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Fetal Surgery for Prenatally Diagnosed Malformations

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Related Policies (if applicable)
None

Disclaimer

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Coverage

Fetal surgery **may be considered medically necessary** for ANY of the following indications:

- Vesico-amniotic shunting as a treatment of bilateral fetal urinary tract obstruction when:
  - Evidence of hydronephrosis due to bilateral urinary tract obstruction; AND
  - Progressive oligohydramnios; AND
  - Adequate renal function; AND
  - No other lethal abnormalities or chromosomal defects.
- Open in-utero resection of malformed pulmonary tissue or placement of a thoraco-amniotic shunt when:
  - 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 pre-eclampsia (i.e., the maternal mirror syndrome) in the mother.
- In-utero removal of sacrococcygeal teratoma when:
  - The fetus is at 32 weeks' gestation or less; AND

- There is evidence of fetal hydrops, placentomegaly, and/or the beginnings of severe pre-eclampsia (i.e., maternal mirror syndrome) in the mother.

- In-utero occlusion of anastomotic vessels (e.g., laser photocoagulation, radiofrequency ablation, and ligation) for twin reversed arterial perfusion (TRAP) sequence**.**
- In-utero laser coagulation of anastomotic vessels in early (<26 weeks gestation), severe twin to twin transfusion syndrome (TTTS).
- Serial amnioreduction for TTTS after 26 weeks gestation.
- In-utero repair of myelomeningocele when:
  - 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; AND
  - Singleton pregnancy; AND
  - Normal fetal karyotype; AND
  - Absence of **ALL** the following:
    a) Fetal anomaly unrelated to the myelomeningocele; and
    b) Severe fetal kyphosis; and
    c) Maternal short cervix (less than or equal to 15 mm); and
    d) Previous pre-term birth; and
    e) Placental abruption; and
    f) Maternal body mass index (BMI) greater than or equal to 35 kg/m^2; and
    g) Contraindications to surgery, including but not limited to previous hysterotomy in the active (upper) uterine segment.

Fetal surgery to perform fetoscopic endoluminal tracheal occlusion (FETO) **may be considered medically necessary** in fetuses with pulmonary hypoplasia due to severe isolated congenital diaphragmatic hernia (CDH) when **ALL** the following conditions are met:

- Singleton pregnancy; AND
- Gestational age less than 29 weeks and 6 days; AND
- Congenital diaphragmatic hernia on the left side with no other major structural or chromosomal defects; AND
- Severe hypoplasia, defined as a quotient of the observed-to-expected lung-to-head ratios of less than 25.0%, irrespective of liver position; AND
- Absence of **ALL** of the following:
  - Maternal contraindications to fetoscopic surgery or severe medical conditions that would make fetal intervention risk full; and
  - Technical limitations precluding fetoscopic surgery including, but not limited to, severe obesity (maternal BMI greater than or equal to 35 kg/m2), or uterine fibroids; and
  - Short cervix (less than or equal to 15 mm); and
  - Müllerian anomalies; and
  - Placenta previa.

Other applications of fetal surgery **are considered experimental, investigational and/or unproven,** including but not limited to the treatment of congenital heart defects, in-utero stem cell transplantation and/or in-utero gene therapy.

Policy Guidelines

None.

Description

Fetal surgery is used for specific congenital abnormalities that are associated with a poor postnatal prognosis. Prenatal surgery typically involves opening the gravid uterus (with a Cesarean surgical incision), surgically correcting the abnormality, and returning the fetus to the uterus and restoring uterine closure. Minimally invasive procedures through single or multiple fetoscopic port incisions are also being developed.

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

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 (CDH) 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 and timing of hernia. 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.

Some fetuses with severe isolated CDH may be appropriate candidates for in-utero fetoscopic endoscopic tracheal occlusion (FETO) although it should only be considered in select fetuses with a poor CDH prognosis. The goal of in-utero treatment in fetuses with severe CDH is to prevent or reverse pulmonary hypoplasia and restore adequate lung growth to improve neonatal survival. Overall, survival has improved with advances in antenatal diagnosis and neonatal care, but affected infants remain at significant risk of morbidity and mortality. (1)

Congenital Cystic Adenomatoid Malformation or Congenital Diaphragmatic Hernia 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 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). Fetuses with developing CCAMs or BPS 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 the power of autonomous growth and a malformation comprised 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, bowel and bladder function,

brain malformation (i.e., hindbrain herniation), cognitive impairment, and disorders of cerebrospinal fluid circulation, i.e., hydrocephalus requiring placement of a ventriculoperitoneal shunt. Traditional treatment consists of surgical repair after term delivery, with ventriculoperitoneal shunting 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. Due to the risks involved related to fetal surgery, it should only be performed at facilities with the special expertise, multidisciplinary teams, and facilities to provide the intensive care required for these patients (2, 3)

Cardiac Malformations

In-utero interventions are being investigated for several potentially lethal congenital heart disorders, including critical aortic stenosis with evolving hypoplastic left heart syndrome (HLHS), HLHS with intact atrial septum, critical pulmonary stenosis or pulmonary atresia. (4) 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 and 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 trial septum is a variant 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.

Twin Reversed Arterial Perfusion (TRAP) Sequence

TRAP sequence refers to a rare complication of monochorionic twin pregnancy in which a twin with an absent or a nonfunctioning heart (acardiac twin) is perfused by its co-twin (pump twin) via placental arterial anastomoses. The acardiac twin usually has a poorly developed heart, upper body and head and is entirely dependent upon the circulatory support from the pump twin. Due to the circulatory burden of supporting its acardiac co-twin, the pump twin is at risk of heart failure and problems related to preterm birth. In addition, TRAP may also occur in monochorionic triplet and higher-order multiple gestations. (5)

Twin to Twin Transfusion Syndrome (TTTS)

Usually developing between 15 and 26 weeks of pregnancy, TTTS is a rare but serious condition that occurs during a twin pregnancy when blood moves from one twin (the “donor twin”) to the other (the “recipient twin”) while in the womb. It is a complication that specifically occurs in identical (monozygotic) twin pregnancies that share the same egg sac (monochorionic) although they may or may not share the same amniotic sac (monoamniotic). Since the fetal

blood supply is disproportionate, it can result in each fetus growing at different rates resulting in the donor twin being smaller, pale, with possible anemia and dehydration. In contrast, the recipient twin may be larger, with redness, elevated blood volume, increased blood pressure causing increased risk of heart failure. (6)

Regulatory Status
Fetal surgery is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration.

Rationale

This medical policy was created in November 2000 and has been updated periodically with literature searches of the PubMed database. The most recent update was with a review of the literature through May 1, 2023.

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. The available literature related to fetal surgery has been summarized below.

Fetal Urinary Tract Obstruction
Systematic Reviews
The 2011 Agency for Healthcare Research and Quality (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. (7) For example, in a follow-up of 18 male children who had survived prenatal vesicoamniotic shunting (follow-up range, 1-14 years), one-third required dialysis or transplantation, and one-half exhibited respiratory, growth and development, or musculoskeletal abnormalities. Despite this, parents and physicians reported the children to be neurodevelopmentally normal, with most having acceptable renal and bladder function and satisfactory self-reported quality of life. (8) 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 protocol for the multicenter randomized PLUTO trial of percutaneous shunting for lower urinary tract obstruction (LUTO) that was designed to assess whether intrauterine vesicoamniotic shunting improved pre- and perinatal health outcomes better than conservative, noninterventional care. (9)

Randomized Controlled Trials

Since publication of the 2011 AHRQ assessment, Morris et al. (2013) published the results of the PLUTO trial. (10) This unblinded RCT included 31 women with male singleton pregnancies, complicated by an isolated LUTO, 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 (11) and was designed to detect a relative risk (RR) 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 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 an intention-to-treat basis and a 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 (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 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 the inability 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 underpowering.

Morris et al. reported on secondary outcomes 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. (12) Secondary outcomes 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 infants 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 infant in the conservative arm had end-stage renal failure at 1 year.

Forty-five women entered 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).

Meta-Analysis

In 2020, Saccone et al. (13) conducted a meta-analysis to evaluate the effectiveness of antenatal intervention for the treatment of lower urinary tract obstruction (LUTO) in improving perinatal survival and postnatal renal function by evaluating 10 articles with a total of 355 fetuses. Overall survival was higher in the vesico-amniotic shunt group compared to the conservative group (Odds Ratio [OR]=2.54, 95% CI, 1.14 to 5.67). 64/112 fetuses (57.1%) survived in the vescico-amniotic shunt group compared to 52/134 (38.8%) in the control group. A total of 5 out of the 10 studies reported on postnatal renal function between 6 months and 2 years of life. Postnatal renal function was higher in the vescico- amniotic shunt group compared to the conservative group (OR=2.09, 95% CI, 0.74 to 5.9). Data from 2 studies reported results of 45 fetuses who underwent fetal cystoscopy; perinatal survival was higher in the cystoscopy group compared to the conservative management group (OR=2.63, 95% CI, 1.07 to 6.47). Normal renal function was noted in 13/34 fetuses in the cystoscopy group versus 12/61 in the conservative management group at 6 month follow-up (OR=1.75, 95% CI 1.05 to 2.92). From this meta-analysis, antenatal bladder drainage appears to improve perinatal survival and other important clinical outcomes in cases of LUTO.

Section Summary: Fetal Urinary Tract Obstruction

Evidence suggests that vesicoamniotic shunting as a therapy for bilateral urinary tract obstruction 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 2003, Harrison et al. (14) 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 premature birth 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. (15) In this subgroup, temporary placement of a detachable balloon to occlude the trachea resulted in a survival rate of 55% (35 cases) compared with 8% survival in a group of contemporary controls treated by postnatal therapy.

Evidence for tracheal obstruction for CDH includes the 2011 AHRQ assessment, which identified 25 publications with 21 unduplicated populations from 10 U.S. sites, 9 European sites, 3 multinational sites, and 5 other countries (total N=335 cases). The single RCT was by Harrison (14) (previously described), with follow-up reported by Cortes et al. in 2005. (16) 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, because survival for CDH with postnatal repair also improved over time. Also noted were results of the Fetal Endoscopic Tracheal Occlusion Task Group in Europe, which used a control group of 86 fetuses with left-sided CDH and liver herniation, managed expectantly and liveborn 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, to 65% survival for LHR of 1.0 to 1.5, and to 83% survival for LHR of 1.6 or more.

Since the 2001 AHRQ assessment, several studies have addressed fetal endoscopic tracheal occlusion (FETO) in CDH. In 2011, Ruano et al. published a small nonrandomized controlled study that evaluated the feasibility of percutaneous FETO with a 1-mm fetoscope. (17) 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 (539%) of 17 of fetal intervention infants and 1 (6%) of 18 of control group infants survived to 28 days, and the authors concluded the intervention was feasible.

In 2012, Ruano et al. (18) conducted a single-center open-label randomized controlled trial on 41 singleton fetuses with severe left or right CDH comparing FETO at 26 to 30 weeks of gestation to usual care (control). Twenty patients were enrolled to FETO and 21 patients to standard postnatal management. Inclusion criteria included no detectable fetal anomalies other than CDH, normal karyotype, fetal lung-to-head ratio < 1.0, and at least one third of the fetal liver herniated into the thoracic cavity as estimated by ultrasound. Postnatal therapy was the same for both treated fetuses and controls. The primary outcome was survival at six months of age. Delivery occurred at 35.6 ±2.4 weeks in the FETO group and at 37.4 ±1.9 weeks in the

control group ($p < 0.01$). In the intention-to-treat analysis, 10/20 (50.0%) infants in the FETO group survived, while 1/21 (4.8%) controls survived (RR 10.5 (95% CI, 1.5–74.7), $p < 0.01$). Additionally, the frequency of severe pulmonary hypertension was significantly lower in the FETO group compared with controls (50.0% versus [vs.] 85.7%, $p = 0.02$) and hemodynamic stabilization occurred earlier in the FETO group than it did in the control group. The authors concluded that FETO improves neonatal survival in cases with isolated severe CDH. The study is limited by the open-labeled design.

In 2014, Rocha et al. published a retrospective case-control study that compared left heart structure size in patients with CDH who underwent FETO with those managed conservatively. (19) 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 FETO 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 FETO who were compared to 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 mL/m^2 vs 12.76 mL/m^2, $p<0.05$), LV length *z* score (-2.05 vs -4, $p<0.01$), left ventricular-right ventricular 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 noted that FETO 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 FETO for CDH. (20) The authors included 3 studies identified as RCTs, including Harrison et al. (2003), Ruano et al. (2011), and Ruano et al. (2012) (noted above). In pooled analysis, patients treated with FETO 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 FETO 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 because Ruano et al. (2011) categorized by its authors as an RCT, was controlled but nonrandomized.

In 2016, Al-Maary et al. (21) evaluated fetal survival after tracheal occlusion in fetuses with severe pulmonary hypoplasia and isolated CDH. PubMed, Cochrane, EMBASE, and Scopus databases were searched for clinical studies on tracheal occlusion and CDH. All studies comparing FETO and a control group were included. The primary outcome was survival, and the secondary outcome was the need for oxygen on discharge. Meta-analysis of outcome measures was performed and odds ratios, RR ratios, and 95% CI were estimated with a fixed-effects model and were reported in accordance with Preferred Reporting Items for systematic reviews and meta-analyses guidance. Five eligible studies describing 211 patients met inclusion criteria

(101 control and 110 FETO). All studies selected isolated severe CDH fetuses with a lung-to-head ratio 1.0 or less and liver herniation into the thoracic cavity. FETO favored survival outcome (OR 13.32; 95% CI, 5.40-32.87). Meta-analysis of the secondary outcome oxygen need at discharge could not be calculated, because it was not reported in all included studies. This review of published literature concluded that FETO improves survival in isolated CDH with severe pulmonary hypoplasia compared with the standard perinatal management.

Deprest et al. (2021a) conducted a multi-center international open-labeled RCT in 80 singleton fetuses with severe isolated left CDH comparing FETO at 27 to 29 weeks of gestation to expectant/usual care. (22) To participate, FETO centers were required to have performed a minimum of 36 fetoscopies annually, have experience with standardized assessment of fetuses with CHD, and to have performed a minimum of 15 FETO procedures at the time the first participant was recruited. The inclusion criteria for the study included a gestational age of < 29 weeks, 6 days, left CDH with no other major structural or chromosomal defects, and severe pulmonary hypoplasia, defined as a quotient of the observed-to-expected lung-to-head ratios of ≤ 25.0%, irrespective of liver position. The exclusion criteria were, among others, an elevated risk of preterm birth (cervical length < 15 mm, müllerian anomalies, or placenta previa). The primary outcome was survival to discharge. The planned sample size was 116 women, but the trial was ended early due to efficacy at interim analysis. In an intention-to-treat analysis that included 80 women, 40% of infants (16 of 40) in the FETO group survived to discharge, as compared with 15% (6 of 40) in the expectant care group (RR 2.67; 95% CI, 1.22 to 6.11; two-sided p = 0.009). Survival to 6 months of age was identical to survival to discharge (RR 2.67; 95% CI, 1.22 to 6.11). The incidence of preterm, prelabor rupture of membranes (ROM) was higher among women in the FETO group than among those in the expectant care group (47% vs.11%; RR, 4.51; 95% CI, 1.83 to 11.9), as was the incidence of preterm birth (75% vs. 29%; RR 2.59; 95% CI, 1.59 to 4.52). There were 2 neonatal deaths, 1 occurred after emergency delivery for placental laceration from fetoscopic balloon removal, and 1 occurred because of failed balloon removal. Among other secondary outcomes, the risk of extracorporeal membrane oxygenation (ECMO) was decreased among infants who had been assigned to FETO (5% vs.29%; RR 0.18; 95% CI, 0.05 to 0.66). The authors concluded that for these select patients, FETO resulted in a significant benefit at discharge that was sustained to 6 months although these findings are limited by the open-labeled study design.

In another open-label trial conducted at multiple centers with FETO experience, Deprest et al. (2021b) randomly assigned women carrying singleton fetuses with a moderate (moderate pulmonary hypoplasia, defined as the quotient of observed to expected lung-to-head ratios of 25.0 to 34.9%, irrespective of liver position, or 35.0 to 44.9% with intrathoracic liver herniation) isolated left CDH to FETO at 30 to 32 weeks of gestation or expectant care. (23) The primary outcomes were survival to discharge and survival without oxygen supplementation at 6 months of age. In an intention-to-treat analysis involving 196 women, 62 of 98 infants in the FETO group (63%) and 49 of 98 infants in the expectant care group (50%) survived to discharge (RR 1.27; 95% CI, 0.99 to 1.63; two-sided P = 0.06). At 6 months of age, 53 of 98 infants (54%) in the FETO group and 43 of 98 infants (44%) in the expectant care group were alive without oxygen supplementation (RR 1.23; 95% CI, 0.93 to 1.65). In the FETO group, the incidence of preterm,

prelabor ROM was higher than among those in the expectant care group (44% vs.12%; RR 3.79; 95% CI, 2.13 to 6.91), as was the incidence of preterm birth (64% vs. 22%, respectively; RR 2.86; 95% CI, 1.94 to 4.34), but FETO was not associated with any other serious maternal complications. There were 2 spontaneous fetal deaths (1 in each group) without obvious cause and 1 neonatal death that was associated with balloon removal. The authors concluded that fetuses with left, moderate CHD did not show a significant increase in survival of infants to NICU discharge or a reduction in the need for oxygen supplementation at 6 months of life among infants assigned to FETO. Additionally, the risk of preterm, prelabor ROM and preterm birth was increased with FETO. The findings of this study are also limited by the open-labeled study design.

A case series reported the results of 24 fetuses with severe CDH who underwent percutaneous FETO with a balloon. (24) Premature prelabor ROM occurred in 16.7% and 33.3% at 28 and 32 weeks, respectively. Seven-day, 28-day, and survival at discharge were 75%, 58.3%, and 50%, respectively. The investigators concluded that FETO may improve survival in highly selected CDH cases.

In 2022, Van Calster et al. (25) performed a re-analysis of the TOTAL trials (22, 23). The re-analysis of the data suggests that FETO increases survival for both moderate and severe lung hypoplasia. The difference between the results for the TOTAL trials, when considered apart, may be because of the difference in the time of balloon insertion. However, the effect of the time point of balloon insertion could not be robustly assessed because of a small sample size and the confounding effect of disease severity. The authors also note that FETO with early balloon insertion strongly increases the risk for preterm delivery.

In 2022 Sferra et al. (26) noted that FETO has shown to improve postnatal survival in a multicenter, randomized controlled trial of infants with severe CDH therefore they sought to evaluate the impact of an integrated prenatal and postnatal care setting on survival outcomes in severe CDH after FETO. This systematic review and meta-analysis and individual participant analysis of FETO outcomes in severe CDH were conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The primary outcome was survival to discharge. Subgroup analyses of patients managed in integrated vs. nonintegrated settings were performed to identify predictors of outcome. The review generated 5 studies (n = 192) for the meta-analysis of FETO vs. expectant prenatal management. Data revealed a significant survival benefit after FETO that was restricted to an integrated setting (OR 2.97, 95% CI 1.69-4.26). There were 9 studies (n = 150) for the individual participant analysis, which showed that FETO managed in an integrated setting had significantly increased survival rates when compared to FETO treated in a nonintegrated setting (70.7% vs. 45.7%, p = 0.003). Multi-level logistic regression identified increased availability of extracorporeal membrane oxygenation (ECMO) as the strongest determinant of postnatal survival (OR=18.8, p = 0.049). Overall, this systematic review shows that institutional integration of prenatal and postnatal care is associated with the highest overall survival in children with severe CDH. These data highlight the importance of a standardized,

multidisciplinary approach, including access to ECMO, as a critical postnatal component in optimizing FETO outcomes in CDH.

In 2023, UpToDate (1) published guidance related to prenatal CDH and recommended that FETO should only be considered in select fetuses with a poor CDH prognosis. Recommended criteria include isolated left CDH, observed/expected lung area to head circumference ratio (o/e LHR) <25 percent, normal microarray, singleton pregnancy, absence of short cervical length, and gestational age 27+0 to 29+6 weeks at the time of the procedure.

Section Summary: Congenital Diaphragmatic Hernia

Most of the literature in fetuses with CDH is comprised of case reports, RCTs, and meta-analysis. Long-term outcomes are not well reported regarding the survival rates of fetuses treated with FETO relative to infants treated at birth. Despite the scarcity of literature, there is growing support in the form of RCTS for the use of FETO demonstrating a positive impact on survival in a carefully selected group of individuals with severe isolated CDH.

Congenital Cystic Adenomatoid Malformation (CCAM) and Bronchopulmonary Sequestration (BPS)

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. (7) Of approximately 401 infants believed to have CCAM, 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. Since 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. (27) 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 of gestation. After delivery, all shunts were in place in the thoracic cavity. Three 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.

Section summary: Congenital Cystic Adenomatoid Malformation (CCAM) and Bronchopulmonary Sequestration (BPS)

CCAM and BPS are the two most common congenital cystic lung lesions. When associated with fetal hydrops before 32 weeks gestation, the survival rate is poor. These individuals may be candidates for open in-utero resection of malformed pulmonary tissue or placement of a thoraco-amniotic shunt as prenatal intervention has resulted in a greater than 50% survival rate.

Sacrococcygeal Teratoma (SCT)

In 1999, the published literature only included 4 cases of fetal surgery for sacrococcygeal teratoma (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 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. (28) Complications other than the fetal death included 1 embolic event, 1 chronic lung disease, and 1 tumor recurrence. The 2011 AHRQ assessment identified 7 retrospective cohorts and case series from 3 academic fetal surgery groups in the United States and the United Kingdom. The 17 fetuses 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, survival rates were 33% to 75%. All fetal and neonatal deaths occurred among patients with hydrops or prodromal cardiovascular changes related to developing hydrops. Challenges in this area are the early and reliable detection of development of hydrops and the timing of the fetal intervention. (7)

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. (29) 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; they 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 noted that, absent treatment, fetal mortality with large fetal vascular SCTs approaches 100%, providing a rationale for fetal intervention.

While the published literature is minimal, given the rarity of the condition, small case series have reported that in-utero surgery may result in prenatal resolution of hydrops, healthy

long-term survival, and normal development (Adzick, 2003b; Hedrick, 2004; Kamata, 2001). These results are impressive given the near-certain fetal mortality if fetal hydrops is left untreated.

Section Summary: Sacrococcygeal Teratoma (SCT)

While evidence is mainly from case reports, case series, and cohort studies, in-utero resection of SCT may reverse the physiologic effects of the tumor and improve fetal survival. Published literature suggest that in-utero surgery may result in prenatal resolution of hydrops, healthy long-term survival, and normal development therefore, in-utero removal of SCT maybe considered medically necessary when the select criteria are met.

Myelomeningocele

Systematic Reviews

As noted in the 2011 AHRQ assessment, more than 200 fetuses with myelomeningocele have undergone open surgical repair in the United States. (7) All 25 reports on open surgery identified in the AHRQ assessment were based on 4 series of patients from 4 academic medical centers in the United States. Two studies had concurrent comparisons. (30, 31) 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 associated with higher rates of oligohydramnios (48% vs 4%), lower gestational ages (33 weeks vs 37 weeks), and no difference in lower extremity function.

Randomized Controlled Trials

In 2011, results of the National Institutes of Health-sponsored Management of Myelomeningocele Study (MOMS), comparing prenatal repair to standard postnatal repair, were published. (32) This RCT began in 2003 and enrolled pregnant women ages 18 years or older whose fetuses had 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 gestation. Follow-up on the children was 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. (7)

The inclusion criteria for MOMS were 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 kg/m^2 or greater, and contraindication to surgery including previous hysterotomy in the active uterine segment. Surgeons had performed at least 15 procedures 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, planned to include 200 subjects, was stopped at 183 subjects when a clear advantage of prenatal intervention was apparent. The 2013 report included 158 women randomized before July 1, 2009. Outcomes up to 30 months were 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 infants in the prenatal surgery group had no evidence of hindbrain herniation vs. 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) of 148.6 (57.5) in the prenatal surgery group (n=64) and 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 in one-third of mothers who had prenatal fetal surgery. 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 trialists 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 cautioned 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 and effects of fetal surgery on bowel and bladder continence, sexual function, and mental capacity are sustained. They warned that trial results should not be generalized to centers with less experience or to patients who do not meet eligibility criteria.

<u>Uncontrolled Series</u>

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). (33) Sixty-one (54%) fetuses 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. (34) Fetal selection criteria included the presence of hindbrain herniation and sonographic evidence of intact neurologic function (i.e., movement of the lower extremities, 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. (30)

In 3 articles, investigators at the University of Pennsylvania reported outcomes of myelomeningocele repair in 54 patients treated before the voluntary moratorium. (35-37) At median follow-up of 66 months (range, 36-113 months), 37 (69%) of 54 walked independently, 13 (24%) of 54 were assisted walkers, and 4 (7%) of 54 were 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 required assistive devices to walk experienced significant deficits in lower-extremity coordination. (36) 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. (37) A survey of 48 families focused on hindbrain herniation-associated brainstem dysfunction (e.g., apnea, neurogenic dysphagia, gastroesophageal reflux disease, neuro-ophthalmologic disturbances). (35) Half of the children required shunting. At a median age of 72 months, 15 non-shunted and 10 shunted children were free of hindbrain herniation symptoms. There were no hindbrain herniation-related deaths, and no children developed severe persistent cyanotic apnea. Most children had no or only mild brainstem dysfunction. The authors concluded that reversal of hindbrain herniation after fetal surgery may reduce the incidence and severity of brainstem dysfunction.

Investigators at a German center retrospectively analyzed expectantly managed patients who received surgical intervention within 2 days of birth at their institution and compared them with outcomes after fetal surgery from other centers, including those previously discussed and to data from historical controls. (38) Patients were born between 1979 and 2009 and had reached a mean (SD) age of 13.3 (8.9) years. Gestational age at birth in the expectantly managed group was 37.8 weeks, significantly higher than in the prenatal surgery patients. In the expectedly managed group, shunt placement was required in 69.8% at mean (SD) age of 16.0 (10.7) days, which was less than for historical controls and comparable to data reported on patients who received fetal surgery. The authors suggested 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 observed 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 cited earlier studies reporting mobility decreases from early childhood to the early teens including 1 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." (39)

Following publication of the MOMS results, Moldenhauer et al. assessed outcomes for a cohort of patients treated at single institution with fetal myelomeningocele repair from 2011 to 2014. (40) A total of 587 patients were referred for potential fetal myelomeningocele repair during the study period, of whom 348 (59.3%) underwent on-site evaluations and 209 (35.6%) were excluded due to noncandidacy for the procedure (BMI >35 kg/m^2, additional fetal anomalies, genetic diagnosis in the fetus, gestational age >26 weeks, preexisting maternal medical condition, multiple pregnancy, no hindbrain herniation on magnetic resonance imaging). A total of 139 (23.7%) patients were considered potential candidates for fetal myelomeningocele repair, of whom 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 (32.3%) of 96 patients and preterm labor occurred in 36 (37.5%) of 96 patients. Sixteen patients had PPROM 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 liveborn at the authors' institution, hindbrain herniation was reversed in 71.1%, and the functional level improved compared with prenatal sonographic bony lesion level in 44 (55%) of 80 neonates assessed. The authors concluded that their experience with fetal myelomeningocele repair was similar to that reported in the MOMS trial.

In 2014, Bennett et al. compared outcomes for a cohort of patients treated with fetal myelomeningocele repair in the post-MOMS era to those treated at the same institution during MOMS. (41) Outcomes were evaluated for 43 patients treated with fetal myelomeningocele repair from 2011 to 2013 and compared to 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 ROM (22% vs 46%, p=0.011) and chorioamnion separation (0% vs 26%, p<0.001). These results suggested that fetal

myelomeningocele repair outcomes in practice can be comparable to or better than those obtained in the MOMS study.

In 2019, Brock et al. (42) evaluated long-term outcomes of 156 children (mean age 7.4 years) from the MOMS trial cohorts to determine differences in urological outcomes. Overall, 62% vs. 87% in the prenatal and postnatal surgery groups, respectively, were placed on clean intermittent catheterization (RR=0.71, 95% CI 0.58-0.86, p<0.001). There was a significant different between the groups in voiding status as 24% in the prenatal group vs. 4% in the postnatal group were reported to be voiding without catheterization (RR=5.8, 95% CI 1.8-18.7; p<0.001). Despite more favorable urologic outcomes in the prenatal surgery group, the study authors emphasize that "urological outcomes alone should not be the sole impetus to perform in-utero closure in children with spina bifida."

In 2020, Houtrow et al. (43) published a long-term study of 161 school-aged (5.9-10.3 years) children from the original MOMS trial who were evaluated by blinded examiners to evaluate psychological and physical difference. Long-term benefits of fetal surgery included improved mobility and independent functioning in addition to fewer surgeries for shunt placement and revision. No differences in cognitive functioning were identified between the 2 cohorts.

In 2022, UpToDate (44) stated that fetal surgery for myelomeningocele can arrest leakage of spinal fluid from the back thereby preventing or reversing herniation of the hindbrain (Chiari II malformation) and reducing the development of hydrocephalus and the need for cerebrospinal fluid (CSF) shunting Fetal surgery is performed at many specialized centers across North America. Because fetal surgery is associated with risks of fetal and maternal complications, UpToDate agreed with recommendations of the American College of Obstetricians and Gynecologists (ACOG) that fetal surgery should only be offered at facilities with the special expertise, multidisciplinary teams, and facilities to provide the intensive care required for these patients. UpToDate stated that the MOMS trial demonstrated evidence of improved motor function in the fetal surgery group and also achieved independent ambulation at 30 months of age compared to those in the postnatal group (45% versus 24%). Children in the fetal surgery group also scored higher of assessments evaluating motor and self-care skills. In addition, both groups had similar cognitive outcomes. It is uncertain whether the rate of bladder dysfunction is lower in patients who undergo fetal repair compared to postnatal repair. If there is an improvement, it does not appear to be dramatic therefore, urologic outcomes alone should not be the sole impetus to perform fetal surgery.

Section Summary: Myelomeningocele

The most direct evidence related to fetal myelomeningocele repair comes from the MOMS study, a RCT that 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 trial.

Cardiac Malformations

The 2011 AHRQ technology assessment (7) included the following evidence on fetal surgery for cardiac malformations:

- Two case series (total 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 (total 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 were from Boston. The 2011 assessment concluded that it is difficult to determine whether the procedure changes long-term outcomes, because 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 several years. Literature was early in development.
- Three case series from 1 U.S. institution (total N=24 patients) addressed the in-utero creation of an atrial septal defect for an intact atrial septum. There were no reports of this procedure performed outside of the U.S. The procedure appears to have technical success; however, mortality remains high, and no controlled trials were available to compare outcomes in patients treated prenatally and 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 is the ability to identify the "right" patient whose care would be compromised by waiting for postnatal repair.

McElhinney et al. analyzed their group's 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. (45) Median gestational age was 23.2 weeks (range, 20-31 weeks). Technical success was achieved in 52 fetuses. Compared with 21 untreated 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 during the study period and became more selective. Larger left heart structures and higher LV pressure at the time of intervention were associated with biventricular outcome. The authors concluded that further investigation is required before it is possible to predict whether fetal intervention will improve 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. (46) 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 HLHS and 3 did not. Rates of longer-term survival and complications were 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. (47) Fetal cardiac intervention was considered for the following echocardiographic findings in patients with isolated cardiac defects (i.e., 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); and 4) pulmonary atresia with intact ventricular septum or critical pulmonary stenosis with impending hypoplastic right heart syndrome (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 (91%) of 22 procedures, with 1 failed aortic and 1 failed pulmonary valvuloplasty. There was 1 fetal death, but 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.

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. (48) Four of the 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. (49) 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, along with 4 neonatal deaths, 2 of which had undergone stenting. No maternal complications were reported.

In 2023, UpToDate published a review on "Fetal cardiac abnormalities: Screening, evaluation, and pregnancy management" (50) that states "In some cases, prenatal diagnosis also provides an opportunity for in-utero interventions. Transplacental medical therapy improves the prognosis of some fetal arrhythmias, particularly tachycardias. Invasive in-utero cardiac intervention (e.g., aortic or pulmonary balloon valvuloplasty, atrial needle septoplasty) may improve the prognosis of some lesions, such as HLHS or severe valvular abnormalities (e.g.,

severe mitral regurgitation, aortic stenosis, pulmonary atresia); however, these interventions are performed at only a few fetal surgery centers and are considered investigational".

Section Summary: Cardiac Malformations

Evidence related to fetal interventions for congenital heart defects (particularly involving 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.

Twin Reversed Arterial Perfusion (TRAP) Sequence

In 2012, Cabassa et al. (51) sought to evaluate a single center experience in the treatment of monochorionic twin pregnancies complicated by TRAP sequence, using radiofrequency ablation (RFA) with expandable needles. Of 11 monochorionic twin pregnancies complicated by TRAP that were referred to the center, 7 underwent intrafetal ablation of the acardiac twin with RFA using expandable needle electrodes. Median gestational age at the intervention was 17(+3) weeks (range 14(+1)-23(+1) weeks). Technical success was obtained in all cases. PPROM occurred in 4/7 (57%) patients. Intrauterine death of the pump twin occurred in one patient at 21(+5) weeks, and one patient opted for termination of pregnancy because of PPROM at 21(+4) weeks. Five fetuses were delivered alive at a median gestational age of 33(+0) weeks (range 31(+0)-39(+5) weeks). All five infants (71%) were alive and had a normal examination at 6 months of age. Investigators concluded that while RFA appears to be a relatively safe and reliable technique in the treatment of Twin Reversed Arterial Perfusion (TRAP) sequence pregnancies, further research is needed to define the best timing of the procedure.

In 2013, Lee et al. (52) retrospectively reviewed the records of all patients who underwent percutaneous RFA of an acardiac twin after referral to 12 North American Fetal Therapy Network (NAFTNet) institutions between 1998 and 2008. The primary outcome was neonatal survival to 30 days of age. Of the 98 patients identified, there were no maternal deaths and no women required blood transfusions. Most women (76 of 98; 78%) stayed in the hospital for ≤1 day after the procedure. Mean gestational age at delivery was 33.4 weeks overall and 36.0 weeks for survivors. Median gestational age at delivery was 37.0 weeks. Survival of the pump twin to 30 days was 80% in the overall cohort. The NAFTNet registry data suggest that radiofrequency ablation of the acardiac twin is an effective treatment for TRAP sequence.

In 2013, Pagani et al. (53) conducted a retrospective cohort study looking at the outcome of TRAP sequence treated with intrafetal laser therapy. Twenty-three cases of TRAP were identified during the study period. Six were managed conservatively and 17 were treated with laser therapy. Among the treated cases, 14 (82%) delivered a healthy twin at a median gestational age of 37 + 1 (interquartile range [IQR], 34 + 0 to 38 + 3) weeks. Ten studies were reviewed in detail and the data were combined with those from the current study. The overall neonatal survival was 80%. Adverse pregnancy outcome was significantly lower when the

treatment was performed before 16 weeks' gestation (19 vs 66%, P = 0.0025). The study data demonstrated a high risk of spontaneous fetal demise in early pregnancy, lack of accurate prognostic markers and improved pregnancy outcome after laser therapy in cases of TRAP.

In 2016, Sugibayashi et al. (54) performed a retrospective study of 40 patients with TRAP sequence who underwent RFA with expandable tines through a multistep coagulation method between 15 and 26 gestational weeks. The primary outcome was neonatal survival to discharge. The overall survival of the pump twin was 85%. The survival rates in monochorionic-monoamniotic (MCMA) pregnancies and monochorionic-diamniotic pregnancies were 66.7% (4/6) and 87.9% (29/33), respectively. One triplet was treated successfully and delivered at 36 weeks of gestation. One of 35 live births (2.9%) had PPROM less than 34 weeks, resulting in infant death. In five intrauterine pump twin deaths, two cases were MCMA twins with cord entanglement and three cases were monochorionic, diamniotic (MCDA) twins with acardius anceps. Reviewers concluded that the study supports the effectiveness of RFA for TRAP sequence after 15 weeks of gestation, and that the presence of MCMA twins or acardius anceps is associated with a high risk of pump twin death after RFA.

In a 2018 retrospective study, Zhang et al. (55) evaluated the treatment of pregnancies in different stages complicated by TRAP sequence. There were four cases in stage Ia, 19 cases in stage IIa, and two cases in stage IIb. Cases in stage Ia were expectantly managed. Among cases in stage IIa, we performed RFA in 10 cases and expectant management in 6 cases, with the remainder of the patients refusing intrauterine treatment. RFA was used to treat one case in stage IIb and the other was managed expectantly. For expectant management group and the RFA group, the survival rates were both 64% (7/11). All pump twins in stage Ia survived and the average gestational age at delivery was 37.9 weeks. In stage IIa, the overall survival rate of the pump twin was 70% (7/10) and the average gestational age at delivery was 35.8 weeks in cases treated by RFA. The survival rate was 50% (3/6) and the average gestational age at delivery was 32.8 weeks in expectantly managed cases in stage IIa. No pump twin survived in stage IIa without treatment (3 cases refused any therapy who were excluded) or in stage IIb. The authors concluded that expectant management is effective for treatment of TRAP sequence in stage Ia, and that in stage IIa, RFA improves the prognosis of pump twins.

In 2020, Shettikeri et al. (56) conducted a single-center cohort study to evaluate outcomes of pregnancies diagnosed with TRAP sequence and treated with interstitial laser therapy or no intervention. Interstitial laser was offered if the blood flow in the acardiac twin was found to be persistent at 2 consecutive examinations or if there were cardiac or hydropic changes in the pump twin at the first examination. A total of 18 cases of TRAP were referred during this period and all were advised regarding fetal therapy if the situation were to deteriorate: 5 couples (27.7%) opted for termination of pregnancy; of the remaining 13, 7 (53.8%) agreed to perform intervention following confirmation of a normal karyotype. Six (85.7%) and 1 (14.3%) laser were performed in the second and third trimesters and all 7 had a normal outcome of the pump twin. There were 6/13 (46.2%) in the expectant group who continued the pregnancy with no intervention, with 2 term live births (33.3%). The authors concluded that there is a high risk of spontaneous loss in untreated pregnancies with TRAP, primarily due to polyhydramnios and

fetal hydrops and in the pregnancies that underwent interstitial laser, there was a more favorable outcome. They also stated that interstitial laser is minimally invasive, safe, and feasible in experienced hands.

In 2022, UpToDate published a review specific to TRAP sequence. (5) For continuing pregnancies, UpToDate offers the following recommendations for the management of TRAP:

- "Pregnancies complicated by TRAP sequence with clinical presentations indicative of a poor prognosis are candidates for intervention via acardiac twin cord occlusion therapy. In-utero treatment improves survival rates to 80 percent or higher.
- Contemporary modalities for cord occlusion therapy for management of TRAP sequence are radiofrequency ablation and bipolar cord coagulation. Intrafetal (or interstitial) laser coagulation is another modality currently being studied for this indication."

Section Summary: TRAP Sequence

Evidence for the treatment of TRAP sequence is limited and consists mostly of retrospective cohort studies, reviews, case series, and registry data however, available data supports improved perinatal survival and favorable clinical outcomes.

Twin to Twin Transfusion Syndrome (TTTS)

In 2008, Roberts et al. performed a Cochrane review to assess which of the treatments for TTTS improves fetal, childhood and maternal outcomes. (57) Three studies (253 women) were included. Laser coagulation resulted in less overall death (48% vs. 59%; RR 0.81; 95% CI, 0.65-1.01 adjusted for clustering; two trials, 364 fetuses), perinatal death (26% vs. 44%; RR, 0.59; 95% CI, 0.40-0.87 adjusted for clustering; one trial, 284 fetuses) and neonatal death (8% vs. 26%; RR, 0.29; 95% CI, 0.14-0.61 adjusted for clustering; one trial, 284 fetuses) when compared with amnioreduction. There was no difference in perinatal outcome between amnioreduction and septostomy. More babies were alive without neurological abnormality at the age of 6 months in the laser group than in the amnioreduction group (52% vs. 31%; RR, 1.66; 95% CI, 1.17-2.35 adjusted for clustering; one trial). There was no difference in the proportion of babies alive at 6 months that had undergone treatment for major neurological abnormality between the laser coagulation and the amnioreduction groups (4% vs. 7%; RR, 0.58; 95% CI, 0.18-1.86 adjusted for clustering; one trial). The results suggest that endoscopic laser coagulation of anastomotic vessels should be considered in the treatment of all stages of TTTS to improve perinatal and neonatal outcome.

Kowitt et al. (2012) conducted a retrospective case-control study to look at the long-term morbidity of monochorionic twins after fetal laser surgery for severe TTS. (58) Of the 38 patients evaluated, 40% (15/38) had at least 1 major sequela, all but 6 of which were fully resolved at a median follow-up of 4.4 years. There were no permanent cardiac, genitourinary, renal, or respiratory sequelae. All major complications were in patients born <29 weeks. There were no significant differences in complications between this cohort of patients and gestational age (GA)-matched control patients. The long-term morbidity of monochorionic twins after fetal laser surgery for severe TTTS is 13%. At a median follow-up of more than 4 years, these children fare no worse than gestational age-matched, non-operated twins and singletons. The degree of

prematurity at birth is the best predictor of temporary or permanent sequela in this group of patients.

In 2014, Roberts et al. conducted a follow-up to their 2008 Cochrane review evaluating the impact of treatment modalities in TTTS. (59) Three studies (253 women and 506 babies) were included. All three trials were judged to be of moderate quality. One study compared amnioreduction with septostomy (71 women), while the other two studies compared amnioreduction with endoscopic laser coagulation (182 women). Although there was no difference in overall death between amnioreduction and laser coagulation (average risk ratio (RR) 0.87; 95% CI 0.55 to 1.38 adjusted for clustering, two trials) or death of at least one infant per pregnancy (RR 0.91; 95% CI 0.75 to 1.09, two trials), or death of both infants per pregnancy (average RR 0.76; 95% 0.27 to 2.10, two trials), more babies were alive without neurological abnormality at the age of six years in the laser group than in the amnioreduction groups (RR 1.57; 95% CI 1.05 to 2.34 adjusted for clustering, one trial). There were no significant differences in the babies alive at six years with major neurological abnormality treated by laser coagulation or amnioreduction (RR 0.97; 95% CI 0.34 to 2.77 adjusted for clustering, one trial). Outcomes for death in this update are different from the previous 2008 update, where improvements in perinatal death and death of both infants per pregnancy were shown in the laser intervention arm. The new trial included in this update exerts an opposite direction of effects to the Eurofetus study, which was previously the only included laser study, hence the difference in outcome. There are no differences in overall death (RR 0.83; 95% CI 0.47 to 1.47, adjusted for clustering, one trial), death of at least one infant per pregnancy (RR 0.80; 95% CI 0.48 to 1.35, one trial), or death of both infants per pregnancy (RR 0.90; 95% CI 0.37 to 2.22, one trial) or gestational age at birth (RR 1.20; 95% CI -0.81 to 3.21, one trial) between amnioreduction and septostomy. The authors concluded that endoscopic laser coagulation of anastomotic vessels should continue to be considered in the treatment of all stages of TTTS to improve neurodevelopmental outcomes.

In 2021, Stirnemann et al. (60) conducted a multi-center, randomized trial to determine if stage 1 TTTS should be managed primarily with intrauterine fetoscopic photocoagulation of placental anastomosis or expectantly. Asymptomatic women with stage 1 TTTS between 16 and 26 weeks of gestation, a cervix of > 15 mm, and access to a surgical center within 48 hours of diagnosis were randomized between expectant management and immediate surgery. In patients allocated to immediate laser treatment, percutaneous laser coagulation of anastomotic vessels was performed within 72 hours. In patients allocated to expectant management, a weekly ultrasound follow-up was planned. Rescue fetoscopic coagulation of anastomoses was offered if the syndrome worsened as seen during a follow-up, either because of progression to a higher Quintero stage or because of the maternal complications of polyhydramnios. The primary outcome was survival at 6 months without severe neurologic morbidity. Severe complications of prematurity and maternal morbidity were secondary outcomes. The trial was stopped at 117 of 200 planned inclusions for slow accrual rate over 7 years: 58 women were allocated to expectant management and 59 to immediate laser treatment. Intact survival was seen in 84 of 109 (77%) expectant cases and in 89 of 114 (78%) (p = 0.88) immediate surgery cases, and severe neurologic morbidity occurred in 5 of 109 (4.6%) and 3 of 114 (2.6%) (p = 0.49) cases in

the expectant and immediate surgery groups. In patients followed expectantly, 24 of 58 (41%) cases remained stable with dual intact survival in 36 of 44 (86%) cases at 6 months. Intact survival was lower following surgery than for the nonprogressive cases, although non-significantly (78% and 71% following immediate and rescue surgery, respectively). The authors concluded that it is unlikely that early fetal surgery is of benefit for stage 1 twin- twin transfusion syndrome in asymptomatic pregnant women with a long cervix and that although expectant management is reasonable for these cases, 60% of the cases will progress and require rapid transfer to a surgical center.

In 2022, Kim et al. (61) conducted a single-center, case series study to assess perinatal outcomes and its associated factors in fetuses with TTTS treated by fetoscopic laser coagulation (FLC). For this retrospective study, all patients with TTTS stage II or higher and those with stage I TTTS coupled with symptomatic polyhydramnios or cardiac dysfunction were eligible for FLC. A total of 172 cases of monochorionic diamniotic twins and 1 case of dichorionic triamniotic triplets were prenatally diagnosed with TTTS and treated with FLC. The median gestational ages at diagnosis and FLC were 20.3 and 20.5 weeks, respectively. The median gestational age of survivors at delivery was 32.5 weeks. The overall at least 1 twin- and double-survival rates within 28 days after birth were 82.1% and 55.5%, respectively. The gestational age at diagnosis and FLC, Quintero stage, inter-twin weight discordance, associated selective intrauterine growth restriction (sIUGR), procedure time, volume of amnioreduction, PPROM within 1 week after FLC, intraoperative intrauterine bleeding, and chorioamnionitis were significant predictive factors of perinatal death. Associated sIUGR, absent end- diastolic flow of umbilical artery, and abnormal cord insertion were significantly associated with donor demise in-utero, whereas lower gestational age at diagnosis and FLC, smaller twins at FLC, pulsatile umbilical vein, and presence of mitral regurgitation were significantly associated with recipient demise in-utero. Since the application of the Solomon technique, the survival rate has improved from 75.4% to 88.8%. The FLC before 17 weeks was associated with PPROM within one week after FLC and lower survival rate, whereas that after 24 weeks was associated with twin anemia-polycythemia sequence and higher survival rate. The authors concluded that FLC is an effective treatment for TTTS and that their study identified several prenatal predictive factors of fetal survival in TTTS treated with FLC.

In 2023, UpToDate (62) a review on the management of patients with TTTS which provide the following recommendations:

- Stage 1 with no tolerable symptoms and cervical length >25 mm

For patients with stage I TTTS with no or tolerable symptoms and cervical length >25 mm, we suggest expectant management rather than invasive therapy (Grade 2C). Weekly ultrasound examinations are suggested to detect progression to more severe disease. Weekly doppler blood flow studies to assess middle cerebral artery peak systolic velocities beginning at 16 weeks and weekly biophysical profile scoring to assess fetal wellbeing beginning at 30 weeks of gestation. Delivery is scheduled at 36 to 37 weeks if TTTS stage and symptoms remain stable.

- Stage I TTTS- Debilitating symptoms or short cervix at 16 to 26 weeks-

For patients with stage I TTTS at 16 to 26 weeks of gestation with debilitating symptoms (e.g., significant respiratory distress and/or preterm contractions) or short cervix (≤25 mm) due to severe polyhydramnios, we recommend fetoscopic laser ablation rather than amnioreduction (Grade1B). Amnioreduction performed as a first-line treatment can result in an inadvertent septostomy or bloody amniotic fluid, which would make subsequent laser treatment difficult to undertake when indicated because of worsening TTTS. Amnioreduction is also more likely to require serial procedures.

- Stage 1 TTTS- Debilitating symptoms or short cervix at >26 weeks

For patients with stage I TTTS at >26 weeks of gestation with debilitating symptoms or short cervix (=25 mm) due to severe polyhydramnios, we suggest amnioreduction rather than laser ablation (Grade 2C). The US FDA investigational device exemption for fetoscopes limits their use to treatment of TTTS at 16 to 26 weeks of gestation, and practically, laser ablation at more advanced gestational ages would be subject to several technical limitations.

- Stage II to IV TTTS-Pregnancies at 16 to 26 weeks –

For patients with stage II to IV TTTS at 16 to 26 weeks of gestation, we recommend laser ablation of placental anastomoses rather than serial amnioreduction (Grade 2B). Laser ablation results in greater prolongation of gestational age, higher neonatal survival, and improved long-term neurologic outcome.

Section Summary: TTTS

Published studies evaluating treatment for twin-to-twin transfusion syndrome (TTTS) consist of prospective, retrospective and randomized trials. Several studies lend support to improved health outcomes, including perinatal survival and survival without neurological complications.

Other Conditions

In-utero fetal surgery has been proposed for other fetal abnormalities, including but not limited to amniotic band syndrome, decompression of the fetal trachea, complete heart block, treatment of hypoplastic left heart syndrome and cleft lip and palate. Evidence in the published, peer-reviewed scientific literature is inadequate to support improved perinatal outcomes with the use of in-utero fetal surgery to treat these conditions. Additional clinical investigation is necessary to evaluate improved patient outcomes and long-term safety and efficacy. (63-65)

There is also interest in the potential use of in-utero hematopoietic stem cell transplantation (HSCT) and/or gene therapy. HSCT is being investigated for use in related stem-cell disorders. Evidence for in-utero stem cell transplantation comes from animal models and from a small number reported cases of in-utero transplantations involving such disorders as X-linked severe combined immune deficiency and hemoglobinopathies (e.g., alpha thalassemia, sickle cell anemia and beta thalassemia). In 2023, UpToDate acknowledged that in-utero HSCT has been performed in an attempt to reduce the possibility of graft rejection by taking advantage of the immunologic immaturity of the fetus although it is controversial since fetal loss is possible. In addition, it is not clear that outcomes are superior to what is routinely achieved when infants are diagnosed with severe combined deficiencies in the neonatal period and protected from infections while awaiting HCT and immune reconstitution. In addition, split chimerism is

common with in-utero HSCT for severe combined immunodeficiency, with generally only T cells engrafting. UpToDate consider HSCT as investigational. (66) To date, there is no proven clear advantage over post-natal stem cell transplantation. Evidence in the published, peer-reviewed scientific literature is inadequate to support improved perinatal outcomes with the use of in-utero hematopoietic stem cell transplantation. Additional clinical investigation is necessary to evaluate improved patient outcomes and long-term safety and efficacy.

In-utero gene therapy is also being considered for disorders that result in irreversible illness or death in the prenatal or neonatal period (e.g., Type 2 Gaucher's Disease, Krabbe's disease, Hurler's Disease). Current evidence is from mainly from animal models and a very small number of reported case reports. Evidence in the published, peer-reviewed scientific literature is inadequate to support improved long-term perinatal outcomes with the use of in-utero gene therapy. Additional clinical investigation is necessary to evaluate improved patient outcomes and long-term safety and efficacy.

Summary of Evidence

Fetal surgery has been researched for many different fetal abnormalities. However, when compared to traditional postnatal therapy, it has been shown to improve outcomes for only a few conditions that include: myelomeningocele repair, twin-to-twin transfusion syndrome (TTTS) , twin reversed arterial perfusion syndrome (TRAP), bilateral urinary-tract obstruction, congenital cystic adenomatoid malformation (CCAM), extralobar pulmonary sequestration, sacrococcygeal teratoma, and in select infants with severe pulmonary hypoplasia due to isolated congenital diaphragmatic hernia (CDH).

Due to 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 other congenital conditions not included in coverage has not been shown to improve long-term health outcomes compared with postnatal treatment. Therefore, the use of in-utero fetal surgery, including in-utero stem cell transplantation and gene therapy for all other conditions are considered experimental, investigational, and/or unproven. Additional studies are needed to identify appropriate candidates and to evaluate long-term outcomes compared with postnatal management.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists (ACOG) and American Academy of Pediatrics (AAP)

ACOG's Committee on Ethics and AAP's Committee on Bioethics issued a committee opinion on maternal-fetal intervention and fetal care centers in 2011 and reaffirmed in 2020. (67) The opinion recommended that:

- Fetal intervention cannot be performed without the explicit informed consent of the pregnant woman.
- Distinctions should be made to prospective parents between which protocols are standard or evidence-based therapies and which are innovative or experimental interventions.

- The informed consent process should involve thorough discussion of the risks and benefits for both the fetus and the pregnant woman.
- Safeguards should be in place to protect women considering fetal research.
- Access to support services such as social services, palliative care and perinatal hospice services, genetic counseling, and ethics consultation should be provided, when appropriate.
- The organization and governance of centers providing fetal interventions should involve a diverse group of professionals, Maternal fetal medicine and neonatologists should be included in this group. including members without direct ties to the center involved.
- Cooperation between fetal care centers should be encouraged to establish collaborative research networks and to support multicenter trials to accumulate more robust short- and long-term maternal and fetal outcome data on all categories of fetal intervention. In addition, the establishment of centers of excellence for those procedures that are particularly challenging and rare may help to optimize fetal and maternal outcomes.

International Fetal Medicine and Surgery Society (IFMSS)

A consensus, endorsed by the IFMSS, proposed the following criteria for fetal surgery (68):

"1. Accurate diagnosis and staging possible, with exclusion of associated anomalies.
2. Natural history of the disease is documented, and prognosis established.
3. Currently no effective postnatal therapy.
4. In utero surgery proven feasible in animal models, reversing deleterious effects of the condition.
5. Interventions performed in specialized multidisciplinary fetal treatment centers within strict protocol and approval of the local Ethics Committee and with informed consent of the mother or parents."

National Institute of Health and Care Excellence (NICE)

The NICE has developed guidelines regarding performance of in-utero surgery to treat some fetal anomalies. According to these guidelines, the following recommendations were given:

- Percutaneous fetal balloon valvuloplasty for pulmonary atresia (69) or aortic stenosis (70) has not been proven safe and effective.
- Percutaneous laser therapy for fetal tumors (i.e., sacrococcygeal teratomas, cervical teratomas, cystic hygromas and congenital cystic adenomatoid malformations [CCAM]) has not been proven safe and effective. (71)
- Intrauterine laser ablation of placental vessels for treatment of twin-to-twin transfusion syndrome has been proven safe and effective. (72)

National Institute of Child Health and Human Development

Myelomeningocele

In 2014, the National Institute of Child Health and Human Development convened the fetal myelomeningocele Maternal-Fetal Management Task Force with representatives from the AAP, ACOG, American Institute of Ultrasound in Medicine, American Pediatric Surgical Association, American Society of Anesthesiologists, American Society of Pediatric Neurosurgeons, IFMSS, American Association of Neurological Surgeons/Congress of Neurological Surgeons, North American Fetal Therapy Network, Society for Maternal-Fetal Medicine, Society of Pediatric

Anesthesia, and Spina Bifida Association. The Task Force provided recommendations about optimal practice criteria for maternal-fetal surgery for myelomeningocele repair. (73)

Recommendations are related to 6 key considerations for teams providing in-utero myelomeningocele repair:

1. Defining a fetal therapy center;
2. Perioperative management for fetal myelomeningocele repair;
3. Long-term care;
4. Counseling;
5. Reporting and monitoring;
6. Access and regionalization.

In general, the authors emphasized the need for access to multidisciplinary teams for prenatal, perinatal, and follow-up care, and recommended that in-utero myelomeningocele repair be performed under strict adherence to the MOMS trial protocol in terms of preoperative evaluation, intraoperative procedure, and immediate postoperative care.

American College of Obstetricians and Gynecologists

In 2013 (reaffirmed 2022) ACOG issued a committee opinion on maternal-fetal surgery for myelomeningocele. (74) This opinion states, "Open maternal–fetal surgery for myelomeningocele repair is a major procedure for the woman and her affected fetus. Although there is demonstrated potential for fetal and pediatric benefit, there are significant maternal implications and complications that may occur acutely, postoperatively, for the duration of the pregnancy, and in subsequent pregnancies. It is a highly technical procedure with potential for significant morbidity and possibly mortality, even with the best and most experienced surgeons. Maternal–fetal surgery for myelomeningocele repair should only be offered to carefully selected patients at facilities with an appropriate level of personnel and resources."

In 2017, ACOG (75) provided a practice bulletin on neural tube defects which provide the following recommendations:

- An individual with a fetus with neural tube defects should be offered the management options of pregnancy termination, expectant management with neonatal surgical repair and in-utero fetal repair for appropriate candidates (level B - recommendation is based on limited or inconsistent scientific evidence).
- Despite the maternal and obstetric risks, in-utero repair is an option for women who meet appropriate criteria. Counseling should be nondirective and include all options, with full disclosure of all potential benefits and risks for the fetus and woman, including implications for future pregnancies (Level C- recommendations are based primarily on consensus and expert opinion).

Society of Obstetricians and Gynaecologists of Canada

In 2021, the Society of Obstetricians and Gynaecologists of Canada (76) issued guidance on the pregnancy management for fetal neural tube defects. They included the following recommendation which they rated as strong with a high quality of evidence: "Once an isolated

open or closed neural tube defect is detected, and diagnostic and genetic testing results (if applicable) are available, families should be offered a choice of 3 obstetrical care management options. In the absence of specific contraindications, families should be given information about the following options: prenatal surgical repair of myelomeningocele and prognosis, postnatal surgical repair of myelomeningocele and prognosis, and pregnancy termination with autopsy (strong, high)."

Society for Maternal-Fetal Medicine (SMFM)
A 2015 SMFM guideline (77) includes fetal needle drainage or thoracoamniotic shunting as a possible treatment for nonimmune hydrops fetalis caused by fetal hydrothorax, chylothorax, large pleural effusion associated with bronchopulmonary sequestration (BPS), and fetal congenital pulmonary airway malformation (CPAM).

In 2022, the SMFM published clinical guidelines for TTTS. (78) Within the guidelines, the SMFM notes perinatal survival for Stage I cases is approximately 86% and that more than three quarters of cases regress or remain stable without invasive intervention. As a result, many of Stage I cases can be managed conservatively. The natural history of an advanced Stage (>III) is poor. When invasive intervention is warranted, fetoscopic laser photocoagulation is considered, by most experts, as the best available approach for Stage II, III and IV TTTS in pregnancies when <26 weeks gestation although it carries numerous possible complications. The SMFM recommends extensive counseling to couples with pregnancies complicated by TTTS to include prognosis, management and treatment options and the possibility of long-term complications after birth, including neurological complications.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this policy are listed in Table 1. Refer to <https://clinicaltrials.gov> for a comprehensive list of clinical trials.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Lower urinary tract obstruction			
NCT01552824	Randomized Controlled Trial of Fetal Cystoscopy Versus Vesico-amniotic Shunting in Severe Lower Urinary Tract Obstructions	60	Jun 2018 (Recruitment status unknown)
Congenital diaphragmatic hernia			
NCT01731509	"Early" Versus "Standard" Fetal Endoscopic Tracheal Occlusion for Severe Congenital Diaphragmatic Hernia - a Randomized Controlled Trial	70	Dec 2016 (No results posted)
NCT00881660	A Prospective Study of the Effectiveness of Fetal Endotracheal Occlusion (FETO) in the	20	Dec 2023 (Active, not recruiting)

	Management of Severe and Extremely Severe Congenital Diaphragmatic Hernia		
Myelomeningocele			
NCT02230072	Minimally Invasive Fetal Neural Tube Defect Repair Study	60	Mar 2024 (Active, not recruiting)
NCT02664207	Extended Criteria for Fetal Myelomeningocele Repair: A Pilot Study	40	Jan 2028 (Recruiting)
NCT03090633	Study of Fetoscopic Repair of Myelomeningocele in Fetuses with Isolated Spina Bifida	30	Apr 2027 (active, not Recruiting)
Fetal Cardiac Surgeries			
NCT01736956	Fetal Intervention for Aortic Stenosis and Evolving Hypoplastic Left Heart Syndrome	9	Oct 2022 (Completed, no results posted)
NCT02852031	National Collaborative to Improve Care of Children with Complex Congenital Heart Disease	1000	May 2028 (Recruiting)
NCT05386173	Effect of Fetal Aortic Valvuloplasty on Outcomes: A Prospective Observational Cohort Study with a Comparison Cohort	200	Dec 2029
Twin Reversed Arterial Perfusion (TRAP) Sequence			
NCT02621645	Early Versus Late Intervention for Twin Reversed Arterial Perfusion Sequence: An Open-label Randomized Controlled Trial: TRAPIST - TRAP Intervention STudy	126	Jun 2022 (No results posted)

NCT: national clinical trial; No: number.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	59001, 59072, 59074, 59076, 59897
HCPCS Codes	S2400, S2401, S2402, S2403, S2404, S2405, S2409, S2411

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
04/01/2024	Reviewed. No changes.
07/15/2023	Document updated with literature review. The following changes were made to Coverage: Expanded the existing experimental, investigational and/or unproven statement to include in-utero stem cell transplantation and/or in-utero gene therapy. Added references 2, 3, 13, 44, 56, 60-62, 77, 78; others updated and/or removed.
12/01/2022	Document updated with literature review. The following changes were made to Coverage: 1) Expanded the criteria for in-utero repair of myelomeningocele; 2) Changed fetal surgery to perform fetoscopic endoluminal tracheal occlusion (FETO) from “experimental, investigational

	and/or unproven" to "may be considered medical necessary" in fetuses with pulmonary hypoplasia due to severe isolated congenital diaphragmatic hernia (CDH) when specific criteria are met; 3) Removed congenital diaphragmatic hernia from the existing experimental, investigational, and/or unproven statement. Added references 1, 2, 18-23, 27, 28, 39-41, 47, 60-64, 67, 68; others updated and/or removed.
03/01/2021	Reviewed. No changes.
03/01/2020	Document updated with literature review. The following changes were made to Coverage: Added conditional coverage for treatment of twin-to-twin transfusion syndrome and twin reversed arterial perfusion sequence. The following references were added and/or updated: 1-2, 10-12, 14-22, 31-32, 37, 39-41, 44-47, and 50.
04/15/2016	Reviewed. No changes.
01/01/2015	Document updated with literature review. Coverage unchanged.
11/01/2012	Document updated with literature review. The entire policy was revised. The following two changes were made to Coverage: 1) In utero repair of myelomeningocele may be considered medically necessary when stated conditions are met; 2) Indications that previously may have been considered medically necessary (vesicoamniotic shunting for urinary tract obstruction, treatment of congenital adenomatoid malformation, extralobar pulmonary sequestration, and sacrococcygeal teratoma) now have specific conditions for medical necessity.
06/01/2008	Revised/updated entire document
03/15/2007	Revised/updated entire document
11/01/2000	New medical document