

Fetal Surgery for Prenatally Diagnosed Malformations

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member’s contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider vesicoamniotic shunting as a treatment of urinary tract obstruction in fetuses under the following conditions to be **eligible for coverage****:

- Evidence of hydronephrosis due to bilateral urinary tract obstruction; AND
- Progressive oligohydramnios; AND
- Adequate renal function; AND
- No other lethal abnormalities or chromosomal defects.

Based on review of available data, the Company may consider open in utero resection of malformed pulmonary tissue or placement of a thoracoamniotic shunt under the following conditions to be **eligible for coverage****:

- Congenital cystic adenomatoid malformation or bronchopulmonary sequestration is identified; AND
- The fetus is at 32 weeks’ gestation or less; AND
- There is evidence of fetal hydrops, placentomegaly, and/or the beginnings of severe preeclampsia (ie, the maternal mirror syndrome) in the mother.

Based on review of available data, the Company may consider in utero removal of sacrococcygeal teratoma under the following conditions to be **eligible for coverage****:

- The fetus is at 32 weeks’ gestation or less; AND
- There is evidence of fetal hydrops, placentomegaly, and/or the beginnings of severe preeclampsia (ie, maternal mirror syndrome) in the mother.

Based on review of available data, the Company may consider in utero repair of myelomeningocele under the following conditions to be **eligible for coverage****:

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- The fetus is at less than 26 weeks' gestation; AND
- Myelomeningocele is present with an upper boundary located between T1 and S1 with evidence of hindbrain herniation.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers in utero repair of myelomeningocele in the following situations to be **investigational**.*

- Fetal anomaly unrelated to myelomeningocele; OR
- Severe fetal kyphosis; OR
- Risk of preterm birth (eg, short cervix less than or equal to 15 mm or previous preterm birth); OR
- Maternal body mass index of 35 or more.

Based on review of available data, the Company considers other applications of fetal surgery, including but not limited to, temporary tracheal occlusion as a treatment of congenital diaphragmatic hernia (CDH) or treatment of congenital heart defects to be **investigational**.*

Policy Guidelines

Amnioreduction and fetoscopic laser therapy as a treatment of twin-twin transfusion are not addressed in this policy.

After 32 weeks of gestation, fetal lung maturity is adequate to permit Cesarean section and management of congenital cystic adenomatoid malformation, bronchopulmonary sequestration, or sacrococcygeal teratoma postnatally.

In utero surgery should be restricted to centers experienced in treating these conditions and staffed by surgeons adequately trained in fetal surgery techniques.

Because of the differing benefits and risks of in utero versus postnatal surgeries, parents should make an informed choice between the procedures.

Background/Overview

Most fetal anatomic malformations are best managed after birth. However, advances in methods of prenatal diagnosis, particularly prenatal ultrasound, have led to a new understanding of the natural history and physiologic outcomes of certain congenital anomalies. Fetal surgery is the logical

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extension of these diagnostic advances, related in part to technical advancement in anesthesia, tocolysis, and hysterotomy.

This policy will pertain to fetal surgery performed for the following clinical conditions.

Fetal Urinary Tract Obstruction

Although few cases of prenatally diagnosed urinary tract obstruction require prenatal intervention, bilateral obstruction can lead to distention of the urinary bladder and is often associated with serious disease such as pulmonary hypoplasia secondary to oligohydramnios. Therefore, fetuses with bilateral obstruction, oligohydramnios, adequate renal function reserve, and no other lethal or chromosomal abnormalities may be candidates for fetal surgery. The most common surgical approach is decompression through percutaneous placement of a shunt or stent. Vesicoamniotic shunting bypasses the obstructed urinary tract, permitting fetal urine to flow into the amniotic space. The goals of shunting are to protect the kidneys from increased pressure in the collecting system and to assure adequate amniotic fluid volume for lung development.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia results from abnormal development of the diaphragm, which permits abdominal viscera to enter the chest, frequently resulting in hypoplasia of the lungs. CDH can vary widely in severity, depending on the size of the hernia and the timing of herniation. For example, late herniation after 25 weeks of gestation may be adequately managed postnatally. In contrast, liver herniation into the chest before 25 weeks of gestation is associated with a poor prognosis, and these fetuses have been considered candidates for fetal surgery. Temporary tracheal occlusion using a balloon is being evaluated for the treatment of CDH. Occluding the trachea of a fetus prevents the normal efflux of fetal lung fluid, which results in a build-up of secretions in the pulmonary tree and increases the size of the lungs, gradually pushing abdominal viscera out of the chest cavity and back into the abdominal cavity. It is believed that this, in turn, will promote better lung maturation. Advances in imaging have resulted in the ability to detect less severe lesions, which has resulted in a decrease in mortality rates for defects detected during pregnancy. Due to these changes over time, concurrent controls are needed to adequately compare pre- and postnatal approaches.

Congenital Cystic Adenomatoid Malformation (Congenital Pulmonary Airway Malformation) or Bronchopulmonary Sequestration

Congenital cystic adenomatoid malformation (CCAM), also referred to as congenital pulmonary airway malformations, and bronchopulmonary sequestration (BPS) are the 2 most common congenital cystic lung lesions and share the characteristic of a segment of lung being replaced by abnormally developing tissue. CCAMs can have connections to the pulmonary tree and contain air, while BPS does not connect to the airway and has blood flow from the aorta rather than the pulmonary circulation. In more severe cases, the malformations can compress adjacent normal lung

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tissue and distort thoracic structure. CCAM lesions typically increase in size in mid-trimester and then in the third trimester either involute or compress the fetal thorax, resulting in hydrops in the infant and sometimes mirror syndrome (a severe form of preeclampsia) in the mother. Mortality is close to 100% when lesions are associated with fetal hydrops (abnormal accumulation of fluid in 2 or more fetal compartments). These patients may be candidates for prenatal surgical resection of a large mass or placement of a thoracoamniotic shunt to decompress the lesion.

Sacrococcygeal Teratoma

Sacrococcygeal teratoma (SCT) is both a neoplasm with autonomous growth and a malformation made up of multiple tissues foreign to the region of origin and lacking organ specificity. It is the most common tumor of the newborn and generally carries a good prognosis in infants born at term. However, in utero fetal mortality approaches 100% with large or vascular tumors, which may become larger than the rest of the fetus. In this small subset, SCT is associated with fetal hydrops, which is related to high output heart failure secondary to arteriovenous shunting. In some cases, mothers of fetuses with hydrops can develop mirror syndrome.

Myelomeningocele

Myelomeningocele is a neural tube defect in which the spinal cord forms abnormally and is left open, exposing the meninges and neural tube to the intrauterine environment. Myelomeningocele is the most common cause of spina bifida, and depending on the location, results in varying degrees of neurologic impairment to the legs and bowel and bladder function, brain malformation (ie, hindbrain herniation), cognitive impairment, and disorders of cerebrospinal fluid circulation, ie, hydrocephalus requiring placement of a ventriculoperitoneal shunt. Traditional treatment consists of surgical repair after term delivery, primarily to prevent infection and further neurologic dysfunction. Fetal surgical repair to cover the exposed spinal canal has been proposed as a means of preventing the deleterious exposure to the intrauterine environment with the hope of improving neurologic function and decreasing the incidence of other problems related to the condition.

Cardiac Malformations

In utero interventions are being investigated for several potentially lethal congenital heart disorders, including critical aortic stenosis with evolving HLHS, HLHS with intact atrial septum, and critical pulmonary stenosis or pulmonary atresia. Critical pulmonary stenosis or atresia with intact ventricular septum is characterized by a very narrow pulmonary valve without a connection between the right and left ventricles. Pulmonary atresia with intact ventricular septum can evolve into right ventricular hypoplasia; fetal pulmonary valvuloplasty may result in biventricular circulation. Critical aortic stenosis with impending HLHS is a very narrow aortic valve that develops early during gestation that may result in HLHS, a complex spectrum of cardiac anomalies characterized by hypoplasia of the left ventricle and aorta, with atretic, stenotic, or hypoplastic atrial and mitral valves. In utero aortic balloon valvuloplasty relieves aortic stenosis with the goal of preserving left ventricular growth and halting the progression to HLHS. HLHS with intact atrial septum is a variant

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of HLHS that occurs in about 22% of all HLHS cases in which blood flow across the foramen ovale is restricted, leading to left atrial hypertension and damage to the pulmonary vasculature, parenchyma, and lymphatics. For HLHS with intact atrial septum, fetal balloon atrial septostomy is designed to reduce the left atrial restriction.

FDA or Other Governmental Regulatory Approval

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The evidence related to the use of fetal surgery is limited by the rarity of the conditions treated and the extremely specialized nature of the procedures, although randomized controlled trials (RCTs) have been conducted for several conditions. The literature related to fetal surgery has been summarized in several systematic reviews. In addition to the 1998 and 1999 TEC Assessments, the Agency for Healthcare Research and Quality (AHRQ) published a technology assessment on fetal surgery in April 2011.

Fetal Urinary Tract Obstruction

Systematic Reviews

The 2011 AHRQ assessment identified 26 publications representing 25 unduplicated reports on fetal interventions for obstructive uropathy. From the 3 prospective cohorts and 8 retrospective cohorts identified, 24 fetuses had placements of shunts, 11 had other treatments for posterior urethral valves, 14 had no fetal intervention, and 13 pregnancies were terminated due to poor prognosis. Overall, 53% to 66% of infants who had shunt placement survived short term. However, more than half of otherwise normal infants who have only isolated bladder outlet tract obstruction and do not have multiple anomalies or syndromes, do not recover normal renal function in childhood, and the majority require dialysis and renal transplantation. In addition, a proportion of affected infants have clusters of syndromic features that are not readily diagnosed prenatally, increasing morbidity among survivors. For example, in a follow-up of 18 male children who had survived prenatal vesicoamniotic shunting (follow-up range, 1-14 years), one-third of the children required dialysis or transplantation, and one-half exhibited respiratory, growth and development, or musculoskeletal abnormalities. In spite of this, parents and physicians reported the children to be neurodevelopmentally normal, with

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most having acceptable renal and bladder function and satisfactory self-reported quality of life. There is a need to better identify appropriate surgical candidates and clarify health outcomes in children who do and do not receive fetal intervention to inform decision making. At the time of the AHRQ assessment, 1 publication described the design of a multicenter randomized trial of percutaneous shunting for lower urinary tract obstruction (PLUTO) that will assess whether intrauterine vesicoamniotic shunting improves pre- and perinatal health outcomes in comparison with conservative, noninterventional care.

Randomized Controlled Trials

Since publication of the 2011 AHRQ assessment, Morris et al published the results of the PLUTO trial. The study was an unblinded RCT that included 31 women with male singleton pregnancies, complicated by an isolated lower urinary tract obstruction, recruited from centers in the United Kingdom, Ireland, and the Netherlands. Inclusion criteria were an ultrasound diagnosis of LUTO (diagnosed on the basis of the visualization of an enlarged bladder and dilated proximal urethra, bilateral or unilateral hydronephrosis, and cystic parenchymal renal disease) about whom the treating physician was uncertain as to the optimum management. Women pregnant with fetuses with other major structural or chromosomal abnormalities were excluded. Women were randomly allocated to either prenatal intervention, consisting of placement of a vesicoamniotic shunt, or control, consisting of usual care. The primary outcome measure was survival to 28 days after birth, with secondary outcomes of survival at 1 and 2 years, and renal function at 28 days, 1 year, and 2 years (measured by serum creatinine, renal ultrasound appearance, and evidence of renal impairment based on need for medical treatment, dialysis, or transplantation). The original planned sample size for the trial of 75 pregnancies in each study group was based on calculations from a meta-analysis reported by the study authors in 2010 and was designed to detect a relative risk of survival with vesicoamniotic shunting of 1.55 with 80% power and an alpha level of 0.05. The study was terminated early due to poor enrollment. Concurrent with the RCT, study authors enrolled eligible subjects who elected not to participate due to either patient or physician preference in an observational registry. There was a high degree of crossover between groups: 3 of 16 women randomized to receive vesicoamniotic shunting did not receive it, and 2 of 15 women randomized to the control group received a vesicoamniotic shunt.

Analyses were conducted on both an intention-to-treat and per-protocol basis. For the study's primary outcome of 28-day survival, there was no significant difference between the groups: of the 16 pregnancies randomly assigned to vesicoamniotic shunting, 8 neonates survived to 28 days, compared with 4 from the 15 pregnancies assigned to the control group (relative risk [RR], 1.88; 95% confidence interval [CI], 0.71 to 4.96; $p=0.27$). Analysis based on treatment received showed a stronger association between shunting and survival (RR=3.2; 95% CI, 1.06 to 9.62; $p=0.03$). The authors conducted a Bayesian analysis, combining data from their trial with elicited priors from experts, and found an 86% probability that vesicoamniotic shunting increased survival at 28 days. Overall, the authors concluded that "survival seemed higher in the fetuses receiving vesicoamniotic

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shunting, but the size and direction of the effect remained uncertain.” While strengths of this study included its randomized controlled design, and tracking of longer (2-year) outcomes, it was limited by its failure to reach enrollment targets and the significant crossover between treatment and control groups. As such, it is difficult to conclude that the lack of significant association between shunting and survival was not due to under powering.

Morris et al reported on secondary outcomes from the PLUTO trial in a complete health technology assessment of the PLUTO trial and the associated registry for patients who elected not to participate in the randomized trial portion. Secondary objectives of the trial included cost-effectiveness of vesicoamniotic shunting compared with conservative management; effect of vesicoamniotic shunting on short-term morbidity; survival and development of chronic renal failure at 1 year of age; identifying prognostic markers of outcome; determining clinicians’ prior beliefs about the effectiveness of vesicoamniotic shunting; and assessing influences on women’s decision making with respect to opting for termination of pregnancy, randomization and the acceptability of the intervention. For the secondary outcomes of the randomized portion of the trial, there were no statistically significant differences in mortality from 28 days to 1 year, although the point estimate for the RR was in the direction of benefit (RR=2.19; 95% CI, 0.69 to 6.94). Of those babies who survived to 1 year, 2 had no evidence of renal impairment (vesicoamniotic shunt arm), while 4 in the vesicoamniotic shunt arm and 2 in the conservative arm required medical management for renal impairment. One baby in the conservative arm had end-stage renal failure at 1 year.

Forty-five women were entered into the concurrent registry; of those, 78% had conservative management. Women who were in the registry cohort differed from those randomized: registry patients who had conservative management were more likely to have a normal (>5th percentile) amniotic fluid volume at diagnosis than those who received vesicoamniotic shunting (p=0.07) or randomized (p=0.05). Women in the registry arm were more likely to be diagnosed at 24 or more weeks among these women than among those in the randomized group (p=0.003).

Section Summary

For fetal vesicoamniotic shunting as a therapy for bilateral urinary tract obstruction, evidence from retrospective and prospective cohort studies summarized in the 2011 AHRQ technology assessment on fetal surgery suggests that vesicoamniotic shunting improves survival, at least in the short term. A subsequent small RCT found limited benefit from the procedure; however, the study’s limitations make it difficult to confidently conclude that vesicoamniotic shunting is associated with no clinical benefit.

Congenital Diaphragmatic Hernia

Tracheal Obstruction for Congenital Diaphragmatic Hernia

In 1999, the TEC Assessment concluded that temporary tracheal obstruction met the TEC criteria as a treatment of CDH, based in part on a case series. However, in 2003, Harrison et al, the same authors

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who reported on the original case series, reported the results of a randomized trial of fetoscopic tracheal occlusion compared with standard postnatal care. Enrollment was stopped at 24 women due to the unexpectedly high 90-day infant survival rate with standard care, and thus the safety monitoring board concluded that further recruitment would not result in a significant difference between the groups. In addition, the fetal surgery group had higher rates of prematurity and lower birth weights. The survival rate in the standard treatment group was 73%, considerably higher than the estimated survival rate of 37% based on historical controls. The survival of infants with a lung-to-head ratio (LHR) greater than 1.0 was 100% in both groups. In contrast, in other publications, survival has been reported to be approximately 10% for children with isolated CDH who have left-sided lesions, liver herniation, and an LHR of less than 1.0 during mid-gestation. In this subgroup, temporary placement of a detachable balloon to occlude the trachea was reported to result in a survival rate of 55% (35 cases), compared with 8% survival in a group of contemporary controls treated by postnatal therapy. Based on the results of the Harrison et al randomized trial, the policy statement was revised to indicate that tracheal occlusion is considered investigational.

More recent evidence for tracheal obstruction for CDH includes a 2011 AHRQ technology assessment which identified 25 publications with 21 unduplicated populations from 10 U.S. sites, 9 European sites, 3 multinational sites, and 5 other countries, for a total of 335 cases. The single RCT was by Harrison et al (previously described), with follow-up reported by Cortes et al in 2005. Growth failure occurred in 56% of controls and 86% of infants who had occlusion. No neurodevelopmental differences were observed between groups with follow-up at 1 or 2 years of age. This randomized study reinforces the importance of a concomitant control group, as the survival for CDH with postnatal repair also improved over time. Also noted were results of the Fetal Endoscopic Tracheal Occlusion (FETO) Task Group in Europe, which is using a control group of 86 fetuses with left-sided CDH and liver herniation, managed expectantly and live born after 30 weeks of gestation. In this control group, the survival rate increased from 0% for LHR of 0.4 to 0.7 to approximately 15% survival for LHR of 0.8 to 0.9, 65% for LHR of 1.0 to 1.5, and 83% survival for LHR of 1.6 or more. This ongoing series currently has an 11% survival for LHR less than 1, which can be used as a reference value for Europe, but not for the United States.

Since publication of the AHRQ assessment, several studies have been published that address fetal endoscopic tracheal occlusion in CDH. In 2011, Ruano et al published a small nonrandomized controlled study to evaluate the feasibility of percutaneous fetal endoscopic tracheal occlusion with a 1-mm fetoscope. Thirty-five women were enrolled from 2006 to 2008, of whom 17 were intended for fetal intervention and 16 underwent successful fetal tracheal occlusion. Nine of 17 (52.9%) of fetal intervention infants and 1 of 18 (5.6%) of control group infants survived to 28 days, and the authors concluded the intervention was feasible.

In a subsequent study reported in 2012, Ruano et al reported a small randomized trial that compared percutaneous FETO with postnatal management in 41 patients whose fetuses had severe CDH (LHR

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<1.0 and at least one-third of the fetal liver herniated into the thoracic cavity). All fetuses in the FETO group were delivered by ex-utero intrapartum therapy to remove the tracheal balloon; controls were delivered by Cesarean section at a maximum gestational age of 38 weeks. The primary outcome, survival to 6 months of age by intention-to-treat analysis, was 50% (10/20) in the fetal surgery group and 4.8% (1/21) in controls (RR=10.5). Mean delivery was about 2 weeks earlier in the fetal surgery group compared with controls (35.6 weeks vs 37.4). There was a trend for a higher frequency of premature delivery (<37 weeks, 50% FETO vs 28.6% controls) and extreme premature delivery (<32 weeks, 15% FETO and 0% controls) in the FETO group. For the 10 survivors in the FETO group, the mean age at hospital discharge was 34.7 days.

In 2014, Rocha et al published a retrospective case-control study to compare left heart structure size in patients with CDH who underwent fetal endoscopic tracheal occlusion with those managed conservatively. Based on observational data that infants born with CDH have small left heart structures, possibly due to direct compression by herniated abdominal organs and/or abnormal orientation of the inferior vena cava and foramen ovale, the authors postulated that increased lung size associated with fetal endoscopic tracheal occlusion may lead to increased left heart structure size in patients with CDH. The study included 9 cases with left-sided CHD and an LHR of 1 or less who underwent fetal endoscopic tracheal occlusion who were compared with 25 similar controls who did not undergo fetal intervention. Mortality did not differ significantly between groups (67% in the fetal intervention group vs 52% in the control group, $p=NS$). At birth, the intervention group had larger left ventricular (LV) end-diastolic volume (indexed to body surface area) (16.8 vs 12.76 mL/m², $p<0.05$), LV length z score (-2.05 vs -4, $p<0.01$), LV:right ventricular (RV) length ratio (1.43 vs 1.04, $p<0.05$), left pulmonary artery diameter z score (+1.71 vs -1.04, $p<0.05$), and better growth of the aortic valve (-2.18 vs -3.3, $p<0.01$). The authors note that fetal endoscopic tracheal occlusion may have benefits in postnatal cardiac output and pulmonary hypertension but that the potential benefits of fetal treatment for CDH are still currently under investigation in several trials and must be weighed against the risks of prematurity and risk to the mother.

In 2014, Shan et al published a systematic review and meta-analysis of RCTs evaluating fetal endoscopic tracheal occlusion for CDH. The authors included 3 studies identified as RCTs, including Harrison et al (2003), Ruano et al (2011), and Ruano et al (2012). In pooled analysis, patients treated with fetal endoscopic tracheal occlusion had higher survival rates than patients treated with standard therapy: 27/48 vs 12/52 (OR for survival with fetal treatment, 5.95; 95% CI, 2.11 to 16.78; $p<0.000$). Patients treated with fetal endoscopic tracheal occlusion had an earlier average gestational age at delivery than patients treated with standard therapy (mean difference, -3.43 weeks; 95% CI, -6.82 to -0.04; $p<0.05$). However, the pooled estimates are difficult to interpret in that 1 study categorized by the authors as an RCT was a controlled but nonrandomized study (Ruano et al [2011]).

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Section Summary

Although early (before 2003) noncomparative studies suggested benefit from fetal endoscopic tracheal occlusion for the treatment of CDH, the most direct evidence related to the effectiveness of this procedure comes from 2 RCTs from 2003 and 2012 which report conflicting findings. The 2012 RCT demonstrated promising findings of improved survival at 6 months post delivery in patients treated with fetal endoscopic tracheal occlusion. However, given the inconclusive results in the randomized trial by Harrison et al, additional study is needed to determine the survival benefit with greater certainty. Longer follow-up is also needed to evaluate morbidity (eg, neurologic and pulmonary outcomes) in survivors.

Congenital Cystic Adenomatoid Malformation (Congenital Pulmonary Airway Malformation) or Bronchopulmonary Sequestration

The 2011 AHRQ assessment identified 17 publications describing 6 distinct cohorts and 4 case series from 7 academic centers in the United States, South America, Europe, and Asia. Of approximately 401 infants believed to have congenital cystic adenomatoid malformations (CCAMs), 54 had thoracoamniotic shunting and 3 had open procedures, with the goal of decompressing the lung lesion. An additional 13 fetuses with BPS were described. In the cohorts, 44% to 100% of infants who had thoracoamniotic shunts survived to birth or through neonatal hospitalization; there was an overall survival rate of 54% in the literature. For fetuses with hydrops, survival was 20% to 30% following surgical treatment compared with 5.7% for untreated hydrops. Because some infants with large CCAMs respond to in utero medical treatment with steroids, failure to respond to steroids may be an entry criterion for future surgical interventions.

In 2014, White et al reported outcomes after the use of a transabdominal, transuterine percutaneous thoracoabdominal shunt creation technique in 5 fetuses with nonimmune hydrops due to fetal thoracic abnormalities. The study was a retrospective review of fetal thoracic abnormality cases treated with percutaneous shunt creation by a combination of interventional radiology and maternal-fetal medicine team at a single institution from 2007 to 2012. Eligible fetuses had to have a thoracic abnormality, no infection, an absence of lethal genetic abnormalities, and have a normal karyotype. All fetuses with type I congenital pulmonary airway malformation (CPAM) received betamethasone to attempt to decrease the CPAM size. Seven shunts were placed in 5 patients. There was 1 case of fetal distress requiring induction of labor at 31 weeks, 2 days gestation. After delivery, all of the shunts were in place in the thoracic cavity. Three of the infants underwent uncomplicated surgical resection of type I CPAMs and were discharged home. Two infants with chylothoraces had bilateral chest tubes placed after delivery and were discharged home after the chylothoraces resolved.

Sacroccygeal Teratoma

At the time of the 1999 TEC Assessment, the published literature included only 4 cases of fetal surgery for SCT. However, in utero surgery resulted in prenatal resolution of hydrops, healthy long-term survival, and normal development in some children. These results were impressive given the

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near-certain fetal mortality when fetal hydrops is left untreated. For example, in a 2004 report of 4 cases of open surgical resection of SCT, Hedrick et al reported 1 neonatal death and 3 survivals with a follow-up range of 20 months to 6 years. Complications other than the fetal death included 1 embolic event, 1 chronic lung disease, and 1 tumor recurrence. The 2011 AHRQ assessment identified a total of 7 retrospective cohorts and case series from 3 academic fetal surgery groups in the United States and the United Kingdom. The 17 fetuses reported to be treated with open surgery were compared with 94 cases with other interventions or no intervention; however, the expectant management cases were less severe. Other ablation methods included alcohol sclerosis (all 3 cases died), radiofrequency ablation (RFA) (4/7 survived), and laser ablation (all 4 died). For open surgical procedures, the survival rates were 33% to 75%. All fetal and neonatal deaths occurred among patients with hydrops or with prodromal cardiovascular changes concerning for developing hydrops. Challenges in this area are the early and reliable detection of development of hydrops and the timing of the fetal intervention.

In 2014, Van Mieghem et al reported a case series of 5 fetuses with SCT treated with fetal interventions, along with a systematic review on fetal therapies for solid SCTs. Cases included in the case series were women presenting between 17 5/7 and 26 4/7 weeks of gestation with fetuses found to have large SCT with evidence of fetal heart failure. Treatment was conducted with fetoscopic laser ablation (n=1), RFA (n=2), or interstitial laser ablation with or without vascular coiling (n=2). Two intrauterine fetal deaths occurred; the remaining 3 cases resulted in preterm labor within 10 days of surgery. Of those surviving to delivery, 1 death occurred and 2 infants survived without procedure-related complications but with complications of prematurity. In the authors' literature review, 21 case reports, case series, and cohort studies were identified, which were generally assessed to be of poor to fair quality. Twenty-nine cases of minimally invasive procedures, with embolization of the SCT vasculature by a variety of therapies, for fetal SCT treatment were identified, which were associated with an overall survival rate of 44%. Twelve cases of open fetal surgery for SCT were identified, with survival of 55%. The authors note that, in the absence of treatment, fetal mortality with large fetal vascular SCTs approaches 100%, providing a rationale for fetal intervention.

Myelomeningocele

Systematic Reviews

As outlined in the 2011 AHRQ assessment, more than 200 fetuses with myelomeningocele have undergone open surgical repair in the United States. All of the 25 reports on open surgery that were identified in the AHRQ assessment were based on 4 series of patients from 4 academic medical centers in the United States. Two of the studies had concurrent comparisons. One of these analyzed the first 29 cases of open myelomeningocele repair at Vanderbilt University Medical Center, finding significant reductions in the need for postnatal shunt placement (51% vs 91%) and reduced hindbrain herniation (38% vs 95%). However, both prospective studies found that in utero repair was

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associated with greater rates of oligohydramnios (48% vs 4%), lower gestational ages (33 vs 37 weeks), and no difference in lower extremity function.

Randomized Controlled Trials

In 2011, results of the National Institutes of Health–sponsored RCTs, the Management of Myelomeningocele Study (MOMS) comparing prenatal repair with standard postnatal repair were published. The trial began in 2003 and was expected to enroll 200 women ages 18 years or older who were pregnant with fetuses with myelomeningocele. Women assigned to have prenatal surgery were scheduled for surgery within 1 to 3 days after they were randomized and stayed near the MOMS center until they delivered by Cesarean section. Women in the postnatal group traveled back to their assigned MOMS center to deliver, also by Cesarean section, around the 37th week of their pregnancies. Follow-up on the children was scheduled to be performed at 1 year and 2.5 years of age to evaluate motor function, developmental progress, and bladder, kidney, and brain development. There was a voluntary moratorium in the United States on conducting in utero repair of myelomeningocele outside of this trial.

The inclusion criteria for MOMS included singleton pregnancy, myelomeningocele with the upper boundary located between T1 and S1, evidence of hindbrain herniation, gestational age of 19.0 to 25.9 weeks at randomization, normal karyotype, U.S. residency, and maternal age at least 18 years. Major exclusion criteria were fetal anomaly unrelated to myelomeningocele, severe kyphosis, risk of preterm birth, placental abruption, body mass index (BMI) of 35 or greater, contradiction to surgery including previous hysterotomy in the active uterine segment. Surgeons had performed at least 15 cases before this randomized study. Primary outcomes were a composite of fetal or neonatal death or the need for a cerebrospinal fluid shunt (shunt placement or meeting criteria for shunt) at 12 months and a composite score of the Mental Development Index of the Bayley Scales of Infant Development II and the child's motor function at 30 months adjusted by level of lesion. Secondary outcomes were surgical and pregnancy complications and neonatal morbidity and mortality. Women were randomized to treatment group in 1:1 ratio.

Recruitment for the trial, planned to include 200 subjects, was stopped at 183 subjects when a clear advantage of prenatal intervention was apparent. The report includes 158 women randomized before July 1, 2009. Outcomes up to 30 months are based on 138 women randomized before December 1, 2007. Groups were similar other than that there were more female fetuses and the lesion level was more severe in the prenatal surgery group. Two perinatal deaths occurred in each treatment group. Both deaths in the prenatal surgery group occurred on the fifth postoperative day, a still birth at 26 weeks and a neonatal death due to prematurity at 23 weeks of gestation. Two neonates in the postnatal surgery group died with severe symptoms of the Chiari II malformation. Fetal or neonatal death or the need for shunt occurred in 68% of infants in the prenatal-surgery group and in 98% of the postnatal-surgery group (RR=0.70; 97.7% CI, 0.58 to 0.84; p<0.001). Shunts were placed in 40% of the prenatal surgery and in 82% of postnatal-surgery groups (p<0.001). At 12 months, 4% of

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infants in the prenatal surgery group had no evidence of hindbrain herniation versus 36% in the postnatal surgery group. There was 1 death in each group between 12 and 30 months (coxsackie septicemia in a child who received prenatal surgery and complications of chemotherapy for choroid plexus carcinoma in a child who received postnatal surgery). The composite of score of Bayley Scales and motor function adjusted by lesion level at 30 months was significantly better in the prenatal surgery group: mean (SD), 148.6 (57.5) in the prenatal surgery group (n=64) versus mean 122.6 (57.2) in the postnatal surgery group (n=70) (p=0.007).

Maternal morbidity and complications related to prenatal surgery included oligohydramnios, chorioamniotic separation, placental abruption, and spontaneous membrane rupture. At delivery, an area of dehiscence or a very thin prenatal uterine surgery scar was seen at delivery in one-third of mothers who had prenatal fetal surgery (all subsequent pregnancies should be delivered by Cesarean section before the onset of labor). The average gestational age of babies in the prenatal surgery group was 34.1 weeks, and 13% were delivered before 30 weeks of gestation. One-fifth of infants in the prenatal surgery group had evidence of respiratory distress syndrome, which was likely related to prematurity. The authors observed that “in the case of infants with low lumbar and sacral sessions, in whom less impairment in lower-limb function may be predicted, the normalization of hindbrain position and the minimization of the need for postnatal placement of cerebral spinal shunt may be the primary indication for surgery.” They caution that the potential benefits of fetal surgery must be balanced against the risks of premature delivery and maternal morbidity and that continued assessment is required to learn if early benefits of prenatal surgery are sustained and the effects of fetal surgery on bowel and bladder continence, sexual function, and mental capacity. They warn that results of this trial should not be generalized to centers with less experience or to patients who do not meet eligibility criteria.

Uncontrolled Series

A 2004 report by Bruner et al described minimum 12-month follow-up of 116 fetuses after intrauterine repair of spina bifida (myelomeningocele or myeloschisis). Sixty-one fetuses (54%) required ventriculoperitoneal shunt placement for hydrocephalus. Statistical analysis revealed that fetuses were less likely to require ventriculoperitoneal shunt placement when surgery was performed at 25 weeks or earlier, when ventricular size was less than 14 mm at the time of surgery, and when the defects were located at L4 or below. Johnson et al reported on the results of a series of 50 fetuses who underwent open fetal closure of a myelomeningocele between 20 and 24 weeks of gestation. Fetal selection criteria included the presence of hindbrain herniation and sonographic evidence of intact neurologic function, ie, movement of the lower extremities and absence of clubfoot deformities. Perinatal survival was 94%, with a mean age at delivery of 34 weeks. All fetuses demonstrated reversal of hindbrain herniation; 43% required ventriculoperitoneal shunting compared with 68% to 100% in historical controls, depending on the location of the myelomeningocele. Another study reporting leg function at longer follow-up showed no difference between patients treated with fetal surgery at 20 to 28 weeks versus traditional surgery.

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In 3 papers, investigators at the University of Pennsylvania reported outcomes of myelomeningocele repair in 54 patients treated before the voluntary moratorium. At median follow-up of 66 months (range, 36-113 months), 37 of 54 (69%) walk independently, 13 of 54 (24%) are assisted walkers, and 4 of 54 (7%) are wheelchair dependent. The strongest factors predicting a lower likelihood to walk independently were higher level lesion (>L4) and the development of clubfoot deformity after fetal intervention. Most independent ambulators, and all children who require assistive devices to walk, experience significant deficits in lower-extremity coordination. Thirty children returned at 5 years of age for neurocognitive examination. In this highly selected group, most children had average preschool neurodevelopmental scores, and children who did not require shunt placement were more likely to have better scores. A survey of 48 families focused on hindbrain herniation (HH)–associated brainstem dysfunction, eg, apnea, neurogenic dysphagia, gastroesophageal reflux disease, neuro-ophthalmologic disturbances. Half of the children required shunting. At a median age of 72 months, 15 nonshunted and 10 shunted children were free of HH symptoms. There were no HH-related deaths, and no children developed severe persistent cyanotic apnea. Most children had no or only mild brainstem dysfunction. The authors conclude that reversal of HH after fetal surgery may help reduce the incidence and severity of brainstem dysfunction.

Investigators at a German center performed a retrospective analysis of expectantly managed patients who received surgical intervention within 2 days of birth at their institution and compared them with reports of outcomes after fetal surgery from other centers including those previously discussed and to data from historical controls. Patients were born between 1979 and 2009 and are now a mean (SD) of 13.3 (8.9) years old. Gestational age at birth in the expectantly managed group was 37.8 weeks, significantly higher than in the prenatal surgery patients. In the expectantly managed group, shunt placement was required in 69.8% at mean (SD) age of 16.0 (10.7) days, which is less than for historical controls and comparable with data reported on patients who received fetal surgery. The authors suggest that inconsistency in clinical criteria for shunting used in studies might contribute to differences in this outcome. Among their expectantly managed patients, 56.4% were assisted walkers and 64.1% attended regular classes, both comparable with historical controls. Noting the discrepancy in the rate of assisted walkers and wheelchair users between expectantly managed patients/historical controls and patients who received surgery, the authors observe that the mean age of the study population was 21.7 years for historical controls, 13.3 years for their population, and only 67.0 months after fetal surgery. They cite earlier papers reporting mobility decreases from early childhood to the early teens including one reporting that “the percentage of patients ambulating the majority of time decreased from 76% at 0-5 years to 46% at 20-25 years, with a flattening beyond 10 years.”

Following publication of the MOMS results, Moldenhauer et al published outcomes for a cohort of patients treated at single institution with fetal myelomeningocele repair from 2011 to 2014. A total of 587 patients were referred for potential fetal myelomeningocele repair during the study period, of which 348 (59.3%) underwent on-site evaluations and 209 (35.6%) were excluded due to

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noncandidacy for the procedure (BMI >35, additional fetal anomalies, genetic diagnosis in the fetus, gestational age >26 weeks, preexisting maternal medical condition, multiple pregnancy, and no HH on magnetic resonance imaging). A total of 139 (23.7%) patients were considered potential candidates for fetal myelomeningocele repair, of which 101 underwent open fetal surgery, 13 had postnatal management, and 25 underwent pregnancy termination. The average gestational age at the time of fetal surgery was 23.4 weeks. Fetal resuscitation (need for intraoperative cardiac compressions and/or administration of atropine, epinephrine, or blood products via the umbilical vein) was successfully performed in 5 cases. Preterm premature rupture of membranes (PPROM) occurred in 31 of 96 (32.3%), and preterm labor occurred in 36 of 96 (37.5%). Sixteen patients had PPRM with preterm labor. The perinatal loss rate was 6.1% (6/98), which included 2 intrauterine demises, 1 diagnosed at the conclusion of fetal myelomeningocele repair and 1 on postoperative day 1, and 4 neonatal deaths. Maternal complications included clinical chorioamnionitis (n=4), persistent oligohydramnios (n=6), pre-eclampsia/gestational hypertension (n=1), and placental abruption (n=2). For the 83 patients who were live born at the authors' institution, HH was reversed in 71.1%, and the functional level improved compared with prenatal sonographic bony lesion level in 44 of 80 (55%) neonates who were assessed. The authors conclude that their experience with fetal myelomeningocele repair was similar to that reported in the MOMS trial.

Bennett et al compared outcomes for a cohort of patients treated with fetal myelomeningocele repair in the post-MOMS era with those treated at the same institution during MOMS. Outcomes were evaluated for 43 patients treated with fetal myelomeningocele repair from 2011 to 2013 and compared with those for 78 patients treated as part of MOMS. During the study time period, the repair technique was modified so that no uterine trocar was used, and uterine entry, manipulation, and closure were modified to reduce amniotic membrane separation. Although the mean gestational age at delivery was similar for the post-MOMS and the MOMS cohort (34.4 weeks vs 34.1 weeks, respectively), a greater proportion of post-MOMS cohort subjects were born after 37 weeks of gestation (39% vs 21%, p=0.03). Post-MOMS cohort subjects had lower incidences of premature rupture of membranes (22% vs 46%, p=0.011) and chorioamnion separation (0% vs 26%, p<0.001). These results suggest that fetal myelomeningocele repair outcomes in practice can be comparable with or better than those obtained in the MOMS study.

Section Summary

The most direct evidence related to fetal myelomeningocele repair comes from an RCT, the MOMS study, which demonstrated significant benefits across multiple outcomes for fetal repair. Single-arm studies have supported these findings. Therefore, fetal myelomeningocele may be considered medically necessary following informed decision making for cases that meet the criteria of the MOMS study.

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Cardiac Malformations

The 2011 AHRQ technology assessment included the following evidence on fetal surgery for cardiac malformations:

- Two case series (n=10) were identified on fetal surgery for pulmonary atresia and intact ventricular septum. The literature was described as scant, reflecting the early formative period of development of procedures for this rare condition.
- Eight prospective case series (n=90) were identified on balloon dilation for critical aortic stenosis. One center in the United Kingdom, 2 centers in Germany, 2 in Brazil, and 1 in the United States performed this procedure. Seventy patients are from Boston. The 2011 technology assessment concluded that it is difficult to determine whether the procedure changes long-term outcomes, since it appears to increase the risk of fetal loss but potentially prevents neonatal deaths. However, it did appear that technical success improves over time within a dedicated team and center. For example, the North American center improved their success rate from 25% to 90% over a period of several years. Overall, the literature was considered to be very early in development.
- Three case series from 1 U.S. institution with a cumulative total of 24 patients were identified on creation in utero of an atrial septal defect for an intact atrial septum. There were no reports of this procedure being performed outside of the United States. The procedure appears to have technical success; however, mortality remains high, and no controlled trials were available to compare outcomes in patients treated prenatally with those treated postnatally.

The AHRQ report concluded that overall, procedures for severe fetal cardiac anomalies are in an early stage. Preliminary work is being reported in a few highly specialized centers that are establishing the groundwork for feasibility and future directions for outcomes research in this area. The authors concluded that the most pressing challenge in this area is the ability to identify the “right” patient whose care would be compromised by waiting to do a postnatal repair.

McElhinney et al analyzed their experience with 70 prenatal balloon aortic valvuloplasties attempted in mid-gestational fetuses between March 2000 and October 2008 for critical aortic stenosis with evolving hypoplastic left heart syndrome (HLHS) to identify factors associated with procedural and postnatal outcomes. Median gestational age was 23.2 weeks (range, 20-31 weeks). Technical success was achieved in 52 fetuses. Compared with 21 untreated comparison fetuses, subsequent prenatal growth of the aortic and mitral valves, but not the left ventricle, was improved after intervention. Nine pregnancies did not reach viable term or preterm birth. Seventeen patients had a biventricular circulation postnatally, 15 of them from birth. Two of these patients had no neonatal intervention. Sixteen were alive at a median age of 2.1 years (range, 4 months to 7 years). The other patient died of unrelated causes. Guidelines for assessing the potential for a biventricular circulation changed over the period of the study and became more selective. Larger left heart structures and higher LV pressure at the time of intervention were associated with biventricular outcome. The authors conclude that further investigation is required before it is possible to predict whether fetal

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intervention will result in improved left heart growth and postnatal survival with a biventricular circulation, and “the potential benefits of fetal intervention must be weighed against the risk of technical failure, fetal demise, aortic regurgitation, and potential long-term adverse events that have yet to be identified.”

In 2013, Marantz et al reported results from a case series of 5 prenatal balloon aortic valvuloplasties for fetuses with aortic stenosis and risk of progression to HLHS. The procedure was technically successful in all cases with no maternal complications or fetal demise. One pregnancy was terminated after the procedure; of the remaining cases, 1 progressed to hypoplastic left heart syndrome and 3 did not. Rates of longer term survival and complications are not provided. The authors conclude that fetal aortic valvuloplasty is safe and feasible.

Pedra et al reported a case series of 22 fetal cardiac interventions for several cardiac conditions in 21 fetuses in Brazil. Fetal cardiac intervention was considered for the following echocardiographic findings in patients with isolated cardiac defects (ie, no other structural abnormality or marker for chromosomal abnormality): (1) critical aortic stenosis with evolving HLHS (n=9); (2) critical aortic stenosis, massive mitral regurgitation, giant left atrium, and hydrops (n=4); (3) HLHS with intact interatrial septum or small patent foramen ovale (n=4); (4) pulmonary atresia with intact ventricular septum or critical pulmonary stenosis with impending hypoplastic right heart syndrome (HRHS) (n=4). Fetal interventions included atrial septostomy, aortic valvuloplasty, pulmonary valvuloplasty, or a combination of aortic septostomy and aortic valvuloplasty in 1 case. Technical success was achieved in 20 of 22 procedures (91%), with 1 failed aortic and 1 failed pulmonary valvuloplasty. There was 1 fetal death, and no maternal complications. Longer term outcomes were generally poor, even among those with successful interventions. Among the 20 with successful fetal interventions, 8 eventually achieved biventricular circulation, with 1 “probable” biventricular circulation, and 12 deaths occurred.

Chaturvedi et al reported outcomes from a series of 10 fetuses who underwent active perinatal management for HLHS with restrictive or intact atrial septum at a single institution from 2000 to 2012. Four of the identified fetuses underwent percutaneous stenting of the atrial septum. No maternal complications occurred. At follow-up, 2 children were alive at 16 and 20 months. Two neonatal deaths occurred in fetuses with the highest left atrial hypertension before intervention and recurrence in utero of left atrial hypertension secondary to stent stenosis.

Kalish et al reported outcomes for 9 fetuses with HLHS with intact atrial septum who underwent prenatal atrial septal stent placement. Atrial septal stent placement was attempted in 9 fetuses, with successful stent deployment in 5, of which 4 demonstrated flow across the stent at the time of intervention. In the remaining 4 cases, stent placement was technically unsuccessful, but in 75% of cases, atrial balloon septoplasty during the same procedure was successful. One fetal death occurred,

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along with 4 neonatal deaths, 2 of which had undergone stenting. No maternal complications were reported.

Section Summary

Evidence related to fetal interventions for congenital heart defects—particularly for evolving HLHS and critical pulmonary stenosis/pulmonary atresia—is limited to small case series. Although postnatal repair/correction of these severe cardiac defects is associated with very high morbidity and mortality, further studies are needed to demonstrate that health outcomes are improved with fetal interventions. Randomized trials are unlikely to be conducted, but comparative studies with concurrent controls would provide further insight into the net benefit of and appropriate patient populations for fetal cardiac interventions.

Other

The use of fetal surgery for other defects is expanding; recent case reports include prenatal correction of cleft lip and palate and decompression of the fetal trachea.

A review of 187 maternal-fetal surgeries performed at the University of California San Francisco Fetal Treatment Center found significant short-term maternal morbidity but no maternal deaths. Postsurgical complications included increased rates of Cesarean birth, treatment in intensive care, prolonged hospitalization, and blood transfusion.

No new studies of fetal surgery for other applications were identified in the 2011 literature update.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov on October 27, 2013, identified several ongoing trials of various fetal surgeries. Most of the surgical procedures are in the early stages of evaluation.

For Lower Urinary Tract Obstruction

- Fetal Cystoscopy Versus Vesico-amniotic Shunting in Severe Lower Urinary Tract Obstructions (CYSTUO) (NCT01552824). This is a phase 2, randomized, unblinded trial to assess whether vesicoamniotic shunting improves outcomes compared with fetal cystoscopy for severe lower urinary tract obstructions. The primary outcome measures are perinatal survival rate and neonatal renal function. Estimated study enrollment is 60 patients and study completion date is listed as May 2015, with follow up to July 2017.

For CDH

- Early FETO for Severe Congenital Diaphragmatic Hernia (NCT01731509). This is a phase 2, randomized, open-label, interventional trial to assess whether early fetal endoscopic tracheal occlusion improves outcomes compared with standard FETO at 26 0/7 weeks to 28 6/7 weeks of gestation. The primary outcome measures are neonatal (30-day) survival rate

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and infant (6-month) survival rate. The estimated study enrollment is 70 patients; the estimated study completion date is listed as December 2016.

- Tracheal Occlusion to Accelerate Lung Growth (TOTAL) Trial for Severe Pulmonary Hypoplasia (NCT01240057). This is a randomized, open label trial to compare fetal endoluminal tracheal occlusion with watchful waiting during pregnancy for the management of left-sided and isolated CDH and severe pulmonary hypoplasia. The primary outcome measure is survival at discharge from neonatal intensive care unit. Enrollment is planned for 148 subjects; the estimated primary study completion date is October 2015, with follow-up through October 2017.
- Fetoscopic Tracheal Balloon Occlusion in Left Diaphragmatic Hernia (NCT00373438). This is a phase 2, randomized, open-label trial to evaluate the effect of fetoscopic tracheal occlusion for the management of left-sided CDH on postnatal extracorporeal membrane oxygenation (ECMO) use. The primary outcome measure is need for postnatal ECMO therapy. Enrollment is planned for 98 subjects; the estimated study completion date was listed as July 2014, but the study status has not been verified since 2009.
- Percutaneous Endoscopic Tracheal Plug/Unplug for CDH (NCT00768703). This is a single-arm, interventional trial to evaluate the safety and efficacy of the Goldvalve balloon for percutaneous temporary tracheal occlusion in severe CDH. The primary outcome measure is fetal lung growth due to successful fetal tracheal occlusion/unocclusion. Enrollment is planned for 10 subjects; the estimated study completion date is September 2015, with follow-up through December 2017.
- Fetal Tracheal Balloon Study in Diaphragmatic Hernia (NCT00966823). This is a single-arm, interventional trial to evaluate the safety and efficacy of detachable endotracheal balloon placement in fetuses with CDH. The primary outcome measure is survival at birth. Enrollment is planned for 15 subjects; the estimated study completion date is January 2015.
- Fetal Endotracheal Occlusion (FETO) in Severe Congenital Diaphragmatic Hernia (NCT00881660). This is a single-arm, interventional trial to evaluate fetal endotracheal occlusion with the Goldvalve Detachable Balloon for treatment of fetuses with severe CDH. The primary outcome measure is feasibility. Enrollment is planned for 15 subjects; the estimated primary study completion date is May 2016, with follow-up through December 2021.

For Myelomeningocele

- Prenatal Surgical Repair of Myelomeningocele PRIUM (NCT 01983345). This is a nonrandomized, open-label, interventional trial to compare open surgical repair of myelomeningocele in the fetus before 26 weeks of gestation to standard care. The primary outcome measure is presence of Arnold-Chiari malformation at birth. Estimated study enrollment is 50 patients; the planned study completion date is September 2019.
- Fetoscopic Meningomyelocele Repair Study (fMMC) (NCT02230072). This is a phase 1, nonrandomized study to evaluate a minimally invasive technique for fetal myelomeningocele

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repair. The primary outcome measure is feasibility. Enrollment is planned for 15 subjects; the estimated primary study completion date is July 2016, with follow-up through January 2021.

For Evolving Hypoplastic Left Heart Syndrome

- Fetal Intervention for Aortic Stenosis and Evolving Hypoplastic Left Heart Syndrome (NCT01736956). This is a phase 1 and phase 2 nonrandomized safety/efficacy study to assess whether fetal balloon aortic valvuloplasty compared with standard care for evolving HLH is associated with improved fetal mitral and LV growth. The primary outcome measure is improved fetal mitral valve and left ventricular growth. Estimated study enrollment is 30 patients and study completion date is listed as October 2017.

Summary of Evidence

Due to a number of factors, including the rarity of the conditions and the small number of centers specializing in fetal interventions, the evidence on fetal surgery is limited. Fetal surgery for many congenital conditions, including CDH and heart defects, has not been shown to improve health outcomes in comparison with postnatal treatment. The available evidence is insufficient to demonstrate that fetal tracheal occlusion for CDH and fetal intervention for evolving HLHS and critical pulmonary stenosis or pulmonary atresia provides improved health outcomes. For these and other applications of fetal surgery that are currently considered investigational, additional studies are needed to identify appropriate candidates and to evaluate longer term outcomes compared with postnatal management.

For conditions leading to fetal hydrops (certain cases of congenital cystic adenomatoid malformation, bronchopulmonary sequestration, sacrococcygeal teratoma), for which mortality approaches 100%, fetal surgery may be considered medically necessary. For bilateral urinary tract obstruction, evidence from retrospective and prospective cohort studies summarized in the 2011 Agency for Healthcare Research and Quality technology assessment on fetal surgery suggests that vesicoamniotic shunting improves survival, at least in the short term. A recent small, randomized controlled trial evaluating the use of vesicoamniotic shunting found limited benefit from the procedure when data were analyzed by intention-to-treat analysis. However, the study's significant limitations, including low enrollment leading to early cessation of the study and significant crossover between treatment and control groups, make it difficult to generalize its finding of no significant benefit from treatment. As such, vesicoamniotic shunting for bilateral urinary tract obstruction may also be considered medically necessary to minimize the effects of this condition on kidney and lung development. Additional studies for these surgeries are needed to better define the appropriate surgical candidates, the most effective timing of the interventions, and the long-term health outcomes in surviving children.

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Data from the MOMS trial show that prenatal repair of myelomeningocele reduces the need for shunting in the first 12 months after delivery and improves a composite measure of mental and motor function, with adjustment for lesion level, at 30 months of age. Prenatal surgery also improves the degree of hindbrain herniation and the likelihood of being able to walk independently when compared with postnatal surgery. The long-term impact on function needs to be evaluated, and benefits must be balanced against risks to mother and child. Thus, fetal surgery may be considered medically necessary following informed decision making for cases of prenatal myelomeningocele that meet the criteria of the MOMS study.

References

1. Schidlow DN, Tworetzky W, Wilkins-Haug LE. Percutaneous fetal cardiac interventions for structural heart disease. *Am J Perinatol*. Aug 2014;31(7):629-636. PMID 24922056
2. Walsh WF, Chescheir NC, Gillam-Krakauer M, et al. Maternal-fetal surgical procedures. Comparative Effectiveness Technical Briefs, No. 5. Rockville (MD): Agency for Healthcare Research and Quality (US) 2011 Apr. Report No. 10(11)-EHC059-EF. <http://www.ncbi.nlm.nih.gov/books/NBK54520/pdf/TOC.pdf>.
3. Biard JM, Johnson MP, Carr MC, et al. Long-term outcomes in children treated by prenatal vesicoamniotic shunting for lower urinary tract obstruction. *Obstet Gynecol*. Sep 2005;106(3):503-508. PMID 16135579
4. Kilby M, Khan K, Morris K, et al. PLUTO trial protocol: percutaneous shunting for lower urinary tract obstruction randomised controlled trial. *BJOG*. Jul 2007;114(7):904-905, e901-904. PMID 17567421
5. Morris RK, Malin GL, Quinlan-Jones E, et al. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. *The Lancet*. 2013;382(9903):1496-1506.
6. Morris RK, Malin GL, Khan KS, et al. Systematic review of the effectiveness of antenatal intervention for the treatment of congenital lower urinary tract obstruction. *BJOG*. Mar 2010;117(4):382-390. PMID 20374578
7. Morris RK, Malin GL, Quinlan-Jones E, et al. The Percutaneous shunting in Lower Urinary Tract Obstruction (PLUTO) study and randomised controlled trial: evaluation of the effectiveness, cost-effectiveness and acceptability of percutaneous vesicoamniotic shunting for lower urinary tract obstruction. *Health Technol Assess*. Dec 2013;17(59):1-232. PMID 24331029
8. Flake AW, Crombleholme TM, Johnson MP, et al. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obstet Gynecol*. Nov 2000;183(5):1059-1066. PMID 11084541
9. Harrison MR, Keller RL, Hawgood SB, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med*. Nov 13 2003;349(20):1916-1924. PMID 14614166

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10. Deprest J, Jani J, Lewi L, et al. Fetoscopic surgery: encouraged by clinical experience and boosted by instrument innovation. *Semin Fetal Neonatal Med.* Dec 2006;11(6):398-412. PMID 17056307
11. Cortes RA, Keller RL, Townsend T, et al. Survival of severe congenital diaphragmatic hernia has morbid consequences. *J Pediatr Surg.* Jan 2005;40(1):36-45; discussion 45-36. PMID 15868556
12. Ruano R, Duarte SA, Pimenta EJdA, et al. Comparison between Fetal Endoscopic Tracheal Occlusion Using a 1.0-mm Fetoscope and Prenatal Expectant Management in Severe Congenital Diaphragmatic Hernia. *Fetal Diagnosis and Therapy.* 2011;29(1):64-70. PMID
13. Ruano R, Yoshisaki CT, da Silva MM, et al. A randomized controlled trial of fetal endoscopic tracheal occlusion versus postnatal management of severe isolated congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol.* Jan 2012;39(1):20-27. PMID 22170862
14. Rocha LA, Byrne FA, Keller RL, et al. Left heart structures in human neonates with congenital diaphragmatic hernia and the effect of fetal endoscopic tracheal occlusion. *Fetal Diagn Ther.* 2014;35(1):36-43. PMID 24356206
15. Shan W, Wu Y, Huang G, et al. Foetal endoscopic tracheal occlusion for severe congenital diaphragmatic hernia--a systemic review and meta-analysis of randomized controlled trials. *J Pak Med Assoc.* Jun 2014;64(6):686-689. PMID 25252491
16. White SB, Tutton SM, Rilling WS, et al. Percutaneous in utero thoracoamniotic shunt creation for fetal thoracic abnormalities leading to nonimmune hydrops. *J Vasc Interv Radiol.* Jun 2014;25(6):889-894. PMID 24702750
17. Hedrick HL, Flake AW, Crombleholme TM, et al. Sacrococcygeal teratoma: prenatal assessment, fetal intervention, and outcome. *J Pediatr Surg.* Mar 2004;39(3):430-438; discussion 430-438. PMID 15017565
18. Van Mieghem T, Al-Ibrahim A, Deprest J, et al. Minimally invasive therapy for fetal sacrococcygeal teratoma: case series and systematic review of the literature. *Ultrasound Obstet Gynecol.* Jun 2014;43(6):611-619. PMID 24488859
19. Tubbs RS, Chambers MR, Smyth MD, et al. Late gestational intrauterine myelomeningocele repair does not improve lower extremity function. *Pediatr Neurosurg.* Mar 2003;38(3):128-132. PMID 12601237
20. Bruner JP, Tulipan N, Paschall RL, et al. Fetal surgery for myelomeningocele and the incidence of shunt-dependent hydrocephalus. *JAMA.* Nov 17 1999;282(19):1819-1825. PMID 10573272
21. Adzick NS, Thom EA, Spong CY, et al. A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele. *N Engl J Med.* Feb 9 2011;364(11):993-1004. PMID 21306277
22. Bruner JP, Tulipan N, Reed G, et al. Intrauterine repair of spina bifida: preoperative predictors of shunt-dependent hydrocephalus. *Am J Obstet Gynecol.* May 2004;190(5):1305-1312. PMID 15167834
23. Johnson MP, Sutton LN, Rintoul N, et al. Fetal myelomeningocele repair: short-term clinical outcomes. *Am J Obstet Gynecol.* Aug 2003;189(2):482-487. PMID 14520222

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24. Danzer E, Finkel RS, Rintoul NE, et al. Reversal of hindbrain herniation after maternal-fetal surgery for myelomeningocele subsequently impacts on brain stem function. *Neuropediatrics*. Dec 2008;39(6):359-362. PMID 19569004
25. Danzer E, Gerdes M, Bebbington MW, et al. Lower extremity neuromotor function and short-term ambulatory potential following in utero myelomeningocele surgery. *Fetal Diagn Ther*. 2009;25(1):47-53. PMID 19174610
26. Danzer E, Gerdes M, Bebbington MW, et al. Preschool neurodevelopmental outcome of children following fetal myelomeningocele closure. *Am J Obstet Gynecol*. May 2010;202(5):450 e451-459. PMID 20347433
27. Mayer S, Weisser M, Till H, et al. Congenital myelomeningocele - do we have to change our management? *Cerebrospinal Fluid Res*. 2010;7:17. PMID 20946644
28. Bowman RM, McLone DG, Grant JA, et al. Spina bifida outcome: a 25-year prospective. *Pediatr Neurosurg*. Mar 2001;34(3):114-120. PMID 11359098
29. Moldenhauer JS, Soni S, Rintoul NE, et al. Fetal Myelomeningocele Repair: The Post-MOMS Experience at the Children's Hospital of Philadelphia. *Fetal Diagn Ther*. Aug 15 2014. PMID 25138132
30. Bennett KA, Carroll MA, Shannon CN, et al. Reducing perinatal complications and preterm delivery for patients undergoing in utero closure of fetal myelomeningocele: further modifications to the multidisciplinary surgical technique. *J Neurosurg Pediatr*. Jul 2014;14(1):108-114. PMID 24784979
31. McElhinney DB, Marshall AC, Wilkins-Haug LE, et al. Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. *Circulation*. Oct 13 2009;120(15):1482-1490. PMID 19786635
32. Marantz P, Aiello H, Grinenco S, et al. Foetal aortic valvuloplasty: experience of five cases. *Cardiology in the Young*. 2013;23(05):675-681.
33. Pedra SR, Peralta CF, Crema L, et al. Fetal interventions for congenital heart disease in Brazil. *Pediatr Cardiol*. Mar 2014;35(3):399-405. PMID 24030590
34. Chaturvedi RR, Ryan G, Seed M, et al. Fetal stenting of the atrial septum: technique and initial results in cardiac lesions with left atrial hypertension. *Int J Cardiol*. Oct 3 2013;168(3):2029-2036. PMID 23481911
35. Kalish BT, Tworetzky W, Benson CB, et al. Technical challenges of atrial septal stent placement in fetuses with hypoplastic left heart syndrome and intact atrial septum. *Catheter Cardiovasc Interv*. Jul 1 2014;84(1):77-85. PMID 23804575
36. Papadopoulos NA, Papadopoulos MA, Kovacs L, et al. Foetal surgery and cleft lip and palate: current status and new perspectives. *Br J Plast Surg*. Jul 2005;58(5):593-607. PMID 15992528
37. Kohl T, Hering R, Bauriedel G, et al. Fetoscopic and ultrasound-guided decompression of the fetal trachea in a human fetus with Fraser syndrome and congenital high airway obstruction syndrome (CHAOS) from laryngeal atresia. *Ultrasound Obstet Gynecol*. Jan 2006;27(1):84-88; discussion 88. PMID 16308883

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38. Golombeck K, Ball RH, Lee H, et al. Maternal morbidity after maternal-fetal surgery. Am J Obstet Gynecol. Mar 2006;194(3):834-839. PMID 16522421
39. Cohen AR, Couto J, Cummings JJ, et al. Position statement on fetal myelomeningocele repair. American Journal of Obstetrics and Gynecology. (0).
40. American College of Obstetricians and Gynecologists Committee on Ethics and the American Academy of Pediatrics Committee on Bioethics. Committee opinion no. 501: Maternal-fetal intervention and fetal care centers. Obstet Gynecol. Aug 2011;118(2 Pt 1):405-410. PMID 21775875
41. American College of O, Gynecologists. ACOG Committee opinion no. 550: maternal-fetal surgery for myelomeningocele. Obstet Gynecol. Jan 2013;121(1):218-219. PMID 23262964

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05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. New policy.
05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. No change to coverage.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. No change to coverage.
05/03/2018	Medical Policy Committee review. Recommend archiving policy.
05/16/2018	Medical Policy Implementation Committee approval. Archived
04/04/2019	Medical Policy Committee review.
04/24/2019	Medical Policy Implementation Committee approval. Brought back to active status.
04/02/2020	Medical Policy Committee review.
04/08/2020	Medical Policy Implementation Committee approval. No change to coverage.
04/01/2021	Medical Policy Committee review.
04/14/2021	Medical Policy Implementation Committee approval. No change to coverage.
04/07/2022	Medical Policy Committee review.
04/13/2022	Medical Policy Implementation Committee approval. No change to coverage.
12/08/2022	Coding update
04/06/2023	Medical Policy Committee review.
04/12/2023	Medical Policy Implementation Committee approval. No change to coverage
04/04/2024	Medical Policy Committee review.
04/10/2024	Medical Policy Implementation Committee approval. No change to coverage
04/03/2025	Medical Policy Committee review.
04/09/2025	Medical Policy Implementation Committee approval. No change to coverage

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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	59076, 59897
HCPCS	S2400, S2401, S2402, S2403, S2404, S2405, S2409
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

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- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.