believe that this approach is untenable given current technical limitations. For example, a mother carrying a 28-week-gestation fetus with a large right-sided CCAM and hydrops was turned down for open fetal surgery by our group because of maternal psychosocial difficulties, and she decided to seek yttrium aluminum garnet (YAG) laser therapy at another medical center. Using a percutaneous technique under ultrasound guidance, a laser fiber was deployed in the fetal right chest, and the procedure was repeated twice during the next 4 weeks. After birth, the baby died of pulmonary hypoplasia and had a severely caved-in right chest with multiple rib fractures as a result of the prenatally applied laser energy. It is possible that laser therapy or techniques such as radiofrequency thermal ablation will be clinically useful for fetal lung lesions associated with fetal hydrops if the result is a decrease in mass effect, but experimental studies in animal models to rigorously test these techniques should be mandatory before clinical trials. Finally, it is possible that administration of a short course of maternal betamethasone may impair CCAM growth in some cases and lead to amelioration of hydrops.

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Congenital diaphragmatic hernia (CDH) is a simple anatomic defect with a devastating physiological consequence: pulmonary hypoplasia. CDH occurs in 1 in 2,200 to 3,500 live births. The defect arises on the right side in 10% of cases and bilaterally in 2%. Nearly all cases are sporadic with the rare exception of familial CDH usually associated with diaphragmatic agenesis. Associated anomalies, such as congenital heart defects, chromosomal anomalies (trisomy 21, 18, and 13), neurologic defects (hydrocephalus, anencephaly, and spina bifida), and other anomalies of the urinary tract and gastrointestinal systems, are seen in 25% to 57% of cases of prenatally diagnosed CDH and 95% of stillborns.

Natural History

Retrospective studies of CDH vary widely in their postnatal mortality rate, and each are flawed by what Harrison has referred to as a “hidden mortality.” This “hidden mortality” arises from deaths occurring in utero, or in the delivery room before transfer to a tertiary center. This issue was addressed in a prospective analysis, which provided invaluable data on the mortality rate of fetal CDH without associated anomalies. The study included 83 cases referred to UCSF between 1989 and 1993 for consideration of fetal therapy with isolated CDH diagnosed before 24 weeks’ gestation. Forty-eight patients (including 7 cases of inexplicable third trimester intrauterine demise) died resulting in an overall 58% mortality rate. Twenty-two of 35 survivors required ECMO, of which 9 patients had significant morbidity. This study clearly documented that patients born with an isolated CDH suffer substantial mortality and morbidity despite accurate prenatal diagnosis and sophisticated neonatal care including maternal transport, planned delivery, and immediate resuscitation at institutions with ECMO capability.

However, this study also showed that 42% of prenatally diagnosed patients are treatable with more conventional postnatal approaches. An accurate prenatal marker was needed to predict postnatal outcome to appropriately select patients for fetal surgery who would do poorly with conventional postnatal therapies. Various prognostic factors for poor outcome have been proposed such as early gestational diagnosis, severe mediastinal shift, polyhydramnios, a small lung-thorax transverse area ratio, left heart underdevelopment, and the presence of stomach in the chest. Unfortunately, none of these features have been uniformly predictive of outcome.

Liver herniation is another important prognostic factor. Although color flow Doppler ultrasound scan can visualize bowing of the ductus venosus to the left of the midline or coursing of the portal branches or hepatic veins to the lateral segment of the left lobe above the level of the diaphragm, ultrasound scan has not always accurately shown liver herniation in the fetus with left-sided CDH. We have shown that ultrafast fetal MRI using rapid HASTE technique is a powerful tool to accurately show liver herniation. The absence of liver herniation indicates a good prognosis with a survival of 93%, whereas liver herniation is associated with 43% survival rate. Although MRI can measure fetal lung volumes, in a study of 41 pregnant women carrying fetuses with left CDH, neither right, left, nor total lung volume measurements by MRI were predictive of survival.

Another prenatal predictor of postnatal outcome for left CDH is the right lung area-to–head circumference ratio (LHR), defined as the 2-dimensional right lung area measured at the level of the 4-chamber view of the heart divided by the head circumference to normalize for gestational age. The LHR measured at 24 to 26 weeks’ gestation has now been assessed retrospectively and prospectively in 2 centers (CHOP and UCSF) and is a useful
The volume of herniated viscera. The spectrum of hypoplasia is directly related to the timing of herniation into the chest. The severity of pulmonary hypertension. Polyhydramnios may arise from reduced capillary bed, predisposes to severe neonatal pulmonary arterioles which, in combination with a reduced preacinar arterioles, arteries, and capillary bed are reduced. In addition, there is an abnormal muscularization of the preacinar pulmonary arterioles which, in combination with a reduced capillary bed, predisposes to severe neonatal pulmonary hypertension. Polyhydramnios may arise from gastric outlet obstruction because of the displacement of the stomach into the chest. The severity of pulmonary hypoplasia is directly related to the timing of herniation and the volume of herniated viscera. The spectrum of CDH varies from neonates with early severe herniation and such extreme pulmonary hypoplasia that they are unsalvageable to patients with relatively mild hypoplasia who can be treated successfully by standard postnatal care. Patients with herniation only late in gestation have minimal pulmonary hypoplasia and a near uniform postnatal survival.

**Surgical Management**

The original approach of complete in utero CDH repair proved technically impossible when liver herniation was present because acute reduction of the liver compromised umbilical venous flow resulting in fetal bradycardia and cardiac arrest. This was disappointing because the most severely affected fetuses with CDH have liver herniation. Although the procedure was feasible in fetuses without liver herniation, a prospective clinical trial at UCSF comparing fetal CDH repair with postnatal therapy showed no difference in survival rate: 75% in the fetal surgery group and 86% in the postnatal therapy group survived. There also was no difference between the 2 groups in duration of ventilatory support, requirement for ECMO, length of hospital stay, or hospital charges. The authors concluded that in utero repair does not improve survival rate over standard postnatal treatment in the subgroup of CDH fetuses without liver herniation, primarily because survival in this subgroup is very favorable without prenatal intervention.

The disappointing experience with complete CDH repair in utero in cases of liver herniation led to the development of fetal tracheal occlusion for severely affected CDH fetuses. It has been recognized for many years that the dynamics of fetal lung fluid affect lung growth: increased fetal lung fluid egress results in pulmonary hypoplasia, whereas decreased fetal lung fluid egress results in large fluid-filled lungs. In 1993, Wilson reported that experimental pulmonary hypoplasia can be prevented by tracheal ligation using a nephrectomized fetal lamb and suggested its potential usefulness in the treatment of fetal CDH. DiFiore et al and Hedrick et al confirmed this concept in a fetal lamb model of CDH. Prenatal tracheal occlusion was shown in the fetal CDH lamb model to induce lung growth with the reduction of herniated viscera and dramatic improvement in lung compliance and gas exchange. The results of these experiments, now replicated in several laboratories, were so compelling that fetal tracheal occlusion has been applied successfully in human fetuses with severe CDH.

Three approaches for fetal tracheal occlusion (TO) have been tried clinically: open fetal surgery and a video-fetoscopic technique using either clips on the trachea (Fetendo Clip) or placement of an intratracheal balloon. Open tracheal clipping is performed through a small hysterotomy exposing only the upper extremities and leaving the fetal head inside the uterus. The fetal trachea is meticulously dissected through a small transverse cervical incision. Great care is taken to avoid injury to the recurrent laryngeal nerves. The occlusion of the trachea is accomplished by applying 2 large hemoclips. In our experience from January 1996 to January 1999, criteria for consideration of open TO required an isolated CDH diagnosed before 25 weeks’ gestation with fetal liver herniation and an LHR less than 1.0. Fifteen fetuses underwent TO at 24 to 28 weeks’ gestation with 5 survivors (33%). Two fetuses were lost to preterm labor. In 13 mothers, postoperative gestation ranged from 19 to 68 days with a mean duration of pregnancy after TO of 38 days. The 5 survivors were hospitalized for an average stay of 76 days. Before birth, lung growth after TO
was not consistent, at times because of the phenomenon of liver lock when the herniated liver became incarcerated in the chest cavity. Despite dramatic lung growth in some fetuses after TO, intensive postnatal management was required frequently because of capillary leak and lung compliance issues. Most deaths were caused by respiratory insufficiency. The 5 survivors range from 4 to 6 years of age. All have been followed up closely and receive yearly developmental assessment. Morbidity in this group included significant neurologic injury in 3 of 5 patients.

Fetendo Clip and fetoscopic balloon placement are 2 techniques pioneered by the UCSF group to obviate a hysterotomy that may contribute to preterm labor. A retrospective review from UCSF compared the outcome of fetal isolated CDH treated with 3 methods: (1) standard postnatal therapy, (2) open tracheal occlusion, and (3) Fetendo Clip. The survival rate reported for each group was 38%, 15%, and 75%, respectively, favoring the Fetendo Clip approach. However, the authors treated fetuses with an LHR up to 1.4, and 5 of 8 fetuses in the Fetendo group had an LHR between 1.0 and 1.4. This subset of patients may have survived with conventional postnatal therapy, making the interpretation of this study difficult. In addition, all 4 Fetendo patients who had to be converted to an open procedure and died are included in the open surgery group. If these cases were included in the Fetendo group, the survival rate for the Fetendo group would have been 50%. The Fetendo Clip technique was complicated by a long operating time, bilateral recurrent laryngeal nerve damage, and amniotic fluid leak. The latter may be related to the requirement for 4 endoscopic ports, which may predispose to membrane rupture. Finally, experimental evidence that the fetoscopic approach minimizes preterm labor is inconclusive, but theoretically the concept is appealing.

There are a number of problems to be solved regarding fetal tracheal occlusion. First, one of the unexpected consequences of fetal tracheal occlusion is induction of surfactant deficiency related to decreased type II pneumocytes. Although the short and long-term clinical significance of this effect is unknown, experimental work has shown that type II pneumocyte numbers rebound with release of tracheal occlusion. However, we have recently that in utero tracheal occlusion with subsequent in utero release of the occlusion does not restore normal postnatal respiratory function in fetal sheep with severe lung hypoplasia associated with CDH.

Second, the enlarged lungs are likely to be “polyalveolar,” a term first applied by Hislop and Reid to a newborn with an enlarged lobe in which several segments had about 5 times the normal alveolar number and showed clinical features of lobar emphysema. The term describes the lung with increased number of alveoli per acinus. Because the development of airway branching in the human fetus is believed to be complete by the end of the pseudoglandular stage (16 weeks), an increase in airway branching is unlikely to be induced by tracheal occlusion, which is performed later in gestation. Thus, it is likely that the components of the lung that grow in response to tracheal occlusion are distal to the terminal bronchiole, resulting in a polyalveolar lung. The long-term function of polyalveolar lung is not known. However, an increase in alveolar number without an increase in airway branching is known to occur in compensatory lung growth after pneumonectomy and in survivors with CDH and unilateral pulmonary aplasia. Emphysema does not necessarily accompany the polyalveolar lung in these circumstances.

The third problem is a variable lung growth response to tracheal occlusion, which is a phenomenon specific to humans. We have shown that the growth response of human fetal CDH lungs to tracheal occlusion is gestation dependent, ie, fetuses occluded late in gestation (26 to 28 weeks) do not respond to tracheal occlusion as consistently as those who undergo occlusion at 24 to 26 weeks. On the other hand, some fetal lungs may respond so quickly as to cause cardiac compression and hydrops within a week after tracheal occlusion, whereas others show no growth response at all. The features responsible for this biological variability in response to tracheal occlusion are poorly understood.

An intraluminal tracheal “plug” that can be placed by a fetoscope is being developed by our group and others. An ideal intraluminal plug could be placed endoscopically using a single port with a percutaneous approach, would consistently obstruct the growing fetal trachea for more than 4 weeks, would not damage the trachea, and could be reversed in utero if necessary or at the time of birth. In theory, the reversibility of the device would be important both to stop rapid lung growth that may result in fetal hydrops and to minimize the potentially detrimental effect of prolonged tracheal occlusion on lung maturation. We are investigating the efficacy of a detachable silicone or latex balloon, an expandable tracheal occlusion device, and an injectable cross-linked hydrogel in fetal animal models, but thus far no technique has fulfilled the above requirements. At the time of this review, we are no longer offering TO clinically while we await results of a NIH-sponsored clinical trial of fetoscopic balloon occlusion versus standard postnatal care performed at UCSF. This trial will be challenging because it is apparent that the survival of the CDH patient treated postnatally is improving because of a new ventilatory management technique referred to as gentle ventilation, which minimizes barotrauma to hypoplastic lungs. Deprest et al in Europe have developed a
percutaneous single port fetoscopic balloon TO technique, but this approach should be tested in a prospective randomized clinical trial.

SACROCCYGEAL TERATOMA

Sacrococcygeal teratoma (SCT), although the most common tumor of the newborn, has an incidence of 1 in 35,000 to 40,000 live births. The occurrence of chromosomal abnormalities or associated congenital anomalies are rare. SCT is uniformly attached to the coccyx and has been classified by the relative amounts of intrapelvic and external tumor using the American Academy of Pediatrics, Surgical Section classification. $^{85}$ Type I is primarily external and has only a small presacral component. Type II is predominantly external but has a significant intrapelvic portion. Type III is partially external but is predominantly intrapelvic with abdominal extension. Type IV is located entirely within the pelvis and abdomen. The value of this classification relates to the case of surgical resection and prenatal detection as well as the likelihood of malignancy. Type I is easy to detect and resect with a very low incidence of malignancy. In contrast, type IV tumors are difficult to diagnose, not amenable to fetal resection, and frequently are malignant when first diagnosed because of prolonged delay in recognition. Fortunately, the majority of tumors are type I or II. Abdominal or pelvic extension of the tumor also is important to determine in terms of the feasibility of fetal surgery. As a result of acoustic shadowing by the fetal pelvic bones, ultrasound scan cannot always define the most cephalad extent of SCT. Ultrafast fetal MRI is superior in delineating the intrapelvic extent of the tumor. $^{86}$

Natural History and Histology

The majority of the newborns with SCT do well after early surgical resection although rarely the tumor undergoes malignant transformation. In contrast, the prognosis of SCT diagnosed before birth has a mortality rate of 30% to 50%. $^{87-89}$ A rapid phase of tumor growth frequently precedes the development of placentomegaly and hydrops, which is a sign of impending fetal demise.

The histologic classification of fetal SCT may change dramatically in utero. Graf et al $^{90}$ reported histologic maturation in fetal SCT between the initial debulking procedure (4 in utero and 1 postnatal at 32 weeks) and subsequent definitive resection. It is unclear whether this was the result of tumor maturation induced by preterm debulking or the natural in utero maturation of fetal SCT.

Pathophysiology

The high mortality rate of fetal SCT is attributed to a variety of mechanisms (Fig 2). The mass effect from the SCT can result in premature delivery or dystocia. Premature delivery is thought to be caused by associated polyhydramnios inducing uterine irritability and premature rupture of the membranes. Dystocia in unsuspected cases is associated frequently with traumatic tumor rupture and hemorrhage during delivery, which usually is fatal. The hemodynamic effects of SCT can be ascribed mainly to a large blood flow to the tumor and in part to anemia caused by hemorrhage into the tumor. The former results in high-output cardiac failure caused by arteriovenous shunting in the tumor and the latter compounds the high output state. A large tumor creates a vascular “steal” from the placenta and the fetus, which has been documented by echocardiographic and Doppler ultrasound measurements. Actual reversal of diastolic flow in the umbilical arteries can be observed as the lower resistance in the tumor “steals” blood flow from the placenta. Abnormalities also occur in left and right ventricular end-diastolic diameters, placental thickness, diameter of the inferior vena cava (IVC), combined ventricular output, descending aortic flow, and umbilical venous flow. $^{91}$ The end stage of placentomegaly and fetal hydrops can lead to the maternal mirror syndrome. As in cases of CCAM, fetal intervention before the related maternal preeclamptic state develops is recommended. $^{92}$

Surgical Management

From 1995 to 2001, we evaluated 26 fetuses with the diagnosis of SCT and performed fetal surgery on 4 cases associated with hydrops. In 1997, we reported the first successful fetal surgical resection of SCT. $^{93}$ In this case, fetal SCT was detected first at 20 weeks’ gestation. The tumor grew rapidly thereafter to become the size of the fetus accompanied by the development of polyhydram-
nios, placentomegaly, and maternal tachycardia and proteinuria. At 26 weeks’ gestation, open surgical resection of the tumor led to the reversal of fetal hydrops and placentomegaly by 10 days after surgery. A 1.33-kg baby girl was delivered at 29 weeks’ gestation and underwent completion coccygectomy. No residual tumor was apparent. At 16 months of age she developed pulmonary metastasis from a germ cell tumor and required chemotherapy and additional surgery. She currently is doing well at age 6 with no evidence of disease. Since that time, 3 additional open fetal surgeries for SCT have been performed at 22 to 26 weeks’ gestation with 2 survivors. These cases show that resection of a large tumor can reverse the pathophysiology of high-output cardiac failure and that early intervention offers the best hope for fetal survival once high-output cardiac failure is documented. If signs of high output cardiac failure are absent, the fetus may be followed up with serial sonography. If placentomegaly or hydrops develops after pulmonary maturation, the fetus should be delivered by emergent cesarian section. Open fetal surgery (Fig 3) is considered in fetuses less than 32 weeks’ gestation when the tumor is anatomically amenable to resection. In the presence of the maternal mirror syndrome, the family is counseled that the best alternative is delivery to prevent life-threatening maternal complications (Fig 4).

Occlusion of feeding arteries to a fetal SCT using a radiofrequency thermal ablation technique or a high-intensity focused ultrasound technique is being evaluated.

Fig 3. Exposure of fetal SCT (A) and resection using a surgical stapler (B).

Fig 4. Algorithm for the fetus with a prenatally diagnosed SCT.
in the laboratory. Although laser therapy has been tried for treatment of human fetal CCAM and SCT we believe further evaluation of its efficacy and safety must be done in the laboratory before clinical application. It may become possible in the future to reverse hydrops caused by fetal SCT using minimally invasive techniques.

Most fetuses with an antenatal diagnosis of congenital anomaly can be treated at an appropriate center with maternal transport, planned delivery, and prompt therapy after birth. Fetal surgery currently is reserved for a small subgroup of patients with extremely poor prognosis, and the initial results are encouraging. Preterm labor after fetal surgery remains an obstacle, and effective pharmacologic control of uterine contractions would be a major breakthrough in this field.

REFERENCES