Anthem

# Clinical UM Guideline

**Subject:** Fetal Surgery for Prenatally Diagnosed Malformations
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## Description

This document addresses the use of surgical techniques to correct or treat fetal malformations in utero, including: vesico-amniotic shunting as a treatment of urinary tract obstruction, repair of myelomeningocele as a treatment of neural tube defect, fetoscopic endoluminal tracheal occlusion as a treatment of congenital diaphragmatic hernia, and fetal aortic valvuloplasty as a treatment of critical aortic stenosis. This document does not address surgery to correct placental or uterine abnormalities including, but not limited to, amnioreduction or laser coagulation therapy to address interfetal transfusion syndrome.

## Clinical Indications

**Medically Necessary:**

Fetal surgery is considered **medically necessary** when ANY of the following criteria sets (I-V) are met:

I. Vesico-amniotic shunting as a treatment of urinary tract obstruction in fetuses when **all** the following conditions are met:
   A. Bilateral obstruction; **and**
   B. Evidence of progressive oligohydramnios; **and**
   C. Adequate renal function reserves; **and**
   D. No other lethal or chromosomal abnormalities.

II. **Either** of the following surgical techniques (A-C) when criteria D **and** E are met:
   A. Open or in-utero resection of malformed pulmonary tissue; **or**
   B. Placement of a thoraco-amniotic shunt as a treatment of either of the following:
      1. Congenital cystic adenomatoid malformation; **or**
      2. Extralobar pulmonary sequestration; **or**
   C. In-utero removal of sacrococcygeal teratoma;
   **and**
   D. Fetus is at 32 weeks gestation, or less; **and**
   E. There is evidence of either of the following:
      1. Fetal hydrops; **or**
      2. Placentamegaly; **or**
      3. The beginnings of severe pre-eclampsia (for example, the maternal mirror syndrome) in the mother.

III. Repair of myelomeningocele when **all** the following conditions are met:
   A. Singleton pregnancy; **and**
   B. Myelomeningocele with the upper boundary of the lesion located between T1 and S1; **and**
   C. Evidence of hindbrain herniation; **and**
   D. Gestational age of 19.0 to 25.9 weeks; **and**
   E. Normal fetal karyotype; **and**
   F. Absence of **all** of the following:
      1. Fetal anomaly unrelated to the myelomeningocele; **and**
      2. Severe fetal kyphosis; **and**
      3. Short cervix (less than or equal to 15 mm); **and**
      4. Previous pre-term birth; **and**
      5. Placental abruption; **and**
      6. Maternal Body Mass Index (BMI) greater than or equal to 35 kg/m$^2$; **and**
      7. Contraindications to surgery, including but not limited to previous hysterotomy in the active (upper) uterine segment.

IV. Fetoscopic endoluminal tracheal occlusion (FETO) when **all** the following conditions are met:
   A. Fetus with pulmonary hypoplasia due to severe isolated congenital diaphragmatic hernia (CDH); **and**
   B. Singleton pregnancy; **and**
   C. Gestational age less than 29 weeks and 6 days; **and**
   D. Congenital diaphragmatic hernia on the left side with no other major structural or chromosomal defects; **and**
   E. 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**
   F. Absence of **all** of the following:
      1. Maternal contraindications to fetoscopic surgery or severe medical conditions that would make fetal intervention riskful; **and**
      2. Technical limitations precluding fetoscopic surgery including, but not limited to, severe obesity (maternal BMI greater than or equal to 35 kg/m$^2$), or uterine fibroids; **and**
      3. Short cervix (less than or equal to 15 mm); **and**
      4. Müllerian anomalies; **and**
      5. Placenta previa.

V. Fetal aortic valvuloplasty when **all** of the following conditions are met:
   A. Severe aortic stenosis; **and**
   B. Midgestation (second trimester); **and**
   C. Evolving hypoplastic left heart syndrome (eHLHS) as evidenced by:
      1. Moderate to severe left ventricular systolic dysfunction; **and**
      2. Abnormal cardiac blood flow as evidenced by:
         a. Retrograde flow in the transverse aortic arch; **or**
         b. Left to right flow across the foramen ovale; **or**
         c. Monophasic mitral valve inflow; **and**

3. Normal-sized mitral valve; **and**
4. Normal-sized to dilated left ventricle;
   **and**

D. Has the potential for postnatal biventricular circulation which includes **either** of the following echocardiographic parameters (1 or 2):
   1. Both a and b:
      a. Left ventricular long-axis z-score ≥-2, **and**
      b. At least 4 of the following:
         i. Left ventricular long-axis z-score > 0; **or**
         ii. Left ventricular short-axis z-score >0; **or**
         iii. Aortic annulus z-score > -3.5; **or**
         iv. Mitral valve annulus z-score > -2; **or**
         v. Aortic stenosis (or mitral regurgitation) maximum systolic gradient ≥ 20 mmHg;
         **or**
   2. Both a and b:
      a. RV/LV length ratio ≥1.094 to <1.135; **and**
      b. MR-Vmax ≥3.14m/s;
      **and**

E. No additional major cardiac or noncardiac malformations; **and**
F. Pregnant person has no contraindications to local/regional anesthesia.

**Not Medically Necessary:**

A. Fetal surgery is considered **not medically necessary** for the conditions indicated above when medically necessary criteria are not met.
B. All other applications of fetal surgery including, but not limited to, aqueductal stenosis are considered **not medically necessary.**

## Coding

*The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.*

**When services may be Medically Necessary when criteria are met:**

**CPT**

| | |
|---|---|
| 59076 | Fetal shunt placement, including ultrasound guidance |
| 59897 | Unlisted fetal invasive procedure, including ultrasound guidance, when performed [when describing a procedure meeting medically necessary criteria] |

**HCPCS**

| | |
|---|---|
| S2400 | Repair, congenital diaphragmatic hernia in the fetus using temporary tracheal occlusion, procedure performed in utero |
| S2401 | Repair, urinary tract obstruction in the fetus, procedure performed in utero |
| S2402 | Repair, congenital cystic adenomatoid malformation in the fetus, procedure performed in utero |
| S2403 | Repair, extralobar pulmonary sequestration in the fetus, procedure performed in utero |
| S2404 | Repair, myelomeningocele in the fetus, procedure performed in utero |
| S2405 | Repair of sacrococcygeal teratoma in the fetus, procedure performed in utero |
| S2409 | Repair, congenital malformation of fetus, procedure performed in utero, not otherwise classified [when describing a procedure meeting medically necessary criteria] |

**ICD-10 Procedure**

| | |
|---|---|
| 10Q00YE-10Q08ZE | Repair nervous system in products of conception [includes codes 10Q00YE, 10Q00ZE, 10Q03YE, 10Q03ZE, 10Q04YE, 10Q04ZE, 10Q07YE, 10Q07ZE, 10Q08YE, 10Q08ZE based on device and approach] |
| 10Q00YF-10Q08ZF | Repair cardiovascular system in products of conception [includes codes 10Q00YF, 10Q00ZF, 10Q03YF, 10Q03ZF, 10Q04YF, 10Q04ZF, 10Q07YF, 10Q07ZF, 10Q08YF, 10Q08ZF based on device and approach] |
| 10Q00YK-10Q08ZK | Repair respiratory system in products of conception [includes codes 10Q00YK, 10Q00ZK, 10Q03YK, 10Q03ZK, 10Q04YK, 10Q04ZK, 10Q07YK, 10Q07ZK, 10Q08YK, 10Q08ZK based on device and approach] |
| 10Q00YR-10Q08ZR | Repair musculoskeletal system in products of conception [includes codes 10Q00YR, 10Q00ZR, 10Q03YR, 10Q03ZR, 10Q04YR, 10Q04ZR, 10Q07YR, 10Q07ZR, 10Q08YR, 10Q08ZR based on device and approach] |
| 10Q00YS-10Q08ZS | Repair urinary system in products of conception [includes codes 10Q00YS, 10Q00ZS, 10Q03YS, 10Q03ZS, 10Q04YS, 10Q04ZS, 10Q07YS, 10Q07ZS, 10Q08YS, 10Q08ZS based on device and approach] |

**ICD-10 Diagnosis**

| | |
|---|---|
| | All diagnoses |

**When services are Not Medically Necessary:**
For the procedure codes listed above when criteria are not met; or when the code describes a procedure indicated in the Clinical Indications section as not medically necessary.

**When services are also Not Medically Necessary:**

**ICD-10 Procedure**

| | |
|---|---|
| 10Q00YG-10Q08ZG | Repair lymphatics and hemic in products of conception [includes codes 10Q00YG, 10Q00ZG, 10Q03YG, 10Q03ZG, 10Q04YG, 10Q04ZG, 10Q07YG, 10Q07ZG, 10Q08YG, 10Q08ZG based on device and approach] |

| | |
|---|---|
| 10Q00YH-10Q08ZH | Repair eye in products of conception [includes codes 10Q00YH, 10Q00ZH, 10Q03YH, 10Q03ZH, 10Q04YH, 10Q04ZH, 10Q07YH, 10Q07ZH, 10Q08YH, 10Q08ZH based on device and approach] |
| 10Q00YJ-10Q08ZJ | Repair ear, nose and sinus in products of conception [includes codes 10Q00YJ, 10Q00ZJ, 10Q03YJ, 10Q03ZJ, 10Q04YJ, 10Q04ZJ, 10Q07YJ, 10Q07ZJ, 10Q08YJ, 10Q08ZJ based on device and approach] |
| 10Q00YL-10Q08ZL | Repair mouth and throat in products of conception [includes codes 10Q00YL, 10Q00ZL, 10Q03YL, 10Q03ZL, 10Q04YL, 10Q04ZL, 10Q07YL, 10Q07ZL, 10Q08YL, 10Q08ZL based on device and approach] |
| 10Q00YM-10Q08ZM | Repair gastrointestinal system in products of conception [includes codes 10Q00YM, 10Q00ZM, 10Q03YM, 10Q03ZM, 10Q04YM, 10Q04ZM, 10Q07YM, 10Q07ZM, 10Q08YM, 10Q08ZM based on device and approach] |
| 10Q00YN-10Q08ZN | Repair hepatobiliary and pancreas in products of conception [includes codes 10Q00YN, 10Q00ZN, 10Q03YN, 10Q03ZN, 10Q04YN, 10Q04ZN, 10Q07YN, 10Q07ZN, 10Q08YN, 10Q08ZN based on device and approach] |
| 10Q00YP-10Q08ZP | Repair endocrine system in products of conception [includes codes 10Q00YP, 10Q00ZP, 10Q03YP, 10Q03ZP, 10Q04YP, 10Q04ZP, 10Q07YP, 10Q07ZP, 10Q08YP, 10Q08ZP based on device and approach] |
| 10Q00YQ-10Q08ZQ | Repair skin in products of conception [includes codes 10Q00YQ, 10Q00ZQ, 10Q03YQ, 10Q03ZQ, 10Q04YQ, 10Q04ZQ, 10Q07YQ, 10Q07ZQ, 10Q08YQ, 10Q08ZQ based on device and approach] |
| 10Q00YT-10Q08ZT | Repair female reproductive system in products of conception [includes codes 10Q00YT, 10Q00ZT, 10Q03YT, 10Q03ZT, 10Q04YT, 10Q04ZT, 10Q07YT, 10Q07ZT, 10Q08YT, 10Q08ZT based on device and approach] |
| 10Q00YV-10Q08ZV | Repair male reproductive system in products of conception [includes codes 10Q00YV, 10Q00ZV, 10Q03YV, 10Q03ZV, 10Q04YV, 10Q04ZV, 10Q07YV, 10Q07ZV, 10Q08YV, 10Q08ZV based on device and approach] |
| 10Q00YY-10Q08ZY | Repair other body system in products of conception [includes codes 10Q00YY, 10Q00ZY, 10Q03YY, 10Q03ZY, 10Q04YY, 10Q04ZY, 10Q07YY, 10Q07ZY, 10Q08YY, 10Q08ZY based on device and approach] |

**ICD-10 Diagnosis**

All diagnoses

## Discussion/General Information

*Description of Birth Defects*

Birth defects, also referred to as congenital anomalies, are abnormalities of structure, function, or body metabolism that are present at the time of birth and frequently lead to mental or physical disabilities. Some birth defects are fatal. There are more than 4000 known birth defects ranging from minor to serious, and although many of them can be treated or cured, they are the leading cause of death in the first year of life. Birth defects can be caused by genetic, environmental, or unknown factors. According to the March of Dimes, about 150,000 babies are born with birth defects each year in the United States. Centers for Disease Control and Prevention (CDC) says that out of every 100 babies born in the United States, 3 have some kind of major birth defect (CDC, 2023).

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 progression and outcomes of certain congenital anomalies. With these advances in diagnostic technology and understanding come additional improvements in surgical and medical procedures to treat birth defects earlier to improve outcomes. Perhaps one of the most significant advances in this field is fetal surgery, which allows doctors to address anatomical abnormalities early in the fetal development process with the goal of lessening significant problems due to the particular abnormality in question.

*Description of Fetal Surgery*

Fetal surgery involves opening a mother's uterus with either a traditional Cesarean surgical incision or through single or multiple incisions through which laparoscopic tools are inserted. When a Cesarean surgical approach is used the fetus is exposed in the maternal abdomen, the fetal abnormality is surgically corrected, and the fetus is returned to the uterus, which is then closed to allow the pregnancy to continue. When a laparoscopic approach is taken, the surgery takes place inside the uterus with the assistance of specialized tools, including a video camera. This is proposed to be a less traumatic method but can only be used under certain circumstances and requires a high degree of surgical skill and experience.

While fetal surgery has been researched as a treatment method for many different abnormalities, only a few conditions have been shown to have improved outcomes when compared to traditional postnatal therapy. Bilateral urinary tract obstruction is often associated with the development of serious health problems including lung disease and loss of amniotic fluid in the uterus. The most common surgical approach is called vesico-amniotic shunting. The shunting procedure bypasses the obstructed urinary tract, permitting fetal urine to flow into the amniotic space decreasing the potential for adverse outcomes. sacrococcygeal teratoma (SCT) associated with fetal hydrops results in near-certain fetal mortality if left untreated. In this case, fetal surgery to remove the tumor may result in resolution of hydrops and increased likelihood of long-term survival. In CDH, intrathoracic herniation of the abdominal viscera impairs normal airway and pulmonary vascular development. FETO has been associated with increased survival among infants with severe pulmonary hypoplasia due to isolated CDH on the left side. Myelomeningocele is a neural tube defect associated with varying degrees of neurological impairment. Surgical repair to the fetus has been proposed to prevent progressive damage during gestation, improve neurological function, and decrease the incidence of associated problems.

*Fetal Urinary Tract Obstruction*

Few cases of prenatally diagnosed urinary tract obstruction require prenatal intervention. However, bilateral obstruction 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 vesico-amniotic shunting by means of shunt or stent placement. The shunting procedure bypasses the obstructed urinary tract, permitting fetal urine to flow into the amniotic space. Small case series have shown improved survival associated with fetal surgery (Freedman, 1999; Sutton, 1999). Long-term follow-up shows that significant proportions of survivors (50%–60%) do not have normal renal function (Biard, 2005; McLorie, 2001). A randomized controlled trial (RCT) published in 2013 by Morris involved 31 participants who were assigned to either surgical intervention (n=16) or

standard care (n=15). The study was closed prematurely due to poor enrollment. Intrauterine death occurred in 1 fetus in each group and pregnancy termination occurred in 3 surgical and 2 control participants. Survival to 28 days was reported in 8 surgical and 4 control participants. In the as-treated analysis, this difference was statistically significant (p=0.03), however, in the intent-to-treat analysis this difference was not statistically significant (relative risk [RR] 1.88, p=0.27). The authors reported substantial short-term and long-term morbidity in both groups, with only 2 babies, both from the surgical group, surviving to 2 years with normal renal function. The authors concluded that, survival appeared higher in the surgical group, but the magnitude and direction of the benefit is unclear and remains to be elucidated, and the likelihood of newborn survival with normal renal function is very low regardless of treatment choice.

Congenital *lower* urinary tract obstruction (LUTO) is typically secondary to a number of other possible conditions including posterior urethral valves (PUV) and urethral atresia. LUTO is the leading cause of pediatric end-stage kidney disease and reportedly has been associated with a mortality rate as high as 45%. The most commonly performed antenatal treatments include serial ultrasound-directed vesicocentesis, vescico-amniotic shunting, fetal cystoscopy and valve ablation. Sacconne and colleagues (2020) conducted a meta-analysis to evaluate the effectiveness of antenatal intervention for the treatment of 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% confidence interval [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. The study authors conclude, “Further randomized trials with long-term follow-up are required to determine the role of antenatal treatment in clinical setting.”

*Congenital Cystic Adenomatoid Malformation (CCAM) and Extralobar Pulmonary Sequestration (EPS)*

CCAM and EPS are the two most common congenital cystic lung lesions. When associated with fetal hydrops before 32 weeks gestation, the survival is poor. These individuals may be candidates for prenatal surgical resection of a large mass or placement of a thoraco-amniotic shunt for a large unilocular cystic lesion. Small case series report that prenatal intervention has resulted in a greater than 50% survival rate (Adzick, 1998; Adzick, 2003a; Adzick, 2003b).

*Sacrococcygeal Teratoma (SCT)*

SCT is both a neoplasm with the power of autonomous growth and a malformation made up of multiple tissues foreign to the region of origin and lacking organ specificity. It is the most common tumor of the newborn. Postnatal SCT carries a good prognosis with morbidity and mortality determined largely by extent of local disease and malignant potential. However, in utero fetal mortality has approached 100% when SCT is associated with fetal hydrops, which is related to high output heart failure secondary to arteriovenous shunting through the tumor. 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.

*Congenital Diaphragmatic Hernia (CDH)*

CDH is a defect that permits abdominal viscera to enter the chest cavity, frequently resulting in hypoplasia of the lungs. CDH can vary widely in severity, depending on the size of the hernia and the timing of herniation. For example, late herniation after 25 weeks of gestation may be adequately managed postnatally. In contrast, liver herniation into the chest prior to 25 weeks of gestation is associated with a poor prognosis; fetuses in which this condition occurs have been considered candidates for fetal surgery. Temporary tracheal occlusion has been investigated as a technique to prevent the normal efflux of fetal lung fluid, which in turn enhances positive pressure in the growing lungs, promoting lung growth and ultimately reducing abdominal viscera back into the abdominal cavity.

In 2023 Tho and colleagues (2023) reported the results of a systematic review and meta-analysis that was designed to estimate the prevalence of symptomatic tracheal complications in infants who underwent FETO for CDH. Presence of one or more of the following was regarded as a tracheal complication: tracheomalacia, stenosis, laceration or tracheomegaly with symptoms such as stridor, effort-induced barking cough, recurrent chest infections or the need for tracheostomy, tracheal suturing, or stenting. Isolated tracheomegaly on routine bronchoscopy or imaging without clinical symptoms was not considered as tracheal morbidity. Statistical analysis was conducted using the metaprop command on Stata V.16.0. A total of 10 studies (449 infants) were included (6 retrospective cohort, 2 randomized controlled trials and 2 prospective cohort studies). A total of 228 infants survived to discharge. Prevalence rates of tracheal complications in infants born alive were 6% (95% CI, 2% to 12%) and 12% (95% CI, 4% to 22%) in those who were still alive at the time of discharge. The spectrum of severity ranged from relatively mild symptoms such as effort-induced barking cough to the need for tracheal/tracheostomy stenting. The researchers found that a significant proportion of FETO survivors have symptomatic tracheal morbidities of varying severity. The authors recommended that facilities that are planning to adopt FETO for managing CDH should consider ongoing surveillance of survivors to enable early identification of upper airway issues. The researchers also point out that new FETO devices that minimize tracheal injury are needed (Tho, 2023).

Deprest and colleagues (2021b) published the results of a randomized open-label trial comparing the effects on postnatal survival of FETO performed at 27 to 29 weeks of gestation to expectant care in a group of participants carrying singleton fetuses with severe isolated CDH on the left side. The study inclusion criteria were a maternal age of 18 years or more, singleton pregnancy, gestational age at randomization of less than 29 weeks 6 days, congenital diaphragmatic hernia on the left side 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 less than 25%, irrespective of liver position. The exclusion criteria were maternal conditions that would make fetal surgery risky, technical limitations precluding fetal surgery (including those caused by severe maternal obesity or uterine fibroids), and an elevated risk of preterm birth (cervical length < 15 mm, müllerian anomalies, or placenta previa). The primary outcome was infant survival to discharge from the neonatal intensive care unit (NICU). The investigators used a group-sequential design with five prespecified interim analyses for superiority. Fetoscopic placement of a tracheal balloon was carried out at 27 weeks 0 days to 29 weeks 6 days gestation. Reversal of occlusion, either by fetoscopy or by ultrasound-guided puncture of the balloon, was scheduled at 34 weeks 0 days to 34 weeks 6 days gestation. Participants assigned to FETO agreed to live near the FETO center for the duration of the tracheal occlusion.

The trial was stopped early for efficacy after the third interim analysis (Deprest, 2021b). The study included 80 participants, 40 in each group. A total of 16 of 40 infants (40%) in the FETO group and 6 of 40 infants (15%) in the expectant care group survived to discharge from the NICU (relative risk [RR], 2.67; 95% CI, 1.22 to 6.11; p=0.009). Survival to 6 months of age was identical to the survival to discharge from the NICU (RR, 2.67; 95% CI, 1.22 to 6.11). Preterm, prelabor rupture of membranes occurred in 19 of 40 women

(47%) in the FETO group and in 4 of 38 (11%) in the expectant care group (RR, 4.51; 95% CI, 1.83 to 11.9). Preterm birth occurred in 30 of 40 women (75%) in the FETO group and in 11 of 38 women (29%) in the expectant care group (RR, 2.59; 95% CI, 1.59 to 4.52). The median gestational age at delivery was 34 weeks 4 days and 38 weeks 3 days in the FETO and expectant care group, respectively, and the median birth weight in the FETO group was 481 g lower than that in the expectant care group.

There were no obvious between-group differences in the incidence of adverse neonatal outcomes (Deprest, 2021b). No maternal complications occurred during FETO. There was 1 case of placental abruption in each group. In the FETO group, there was 1 case of procedure-related fetoscopic placental laceration from balloon removal that resulted in neonatal death during resuscitation. One participant, who moved away from the FETO center, presented to her local unit at 33 weeks 6 days gestation in preterm labor and with intact membranes; postnatal puncture was unsuccessful and resulted in neonatal death. Additionally, the investigators identified five spontaneous balloon deflations which could potentially compromise any intended therapeutic effect. Tracheomalacia was diagnosed at 10 months of age in 1 infant. The same child, still dependent on oxygen at 3 years of age, had two cardiac operations for a ventricular septal defect that was not detected before birth, and assisted ventilation for 240 days. An adverse event of significant concern is an inability to remove the balloon, leading to rapid neonatal death. Deprest and colleagues (2021b) note that this is more likely to occur if the balloon removal becomes an emergency, rather than a planned procedure. Balloons were removed in 9 fetuses at a non-FETO center by an inexperienced team and the removal was problematic in 3 of the fetuses. In the trial, participants assigned to FETO agreed to live near the FETO center for the duration of tracheal occlusion. If preterm birth was imminent, emergency balloon retrieval was performed in utero, at the time of delivery while the umbilical cord still connected the infant to the placenta, or by direct puncture immediately after delivery. The authors further emphasize that because the trial involved experienced fetal surgery units, the findings should not be generalized to centers without extensive experience in fetoscopy and FETO or to centers that cannot ensure availability of a team that can perform safe and effective balloon retrieval. Ideally, FETO should be performed at a center with a dedicated, multidisciplinary Fetal Care Team that is equipped to provide support in the medical, social, and ethical considerations of undergoing FETO procedures. The results of this study are promising. Further study is needed to evaluate the impact of FETO on longer-term health outcomes as compared with expectant care for severe congenital diaphragmatic hernia.

In another randomized open-label trial, Deprest and colleagues (2021a) compared the effects of FETO performed at 30 to 32 weeks of gestation to expectant care in women carrying singleton fetuses with moderate isolated congenital diaphragmatic hernia on the left side. The primary outcomes were infant survival to discharge from a NICU and survival without oxygen supplementation at 6 months of age. The trial was not stopped early for superiority. In an intention-to-treat analysis, 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). The percentages of infants who survived without oxygen supplementation at 6 months of age were 54% (53 of 98 infants) for the FETO group and 44% (43 of 98 infants) for the expectant care group. Two unexplained fetal deaths occurred in the FETO group and 1 in the expectant care group. The incidence of preterm, prelabor rupture of membranes was 44% in the FETO group and 12% in the expectant care group. The incidence of preterm birth was 64% for the FETO group and 22% for the expectant care group. There were two problematic balloon removals, one of which resulted in death of the infant. The results 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 age among infants assigned to FETO. Further study is needed to assess potential strategies to reduce FETO-associated complications, treatment criteria, and longer-term outcomes in individuals with moderate isolated CDH on the left side.

In a retrospective case series study, 28 fetuses with CDH and intrafetal fluid effusions and severe pulmonary hypoplasia had fetoscopic endoluminal tracheal occlusion (FETO) attempted (Van Mieghem, 2012). A total of 21 participants had CDH as their only complication, while the remaining 7 cases had additional congenital anomalies. A total of 3 pregnancies were terminated early and 19 cases underwent technically successful FETO, which was the sole intervention in 13 cases. No FETO was done in 5 cases. Thoracic drainage procedures were performed in 6 participants. Postoperatively, 16 cases had stable effusions, and 3 had progressive ascites, hydrothorax and subcutaneous edema. No cases of fetal death were reported. Neonatal survival in the 25 remaining cases was 36% (n=9). Survival was similar in the FETO group (6/15) and no FETO group (2/5) (p=1.0).

A single-center RCT conducted in Brazil by Ruano and colleagues (2012) involved 38 subjects with CDH. Fetuses had no other detectable anomalies, fetal lung-to-head ratio < 1.0 and sonographic evidence of at least one-third of the fetal liver herniated into the thoracic cavity. Participants were randomized to undergo either FETO (n=20) or standard postnatal care (n=21). One participant in the FETO group and 2 in the control declined the assigned treatment; all 3 fetuses subsequently died before delivery. Balloon rupture was reported in 2 FETO cases, but a second balloon was placed with no subsequent related adverse events reported. Premature rupture of membranes at both < 32 and < 37 weeks was not different between groups. While gestational age at delivery was significantly earlier in the FETO group (p<0.01), overall, there were no differences in rates of prematurity between groups. In the received-treatment analysis, 10/19 (52.5%) of the infants in the FETO group and 1/19 (5.3%) of the infants in the control group survived (p<0.01). In the intent-to-treat analysis, 50% (10/20) in the FETO group survived to 6 months (primary outcome measure) while only 4.8% (1/21) in the control group survived to at least 6 months (p<0.01). Severe pulmonary hypertension was noted in 50% (10/20) of the FETO group and in 85.7% (18/21) of the control group (p=0.02). In the received-treatment analysis, 12 FETO participants and 4 controls received postnatal surgical repair (81% received a prosthetic patch). While these results are promising, additional multi-center studies with larger sample sizes are needed.

A randomized study comparing tracheal occlusion with conventional postoperative care was terminated early due to lack of improvement in survival or morbidity rates (Harrison, 2003). Jani and colleagues (2009) reported on a case series study involving 210 fetuses with CDH treated with fetoscopic endoluminal tracheal occlusion (FETO). This study reported a high number of prelabor rupture of membranes (47.1%) and preterm deliveries (30.9%). Out of 210 cases, 204 (97.1%) babies were live births, and 98 (48.0%) were discharged from the hospital alive. A total of 10 deaths were reported being directly related to removal of the occlusal device. There was no comparison group used in this study.

A report by AHRQ (2011) similarly concluded that the bulk of CDH literature is comprised of case reports, and long-term outcomes are not well reported regarding the survival rates of fetuses treated with tracheal occlusion 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.

*Myelomeningocele*

Myelomeningocele is a neural tube defect in which the spinal cord and its coverings protrude through the skin in the lower back. Children with this disorder have varying degrees of neurologic impairment to the legs and bowel and bladder function, brain malformation, and disorders of cerebrospinal fluid circulation. Traditional treatment of the condition consists of surgical repair after term delivery. Surgical repair to the fetus has been proposed as a means of improving neurologic function and decreasing the incidence of other problems related to the condition. Two case series reporting short-term outcomes up to 6 months have shown improvement in anatomic hindbrain herniation and a lower incidence of hydrocephalus requiring ventriculoperitoneal shunt (Adzick, 2003b; Tulipan, 1999). A study reporting leg function at longer follow-up showed no difference between individuals treated with fetal surgery versus traditional surgery (Tulipan, 1999). Both case series show that the incidence of premature delivery is increased in the fetal surgery groups (Bruner, 1999; Sutton, 1999). A systematic review of 11 studies comprised of 518 women who received fetal

myelomeningocele repair, reported an average overall rate of maternal and obstetric complications of 78.6%, the majority being obstetric complications, including chorioamniotic membrane separation (65.6%), oligohydramnios (13.0%), placental abruption (5.0%), spontaneous or preterm premature membrane rupture (42.0%), and early preterm delivery (11.3%). The most common medical complications were pulmonary edema (2.8%), gestational diabetes (3.7%), preeclampsia (3.7%), and need for blood transfusions (3.2%). Authors emphasize that overall lack of published data on maternal and obstetric complications related to myelomeningocele repair and highlight that “maternal health hazard will continue to be an issue of crucial importance and further studies are required.” (Licci, 2019).

Adzik and colleagues in the Management of Myelomeningocele Study (MOMS) group published the results of a large RCT that included 138 participants who completed up to 30 months follow-up (2011). This study randomized participants to receive myelomeningocele repair either in utero (fetal surgery group) or following delivery (perinatal group). The first primary outcome, fetal death or the need for cerebrospinal fluid shunt by the age of 12 months was significantly better in the fetal surgery group with 68% vs. 98% of participants requiring shunts, respectively ($p<0.001$). The rate of actual shunt placement was 40% for the in utero group vs. 82% in the perinatal group. Additionally, at 12 months of age, the fetal surgery group demonstrated significantly fewer infants with any evidence of hindbrain herniation (64% vs. 96%, $p<0.001$), brain stem kinking (20% vs. 46%, $p<0.001$), abnormal fourth ventricle location (46% vs. 72%, $p<0.002$), and syringomyelia (39% vs. 58%, $p<0.03$). The main secondary outcome was a composite score made up of data from the Bayley Mental Developmental Index and the difference between the functional and anatomical lesion was calculated at 30 months and was significantly better in the fetal surgery group (mean 148.6 vs. mean 122.6, $p<0.007$). In the post hoc analysis, the authors reported that participants in the fetal surgery group were more likely to have a level of function two or more levels better than their anatomical level (32% vs, 12%, $p<0.005$), and were also more likely to ambulate without orthotics or other devices (42% vs. 21%, $p<0.01$). Interestingly, the participants in the fetal surgery group had significantly better motor function scores on the Bayley and Peabody motor scales, despite having more severe anatomical lesion levels at baseline. There were no significant differences in cognitive function between groups. The report also stated that the fetal surgery group had significantly higher rates of pre-term birth (79% vs. 15%), spontaneous membrane rupture (46% vs. 8%, $p<0.001$), oligohydramnios (21% vs. 4%, $p=0.001$), and maternal transfusion (9% vs. 1%, $p=0.03$). Evaluating this data, it is clear that there appears to be potentially significant benefits to the fetus with fetal surgery for myelomeningocele. However, these benefits must be balanced with the possible risks of maternal and pregnancy complications. Prompted by publication of the MOMS trial, the fetal myelomeningocele Maternal-Fetal Management Task Force (convened by the Eunice Kennedy Shriver National Institute of Child Health and Human Development) recently published a position statement on optimal practice criteria for facilities and practitioners performing this procedure (Cohen, 2014). A post-hoc analysis of 30-month cohort data from the MOMS trial, validated that cognitive and motor function outcomes favored in-utero repair of myelomeningocele over postnatal procedures (Farmer, 2018). Based on the MOM’s study, the American College of Obstetricians and Gynecologists (ACOG)’s practice bulletin on Neural Tube Defects includes a recommendation for fetal surgery for myelomeningocele in eligible women and fetuses (ACOG, 2017).

In 2020, Houtrow and colleagues 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 determine neuropsychological and physical difference. Long-term benefits of fetal surgery identified included improved mobility and independent functioning in addition to fewer surgeries for shunt placement and revision. There was no difference detected in cognitive functioning between the two cohorts. Similarly, Brock and colleagues (2019) 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 difference 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 2021, the Society of Obstetricians and Gynaecologists of Canada (Wilson, 2021) 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).

*Critical Aortic Stenosis*

Aortic stenosis is narrowing of the aortic valve which develops early in pregnancy. Fetal critical aortic stenosis (CAS) is a malformation of the fetus in which aortic stenosis progresses and causes hypoplasia of the left heart and insufficient systemic circulation. As a result of the decreased left ventricular output, the right ventricle supports a greater share of the fetal cardiac output.

The development of hypoplastic left heart syndrome (HLHS) secondary to CAS occurs at midgestation and involves cardiac anomalies with stenosis or atresia of the mitral and/or aortic valve leading to hypoplasia of the left ventricle and the ascending aorta. Without adequate treatment, HLHS is always lethal. HLHS is one of the most severe types of congenital heart disease diagnosed during pregnancy. The incidence of HLHS is estimated to be approximately 0.16 to 0.36 per 1000 live births and accounts for 4.8–9% of all cases of congenital heart disease (Graupner, 2019).

Early intervention with fetal aortic valvuloplasty (FAV) has been explored as a means to protect the fetus from HLHS by enabling biventricular circulation (BVC) and thereby avoiding staged univentricular palliation, improving left heart hemodynamics and growth of aortic and mitral valves as well as improving short-term and long-term mortality and morbidity. However, this intrauterine, ultrasound-guided transcatheter procedure poses significant risks to the fetus as well as some risk to the mother.

The available evidence addressing FAV as a treatment for CAS is generally limited to non-randomized studies, retrospective reviews, systematic reviews and meta-analyses. Several studies have described the biventricular (BV) outcome rate in fetuses who have undergone FAV as a treatment of CAS.

Mendel and colleagues (2023) reported the results of a systematic review and meta-analysis that explored the outcomes of FAV in fetuses with CAS. The primary endpoint was overall mortality. R software was used to estimate the overall proportion of each outcome using random-effects model of proportional meta-analysis. A total of 389 fetal participants and 10 observational non-randomized studies were included in the qualitative and quantitative analysis. FAV was successfully performed in 84% of participants and revealed a successful conversion to BV circulation (BVC) rate of 33% with a mortality rate of 20%. Most studies reported this procedure was performed in fetuses 23 or 26 weeks of gestation. The two most common fetal complications requiring treatment were bradycardia and pleural effusion, occurring in 50-60% of participants. With regard to maternal complications, only placental abruption in a single participant was reported. Three studies reported no fetal or maternal complications. The authors concluded that FAV has a high technical success rate with the ability to achieve BVC and a low rate of procedure-related mortality when carried out by experienced practitioners.

Diniz and colleagues (2023) conducted a systematic review to determine the benefits and risks of fetal surgery for congenital cardiac defects including CAS. This study found that the FAV enables growth of the left ventricle and increases left ventricular pressure. However, the procedure has a high complication rate, along with considerable morbidity and mortality. The significant risk of complications can be reduced by the surgeon's technical expertise and well-structured hospital facilities.

Tulzer and colleagues (2023) reported on their experience with FAV in fetuses with CAS and evolving HLHS, including short- and medium-term postnatal outcome. The researchers conducted a retrospective review of all fetuses with CAS and evolving HLHS undergoing FAV at a single institution between December 2001 and September 2020. Echocardiograms and the charts of participants were analyzed for pre-FAV ventricular and valvular dimensions and hemodynamics and for postnatal procedures and outcomes. The primary endpoints were type of circulation 28 days following birth and at 1 year of age. Classification and regression-tree analysis was carried out to investigate the predictive capacity of pre-FAV parameters for BV circulation at 1 year of age. The researchers also sought to improve selection criteria for FAV by identifying preprocedural predictors of BV outcome.

During the study period, 103 fetuses had 125 FAVs, of which 87.4% had a technically successful procedure. Technical success per fetus was higher in the more recent timeframe (since 2014) than in the earlier period (96.2% [51/53] vs. 78.0% [39/50]; p=0.0068). A total of 80 fetuses were liveborn after successful intervention and received further treatment. BV outcome at 1 year of age was achieved in 55% of liveborn participants after successful FAV, which is significantly higher than the BV-outcome rate (23.7%) previously reported by Gardiner (2016) in a natural history cohort fulfilling the same criteria for eHLHS (p=0.0015). Decision-tree analysis based on the ratio of right to left ventricular (RV/LV) length combined with LV pressure (mitral valve regurgitation maximum velocity [MR-Vmax]) revealed a sensitivity of 96.97% and a specificity of 94.44% for predicting BVC without signs of pulmonary arterial hypertension at 1 year of age. The highest probability for BVC was predicted for fetuses with a pre-FAV RV/LV length ratio of < 1.094 (96.4%) and for those fetuses with a RV/LV length ratio ≥ 1.094 to < 1.135 combined with a MR-Vmax of ≥ 3.14 m/s (100%).

Vorisek and colleagues (2022) reported the results of a systematic review and meta-analysis that investigated the type of postnatal circulation achieved following FAV. The systematic review was comprised of seven cohort studies (one prospective and six retrospective studies, of which Freud [2014] and Kovacevic [2018] are summarized below in this document), involving a total of 266 fetuses, along with three studies (n=29) that included fetuses with hydrops. The median follow-up was from 12 months to 13.2 years. The researchers found that BVC was achieved in 46%, which increased to 52% when participants underwent technically successful FAV for AS (defined as the presence of flow across the AV after balloon inflation). The authors pointed out study limitations which included a lack of RCTs, small sample sizes, incomplete follow-up, heterogeneity in inclusion criteria and surgical techniques, as well as a lack of well-defined postnatal circulation outcomes. The authors concluded that while the study demonstrated a BVC rate of 46% among liveborn participants with AS who underwent FAV, the results should be interpreted cautiously in light of the study limitations. The authors acknowledged that well-designed international collaborative RCTs with standardized selection criteria and evaluation of outcomes beyond the neonatal period are needed to conclusively determine the postnatal circulation outcome following FAV.

Walter (2022) retrospectively assessed the course and outcome of FAV in fetuses with severe AS at a single tertiary center for fetal medicine over a 10 year period. In the study, period fetuses with severe AS were considered suitable for FAV provided they had markedly elevated left ventricular pressures (maximum velocity of mitral regurgitation (MR Vmax) > 250 cm/s and/or maximum velocity of aortic stenosis (AS Vmax) > 250 cm/s, retrograde flow in the transverse aortic arch; and a left ventricular length Z-score >−1. A total of 29 fetuses with AS were treated with 38 FAVs. When reinterventions are included, 82.7% of fetuses received a technically successful FAV. Procedure related death occurred in 3 (10.3%) cases, spontaneous fetal death in 2 (6.9%), and termination of pregnancy was carried out in 3 cases (10.3%). Of the 21 live births (72.4%), 4 died in infancy. Among the remaining survivors, 8/17 (47.1%) had a biventricular outcome at the age of 1 year, 8/17 (47.1%) were univentricular and 1 infant (5.9%) had biventricular outcome at the age of 8 months. Fetuses with BVC had significantly greater left ventricular (LV) length Z-scores (p=0.031), and lower tricuspid to mitral valve (TV/MV) ratios (p=0.003). The researchers concluded that FAV has a high technical success rate and a low rate of procedure related mortality when performed in experienced hands. The success rate of BVC at 1 year of age is moderate and seems to depend rather on the center's experience and postnatal surgical strategies than solely on prenatal selection criteria. The researchers also concluded that due to the lack of randomized controlled trials, FAV should be considered an experimental surgical intervention.

Pickard and colleagues (2020) completed and reported the results of a retrospective analysis of 143 fetuses who underwent FAV from 2000-2017 and a secondary analysis of the Pediatric Heart Network Single Ventricle Reconstruction trial. Using these results, the researchers developed a decision model to approximate the probability of transplant-free survival from fetal diagnosis to age 6 and postnatal restricted mean transplant-free survival time (RMST). FAV was technically successful in 120 (84%) fetuses with fetal demise occurring in 12 (8%) of whom 9 fetal losses were attributed directly to the FAV procedure. BVC following technically successful FAV was achieved in 56/111 (50%) liveborn infants but in only 16% of the 19 patients with unsuccessful FAV. The model estimated overlapping probabilities of transplant-free survival to age 6 at 75% (95% CI, 67% - 82%) with FAV versus 72% (95% CI, 61% - 82%) with expectant fetal management, resulting in a RMST benefit of 1.2 months. When limiting analyses to the improved FAV experience since 2009 to mirror current practice, probability of technical success (94%), fetal demise (4%), and biventricular circulation (66%), the model projected that FAV increased the probability of survival to age 6 to 82% (95% CI, 73% - 89%). Expectant management is favored if the probability of biventricular circulation fell below 26% or the risk of fetal demise exceeded 12%, but FAV remained favored over plausible recent range of technical success. Because no significant maternal complications related to FAV have occurred in the study population, the model did not consider FAV-related maternal risk. The model suggests that FAV provides a modest, medium-term survival benefit over expectant fetal management, however, careful patient selection and low risk of fetal demise with FAV are critical factors for obtaining a survival benefit.

Friedman and colleagues (2018) carried out a study to determine whether technical success and biventricular outcome after FAV have changed from an earlier (2000–2008) to a more recent (2009–2015) era and identify pre-FAV predictors of biventricular outcome. The researchers evaluated procedural and postnatal outcomes in 123 fetuses that underwent FAV for evolving HLHS at Boston Children's Hospital between 2000 and 2015. The primary outcome measure was circulation type (BVC or single ventricle circulation) at the time of neonatal hospital discharge. Classification and regression tree (CART) analysis was carried out to construct a stratification algorithm to predict BVC based on pre-FAV fetal variables. FAV was technically successful in 101/123 (82%) fetuses, with a higher technical success rate in the more recent era than in the earlier one (49/52 [94%] vs. 52/71 [73%]; p=0.003). In liveborn participants, the incidence of BVC outcome was higher in the recent than in the earlier era, both in the entire liveborn cohort (29/49 [59%] vs. 16/62 [26%]; p=0.001) and in those in whom the procedure was technically successful (27/46 [59%] vs. 15/47 [32%]; p=0.007). Independent predictors of BVC were higher left ventricular (LV) pressure, larger ascending aorta, better LV diastolic function and higher LV long-axis Z-score. On CART analysis, fetuses with LV pressure > 47 mmHg and ascending aorta Z-score ≥ 0.57 had a 92% probability of BVC outcome (n=24). Those with a lower LV pressure, or mitral dimension Z-score < 0.1 and mitral valve inflow time Z-score < –2 (n=34) were unlikely to have BVC. The authors acknowledge that this study has limitations including but not limited to the primary outcome measure, BVC through the neonatal period, is dependent on postnatal decision-making and is a short-term outcome. Variability in postnatal decision-making, especially with regard to initial management strategy, was unavoidable, as newborns were cared for at multiple institutions and over a 15-year time period.

Kovacevic and colleagues (2018) conducted a retrospective multicenter study to assess the efficacy of FAV by comparing survival

and postnatal circulation between fetuses that underwent FAV and those that did not. Primary outcomes were overall survival, BVC survival and survival after birth. Secondary outcomes measures included hemodynamic change and left heart growth. A propensity score model was created including 54/67 FAV and 60/147 natural history (NH) fetuses. Analyses were performed using logistic, Cox or linear regression models with inverse probability of treatment weighting (IPTW) restricted to fetuses with a propensity score of 0.14-0.9, to create a final cohort for analysis of 42 FAV and 29 NH cases. The study demonstrated that FAV was technically successful in 59/67 fetuses at a median age of 26 (21-34) weeks gestation. There were 7/72 (10%) procedure-related fetal losses, and 22/53 (42%) FAV babies were delivered at < 37 weeks. IPTW showed improved survival of liveborn infants following FV (hazard ratio, 0.38; 95% CI, 0.23-0.64; p=0.0001), after adjusting for circulation and postnatal surgical center. Similar BVC outcome rates were reported in fetuses who underwent FAV vs. those with no intervention (36% and 38%, respectively). Successful FAV cases displayed improved hemodynamic response and less deterioration of left heart growth compared with NH cases (p≤0.01). While the proportion of those achieving a BVC outcome was similar in both groups, FAV survivors demonstrated improved survival independent of final circulation to 10 years' follow-up. While the researchers reported improved hemodynamics in the intervention group, an increased rate of preterm delivery (42%) was observed in comparison with 26% in the natural-history group. The researchers recommended a carefully designed trial incorporating appropriate and integrated fetal and postnatal management strategies to account for center-specific practices, so that the benefits achieved by fetal therapy vs surgical strategy can be clearly established.

Wohlmuth and colleagues (2014) retrospectively evaluated the maternal aspects, pregnancy-associated risks and adverse events in women who had undergone intrauterine cardiac interventions. Between October 2000 and December 2012, 53 fetal cardiac interventions were completed in 47 fetuses (43 aortic valve dilations in 39 participants, 7 pulmonary valve dilations in 6 participants and 3 balloon atrioseptostomies in 2 participants). Median gestational age at the time of intervention was 26 + 4 (range, 20 + 3 to 33 + 1) weeks. Interventions were performed using an ultrasound-guided percutaneous approach under general anesthesia. The medical records and patient charts were reviewed retrospectively. At the preoperative assessment, all women were considered healthy. A total of 39 (83%) women continued pregnancy until term and 8 of 47 participants had experienced an intrauterine fetal death (IUFD) and were induced. Postoperative nausea was described in 29.8% of participants and abdominal pain in 36.2% of participants on the day of surgery. Preterm contractions were observed in 2 participants; no preterm prelabor rupture of membranes occurred. One participant with IUFD experienced severe postpartum hemorrhage and subsequent induction; however, this was unrelated to the fetal aortic valvuloplasty procedure. No intensive care unit admissions and no major anesthesia-associated complications (aspiration, anaphylactic reaction, cardiovascular collapse, laryngeal damage, damage to teeth, awareness or hypoxic brain damage) were reported. There were no maternal mortalities. A significant learning curve was observed in terms of the duration of the surgical intervention. The researchers concluded percutaneous needle-guided fetal cardiac intervention appears to be a safe procedure for the mother. In 53 procedures no major maternal complication directly related to the surgical intervention was observed.

Freud and colleagues (2014) reported the postnatal outcomes of 100 participants who underwent FAV for evolving HLHS. A total of 100 participants who underwent FAV for severe midgestation AS with evolving HLHS from March 2000 to January 2013 were included in the study. Clinical records were reviewed, and participants were categorized based on postnatal management as BV or HLHS. A total of 84 fetuses were live-born, and 38 had a BV circulation (31 from birth, 7 converted after initial univentricular palliation). Left-sided structures, namely aortic and mitral valve sizes and LV volume were significantly larger in the BV group at the time of birth (p-values <0.01). After a median follow-up of 5.4 years, freedom from cardiac death among all BV participants was 96 ± 4% at 5 years and 84 ± 12% at 10 years, which was better than HLHS patients (log-rank p=0.04). There was no cardiac mortality in the participants with BV circulation from birth. All but 1 of the BV participants required postnatal intervention; 42% underwent aortic and/or mitral valve replacement. On most recent echocardiogram, the median LV end-diastolic volume z-score was +1.7 (range: -1.3, +8.2), and 80% had normal ejection fraction. The authors concluded that short- and intermediate-term survival among participants who underwent FAV and achieved a BV circulation postnatally is encouraging, but because morbidity still exists, ongoing assessment is warranted.

Artz and colleagues provided data from a small case series in Austria of 23 fetal participants with CAS (2011). Aortic valvuloplasty was attempted in all participants, with success reported in 16 (69.6%); 15 of these procedures were judged to be technically successful with 1 intrauterine death in this group. In 8 fetuses the intervention was not successful, with intrauterine fetal death in 2 of these cases. In 10 of the 15 successfully treated and live born fetuses, BVC was achieved postnatally. Complications included severe sustained bradycardia requiring intracardiac treatment with epinephrine. Other complications included hemopericardium, left ventricular thrombus, and balloon tear off. At median follow-up of 27 months, 40% of the 10 newborns that achieved BVC required only AV balloon dilatation in the first prenatal week and no further surgery. Although in this small series, fetal aortic valvuloplasty was performed successfully in two-thirds of selected fetuses with CAS, further study of the long-term outcome is needed to judge the permanent function of the left ventricle after this intrauterine intervention.

McElhinney and colleagues (2009) described the outcomes of aortic valvuloplasty in 70 fetuses with severe AS and evolving HLHS. The procedure was reported to be successful in 52 (74%) cases. In 20 participants with significant aortic regurgitation following valvuloplasty, all but 1 had resolution. The remaining participant had persistent regurgitation through the newborn evaluation. Within the study group, 1 pregnancy was terminated and 8 (13%) did not reach a viable term or preterm birth. Another 6 pregnancies ended in fetal death or preterm stillbirth, another 2 were live births, but were nonviable due to extreme prematurity. Of the remaining 61 participants, 5 were delivered preterm, 54 were delivered at term, and 2 were still in utero at time of publication. Overall, 67% of participants had a technically successful valvuloplasty and were born viable. In the group of 14 participants with unsuccessful procedures but born at a viable age, 11 (78.6%) were alive at time of publication. At the time of birth, 15 participants with successful interventions had biventricular circulation (30%). The remaining 30 participants underwent further procedures postnatally, and 6 died. Only 2 of the remaining 24 participants converted to biventricular circulation. Larger left heart structures and higher left ventricular pressure at the time of the aortic valvuloplasty were associated with a biventricular outcome postpartum. Using a multi-variable threshold scoring system, the researchers were able to discriminate fetuses with a biventricular outcome with 100 % sensitivity and modest positive-predictive value. The authors concluded that technically successful aortic valvuloplasty modifies left heart valvar growth in fetuses with AS and evolving HLHS and, in a subgroup of cases, appeared to play a role in a biventricular outcome after birth. Fetal aortic valvuloplasty poses significant risks to the fetus and the mother. The authors also found that fetuses undergoing in-utero aortic valvuloplasty with an unfavorable multi-variable threshold score at the time of intervention are very unlikely to achieve a biventricular circulation postnatally.

In a retrospective study, Selamet Tierney and colleagues (2007) reported the effects of mid-gestation fetal balloon aortic valvuloplasty on subsequent fetal left ventricular function. A total of 42 fetuses had attempted aortic valvuloplasty, 12 were excluded from analysis due to inadequate follow-up data, pregnancy termination or fetal demise. Study fetuses (n=30) had pre-procedure echocardiography at a median gestational age of 23 weeks and were followed for a median of 66 ± 23 days post-intervention. In 26 of the 30 study fetuses, aortic valvuloplasty was reported to be technically successful. A control group was used which included the 4 fetuses that underwent technically unsuccessful aortic valvuloplasty plus 14 control fetuses that did not undergo the intervention. Left ventricular ejection fraction increased from 19 ± 10% pre-intervention to 39 ± 14% post-intervention (p<0.001). Other improvements in Doppler cardiac characteristics were also noted in the study group, but not in the control group. The authors caution that further study is necessary to determine if changes in left heart physiology after in-utero aortic valvuloplasty can be used to predict postnatal outcome.

Makikallio and colleagues (2006) conducted a study to define echocardiographic features associated with progression of midgestation fetal AS to HLHS. Researchers reviewed the fetal echocardiograms of 43 fetuses diagnosed with AS and normal left ventricular (LV)

length at ≤ 30 weeks' gestation. Of 23 live-born participants with available follow-up data, 17 had HLHS and 6 had a biventricular circulation. At the time of diagnosis, LV length, aortic valve, mitral valve and ascending aortic diameter Z-scores did not differ between fetuses that went on to develop HLHS and those that maintained a biventricular circulation postnatally. However, all of the fetuses that progressed to HLHS had retrograde flow in the transverse aortic arch (TAA), 88% had left-to-right flow across the foramen ovale, 91% had monophasic mitral inflow, and 94% had considerable LV dysfunction. Contrary to these findings, all 6 fetuses with a biventricular circulation postnatally had antegrade flow in the TAA, biphasic mitral inflow, and normal LV function. With progressing gestation, growth arrest of left heart structures became evident in fetuses developing HLHS. The authors concluded that in midgestation fetuses with AS and normal LV length, reversed flow in the TAA and foramen ovale, monophasic mitral inflow, and LV dysfunction signal the progression to HLHS. These physiological features may help improve patient selection for fetal intervention to prevent the progression of AS to HLHS.

Tworetsky and colleagues (2004) reported the results of a program to relieve fetal AS, preserve left heart function and flow in utero and perhaps prevent HLHS altogether. In this study, researchers offered fetal AS dilation to 24 mothers whose fetuses had AS. At least three echocardiographers assigned a high probability that all 24 fetuses would progress to HLHS if surgical intervention was not provided. After a discussion of the risk and benefits of the procedure, four sets of parents (4 of 24, 16%) declined further intervention. A total of 20 fetuses (21 to 29 weeks' gestation) underwent attempted AS dilation, with technical success in 14 participants. Three of the first 4 attempts were technically unsuccessful and shared several common features including suboptimal fetal positioning, inability to manipulate the wire across the aortic valve, and a cannula angle that directed the wire either toward or posterior to the ventricular septum instead of toward the aortic valve. Serial fetal echocardiograms following the intervention demonstrated ongoing left heart growth in successful cases and growth arrest of the left heart structures in unsuccessful cases and in those who declined the intervention. Resumed left heart growth resulted in biventricular circulation at birth in 3 babies. The researchers concluded that fetal echocardiography can be used to identify midgestation fetuses with AS who are at elevated risk for developing HLHS. While aortic valve dilation may prevent left heart growth arrest and may result in normal ventricular anatomy and function at birth, successful aortic valve dilation requires ideal positioning of the fetus and the cannula.

Fetal complications occurred frequently during or shortly following the intervention. They included fetal demise 1 day after a technically successful intervention in a fetus with severe hydrops. There was a second fetal demise 1 day after an unsuccessful intervention, thought to the result of fetal stress and prolonged anesthesia time, and an additional death 3 days after the procedure in a fetus who experienced severe bradycardia during a technically successful dilation. That fetus also had moderate to severe mitral regurgitation. There was 1 previable delivery as a result of incompetent cervix 3 weeks following the intervention (interval cervical monitoring by ultrasound had been normal). Two balloons ruptured during a second or third inflation after being repositioned in the participant. In 1 fetus, a balloon fragment was missing when the balloon was removed through the cannula. Intraoperative fetal bradycardia occurred in 15 cases, requiring administration of epinephrine in 11 participants with recovery of normal heart rate in all. Two fetuses experienced a small pericardial effusion that resolved spontaneously within several hours. Maternal respiratory compromise requiring the administration of oxygen occurred in the participant presenting with fetal hydrops and responded to diuresis on postoperative day 1. None of the mothers experienced hemorrhage that required blood transfusion, postoperative infection, or thrombotic events (Tworetsky, 2004).

Fetuses with prenatally diagnosed CAS and eHLHS are at significant risk of morbidity and mortality. With the advent of the ability to identify prenatal anatomic and physiologic characteristics predictive of the development of HLHS, FAV is generally accepted by the practicing medical community as an appropriate surgical intervention to prevent progression of CAS to eHLHS in carefully selected individuals. While FAV poses significant risks to the fetus as well as some risk to the mother, FAV is grounded on the premise that biventricular circulation returns a better prognosis over the course of the child's life. Given the uniform lethality of the untreated disease and the significant mortality associated with postnatal management, FAV may be considered justifiable in carefully selected individuals. The technical success of intrauterine FAV has improved over time and appears to be related to experience of the medical facility and fetal surgery team. FAV should be carried out at a facility with a dedicated, multidisciplinary Fetal Care Team that is prepared to provide support in the medical, social, and ethical considerations of undergoing a FAV procedure.

## Definitions

Aqueductal stenosis: The most common cause of congenital hydrocephalus, a condition caused by a narrowing of the Aqueduct of Sylvius which is a space that connects the third and fourth ventricles of the brain and allows the flow of cerebrospinal fluid.

Body Mass Index (BMI): Weight in kilograms divided by the square of the height in meters.

Congenital cystic adenomatoid malformation: A benign (non-cancerous) mass of abnormal lung tissue, usually located in one lobe of the lung. This condition is caused by overgrowth of abnormal lung tissue that may form fluid filled cysts that do not function as normal lung tissue.

Congenital diaphragmatic hernia: A condition where there is a hole in the diaphragm, the muscle that separates the chest and abdominal cavities, through which the organs in the abdomen pass through and compress the lungs and heart.

Extralobar pulmonary sequestration: A condition where a portion of a normal lung lacks the usual connections to the rest of the lung, including air passages and blood flow. If uncorrected this portion of the lung cannot perform normal respiratory functions.

Fetal hydrops: A condition characterized by the presence of a generalized collection of extra fluid under the skin of a fetus and in one or more body cavities.

Fetal surgery: A surgical procedure performed on an unborn child while still in the mother's uterus, to correct congenital deformities that have significant health impact.

Fibroelastosis: The proliferation of fibroelastic tissue in an organ (for example, the left ventricle of the heart) or tissue of the body.

Hindbrain herniation: A condition where a posterior portion of the brain inappropriately protrudes through the spinal cord opening in the base of the skull (the foramen magnum). This condition is referred to as a "Chiari Malformation" (CM) and may be classified as Type I, Type II or Type III. Type I involves the extension of the cerebellar tonsils (the lower part of the cerebellum) into the foramen magnum, without involving the brain stem. Type II, also called classic CM, involves the extension of both cerebellar and brain stem tissue into the foramen magnum. Type III is the most serious form of CM since the cerebellum and brain stem protrude through the foramen magnum and into the spinal cord.

Hypoplastic left heart syndrome (HLHS): A complex, congenital cardiac condition typified by a diminutive left ventricle and small left-sided structures incapable of supporting the systemic circulation. If left untreated, HLHS is generally fatal.

Karyotype: The characterization of an individual's chromosomes, including number, type, shape, etc.

Kyphosis: An abnormal forward rounding of the upper portion of the spine. Individuals with this condition may appear to have a "hump."

Maternal mirror syndrome: The occurrence of fetal and placental hydrops with maternal pre-eclampsia; it is called “mirror syndrome” because the edema in the mother mirrors that in the fetus (also known as Mirror Syndrome or Ballantyne’s Syndrome).

Myelomeningocele: A condition where the backbone and spinal canal of a fetus do not close before birth. This can result in the spinal cord and it’s covering membranes protruding out of the infant's back. This is the most common cause of spina bifida. Nearly all individuals with myelomeningocele have a Chiari II malformation.

Oligohydramnios: A condition characterized by too little amniotic fluid within the amniotic sack surrounding the fetus. Certain birth defects such as kidney and urinary tract problems and ruptured membranes are the most common cause for his condition.

Placental abruption: A condition where a placenta either partially or completely peels away from the inner wall of the uterus before delivery.

Placentamegaly: A condition where the mother’s placenta is abnormally enlarged.

Pre-eclampsia: Also referred to as toxemia**,** a condition characterized by maternal high blood pressure, swelling, high concentrations of protein in maternal urine; this condition may interfere with adequate blood supply to the fetus.

Sacrococcygeal teratoma: A type of tumor that develops in fetuses in the lower-most portion of the back, just above the buttocks. Most frequently these are benign tumors but the odds of malignancy increases with increasing age, necessitating removal at the earliest possible opportunity.

Tracheal occlusion: A condition where the main airway to the lungs is blocked, most frequently due to diaphragmatichernia.

Thoraco-amniotic shunt: A tube that drains the fluid from the chest into the amniotic sac. Fluid accumulation in the chest may be due to congenital cystic adenomatoid malformation or extralobar pulmonary sequestration.

Urinary tract obstruction: A condition where the flow of urine through the urinary tract is blocked.

Vesico-amniotic shunting: A treatment for fetal urinary tract obstruction, where a tube is inserted into the urinary tract above the obstruction and passed through the abdominal wall to drain into the amniotic sac.

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## Index



**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

## History

| Status | Date | Action |
|---|---|---|
| New | 02/15/2024 | Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development. Moved contents of SURG.00036 Fetal Surgery for Prenatally Diagnosed Malformations to clinical utilization management guideline document with the same title. Reformatted Clinical Indications section and added medically necessary criteria for fetal aortic valvuloplasty. Updated Coding, Discussion/General Information, References and Websites for Additional Information sections. |