Fetal Surgery

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Abstract

Maternal fetal surgery for correction of an anatomic defect was first performed 30 years ago by Michael Harrison. At that time, the concept of the fetus as a patient was the subject of philosophical and ethical debate and the rationale and pre-requisites for prenatal surgical treatment were in evolution. Over the past three decades, the concept of the fetus as a patient has become commonly accepted and the ethical framework for maternal fetal intervention is now well developed. Improvements in prenatal diagnosis now provide certainty for the primary diagnosis and, in competent hands, can identify or exclude virtually all significant associated anomalies. Clinical experience with prenatally diagnosed fetuses has provided insight into the natural history of specific anomalies, improved our ability to predict the outcome for an individual fetus, and allowed more accurate selection of fetuses that will benefit from prenatal surgery. While application of open fetal surgery has remained limited to only a few anomalies, it is important to appreciate that the development of this field has accelerated

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P.D. Losty et al. (eds.), *Rickham's Neonatal Surgery*, https://doi.org/10.1007/978-1-4471-4721-3_14

technological progress in prenatal diagnosis and intervention, led to improved understanding of the pathophysiology and natural history of candidate disorders, allowed comprehensive counseling of prospective parents in centers with focused expertise in fetal anomalies, and driven the evolution of less invasive therapeutic approaches. In this chapter we will discuss the rationale and current indications for open fetal surgery, the evidence supporting its efficacy, and basic physiologic and technical considerations common to all fetal surgical interventions.

Keywords
Fetal surgery • Birth defects • Fetus • Outcomes

Maternal fetal surgery for correction of an anatomic defect was first performed 30 years ago by Michael Harrison [1]. At that time, the concept of the fetus as a patient was the subject of philosophical and ethical debate [2] and the rationale and pre-requisites for prenatal surgical treatment were in evolution. Over the past three decades, the concept of the fetus as a patient has become commonly accepted and the ethical framework for maternal fetal intervention is now well developed [3]. Improvements in prenatal diagnosis now provide certainty for the primary diagnosis and, in competent hands, can identify or exclude virtually all significant associated anomalies. Clinical experience with prenatally diagnosed fetuses has provided insight into the natural history of specific anomalies, improved our ability to predict the outcome for an individual fetus, and allowed more accurate selection of fetuses that will benefit from prenatal surgery. While application of open fetal surgery has remained limited to only a few anomalies, it is important to appreciate that the development of this field has accelerated technological progress in prenatal diagnosis and intervention, led to improved understanding of the pathophysiology and natural history of candidate disorders, allowed comprehensive counseling of prospective parents in centers with focused expertise in fetal anomalies, and driven the evolution of less invasive therapeutic approaches. In this chapter we will discuss the rationale and current indications for open fetal surgery, the evidence supporting its efficacy, and basic physiologic and technical considerations common to all fetal surgical interventions.

14.1 Rationale and Foundation for Fetal Surgery

Observations by clinicians of neonates with specific anatomic defects born with secondary irreversible organ damage led to the conclusion that the damage occurred before birth and the compelling rationale that the only way to prevent that damage, was to correct the defect by fetal intervention. This led to experimental validation of the pathophysiology of specific fetal defects in the lamb model and to the development of techniques for their prenatal surgical correction [4–6]. Finally, pre-clinical studies in the primate model defined the anesthetic, tocolytic, and technical methods and devices [7] that proved essential for clinical translation [8–10]. Ultimately, these efforts supported the first systematic clinical application of fetal surgery in the early 1980's.

The pre-requisites for fetal surgery were developed during this formative period and, with slight modification, still apply today (Table 14.1). However, with advances in prenatal diagnosis, increased prenatal experience, and technical progress in fetal surgery, our ability to meet these

Table 14.1 Prerequisites for fetal surgery

• Accurate Prenatal Diagnosis
• No Associated Anomalies
• Defined Natural History
• Correctable Lesion Leading to Fetal Death or Organ Destruction
• Technical Feasibility

criteria for specific anomalies has improved dramatically. For instance, the requirement for an accurate prenatal diagnosis and the exclusion of associated anomalies is now practically taken for granted. The armamentarium for examining the fetus in the womb, including high resolution ultrasound (2D, 3D and 4D), haste MRI, and fetal echocardiography, when expertly applied, are capable of detecting essentially any significant fetal structural anomaly. When combined with maternal serum screening, karyotype analysis, and molecular diagnostic techniques, the likelihood of missing an associated anomaly or performing an intervention on an unrecognized syndromic fetus has been dramatically reduced. In addition, with accumulated experience and normograms for many fetal parameters, the limits of normality and abnormality have been clarified, allowing appropriate interpretation of normal variation (for instance, minimal renal pelviectasis). The presumed pathophysiology of specific anatomic defects has been confirmed either in animal models when possible, or by clinical observation, and the ability to reverse the pathophysiology by fetal surgical correction has been validated. Finally, significant progress in our ability to safely operate on the mother and her fetus has been made. Advances in the technical aspects of fetal intervention, maternal anesthesia, tocolysis and the accumulation of clinical experience have evolved to the point where open fetal surgery can be performed in experienced centers with a minimum of maternal morbidity, and to this date no maternal mortality [11]. Nevertheless, fetal surgical interventions have until recently been limited to fetal anomalies perceived to be lethal because of the potential risk of this major surgical procedure to the usually young, healthy mother. The fetal surgical treatment of myelomeningocele (MMC), a non-lethal disorder, has extended the original pre-requisites for fetal surgery to disorders causing irreversible organ damage with associated quality of life impacting morbidities prior to birth.

Despite this progress, fetal surgery remains controversial. The controversies primarily relate to our understanding of the "natural history" of specific anomalies, and whether we can accurately select fetuses that will benefit from fetal intervention. Our knowledge of the natural history of many disorders without fetal treatment has improved allowing accurate selection of fetuses that might benefit from fetal intervention. The natural history of Congenital Pulmonary Airway Malformation (CPAM), fetal Sacrococcygeal Teratoma (SCT), and Lower Urinary Tract Obstruction (LUTO) for instance, are relatively well understood. However, the natural history remains controversial for Congenital Diaphragmatic Hernia (CDH) and cardiac outflow tract anomalies making interpretation of the results of fetal therapy more difficult. The importance of randomized controlled trials (RCT) to resolve these controversies cannot be overemphasized and the design and implementation of such trials is a current focus for fetal treatment centers [12, 13]. Challenges in performing RCTs include the rarity of appropriate subjects, ethical challenges, and the resources required for organization, financing, and impartial evaluation of results obtained. The future of fetal intervention depends upon developing evidence based support for fetal interventional procedures which will be a major focus in coming years.

Currently, there is a relatively limited list of fetal anomalies for which a compelling rationale exists for fetal intervention. Anatomic anomalies that are currently treated by fetal intervention and their associated pathophysiology are shown in Table 14.2. However, there are basic considerations common to all fetal surgery that will be discussed as a basis for discussion of specific anomalies.

Table 14.2 Anatomic anomalies treated by fetal intervention

Anomaly	Pathophysiologic consequences	Fetal treatment
Cystic adenomatoid malformation	Hydrops; Lung hypoplasia	Open surgery or Thoracoamniotic shunt
Sacrococcygeal teratoma	High output cardiac failure	Open surgery; Tumor debulking
Myelomeningocele	Spinal chord damage; Brain stem compression; Hydrocephalus	Open Surgery; Defect closure

14.2 Basic Considerations that are Common to all Open Fetal Surgery

14.2.1 Ethical Considerations and Preoperative Management

Fetal surgery is unique in its involvement of a healthy patient who undertakes considerable surgical risk without expectation of direct benefit, creating a unique subset of ethical concerns. Such concerns have been explored and an ethical framework has been well established [14]. In general, the fetus achieves independent moral status as a patient once he/she reaches the point of viability. The pre-viable fetus, then, is a patient only when the pregnant woman chooses to continue her pregnancy and presents for treatment on behalf of her fetus. For the eligible fetus, the risks of such a procedure are clearly offset by the considerable benefit of salvage, but the fetus cannot be considered to be an independent or autonomous decision-maker, and the beneficence-based obligation to the fetus must be balanced with both beneficence-based and autonomy-based obligations to the mother. Thus, the fetus is not a separate patient, and maternal safety is a primary concern in considering fetal intervention.

Furthermore, the mother is under no obligation to present her fetus for treatment, and she must be provided all necessary information for truly informed consent. The treatment team has a responsibility to consider the risks to the mother in the context of the likelihood of fetal loss or severe, reversible disability. For this reason, both fetal and maternal factors can be contraindications to open fetal surgery, including chromosomal abnormalities, significant anatomic abnormalities, maternal obesity, heavy smoking history or other medical conditions. Patient selection should take place through multidisciplinary evaluation following a screening process including detailed ultrasonographic examination for characterization of the defect and any other abnormalities, ultra-fast fetal MRI for anatomic definition, fetal echocardiogram to assess heart function and detect any cardiac abnormality, and karyotyping and/or more high resolution genetic analysis. Following this evaluation, cases should be reviewed by a multidisciplinary team of fetal surgeons, obstetricians, anesthesiologists, radiologists, a nurse coordinator, geneticist, and social workers.

Eligible families must undergo extensive counseling to discuss the proposed surgical procedure, postoperative and postnatal care. A team meeting provides an appropriate forum for the family to learn about the procedure and its risks, benefits and alternatives. Depending upon gestational age, all appropriate options should be discussed in a non-directive manner, including termination, expectant management with palliative or best available postnatal treatment, and prenatal therapy. Parents must understand the likely outcomes of all possibilities, as well as the risks involved. For any fetal surgery, complications may include preterm labor, premature rupture of membranes, chorioamnionitis, uterine rupture, medication side effects, risk of fetal demise, as well as surgical complications and future reproductive issues. The mother must be counseled regarding the need for caesarean section in this and all future pregnancies, and care must be taken to “allow” families to opt for non-surgical management.

14.2.2 General Principles of Open Fetal Surgery

14.2.2.1 Personnel and Equipment

Care of the fetal surgery patient requires a multidisciplinary team with clearly defined roles, as well as highly specialized equipment. Because the mother and fetus have separate, though co-dependent anesthetic concerns, both an obstetric anesthesiologist and a pediatric anesthesiologist are necessary. A sonographer and an echocardiographer should be an integral part of the surgery team, and a high-resolution ultrasound machine with color Doppler should be used to identify fetal and placental anatomy and to assess for potential hazards such as velamentous cord insertion. Ultrasound images before and after maternal incision are used to select the optimal site for hysterotomy. During the procedure, continuous echocardiography should be used in combination with pulse oximetry, when possible, to monitor fetal heart rate, cardiac function, and volume status. An OR nursing team trained in fetal surgical procedures and familiar with the specialized instrumentation is of critical importance. The surgical team should be led by a pediatric surgeon or a perinatologist with specific training in fetal surgical techniques. In our institution, two pediatric surgeons with experience in all aspects of fetal therapy are scrubbed on all fetal surgical procedures, to assure maximal expertise with these uncommon procedures.

14.2.2.2 Anesthesia

Patients should be admitted prior to the planned procedure for monitoring and initiation of tocolysis with Indomethecin. Antibiotics should also be administered preoperatively to decrease the risk of maternal complications and chorioamnionitis. At the time of the procedure, anesthetic management should be initiated with placement of an epidural catheter to assist in both intra-operative and post-operative pain management. Typically, a Fentanyl/Bupivicaine mixture provides optimal pain control and reduces uterine irritability. General anesthesia is induced with inhalational agents, generally at a MAC of 2–2.5, sufficient to provide uterine relaxation. Maternal monitoring should include a radial arterial line, frequent cuff pressures, multiple large bore IV catheters, a foley catheter, pulse oximetry, and continuous EKG. Fluid management strategies should be aimed at euvolemia, given the predilection to postoperative non-cardiac pulmonary edema in the pregnant patient.

14.2.2.3 Positioning and Draping

Patients should be positioned supine with a left lateral tilt provided by a roll under the right side, in order to maximize venous return by preventing inferior vena caval compression by the uterus. Skin prep should include mid-abdomen to mid-thigh, and the operative field can be squared with sterile towels and covered with a fenestrated and pocketed drape.

14.2.2.4 Incision and Exposure

In general, the uterus is exposed through a low transverse abdominal incision. Placental position may guide the fascial incision. In general, subcutaneous flaps can be raised and the fascia may be divided in the midline from the umbilicus to the symphysis pubis. For posterior placentas, a ring retractor can then be positioned for retraction of the abdominal wall. A late gestational uterus with an anterior placenta may dictate that the fascia be divided transversely to allow anterior rotation of the uterus and a posterior hysterotomy.

14.2.2.5 Opening the Gravid Uterus

Prior to hysterotomy, the uterus is palpated to determine whether sufficient relaxation has been achieved. Transuterine ultrasound is used to confirm fetal and placental position prior to hysterotomy. Under ultrasound guidance, electrocautery is used to map the placental margins on the surface of the uterus and a safe site for hysterotomy (>6 cm from the placenta) is determined, avoiding uterine vasculature. Unlike a standard caesarean section, the lower segment of the uterus is avoided due to increased risk of amniotic fluid leak, chorioamnionitis and preterm labor.

Once a site is chosen, opposing 0 PDS traction sutures are placed through the uterine wall and fetal membranes under ultrasound guidance. Using electrocautery, a 2 cm incision is made in the myometrium between the sutures and the membranes are visualized and opened in a controlled fashion. A specialized uterine stapler is then placed through the fetal membranes and the stapler is fired once in either direction. It is important to use a uterine stapler intended for fetal surgery, as it compresses the myometrium and controls the membranes to minimize blood loss during hysterotomy while maintaining membrane integrity for closure. Absorbable staples are used to avoid subsequent fertility issues. Using a Level I rapid infuser, warmed Lactated Ringer's solution is infused into the amniotic space via a catheter to maintain amniotic fluid volumes and fetal temperature, while preventing cord compression. When an extremity is available (CPAM, SCT) a fetal peripheral intravenous line is then placed for infusion of fluids, blood, or medications.

14.2.2.6 Closure of the Gravid Uterus

Proper uterine closure is critically important, as the fetus must be returned to the amniotic space in such a way as to allow gestation to continue as normally as possible. The closure must have adequate strength to prevent uterine rupture, must be watertight to prevent amniotic fluid leaks, and must not contribute to preterm labor or future infertility. A two-layer closure should be performed, using double-armed full thickness 0 PDS stay sutures approximately 2 cm apart and 2 cm back from the staple line and a running 2–0 PDS suture through myometrium and membranes. Prior to completing the running layer, approximately 400 cc of warmed Lactated Ringer's solution containing 500 mg of Oxacillin should be instilled into the amniotic cavity and adequate amniotic fluid volumes should be confirmed by ultrasound. An omental flap should be used to buttress the uterine closure, and the maternal laparotomy should be closed in layers. Skin closure should be performed with an absorbable subcuticular layer, and dressings should consist only of a transparent Tegaderm, in order to allow continued fetal monitoring by ultrasound postoperatively.

14.2.2.7 Tocolysis and Postoperative Care

Preterm labor can compromise even the most carefully conducted intervention, and adequate tocolysis is of paramount importance to the success of any open fetal surgical procedure. Preoperative placement of an epidural catheter provides analgesia once the uterine relaxing effects of inhaled anesthesia have worn off, preventing a maternal stress response and uterine irritability. Placement of an Indomethacin suppository preoperatively begins the process, and a loading dose of 6 g IV magnesium sulfate is administered during hysterotomy closure. A maintenance infusion of magnesium sulfate is continued at 2–4 g/h for 18–24 h postoperatively, and Indomethacin suppositories are placed every 6 h postoperatively through 24 h. Patients must be closely monitored for signs of magnesium toxicity and serum magnesium levels should be checked frequently during this period. In addition, daily fetal echocardiography is required to detect any signs of Indomethacin toxicity, which can manifest as ductal constriction, oligohydramnios or tricuspid regurgitation. Uterine activity is monitored by tocodynamometer, and fetal heart rate is followed for any signs of distress. Daily ultrasound performed during the inpatient hospitalization assesses for fetal movement, amniotic fluid and membrane status, and serial anatomic evaluation.

During the postoperative period, fluid status must be carefully managed. Both the physiology of pregnancy and the magnesium sulfate regimen predispose the patient to noncardiogenic pulmonary edema, one of the most serious complications observed in otherwise healthy mothers. Empiric furosemide diuresis can be added if signs of pulmonary edema develop. After 48 h, patients begin a tocolytic regimen of 10–20 mg oral Nifedipine every 6 h, which is continued through delivery. Patients can usually be discharged by postoperative day 4, but should be required to remain on modified bedrest for the first 2 weeks after discharge. In the absence of uterine irritability, patients can then be allowed moderate activity, though they should remain nearby and return for twice-weekly ultrasounds

with obstetrical assessment. Once the fetus reaches 36 weeks' gestation, lung maturity is assessed by amniocentesis, and caesarean section is performed once the lungs are mature.

14.3 Anatomic Anomalies Currently Treated by Open Fetal Surgery

14.3.1 Fetal Lung Lesions

Fetal lung lesions represent a spectrum of pulmonary maldevelopment and for the purpose of discussion can be divided into four classifications: Congenital Pulmonary Airway Malformations (CPAM); Extralobar Bronchopulmonary Sequestration (BPS); Intralobar BPS; and Hybrid Lesions. It is important to realize that CPAMs may have features suggestive of BPS, such as systemic blood supply (hybrid lesions) or BPS may contain CPAM histology often suggested by a cyst within an extralobar BPS. In addition, lobar or segmental bronchial stenosis or atresia may be present suggesting an etiologic link with obstruction. CPAM is a hamartomatous tumor that is thought to arise from aberrant events during lung branching morphogenesis [15]. Grossly CPAMs appear as a discrete intraparenchymal masses that derive their blood supply from the pulmonary circulation and can contain cysts of any size ranging from the visually imperceptible (microcystic CCAM) to the predominantly cystic (macrocystic CCAM). Histologically CCAM is characterized by an overgrowth of one or several components of lung tissue with typically bronchial and epithelial elements. Bronchopulmonary Sequestration (BPS) consists of a mass of nonfunctional lung tissue that arises as an aberrant outpouching from the developing foregut. Characteristic features include the absence of a communicating bronchus and aberrant systemic blood supply. Intralobar sequestration shares a visceral pleural lining with usually a lower pulmonary lobe and may be aerated by intra-alveolar communications. The combination of systemic vascular inflow with pulmonary venous outflow in these lesions often results in a high-flow, low-resistance circuit leading to cardiac failure in childhood.

The differential diagnosis of fetal lung lesions also includes bronchogenic cysts, congenital lobar emphysema, segmental bronchial stenosis, bronchial atresia, unilateral lung agenesis, congenital diaphragmatic hernia (particularly right sided), mediastinal tumors, and congenital high airway obstruction (CHAOS). Detailed ultrasonographic features including lesion volume, consistency, location, arterial blood supply, and venous drainage will usually provide a definitive diagnosis.

14.3.1.1 Pathophysiology and Natural History

The natural history of postnatally recognized CCAM includes recurrent pulmonary infection that is resistant to antibiotic treatment, pneumothorax, and ultimately a propensity for malignant degeneration [16–18]. For these reasons we recommend resection of all CCAMs even when asymptomatic. The postnatal natural history of BPS is dependent upon whether they are intralobar or extralobar. Intralobar BPS should always be resected due to likely events of infection or high output cardiac failure. Extralobar BPS should be resected if there appears to be risk for cardiac failure, there is significant mass effect, or lymphatic congestion results in associated pleural effusion. In contrast to postnatally diagnosed lesions, the natural history of prenatal cystic lung lesions is relatively unpredictable. Approximately 15–20% of fetal CPAM lesions will decrease in size and 2/3rds of BPS lesions shrink considerably prior to birth [19, 20]. Despite a relative or absolute decrease in size and a tendency to become iso-echogenic with lung tissue by ultrasound examination in the third trimester, few if any of these lesions truly disappear and postnatal CT scan will confirm the persistence of the lesion after birth. Other CPAMs will grow dramatically during gestation with secondary compression of the surrounding lung and mediastinal structures. This may result in heart failure (hydrops) in the fetus or the presence of a large mass preventing ventilation at term. In addition, there is a low incidence of significant pulmonary hypoplasia

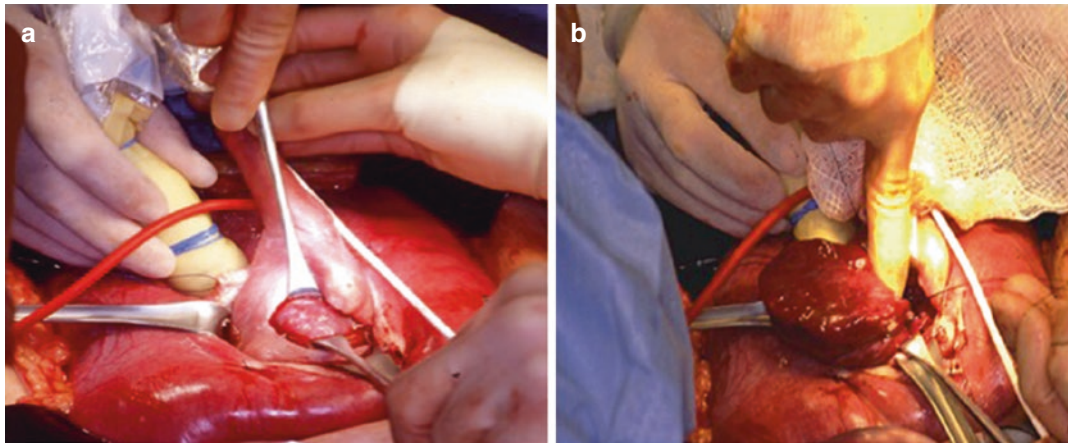

Fig. 14.1 (**a**) Resection of a fetal CPAM. The picture illustrates the fetal position with the arm and chest wall exposed and the head within the uterus. Continuous echocardiographic monitoring is performed during the procedure and an IC and pulse oximeter are placed on the exposed hand. A thoracotomy has been performed and the tumor can be seen bulging out of the incision. (**b**) A hilar dissection is performed. Here the pulmonary artery and bronchus have already been divided and the pulmonary vein is being ligated prior to removal of the tumor

that may impact survival after birth. The evolution of hydrops associated with CPAM is nearly uniformly fatal without intervention and is the sole indication for fetal surgery [19]. Given the uncertain natural history of these lesions, and the requirement for early intervention when hydrops develops, it was important to develop predictive parameters for the development of hydrops. One such parameter is the CPAM volume (using the formula for a prolate ellipse—length × height × width × 0.52) divided by the head circumference (to control for gestational age) ratio, called the CVR [21]. By serial measurement of the CVR, we have determined that most CPAMs follow a predictable growth profile, increasing in size until they plateau at around 28 weeks gestation. A CVR on presentation of ≥1.6 in a microcystic CPAM predicts an 80% likelihood of the development of hydrops, and these fetuses require very close sonographic surveillance (2–3 times per week) to monitor for signs of hydrops. A CVR of <1.6 portends a low likelihood of hydrops and we recommend initial weekly surveillance with decreasing frequency after 28 weeks. CPAMs with a predominant macrocystic component must be observed frequently throughout pregnancy as their growth is less predictable than microcystic CPAMs and we have observed rapid growth after 28 weeks in a few cases.

14.3.1.2 Fetal Intervention for Lung Lesions

Fetal intervention for CPAM is one of the unequivocal success stories of fetal surgery. The majority of lung lesions require no fetal intervention and can be managed postnatally as described above with excellent outcomes [22]. CPAMs that present with CVRs of ≥1.6 are a high risk category and require close surveillance. We [23] and others [24, 25] have observed growth arrest of microcystic CPAMs with steroid therapy reducing the need for fetal surgical resection. At the present time, we empirically treat CPAMs at risk for evolution of hydrops, or in early stages of hydrops, with steroids prior to fetal intervention. If signs of hydrops persist or progress in the fetus less than 32 weeks gestation, fetal surgery is indicated, either open resection for microcystic lesions (Fig. 14.1), or thoracoamniotic shunt placement for macrocystic lesions with a single dominant cyst or multiple communicating cysts. If hydrops develops in a fetus after 32 weeks gestation, or if there is persistence of major mediastinal shift closer to term, we recommend delivery and resection by the Ex Utero Intrapartum Treatment (EXIT) procedure [26]. The results of fetal therapy for hydrops induced by fetal lung lesions have significantly improved upon the natural history. Of 24 fetuses undergoing open fetal

surgery at the Children's Hospital of Philadelphia between 21 and 31 weeks gestation, there are 13 healthy survivors with 1–16 years of follow up. Resections involved a single lobectomy in 18 cases, right middle and lower lobectomies in 4 cases, extralobar BPS resection in 1 case, and 1 left pneumonectomy for CCAM. In survivors resection resulted in resolution of hydrops within 1–2 weeks after resection and impressive compensatory lung growth prior to delivery. Follow up developmental testing has been normal in all survivors. The results of thoracoamniotic shunt placement for hydrops due to CCAMs with a predominant cyst are even better with good quality of life survival of approximately 75% of shunted patients.

14.3.2 Sacrococcygeal Teratoma

A particularly challenging fetal anomaly requiring expertise in its pre and perinatal management is Sacrococcygeal Teratoma (SCT) [27, 28]. SCT is a teratoma arising from the presacral area that occurs in 1/30,000–1/40,000 live births. SCTs have malignant potential but are predominantly benign at birth. By definition they are comprised of elements from all three germ layers on microscopic examination and usually contain cystic and solid elements. Fetal karyotype is usually normal and there are usually no associated anomalies. SCTs have been classified (AAP Surgical Section Classification) based on the anatomic distribution of the tumor [29]. Type I SCT is predominantly external with a minimal presacral component. Type IV SCT is predominantly presacral with extension into the pelvis and abdomen and Types II and III are intermediate between these extremes. The majority of SCTs are Types I or II. Type IV is of significance because it can be missed after birth if not detected prenatally with subsequent presentation with pelvic outlet obstruction or malignancy.

14.3.2.1 Pathophysiology and Natural History

The natural history of prenatally diagnosed SCT is considerably worse than that after delivery [30]. After birth, the majority of patients with SCT do well after early surgical resection, which must include the coccyx to prevent recurrence of the tumor. In contrast, the mortality associated with prenatally diagnosed SCT ranges from 30% to 50%. The high mortality rate of fetal SCT can be attributed to a variety of mechanisms all of which relate to the size or blood flow of the tumor. Mass effect can result in preterm labor and/or dystocia and these were common mechanisms of fetal demise prior to the advent of prenatal diagnosis. SCTs can hemorrhage internally resulting in rapid enlargement of the tumor and fetal anemia, or rupture and bleed into the amniotic fluid resulting in fetal anemia or sudden death. Finally, predominantly solid SCT have high associated blood flow with arteriovenous shunting. This represents a low resistance vascular steal from the fetus and placenta and can ultimately result in high output cardiac failure [31]. Serial echocardiographic assessment can document the evolution of high output failure with increasing combined cardiac outputs and descending aortic blood flow, increasing left and right ventricular end diastolic diameters, increasing inferior vena caval diameter, and increasing placental thickness [32]. Fetal hydrops and placentomegaly may subsequently occur with the end result being fetal demise and often the maternal mirror syndrome. The evolution of hydrops secondary to high output cardiac failure in the immature fetus with SCT is associated with near 100% mortality and is the sole indication for fetal resection of these tumors.

14.3.2.2 Fetal Intervention for SCT

The fetus presenting with a large predominantly solid SCT is at high risk for progression to hydrops [33]. We recommend frequent surveillance by sonography and echocardiography with measurement of the cardiovascular parameters noted above. This may be as often as 3 times per week in the fetus verging on hydrops as they can decompensate rapidly and success of fetal treatment is dependent upon intervention before progression of hydrops. Fetal debulking of the tumor to remove the vascular steal is recommended when the evolution of high output cardiac failure

is recognized at prior to 28 weeks gestation in a fetus with Type I SCT. Timing of intervention is critical and should be recommended when the first overt evidence of hydrops occurs. The presence of advanced hydrops and/or the presence of placentomegaly are contraindications for fetal intervention. A significant number of pregnancies complicated by high-risk SCT will manifest signs of fetal or maternal decompensation, or both, between 27 and 32 weeks of gestation. In this grey zone between fetal intervention and adequate maturation for delivery, we have moved toward pre-emptive delivery by the EXIT procedure with debulking of the tumor on placental support [28]. Once the cardiac failure has resolved and the infant has been stabilized after birth, a formal resection of the residual tumor and coccyx can be performed. After fetal resection of the SCT, hydrops will generally resolve within 2–3 weeks. Since 1995, we have operated on 7 anatomically appropriate fetuses with SCT and associated high output failure with 5 survivors. One survivor has required postnatal treatment of pulmonary metastases of germ cell tumor but at 11 years of age has no evidence of disease. Another survivor had significant morbidity likely related to emboli at the time of tumor resection. The other three survivors remain healthy. These cases demonstrate that fetal resection of a large tumor can reverse the pathophysiology of high output cardiac failure in carefully selected cases and that early intervention offers the best hope of survival once high output failure is documented. However, SCT remains one of the most difficult and challenging fetal anomalies to manage and parents should be counseled appropriately. Our algorithm for pre and perinatal management of high risk fetal SCT is shown in Fig. 14.2.

14.3.3 Fetal Myelomeningocele

Myelomeningocele (MMC) or open spina bifida is a common and devastating congenital anomaly for which there is no satisfactory postnatal treatment. It is the first non-fatal anomaly considered for fetal surgical intervention necessitating a careful analysis of risks and benefit. It is

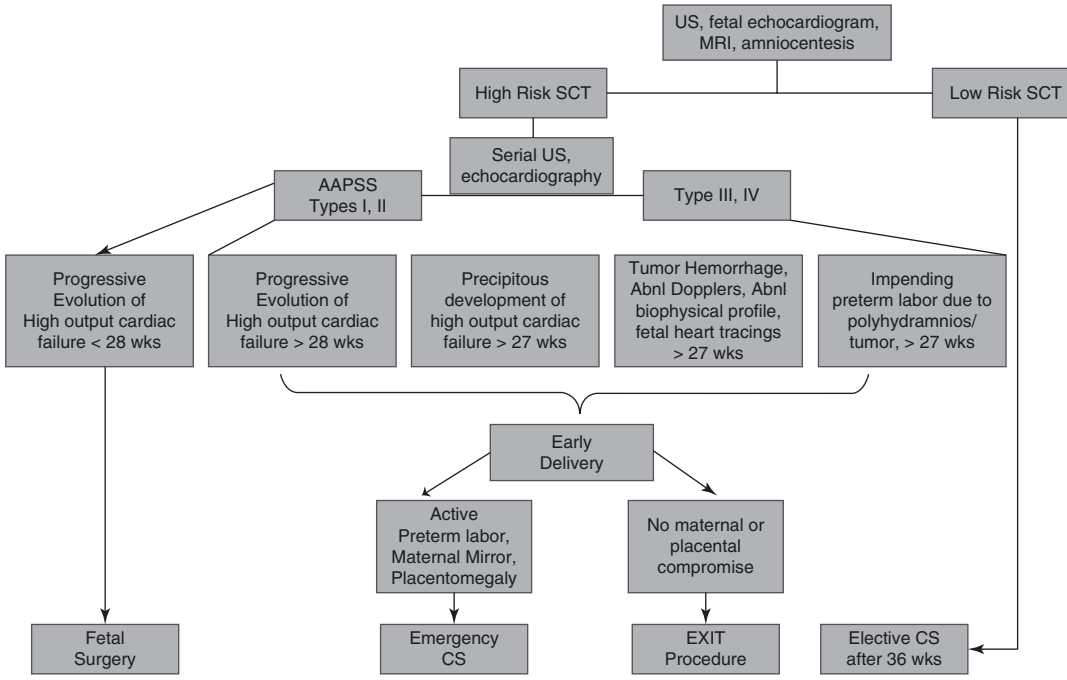

Fig. 14.2 CHOP Algorithm for pre and perinatal management of fetal SCT. (Reprinted with permission from Ref. [28])

characterized by protrusion of meninges and neural elements through a defect in the vertebral arches with secondary complications of lifelong paralysis and varying degrees of mental retardation, bowel and bladder dysfunction, and orthopedic disabilities [34]. MMC has been determined to have both genetic and micronutrient causes. While substantial progress could be made in preventing this disorder through folic acid supplementation, MMC still effects approximately 1/2000 live births and this figure does not include the 23% of MMC pregnancies in which the fetus is aborted [35–38].

14.3.3.1 Pathophysiology and Natural History

There is experimental and clinical evidence implicating the "two hit hypothesis" in the pathophysiology of MMC recently reviewed by Adzick [13]. The first "hit" is failure of neurulation resulting in an open spinal defect. Interestingly, there is minimal evidence for primary neural injury during this phase of the pathogenesis. The second "hit" results from exposure of the neural elements to the amniotic fluid and mechanical effects within the intrauterine environment. This is where evidence suggests the neural damage occurs and this evidence constitutes the rationale for fetal coverage of the MMC defect. A secondary result of the open spinal defect is the Arnold-Chiari malformation which is responsible for a significant component of the morbidity and mortality of MMC. Loss of cerebral spinal fluid through the defect results in a sump effect that causes descent of the hindbrain into the posterior fossa with secondary brainstem compression. With current postnatal treatment nearly 14% of all MMC neonates do not survive past 5 years of age, with the mortality rising to 35% of those with symptoms of brainstem compression from the Arnold-Chiari malformation. Whereas 70% of patients have an IQ >80, only half are able to live independently as adults, even with adapted accommodations [39, 40]. In addition to the motor and sensory deficits due to the spinal cord lesion, MMC patients have significant complications from hydrocephalus, the Arnold-Chiari II malformation, and tethering of the cord at the site of surgical repair. Hydrocephalus occurs in more than 85% of patients with MMC and at least 80% require placement of shunts to prevent neurologic and intellectual compromise associated with hydrocephalus. The rate of shunt related complications and morbidity is high contributing significantly to the overall morbidity of MMC. Thus it is clear that improvements in treatment are desperately needed.

14.3.3.2 Fetal Intervention for MMC

The rationale for open fetal MMC repair is based upon the prevention of neurologic deficits and associated morbidities. With evidence from animal models supporting the likelihood of improved functional outcomes, the first attempts at human MMC repair were reported in the late 1990s. The first endoscopic attempts at MMC repair were reported in 1997 with no apparent improvement in clinical outcome [41]. A subsequent report comparing outcomes between endoscopic and open repair demonstrated superior results with the open approach [42], and thus far attempts at endoscopic repair have not been proven effective in a well designed study. The first successful open fetal surgery for MMC demonstrating improved neurologic function was performed at CHOP in 1998 [43], and was followed by two studies of open MMC repairs reported in 1999 ($n = 10$) [44] and 2003 ($n = 50$) [45] at CHOP. The technique consists of excision of the MMC sac with preservation of the neural placode, closure of mobilized paravertebral myofascial flaps which are lined by Dura, and direct closure of the skin if possible with the use of an alloderm patch in larger defects. In these series overall survival was 90 and 94% respectively, with partial or complete reversal of hindbrain herniation in 100% of fetuses within 3 weeks of operation (Fig. 14.3), and VP shunt rates were significantly lower than expected based on historical controls.

Based on these promising initial results for open MMC repair, a group of three centers in the United States undertook a randomized clinical trial comparing prenatal open MMC surgery with postnatal surgery, the Management of Myelomeningocele Study (MOMS), in 2003. The study was carried out at CHOP, Vanderbilt University and UCSF, with an independent Data

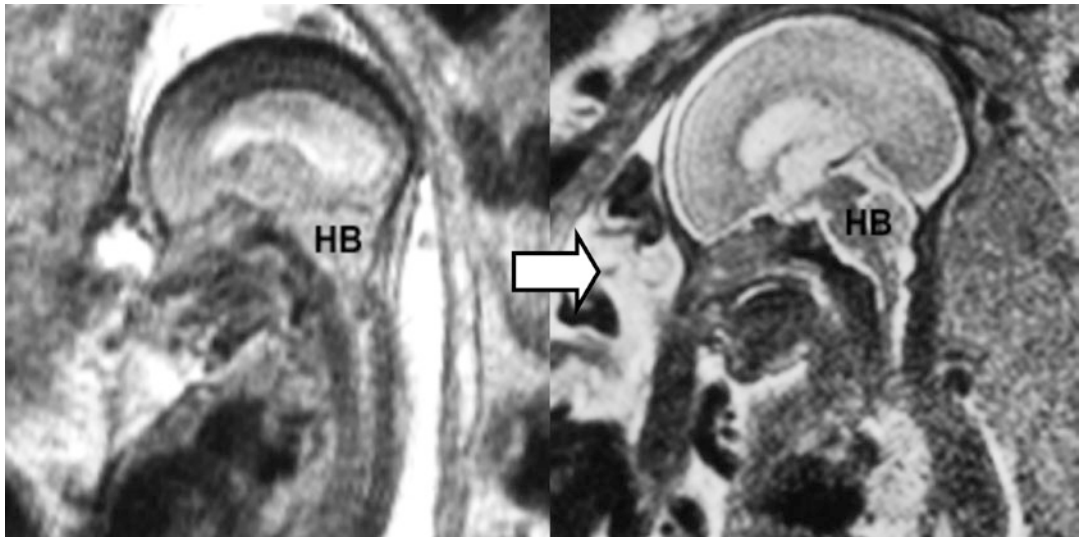

Fig. 14.3 (**a**) MRI appearance of hindbrain herniation in Arnold-Chiari II malformation. (**b**) Reversal of hindbrain herniation 3 weeks after fetal repair of MMC. Fluid spaces in the cisterna magna are uniformly restored after fetal repair. (**c**) Algorithm for management of fetal MMC

and Study Coordinating Center at George Washington University Biostatistics Center. While the trial was being conducted, a moratorium on open fetal MMC repair outside the trial was agreed upon by other fetal centers in the US. The study was powered to recruit 200 patients but was halted in December 2010 when a planned interim analysis demonstrated clear benefit for prenatal surgery after randomization of 183 patients. The results were reported in 2011 [46] and included 158 women randomized prior to July 1, 2009, with 78 in the prenatal group and 90 in the postnatal repair group. The inclusion criteria required that the fetus be 19–25.9 weeks of gestation, with MMC located between T1-S1, with evidence of hindbrain herniation, and normal karyotype without evidence of other abnormalities. The first primary endpoint of the study was a composite of fetal or neonatal death and the need for a CSF shunt at 12 months of age. Sixty-eight percent of the prenatal surgery group versus 98% of the postnatal group fulfilled the primary endpoint, with actual shunt rates of 40% versus 82% respectively. At 12 months of age, rates of moderate or severe hindbrain herniation were significantly lower in the prenatal group (25%) compared the postnatal group (67%). The secondary outcome was a score derived from the Bayley Mental Development Index and the difference between the functional and anatomic level of the lesion at 30 months of age, and was significantly better in the prenatal group versus postnatal repair. Children in the prenatal group were significantly more likely to walk without the use of orthotics or devices (42% vs. 21%), and scored significantly higher in parent-reported self-care and mobility scores. Importantly, prenatal surgery was associated with higher rates of prematurity and maternal morbidity, though infant mortality rates were equal and no maternal mortalities occurred.

Long-term follow-up on neurodevelopmental outcomes at age 5 through 9 of the MOMS cohort (MOMS II) will be a fundamental component of evaluation of the overall efficacy of prenatal therapy for MMC. Results of 5-year follow-up on the cohort of patients treated at CHOP prior to the MOMS trial were recently reported [47]. The majority of children achieved complete independence in cognitive (84%) and mobility (68%) scores, but continued to require significant assistance in self-care. Improved understanding of long-term functional limitations will allow for more effective interventions to maximize clinical outcomes following MMC repair.

14.3.4 Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) occurs in 1 in 3000 to 1 in 5000 live births and is associated with high rates of morbidity and mortality due to pulmonary underdevelopment resulting from the anatomic defect. CDH was one of the first anomalies considered for fetal intervention, however the early experiences with open fetal surgery and tracheal occlusion have produced mixed results and raised controversies regarding the natural history of the anomaly and identification of patients likely to benefit from prenatal therapy.

14.3.4.1 Pathophysiology and Natural History

CDH results from failure of closure of the foramen of Bochdalek between 8 and 10 weeks of gestation. The cause of that failure is the subject of active investigation, with strong evidence implicating genetic factors including disruption of retinoid signaling [48]. Herniation of abdominal contents into the thoracic space results in pulmonary hypoplasia (PH) due to interference with branching morphogenesis during lung development, resulting in a reduction in the number of airways, alveolar, and vascular structures, in turn leading to decreased surface area for gas exchange and fixed increased vascular resistance [49]. Pulmonary vasculature in CDH is also grossly abnormal, with hypermuscular peripheral pulmonary arteries resulting in increased pulmonary vasoreactivity and persistent pulmonary hypertension (PPH). As hypoxemia and acidosis stimulate further pulmonary vasospasm, patients may decompensate rapidly and prove refractory to ventilation by conventional modalities [50]. Improvements in neonatal management, including immediate intubation and ventilation with low peak pressures, blood pressure support, delayed surgery, and extracorporeal membrane oxygenation (ECMO), have resulted in improved outcomes [51]. However, CDH resulting in severe pulmonary insufficiency remains a clinical problem with no adequate postnatal treatment option. The frustration of physicians and surgeons observing the effects of this prenatal insult has prompted considerable exploration of fetal interventions to prevent or reverse pulmonary hypoplasia and restore sufficient lung mass for neonatal survival.

14.3.4.2 Fetal Intervention for CDH

To meet the fundamental criteria for consideration of fetal intervention, the natural history of the condition must be well-described. While advances in prenatal imaging have led to detailed analysis of the anatomic abnormalities encountered in CDH, controversy exists regarding their prognostic power. The most significant prognostic factor for poor outcome is a finding of herniation of the liver into the thorax ('liver-up'), which is associated with a 55% mortality rate compared to mortality of 26% in 'liver-down' cases [52]. Measurements of lung volume, whether by direct measurement or lung-to-head ratio (LHR), calculated using the contralateral lung at the level of the four-chamber view of the heart [53, 54], or "observed to expected" LHR or lung volume determined by US or MRI, do not provide additional independent predictive value for mortality over liver herniation, but do provide additional evidence of severity. With improving survival and no validated prenatal prognostic indicator of morbidity, selection of a group with a defined expected mortality or quality-of-life-impacting morbidity for fetal intervention poses a significant challenge to trial design and analysis.

Initial trials of prenatal treatment employed open fetal surgery and a patch repair of the diaphragmatic defect, however fetuses with liver herniation could not be salvaged by this approach due to kinking of the umbilical vein resulting in intrauterine demise [55]. While no differences in survival were found in 'liver-down' CDH repaired in utero compared to postnatal repair, these patients were later determined to have favorable outcomes with postnatal therapy, and the open approach was ultimately abandoned. More recently, tracheal occlusion (TO) has been studied as a potential treatment for CDH-induced pulmonary hypoplasia. The lungs are net producers of amniotic fluid, and lung fluid volumes are normally regulated by fetal laryngeal tone. In

animal models, pulmonary hypoplasia may be induced by shunting of fluid from the lungs to the amniotic space, while obstruction of tracheal outflow generates large fetal lungs [56]. Fetal lamb models of TO in CDH demonstrated accelerated lung growth and improved pulmonary function [57, 58], although these studies raised concerns regarding lung maturity as measured by surfactant production and type II pneumocyte levels [59]. Based on the experimental data in animals, clinical trials were initiated at UCSF in the late 1990s, with an uncontrolled case series suggesting benefit for TO by a fetoscopic approach in CDH [60]. A subsequent RCT at UCSF demonstrated no benefit in the TO group [61], and an interim prospective trial at CHOP observed that even in cases when lung growth occurred, many of the neonates had severe respiratory compromise raising doubts about the biology of TO in severe CDH [62]. These results led to diminished interest in pursuing TO in North America. However, Jan Deprest and the Eurofetus study group have developed a minimally-invasive approach to TO utilizing a deployable balloon through a single small trocar, and have reported promising initial results [63]. However, there are serious flaws in this data including a 28% rate of primary repair of the diaphragm, suggesting the patients were not as severe as the selection criteria would suggest, no concurrent controls, and a simultaneous improvement in CDH survival in Europe due to adoption of permissive hypercapnia techniques during the decade of these reports [64]. Recently a multi-center RCT, the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) Trial was initiated by Eurofetus and the results of this trial are anticipated with interest. A US consortium to investigate FETO is currently being organized to augment the European trial.

14.4 Other Invasive Maternal/ Fetal Procedures

While the most common fetal anomalies treated by open fetal surgery are emphasized above, the spectrum of fetal intervention includes not only open fetal surgery, but also minimally invasive fetal surgeries such as shunting or fetoscopic procedures, as well as the Ex Utero Intrapartum Treatment (EXIT) procedure.

Fetoscopy first became available in the 1970's, and was initially used primarily as a diagnostic tool. With the development of more sophisticated camera equipment and specialized endoscopic tools, minimally invasive interventions have become not only feasible, but widely applied. Procedures performed in this manner range from laser coagulation of placental anastomoses in TTTS to balloon tracheal occlusion for CDH. Complications of these procedures may include bleeding, separation or rupture of fetal membranes, chorioamnionitis or preterm delivery. Most fetoscopic procedures can be performed entirely percutaneously, minimizing maternal and fetal risks. Such cases usually require only local anesthesia, while procedures which could cause fetal pain generally involve intraumbilical or usually intramuscular administration of opioid and/or muscle relaxant. Similarly, the lack of a hysterotomy obviates the need for extensive tocolysis, and most procedures are performed with only a single dose of indomethacin or nifedipine, if any tocolysis is required. Randomized controlled trials have demonstrated benefit for fetoscopic laser ablation in TTTS [65] and are currently being conducted for fetoscopic tracheal occlusion for CDH.

The EXIT procedure was originally used to deal with surgically applied clips in the early experience with TO for treatment of CDH [66] and was subsequently applied to the difficult airway in cases of large anterior neck mass. The indications for the procedure have now expanded [67], and it is used in any case in which difficulty obtaining an airway after birth is expected or in some circumstances where instability immediately after seperation from the placenta is anticipated (massive SCT with hydrops). Some such indications include not only giant anterior neck masses, but congenital high airway obstruction syndrome (CHAOS), hypoplastic craniofacial syndrome, thoracic masses, mediastinal tumors, pleural effusions, large CCAM's, premature infants with large SCTs, or as a bridge to extracorporeal membrane oxygenation (ECMO) for

severe CDH with a combined cardiac defect or other cyanotic lesion, minimizing any time during which the fetus might be hypoxic or acidotic.

During an EXIT procedure, the mother is positioned supine with a left lateral tilt to maximize venous return and maximize blood supply to the uterus and placenta. A deep general anesthetic is maintained with halogenated agents to achieve uterine relaxation. Although inhaled agents cross the placenta and may provide sufficient fetal anesthesia, fetal anesthesia is supplemented by an intramuscular dose of narcotic and a paralytic agent to prevent fetal discomfort and breathing during the procedure. Careful mapping by ultrasound of the placental edges is performed and the uterus is opened with the same absorbable stapler used in open fetal surgery to control blood loss during the procedure. A peripheral intravenous line is always established for fluid resuscitation, blood transfusion, and drug administration if necessary. A pulse oximeter should be applied to the exposed fetal hand in order to monitor oxygenation during the procedure, and continuous transthoracic fetal echocardiography provides constant assessment of fetal cardiac function and volume status. Infusion of warmed Lactated Ringer's solution is used to maintain uterine volume and to prevent spasm of the cord vessels, and the fetus is maintained on placental circulation while an airway is established. In cases of giant fetal neck masses, tracheal anatomy may be significantly distorted or compressed, and the carina may be displaced superiorly, yielding a small window through which to establish an airway. Rigid bronchoscopy and/or operative tracheostomy may be sufficient, but in some cases decompression of a cystic mass or partial tumor resection may be required.

Success of this procedure rests upon adequate uterine relaxation to maintain utero-placental blood flow and prevent placental separation. This relaxation can cause bleeding complications postoperatively, and Oxytocin is routinely administered immediately following division of the fetal cord. Maternal risks inherent to this procedure include hemorrhage, scar dehiscence or uterine rupture in a subsequent pregnancy (due often to classical cesarean incision required to avoid the placenta or atraumatically deliver a large tumor), and wound infection. Generally, the fetus is felt to be able to be maintained on placental circulation for around 60 min, though procedures as long as 2.5 h have been performed successfully [68]. Fetal risks of this procedure include bradycardia, hypoxic/anoxic brain injury, hemorrhage and death. These complications may occur due to cord compression, placental abruption, or loss of myometrial relaxation all of which result in inadequate uteroplacental gas exchange. Nevertheless, in competent hands the EXIT procedure has been applied with excellent results and minimal maternal or fetal morbity and is an essential component of the Fetal Treatment Center armamentarium.

14.5 Efficacy and Future of Fetal Surgery

The anomalies discussed in this chapter represent the full spectrum of efficacy in fetal surgery. In some cases, fetal surgery has clearly altered the natural history of the disease and improved outcomes (CPAM, TTTS, MMC). For some lesions there is too limited an experience for definitive statements to be made (SCT). For CDH, fetal intervention remains controversial as interventions have not yet shown benefit and selection of a cohort appropriate for fetal therapy has become increasingly difficult as improvements in postnatal management have increased survival rates even in severely affected fetuses.

Dramatic progress has been made in imaging and diagnosis of fetal anomalies, and technical development continues to allow more minimally invasive forms of therapy. As imaging modalities become more sophisticated, our capabilities for image-guided intervention will move to ever earlier gestational time points. In doing so, preterm labor and premature delivery can likely be decreased, though improvements in tocolysis should be a priority to optimize patient outcomes. In the future, randomized controlled trials must be conducted where appropriate to establish clear benefit to patients, allowing fetal surgery to transition from experimental therapy to standard of care.

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