Intrauterine Fetal Surgery (for Kentucky Only)

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Instructions for Use

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Related Policies
None

Application

This Medical Policy only applies to the state of Kentucky.

Coverage Rationale

Intrauterine fetal surgery (IUFS) is proven and medically necessary for treating the following conditions:

- Congenital Cystic Adenomatoid Malformation (CCAM) and Extralobar Pulmonary Sequestration (EPS): Fetal lobectomy or thoracoamniotic shunt placement for CCAM and thoracoamniotic shunt placement for EPS
- Pleural Effusion: thoracoamniotic shunt placement
- Sacrococcygeal Teratoma (SCT): SCT resection
- Urinary Tract Obstruction (UTO): Urinary decompression via vesicoamniotic shunt placement
- Twin-Twin Transfusion Syndrome (TTTS): Fetoscopic laser surgery (Stages II, III, IV in pregnancies at < 26 weeks of gestation)
- Twin Reversed Arterial Perfusion (TRAP): Ablation or occlusion of anastomotic vessels (e.g., laser coagulation or radiofrequency ablation)
- Myelomeningocele (MMC) repair

Fetoscopic endoluminal tracheal occlusion (FETO) is proven and medically necessary for the intrauterine treatment of congenital diaphragmatic hernia (CDH) when the following criteria are met:

- Diagnosis of CDH before 30 weeks of gestation
- Severe pulmonary hypoplasia defined as a quotient of the observed-to-expected lung-to-head ratios of less than 25.0%
- No other major structural or chromosomal defects are present

Due to insufficient evidence of efficacy, IUFS is unproven and not medically necessary for treating all other conditions, including but not limited to:

- Congenital diaphragmatic hernia when the FETO criteria above are not met or for other approaches to intrauterine CDH surgery Congenital heart disease (CHD)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
59072	Fetal umbilical cord occlusion, including ultrasound guidance
59074	Fetal fluid drainage (e.g., vesicocentesis, thoracocentesis, paracentesis), including ultrasound guidance
59076	Fetal shunt placement, including ultrasound guidance
59897	Unlisted fetal invasive procedure, including ultrasound guidance, when performed

HCPCS Code	Description
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
S2411	Fetoscopic laser therapy for treatment of twin-to-twin transfusion syndrome

Description of Services

This policy addresses the use of intrauterine fetal surgery (IUFS), an open surgical treatment of fetuses with specific life-threatening conditions that involve a fetal malformation. During IUFS, a hysterotomy is performed, and the fetus is partially removed to correct a fetal malformation.

IUFS uses minimally invasive techniques (i.e., small incisions) and instruments to correct the fetal malformation. The primary medical conditions indicated for IUFS include the following:

- Congenital cystic adenomatoid malformation
- Congenital diaphragmatic hernia
- Congenital heart disease
- Extralobar pulmonary sequestration
- Myelomeningocele repair
- Sacrococcygeal teratoma
- Twin-twin transfusion syndrome
- Twin reversed arterial perfusion syndrome
- Urinary tract obstruction

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

Congenital cystic adenomatoid malformation (CCAM), also known as congenital pulmonary airway malformation, and bronchopulmonary sequestration (BPS) are rare congenital cystic lesions of the lung in fetuses. CCAMs derive their blood supply through the pulmonary circulation, while BPS does not have a connection to the tracheobronchial tree and receives arterial flow directly from the aorta. Depending on the size of the lesion, other possible findings include polyhydramnios, mediastinal shift, pleural effusions, and hydrops. Large lesions may compress residual tissue, thus increasing the risk of

pulmonary hypoplasia. The fetal intervention for these lesions is to permanently reduce the space-occupying effect of the lesion and includes fetal lobectomy or thoracoamniotic shunt placement for CCAM and thoracoamniotic shunt placement for EPS (Sfakianaki and Copel 2012, Witlox et al., 2019).

Congenital Diaphragmatic Hernia (CDH)

CDH results from abnormal development of the diaphragm, which allows abdominal organs like the bowel, stomach, and liver to protrude into the chest cavity. Fetuses diagnosed in utero as a result of maternal symptoms have a high mortality risk. Less invasive fetal procedures are being developed that focus on methods to accomplish tracheal occlusion (Walsh et al., 2011).

Congenital Heart Disease

In utero procedures are performed for cardiac conditions such as pulmonary atresia with intact ventricular septum, critical aortic stenosis with impending hypoplastic left heart syndrome, and hypoplastic left heart syndrome with intact atrial septum. All of these conditions, if untreated either in utero or soon after birth, are fatal (Walsh et al., 2011).

Myelomeningocele (MMC)

MMC (also known as spinal bifida) is a neural tube defect in which the spinal cord forms but remains open. Although MMC is rarely fatal, individuals affected with it have a range of disabilities, including paraplegia, hydrocephalus, skeletal deformities, bowel and bladder incontinence and cognitive impairment. Standard therapy is postnatal surgical closure of the MMC followed by shunting for hydrocephalus if needed (Walsh et al., 2011).

Pleural Effusion

Fetal pleural effusion is a rare condition characterized by an accumulation of fluid in the fetal thorax. Pleural effusions are either primary or secondary, depending on the underlying etiology. When fetal pleural effusions are large or bilateral, they can compromise lung development, leading to pulmonary hypoplasia. Polyhydramnios and secondary fetal hydrops may occur and results in a poor prognosis. Thoracoamniotic shunting is used to drain the pleural effusion into the amniotic cavity and prevent or reverse hydrops (Chon et al., 2019, Jeong et al., 2015).

Sacrococcygeal Teratoma (SCT)

Fetuses with large, vascular SCTs have a high incidence of prenatal mortality from high-output cardiac failure or spontaneous hemorrhage of the growing tumor. Fetal surgical procedures for SCT have focused on the small subgroup of fetuses with SCT and hydrops because untreated cases are expected to die in utero or at birth. In severe cases, SCT with hydrops is associated with a maternal risk of developing mirror syndrome, a severe form of preeclampsia (Walsh et al., 2011).

Thoracic Lesions

Congenital cystic adenomatoid malformation (CCAM) and bronchopulmonary sequestration are congenital anomalies of the lung. Appropriate candidates for in utero treatment include a small subset of fetuses with congenital pulmonary airway malformations. In this subset, the fetal mediastinum is compressed, leading to impaired venous return with resulting fetal hydrops, secondary to cardiac failure (Walsh et al., 2011).

Twin Reversed Arterial Perfusion (TRAP)

TRAP sequence is a condition in which an acardiac/acephalic twin receives all of its blood supply from a normal twin, the so-called “pump” twin. Blood enters the acardiac twin through a retrograde flow via the umbilical artery and exits via the umbilical vein. The extra work places an increased demand on the heart of the pump twin, resulting in cardiac failure. Twin death occurs more frequently when the size of the acardiac twin is greater than half that of the pump twin. The goal of fetal surgery is to interrupt blood supply to the non-viable twin.

Twin-Twin Transfusion Syndrome (TTTS)

In TTTS, twins share a single chorionic membrane and a single placenta but have separate amniotic sacs. Women with severe TTTS who have not undergone treatment before 26 weeks will usually experience loss of both fetuses. However, if both twins survive, they often experience severe neurologic compromise and organ failure. Treatment options include amnioreduction to relieve pressure and uterine size, termination of the sicker twin, or fetoscopic laser ablation of the communicating vessels. In

nonselective ablation, all vessels crossing the dividing membrane are ablated, whereas selective ablation is limited to certain vessels connecting the two fetuses (Walsh et al., 2011).

Urinary Tract Obstruction (UTO)

Fetal UTO interferes with normal development of the kidneys and lungs, particularly when involving the lower urinary tract. Goals of fetal surgery have emphasized decompression procedures, such as percutaneous shunting, rather than repair of the specific lesion. The goal of decompression of the distended portion of the urinary tract is to protect function of the remaining kidney and to promote lung development (Walsh et al., 2011).

Clinical Evidence

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

Litwińska et al. (2017) conducted a retrospective case series and literature review of 12 fetuses with a large thoracic cyst treated with thoracoamniotic shunting between 2004 and 2014 in a tertiary fetal therapy center. In all cases the thoracic cyst was associated with major mediastinal shift, the CCAM volume ratio (CVR) was >1.6, and in 8 cases there was associated hydrops. Shunt insertion was successfully carried out in all cases at a median gestational age of 24 weeks (range 18-34). In ten cases there was live birth at a median age of 38 weeks (range 35-41), but in two hydropic fetuses there was intrauterine death. A literature search identified a total of 98 fetuses with CCAM treated with thoracoamniotic shunting between 1987 and 2016. In the combined data from the previous and the current study, the survival rate was 77% for hydropic and 90% for nonhydropic fetuses. The authors concluded that the role of thoracoamniotic shunting in macrocystic lung lesions associated with hydrops is well accepted, and that intrauterine intervention is also likely to be beneficial in the subgroup of nonhydropic fetuses with a CVR >1.6.

Knox et al. (2006) conducted a systematic review to determine the effect of in-utero pulmonary drainage on perinatal survival in fetuses with primary hydrothoraces and/or congenital cystic lung lesions. A search was conducted in MEDLINE (1966-2004), EMBASE (1988-2004) and the Cochrane Library (2004 issue 2). Selected studies compared the effect of prenatal pulmonary drainage (shunt, surgery, or drainage) on perinatal survival to no treatment, in fetuses with ultrasonic evidence of lung pathology. Of a total of 7,958 articles, there were 16 controlled observational studies that included 608 fetuses. Pooled odds ratios (ORs) were used as summary measures of effect and the results were stratified according to predicted fetal prognoses. Pulmonary drainage did not improve perinatal survival in cystic lung lesions compared with no drainage (OR 0.56, 95% CI 0.32-0.97, p = 0.04) overall. However, there was an improvement with this therapy in a subgroup of fetuses with fetal hydrops fetalis (OR 19.28, 95% CI 3.67-101.27, p = 0.0005) however, this was not observed in the subgroup uncomplicated by fetal hydrops fetalis (OR 0.04, 95% CI 0.01-0.32, p = 0.002). The authors concluded that percutaneous, in-utero pulmonary drainage in fetuses with ultrasonic evidence of congenital pulmonary cystic malformations is associated with improved perinatal survival among fetuses with hydrops fetalis.

Clinical Practice Guidelines

Society for Maternal-Fetal Medicine (SMFM)

A SMFM guideline 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, and fetal congenital pulmonary airway malformation (2015).

Pleural Effusion

Chon et al. (2019) conducted a single-center case series analysis to describe postnatal outcomes in survivors after TA shunt placement for congenital pleural effusions. At this center, patients with a dominant unilateral or bilateral pleural effusion complicated by hydrops fetalis were offered TAS placement. The term “dominant” was reserved for fetuses with pleural effusions that were the first to develop or that were relatively more prominent than any remaining fetal effusions, and that were suspected to be the primary underlying cause of the cardiovascular compromise leading to the hydrops. Over a ten-year period, a total of 29 patients with pleural effusion with secondary hydrops underwent TAS placement. The gestational age at the initial TAS placement was 27.6 (20.3-36.9) weeks. Before delivery, hydrops resolved in 17 (58.6%) patients. The delivery gestational age was 35.7 (25.4-41.0) weeks, and the overall survival rate was 72.4%. Of the 21 survivors, 19 (90.5%) required admission to the neonatal intensive care unit for 15 (5-64) days. All survivors had postnatal resolution of the pleural effusions. At the time of

last reported follow-up, all 21 children were long-term survivors, with a median age of survivorship of 3 years 3 months. (9 mos.-7 years 6 months.). The authors concluded TA shunting in fetuses with a dominant pleural effusion(s) and secondary hydrops resulted in a 72% survival rate. Nearly all survivors required admission to the neonatal intensive care unit. However, a majority did not have significant long-term morbidity.

Jeong et al. (2015) conducted a single-center case series analysis to evaluate outcomes of fetal pleural effusion after TA shunting. A total of 68 singleton pregnancies with massive fetal pleural effusion were included. Of those, three were lost to follow-up and two fetuses died in utero. The median gestational age at shunting was 28.3 weeks (range, 18.5-34.1 weeks). Of the 65 fetuses, 50 (76.9%) were hydropic, of which hydrops resolved following shunting in 29 fetuses (58.0%). Among the 63 live births, the median gestational age at delivery was 33.6 weeks (range, 26.2-40.0 weeks), with 36 fetuses (57.1%) delivered preterm. The overall survival rate was 75.4% (49/65), and in a subgroup analysis, the survival rate was highest for non-hydropic fetuses (14/15, 93.3%), followed by fetuses whose hydrops resolved (25/29, 86.2%) and remained after shunting (10/21, 47.6%). The authors concluded that TA shunting can be helpful for fetuses with massive pleural effusion. While fetal hydrops can occur in such cases, perinatal outcomes can be improved by successful shunting.

Peranteau et al. (2015) conducted a single-center case series analysis of fetuses diagnosed with a congenital lung lesion or pleural effusion (PE) that underwent thoracoamniotic shunt (TA) placement. Ninety-seven shunts were placed in 75 fetuses. Average gestational age at shunt placement and birth was 25 ± 3 weeks and 34 ± 5 weeks, respectively. Shunt placement resulted in a 55 ± 21% decrease in macrocystic lung lesion volume and complete or partial drainage of the PE in 29% and 71% of fetuses. Fifty-two (69%) fetuses presented with hydrops, which resolved following shunt placement in 83%. Survival was 68%, which correlated with GA at birth, % reduction in lesion size, unilateral pleural effusions, and hydrops resolution. Surviving infants had prolonged NICU courses and often required either surgical resection or tube thoracostomy in the perinatal period. The authors concluded that TA shunts provide a therapeutic option for select fetuses with large macrocystic lung lesions or PEs at risk for hydrops and/or pulmonary hypoplasia. Survival after shunting depends on gestational age at birth, reduction in mass size, and hydrops resolution.

Yinon et al. (2010) conducted a case series analysis to evaluate perinatal outcome of fetuses with primary pleural effusions following pleuroamniotic shunting. A total of 88 fetuses with large pleural effusions were referred to a tertiary fetal medicine unit and after thorough evaluation, underwent pleuroamniotic shunting. At presentation, 59 (67.0%) fetuses were hydropic and 67 (76.1%) had bilateral effusions. In 17 (19.3%) fetuses, pleural fluid was aspirated prior to shunting and in 71 (80.7%), shunts were inserted directly as the first procedure. The mean gestational age at shunting was 27.6 (range, 18–37) weeks and at delivery 34.2 (range, 19–42) weeks. Seventy-four (84.1%) babies were born alive and of those, 52 (70.3%) survived the neonatal period. Of 59 hydropic fetuses, 10 (16.9%) died in utero and 18 neonates (30.5%) died, resulting in perinatal survival of 52.5%, whereas of 29 non-hydropic fetuses, perinatal survival was 72.4%. Hydrops resolved following shunting in 28 fetuses, of whom 71% survived, compared to 35% survival in 31 fetuses where hydrops persisted (p = 0.006). Of 22 neonatal deaths, seven were related to pulmonary hypoplasia, five to genetic syndromes, two to aneuploidy and one to a congenital anomaly. Overall, 13 (14.8%) were diagnosed with a chromosomal, genetic, or other condition, several of which could not have been diagnosed antenatally. The authors concluded that carefully selected fetuses with primary pleural effusions can benefit from pleuroamniotic shunting, allowing hydrops to resolve with a survival rate of almost 60%.

Sacrococcygeal Teratoma (SCT)

Simonini et al. (2021) conducted a single-center case series study to describe evaluation and outcomes of pregnancies with prenatally diagnosed fetal teratomas of various locations. Data was obtained from the center's perinatal database, neonatal records, or autopsy findings. Perinatal survival and, when available, long-term outcome were compared in different groups of tumor locations. A total of 79 cases of fetal teratomas were included in the study. Of those, the most frequent tumor location was the sacrococcygeal region (n = 47, 59.5%). Among the 47 cases with tumors in the sacrococcygeal region, ultrasound findings showed 21 cases with cardiac compromise, 14 with middle cerebral artery peak systolic velocity values greater than 1.5 multiples of the median and 18 with polyhydramnios. For this subset of cases, prenatal interventions included amniotic fluid drainage (n = 7), tumor puncture (n = 7), radiofrequency ablation (n = 3), intra-uterine transfusion (n = 3), and ascites puncture (n = 2). Outcomes of those cases included alive and well (n = 30), termination of pregnancy (n = 9), neonatal death (n = 6), intrauterine death (n = 1), and no follow-up (n = 1). Across all types of fetal teratomas, preterm birth before 37 and early preterm birth before 32 weeks occurred in 72.7% and 29.1%, respectively. Major causes of perinatal death were tumor bleeding in sacrococcygeal teratomas (SCTs) and respiratory failure in cervical and oropharyngeal teratomas. The authors concluded that to achieve best outcome for children with teratomas, it is important to recognize specific complication patterns during pregnancy and to meet them with a multidisciplinary approach. They also stated that the need for intervention is high

throughout gestation and ranges from fetal pericardiocentesis, to amniotic fluid drainage, or cyst puncture in order to facilitate delivery, experience with successful minimal-invasive treatment in cases with high cardiac output failure still remains limited, and that additional imaging by MRI should be considered in particular in tumors of the neck and oropharynx however, is not in general superior to prenatal ultrasound, which offers very high sensitivity in the diagnosis and spatial extension of fetal teratomas.

Sananes et al. conducted a retrospective multicenter cohort study in 13 fetuses with high-risk large SCTs between 2004-2010. Additionally, the researchers performed a systematic literature review of all cases that underwent tumor ablation in order to compare the survival rates after 'vascular' and 'interstitial' ablation. Study objectives were to evaluate the efficacy of minimally invasive ablation of high-risk large SCTs and to compare the efficacy of the vascular versus interstitial tumor approach. Five of the 13 underwent tumor ablation. The estimated difference in hydrops resolution rate and survival rate between the fetal intervention and the no fetal intervention groups was 44.6% and 31%, respectively. The five cases were then analyzed with 28 cases from the literature. Researchers estimated the difference in survival rate and in hydrops resolution rate between the vascular and interstitial ablation groups was 19.8% and 36.7%, respectively. The authors concluded that minimally invasive surgery seemed to improve perinatal outcome in cases of high-risk large fetal SCT. Their findings also suggested that vascular ablation may improve outcome and may be more effective than interstitial tumor ablation. Further investigation in a larger multicenter prospective study is needed (2016).

Fetal surgery is not considered appropriate in the presence of the maternal mirror syndrome or in cases of advanced high-output cardiac failure (Hedrick et al., 2004).

Urinary Tract Obstruction (UTO)

Nassr et al. (2017) conducted an updated systematic review and meta-analysis to evaluate the effect of vesicoamniotic shunt (VAS) as treatment for fetal lower urinary tract obstruction (LUTO). The primary outcomes were perinatal and postnatal survival rates. The secondary outcome was the effect of treatment with a VAS on postnatal renal function compared with conservative prenatal management. A search was conducted using the following databases: Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews and Scopus. Cohort studies and clinical trials were included. However, case series were also included if the intervention and conservative management could be identified after the exclusion of cases that underwent elective termination of pregnancy (TOP). Single-arm studies and studies that did not report survival were excluded. All included studies were required to clearly define LUTO as the presence of an enlarged fetal bladder and bilateral hydronephrosis. Results from a total of nine studies (four retrospective cohort, one combined prospective and retrospective cohort, one randomized trial, and two that did not specify the method of data collection) were pooled for the meta-analysis. The results revealed that 64 of the 112 fetuses in the VAS arm survived compared with 52 of the 134 fetuses in the conservative arm (57.1% vs. 38.8%, $p < 0.01$). The pooled estimate of survival was different in the two arms, favoring VAS (OR, 2.54 (95% CI, 1.14–5.67)). There was no difference in six-month or 12-month survival (OR, 1.77 (95% CI, 0.25–12.71)) or two-year survival (OR, 1.81 (95% CI, 0.09–38.03)). Furthermore, there was no difference in postnatal renal function between fetuses that underwent VAS and those that did not (OR, 2.09 (95% CI, 0.74–5.94)). The authors concluded that data available for this meta-analysis appears to support an advantage for perinatal survival in fetuses treated with VAS compared with conservative management, and that one to two-year survival and long-term renal function after a VAS procedure remains uncertain. However, multi-center, randomized controlled trials evaluating VAS treatment with various levels of LUTO severity are also needed.

Twin-Twin Transfusion Syndrome (TTTS)

Kim et al. (2021) conducted a single-center, case series study to assess perinatal outcomes and its associated factors in fetuses with twin-to-twin transfusion syndrome (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 A total of 172 cases of monochorionic diamniotic twins and one case of dichorionic triamniotic triplets were prenatally diagnosed with TTTS and treated with FLC. The median gestational ages (GAs) at diagnosis and FLC were 20.3 and 20.5 weeks, respectively. The median GA of survivors at delivery was 32.5 weeks. The overall at least one twin- and double-survival rates within 28 days after birth were 82.1% and 55.5%, respectively. The GAs at diagnosis and FLC, Quintero stage, inter-twin weight discordance, associated selective intrauterine growth restriction (sIUGR), procedure time, volume of amnioreduction, preterm prelabor rupture of membranes (PPROM) within one 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 GA 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.

Stirnemann et al. (2021) conducted a multi-center, randomized trial to determine if stage 1 twin-twin transfusion syndrome (TTTS) should be managed primarily with intrauterine fetoscopic photocoagulation of placental anastomosis or expectantly. Asymptomatic women with stage 1 twin-twin transfusion syndrome 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 six 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 seven 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 five of 109 (4.6%) and three of 114 (2.6%) (p = 0.49) cases in the expectant and immediate surgery groups, respectively. 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 nonsignificantly (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.

Ozawa et al. (2017) conducted a prospective case series interventional study to investigate the feasibility and safety of fetoscopic laser photocoagulation (FLP) for amniotic fluid discordance (AFD) bordering on TTTS with an absent or reverse end-diastolic velocity in the umbilical artery, as well as evaluating the perinatal and long-term outcomes. Surgical intervention took place on the fetuses of 11 women during weeks 20-25 of gestation. Neurodevelopmental outcome was evaluated at six months and at 3 years of age. There were nine cases of selective intrauterine growth restriction in which the growth discordant rate exceeded 25%. The survival rates of the donor and recipient twins were 27.3% and 100%, respectively. None of the surviving donor twins and two of the 11 recipient twins had hemiplegia at 6 months of age. One additional recipient twin had developmental delay at 3 years of age. Researchers concluded that FLP does not seem to be a promising treatment option for AFD bordering on TTTS. While feasible without complications, donor twin death occurred frequently and there were some cases of neurodevelopmental abnormalities in the surviving recipient twin.

Salomon et al. (2017) conducted a long-term follow-up study of 256 fetuses with TTTS that were enrolled in the Eurofoetus trial. The Eurofeoetus trial (Senat, 2004) was a multi-center, randomized clinical trial that compared treatment with fetoscopic selective laser coagulation (FSLC; n = 136) versus serial amniodrainage (AD; n = 120). The follow-up study evaluated the neurological and neurodevelopmental outcomes up to age 6. Survivors were evaluated by standardized neurological examination and by Ages and Stages Questionnaires (ASQ). The primary outcome was a composite of death and major neurological impairment. In the FSLC group, 37% (n = 50) and 9% (n = 13) of fetuses died in utero and in the neonatal period, respectively. In the AD group, there were 39% (n = 47) and 22% (n = 26) died in utero and in the neonatal period, respectively. A total of 120 children (47%) were alive at the age of 6 months and were followed up to 6 years of age. At the time of diagnosis, only treatment and Quintero stage were predictors of a poor outcome (hazard ratio, 0.61; 95% CI, 0.41–0.90; p = 0.01 and hazard ratio, 3.23; 95% CI, 2.19–4.76; p < 0.001, respectively). At the end of follow-up, 60 (82%) and 33 (70%) of the children had a normal neurological evaluation in the FSLC and AD treatment groups, respectively (p = 0.12). Children treated by FSLC had higher ASQ scores at the end of follow-up (p = 0.04). The authors concluded that TTTS treated with FSLC is associated with a lower incidence of fetal death and long-term major neurological impairment than treatment with AD.

Roberts et al. (2014) conducted an updated systematic review to evaluate the impact of treatment modalities in twin-twin transfusion syndrome. A search was performed using the Cochrane Pregnancy and Childbirth Group's Trials Register (May 2013), the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, proceedings of major conferences and weekly current awareness alerts from an additional 40 journals. A total of three studies (253 women and 506 babies) were included.

Two studies compared amnioreduction with endoscopic laser coagulation (182 women, Senat 2004 [Eurofoetus trial] and Crombleholme 2007 [NIHCD]) and one study compared amnioreduction with septostomy (71 women, Moise 2005). When amnioreduction was compared with laser coagulation, although there was no difference in overall death between amnioreduction and laser coagulation (average risk ratio (RR) 0.87; 95% confidence interval (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). In this updated review, outcomes for death are different from the previous review (Roberts 2008), where improvements in perinatal death and death of both infants per pregnancy were shown in the laser intervention arm. The NIHCD trial included in this update exerts an opposite direction of effects to the Eurofetus study, which was previously the only included laser study, therefore the difference in outcome. When amnioreduction was compared with septostomy, there were 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 twin-twin transfusion syndrome to improve neurodevelopmental outcomes, and that further research assessing long-term outcomes of TTTS survivors is still needed.

A systematic review and meta-analysis were conducted by Rossi and D'Addario (2008) to review the controversy on laser therapy (LT) versus serial amnioreduction (SA) performed for TTTS. Inclusion criteria were diamniotic monochorionic pregnancy, TTTS diagnosed with standard parameters, and peri- and neonatal outcomes well defined. Ten articles published between 1997-2007 provided 611 cases of TTTS (LT: 70%; SA: 30%) with four studies comparing the two treatments (395 cases: LT, 58%; SA, 42%). The meta-analysis showed that LT was associated with better outcomes than SA.

Graef et al. conducted a case series evaluation of 167 children (median age 3 years, 2 months) to investigate long-term neurodevelopment after intrauterine laser coagulation for TTTS. A total of 145 children (86.8%) demonstrated normal development, 12 children (7.2%) showed minor neurological abnormalities, and 10 children (6%) demonstrated major neurological abnormalities. The investigators concluded that intrauterine laser coagulation was the relatively best treatment option for severe TTTS (2006).

A National Institute for Health and Care Excellence (NICE) interventional procedures guideline states that current evidence on the safety and efficacy of intrauterine laser ablation of placental vessels for the treatment of TTTS appears adequate to support the use of this procedure provided that the normal arrangements are in place for clinical governance (2006).

Clinical Practice Guidelines

Society for Maternal-Fetal Medicine (SMFM)

A SMFM clinical guideline states that over 75% of stage I TTTS cases remain stable or regress without invasive intervention, with perinatal survival of about 86%. Therefore, many patients with stage I TTTS can often be managed expectantly. For stages II-IV, fetoscopic laser photocoagulation of placental anastomoses is considered by most experts to be the best available approach in continuing pregnancies at < 26 weeks. However, expectant management and amnioreduction remain two options for TTTS > stage I at < 26 weeks when the patient does not have the ability to travel to a center that performs fetoscopic laser photocoagulation. Published meta-analysis data have demonstrated no significant survival benefit, and long-term neurologic outcomes in the Eurofetus trial were not different between the laser and non-laser groups. Laser-treated TTTS has been shown to be associated with a perinatal mortality rate of 30-50%, and a 5-20% chance of long-term neurologic handicap. For stage ≥ III TTTS and for those undergoing invasive interventions, steroids for fetal maturation should be considered at 24 0/7 to 33 6/7 weeks (2013).

Twin Reversed Arterial Perfusion (TRAP)

Shettikeri et al. (2020) conducted a single-center cohort study to evaluate outcomes of pregnancies diagnosed with twin reversed arterial perfusion (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 two 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 counselled regarding fetal therapy if the situation were to deteriorate: five 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%) lasers were performed in the second and third trimesters, respectively; all seven 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 two 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.

Zhang et al. (2018) conducted a single-center retrospective case series analysis evaluating 25 patients with pregnancies complicated by different stages of TRAP. All patients were diagnosed by ultrasound and categorized into three groups (Ia, IIa and IIb). Patients were expectantly managed or underwent RFA (radiofrequency ablation) according to the degree to which the pump twin was affected and the abdominal circumference ratio between the acardiac and pump twin. For stage Ia cases without obvious blood flow to the acardiac twin, expectant management was preferred. For stage IIa and IIb cases, RFA (radiofrequency ablation) or expectant management was performed according to the condition of the TRAP. The primary outcome was perinatal outcome: live birth, IUFD (intrauterine fetal demise) or labor induction. Secondary outcomes included gestational age at delivery and complications. 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 the stage IIa cases, 10/19 underwent RFA (radiofrequency ablation) and 6/19 received expectant management, with the remaining three patients refusing any therapy and excluded from the analysis. Among the stage IIb cases, one underwent RFA, and one was managed expectantly. The total survival rate when the pump twin received treatment was 64% (14/22). For the 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 cases, 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 or in stage IIb. The authors concluded that expectant management is an effective for treatment of TRAP sequence in stage Ia and that in cases with stage IIa TRAP, RFA improves the prognosis of pump twins.

Cabassa et al. (2013) conducted a case series review to evaluate the treatment of monochorionic twin pregnancies complicated by TRAP using RFA. Between July 2007 and October 2010, 11 monochorionic twin pregnancies complicated by TRAP were identified. A total of seven patients underwent intrafetal ablation of the acardiac twin with RFA. Median gestational age at the intervention was 17 weeks. A total of five fetuses (71%) were delivered at a median gestational age of 33 weeks; all were alive and had a normal examination at 6 months of age. The overall neonatal survival was 85%. The authors noted that further research is needed to define the best timing of the procedure.

Lee et al. (2013) reported the North American Fetal Therapy Network (NAFTNet) Registry data on the outcomes of using radiofrequency ablation (RFA) to treat TRAP. This was a retrospective review of all patients who underwent percutaneous RFA of an acardiac twin after referral to a NAFTNet institution. The primary outcome was neonatal survival to 30 days of age. Of the 98 patients identified, there were no maternal deaths. Mean gestational age at delivery was 33.4 weeks overall and 36.0 weeks for survivors. Median gestational age at delivery was 37 weeks. Survival of the pump twin to 30 days was 80% in the overall cohort. The authors concluded that this data suggests that RFA of the acardiac twin is an effective treatment for TRAP sequence.

Pagani et al. (2013) conducted a retrospective cohort study and meta-analysis of intrafetal laser treatment for TRAP sequence. A total of 23 cases of TRAP were identified during the study period. Of these, six were managed conservatively and 17 were treated with laser therapy. All cases managed conservatively were complicated by intrauterine death (IUD) at a median gestational age of 14 weeks. Among the treated cases, 14 (82%) delivered a healthy twin at a median gestational age of 37 weeks. The overall neonatal survival was 80%. Adverse pregnancy outcome was significantly lower when the treatment was performed before 16 weeks' gestation.

Myelomeningocele (MMC)

Relating to MMC, a 2018 Hayes report (consisting of an RCT and six cohort studies) suggests that prenatal MMC repair significantly decreases the need for shunts and may decrease hindbrain herniation compared with postnatal MMC repair.

Kabagambe et al. (2018) conducted a systematic review and meta-analysis to evaluate obstetrical, neonatal and 12–month neurological outcomes of patients with myelomeningocele (MMC) who underwent fetoscopic vs. open in utero repair. This

study focused on medical literature published after the MOMS study (Adzick 2011). Using predetermined terms, a search was conducted in PubMed and Embase. Studies that reported fetal, obstetrical, or postnatal outcomes after in utero repair of MMC and published between January 1, 2011 and August 13, 2016 were eligible. After reviewing the identified articles, 11 retrospective or nonrandomized prospective cohort studies were included in the final analysis. Of the 11 studies, five reported outcomes using fetoscopic MMC repair (n = 179) and six were with open fetal repair (n = 257). One study, Belfort (2017), reported fetoscopic MMC repair via maternal laparotomy rather than percutaneous access and since this approach differed, fetoscopic results were reported with and without this study's results. The meta-analysis revealed no difference in mortality or the rate of shunt placement for hydrocephalus. Percutaneous fetoscopic repair was associated with higher rates of premature rupture of membranes (91 vs. 36%, $p < 0.01$) and preterm birth (96 vs. 81%, $p = 0.04$) compared to open repair however, fetoscopic repair via maternal laparotomy reduced preterm birth. The rate of dehiscence and leakage from the MMC repair site was higher after both types of fetoscopic surgery (30 vs. 7%, $p < 0.01$), while the rate of uterine dehiscence was higher after open repair (11 vs. 0%, $p < 0.01$). The authors concluded that fetoscopic repair is a promising alternative to open fetal MMC repair with a lower risk of uterine dehiscence; however, fetoscopic techniques should be optimized to overcome the high rate of dehiscence and leakage at the MMC repair site, and that a fetoscopic approach via maternal laparotomy reduces the risk of preterm birth.

The Management of Myelomeningocele Study (MOMS) compared outcomes of prenatal versus postnatal repair of MMC. Patients (n = 183) were randomized to undergo either prenatal surgery before 26 weeks of gestation or standard postnatal repair. Primary outcomes were fetal or neonatal death, the need for a cerebrospinal shunt by the age of 12 months and mental development and motor function at 30 months. The children of 158 patients were available for evaluation at 12 months. The children of 134 patients were available for evaluation at 30 months. The trial was stopped after recruiting 183 of the planned 200 patients due to demonstrated efficacy of prenatal versus postnatal repair. Despite having more severe lesions and an increased risk of preterm delivery, the study found that the prenatal surgery group had significantly better outcomes than the postnatal surgery group. Prenatal surgery for MMC decreased the risk of death or need for shunting by the age of 12 months. Prenatal surgery also improved scores on a composite measure of mental and motor function at 30 months. However, prenatal surgery was associated with an increased risk of preterm delivery and uterine dehiscence at delivery. The authors noted that the potential benefits of prenatal surgery must be balanced against the risks of prematurity and maternal morbidity (Adzick, 2011). This study was included in the Hayes report (2018).

Danzer et al. (2009) evaluated lower extremity neuromotor function (LENF) and short-term ambulatory potential following fetal MMC (fMMC) closure in a retrospective chart review of 54 children. Neonatal LENF was compared to predicted function based on spinal lesion level assigned by prenatal ultrasound. A total of 31 out of 54 of fMMC children (57.4%) had better than predicted, 13/54 (24.1%) same as predicted and 10/54 (18.5%) worse than predicted LENF at birth. At a median follow-up age of 66 months, 37/54 (69%) walk independently, 13/54 (24%) are assisted walkers, and 4/54 (7%) are wheelchair dependent. Despite the observed improved ambulatory status, structured evaluation of coordinative skills revealed that the majority of independent walkers and all children that require assistive devices to walk experience significant deficits in lower extremity coordination. The investigators concluded that fMMC surgery results in better than predicted LENF at birth and short-term ambulatory status. However, fMMC children continue to demonstrate deficits in movement coordination that are characteristic for children with spina bifida.

Danzer et al. (2008) evaluated the incidence and clinical implications of the development of cutaneously derived intradural inclusion cysts following fMMC closure in retrospective databases and responses to a parental questionnaire. The investigators found that cutaneously derived intradural inclusion cysts can develop following fMMC surgery. Deterioration of bladder function, risk of recurrence, and loss of lower extremity function appear to be the most important long-term complications of inclusion cysts in children with fMMCs.

Koh et al. (2006) compared urodynamic findings in patients who underwent prenatal closure of MMC (n = 5) with those of patients who underwent postnatal closure (n = 88). All five prenatally treated patients had lower lumbosacral lesions on neurological examination. In comparison, 34 of the 88 patients in the postnatal cohort (39%) lacked sphincter activity at newborn examination, with similar findings noted at one-year evaluation. In terms of bladder function, all five patients in the prenatal cohort showed detrusor overactivity, compared to 33 of the 88 patients (38%) in the postnatal cohort at the newborn examination, with similar findings at one-year evaluation. The investigators concluded that fetal closure of MMC is associated with a higher incidence of complete denervation of the external urethral sphincter and detrusor overactivity compared to postnatal closure.

Clinical Practice Guidelines

American College of Obstetricians and Gynecologists (ACOG)

ACOG's Maternal-Fetal Management Task Force published a position statement (Cohen et al., 2014) regarding fMMC repair with the goal of developing "optimal practice criteria for medical and surgical leadership." Members of the task force reported the following:

- "fMMC repairs should be performed in established fetal therapy centers using a multidisciplinary team approach.
- The fetal surgery team must have experience working together and individual members have a level of expertise in their field.
- The level of fetal surgical technical expertise demanded requires an adequate annual volume of open fetal and ex utero intrapartum treatment (EXIT) procedures to maintain competency.
- The level of technical expertise in fMMC repair requires an initial experience of at least five cases and an ongoing adequate annual volume of cases evaluated for fetal surgery to maintain competency.
- Centers developing new programs must receive guidance and training from established programs and experienced individuals.
- The MOMS protocol should be followed for preoperative, intraoperative, and immediate postoperative care. This applies to inclusion and exclusion criteria for in utero MMC repair.
- Modification of the long-term postoperative and delivery care is acceptable in certain circumstances.
- Modifications to the perioperative protocol are only permissible after the results of fMMC repair performed by an expanded number of centers have been shown to be consistent with the results obtained in the MOMS trial. Such modifications would, ideally, be developed by means of a series of cooperative trials.
- Ongoing neonatal and pediatric care should be performed in multidisciplinary spina bifida clinics. This can be done at outside centers but must be standardized.
- Counseling should be full disclosure and nondirective in nature. It should also include reproductive implications for future pregnancies.
- A reflective period of at least 24 hours is recommended.
- Short-term and long-term outcomes data from all centers should be kept in a national registry with periodic review.
- Centers performing open MMC repair must maintain a collaborative approach to outcomes reporting and future research, including participating in the long-term outcomes data collection and evaluation. Close links between fetal centers throughout the country and community providers are essential."

An ACOG practice bulletin states that 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 the implications for future pregnancies (2017).

An ACOG committee opinion states open maternal–fetal surgery for MMC 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 MMC repair should only be offered to carefully selected patients at facilities with an appropriate level of personnel and resources (2017).

Congenital Diaphragmatic Hernia (CDH)

Deprest et al. (2021a) conducted a multi-center international open-labeled RCT in 80 singleton fetuses with severe isolated left CDH comparing fetoscopic endoluminal tracheal occlusion (FETO) at 27 to 29 weeks of gestation to expectant/usual care. To participate, FETO centers were required to have performed a minimum of 36 fetoscopies per year, 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 less than 29 weeks, 6 days, left congenital diaphragmatic hernia 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 initially 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 (relative risk, 2.67; 95% confidence interval [CI], 1.22 to 6.11; two-sided p = 0.009). Survival to 6 months of age was identical to the survival to discharge (relative

risk, 2.67; 95% CI, 1.22 to 6.11). The incidence of preterm, prelabor rupture of membranes was higher among women in the FETO group than among those in the expectant care group (47% vs. 11%; relative risk, 4.51; 95% CI, 1.83 to 11.9), as was the incidence of preterm birth (75% vs. 29%; relative risk, 2.59; 95% CI, 1.59 to 4.52). There were two neonatal deaths, one occurred after emergency delivery for placental laceration from fetoscopic balloon removal, and one 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%; relative risk: 0.18; 95% CI, 0.05 to 0.66). The authors concluded that for these patients, FETO resulted in a significant benefit at discharge that was sustained at six months. The 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. The primary outcomes were survival to discharge and survival without oxygen supplementation at six 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 (relative risk, 1.27; 95% confidence interval [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 (relative risk, 1.23; 95% CI, 0.93 to 1.65). In the FETO group, the incidence of preterm, prelabor rupture of membranes was higher than among those in the expectant care group (44% vs. 12%; relative risk, 3.79; 95% CI, 2.13 to 6.91), as was the incidence of preterm birth (64% vs. 22%, respectively; relative risk, 2.86; 95% CI, 1.94 to 4.34), but FETO was not associated with any other serious maternal complications. There were two spontaneous fetal deaths (one in each group) without obvious cause and one 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 rupture of membranes and preterm birth was increased with FETO. The findings of this study are also limited by the open-labeled study design.

A 2018 Hayes report concludes that FETO for fetuses with mild CDH, cannot be evaluated due to a lack of evidence in the peer reviewed literature. The evidence also suggests that FETO may not benefit fetuses with moderate CDH, although this was only evaluated in a single RCT and thus the evidence is insufficient. In fetuses with severe CDH, there may be clinical benefits over postnatal treatment alone in terms of improved survival and a reduction in severe pulmonary hypertension in infants; however, reviewed evidence is limited to three fair-quality RCTs.

A systematic review and meta-analysis by Grivell et al. (2015) compared the effects of prenatal versus postnatal interventions for CDH on perinatal mortality and morbidity, longer-term infant outcomes, and maternal morbidity. The review also looked to compare the effects of different prenatal interventions with each other. Three studies were included involving 97 women. Two trials examined in utero FETO with standard (postnatal) care in fetuses with severe diaphragmatic hernia. One trial examined the effect of antenatal corticosteroids versus placebo. The authors concluded that there is currently insufficient evidence to recommend in utero intervention for fetuses with CDH as a part of routine clinical practice. Only one of the studies adequately reported on perinatal mortality, but there were no data suitable for inclusion in the analysis. More studies are needed to further examine the effect of both in utero FETO and the use of antenatal corticosteroids on important neonatal outcomes and long-term infant survival and health.

Ruano et al. (2012) conducted a single-center open-label randomized controlled trial on 41 singleton fetuses with severe left or right CDH comparing fetoscopic endoluminal tracheal occlusion (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 (relative risk (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% 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.

Kunisaki et al. (2007) conducted a retrospective cohort analysis to evaluate whether the EXIT to ECMO procedure is a reasonable approach for managing patients antenatally diagnosed with severe CDH. Fourteen patients underwent EXIT with a trial of ventilation. Fetuses with poor preductal oxygen saturations despite mechanical ventilation received ECMO before their delivery. Three neonates passed the ventilation trial and survived, but two of them required ECMO within 48 hours. The remaining 11 fetuses received ECMO before their delivery. Overall survival after EXIT-to-ECMO was 64%. At one-year follow-up, all survivors had weaned off supplemental oxygen, but 57% required diuretics and/or bronchodilators. The investigators concluded that the EXIT-to-ECMO procedure is associated with favorable survival rates and acceptable pulmonary morbidity in fetuses expected to have a poor prognosis under conventional management.

A case series reported the results of 24 fetuses with severe CDH who underwent percutaneous FETO with a balloon. Premature prelabor rupture of the membrane 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 (Deprest et al., 2006).

Hirose et al. (2004) conducted a retrospective review of 52 patients who underwent an EXIT procedure. Fifty-one of 52 patients were born alive. At the time of the study, 27 of 52 patients (52%) were alive. All deaths have been in patients with CDH. The investigators concluded that the EXIT procedures can be performed with minimal maternal morbidity and with good outcomes.

Congenital Heart Disease (CHD)

Kovacevic et al. (2018) conducted a multi-center, retrospective, cohort analysis of fetuses with aortic stenosis that underwent fetal valvuloplasty (FV) compared with fetuses with similar characteristics but did not undergo FV. The primary outcomes were overall survival, biventricular (BV)-circulation survival, and survival after birth. Secondary outcomes were hemodynamic change and left heart growth. To enable retrospective pseudorandomization, a two-stage propensity score process was undertaken. First, propensity scores were derived from clinically relevant variables and then, propensity score cases were weighted, and matching was restricted to those with a score between 0.14 – 0.9. The propensity score model was created with 54/67 FV and 60/147 natural history (NH) fetuses, and the final analytic cohort was comprised of 42 FV fetuses and 29 NH fetuses. FV was successful in 59/67 fetuses at a median age of 26 (21-34) weeks. There were 7/72 (10%) procedure-related losses, and 22/53 (42%) FV babies were delivered at < 37 weeks. After adjusting for circulation and postnatal surgical center, the inverse probability of treatment weighting demonstrated improved survival of liveborn infants following FV (hazard ratio, 0.38; 95% CI, 0.23-0.64; p = 0.0001). Similar proportions had BV circulation (36% for the FV cohort and 38% for the NH cohort) and survival was similar between final circulations. Successful FV cases showed improved hemodynamic response and less deterioration of left heart growth compared with NH cases (p ≤ 0.01). The authors concluded that their results showed improvements in fetal hemodynamics and preservation of left heart growth following successful FV compared with NH. Although the proportion of those achieving a BV circulation outcome was similar in both cohorts, fetuses that survived showed improved survival independent of final circulation up to 10 years of follow-up. However, FV is associated with a 10% procedure-related loss and increased prematurity and therefore, the risk of FV compared to its benefit remains uncertain, and additional trials are still needed.

A 2018 NICE interventional procedures guideline states that current evidence on the safety and efficacy of percutaneous balloon valvuloplasty for fetal critical aortic stenosis is limited in quantity and the results are inconsistent. Therefore, this procedure should only be used in the context of research.

Araujo Júnior et al. (2016) completed a systematic review and meta-analysis to assess perinatal outcomes and intrauterine complications following fetal intervention for CHD. Outcome measures included fetal death, live birth, preterm delivery < 37 weeks' gestation, and neonatal death. Intrauterine complications that were assessed included bradycardia requiring treatment and hemopericardium requiring drainage. Out of 2,279 records identified in the database search, 29 studies (11 retrospective cohort and 18 case reports) were considered eligible for analysis. Fetal death after treatment of CHD by aortic valvuloplasty was reported in three studies, with a rate of 31%; after pulmonary valvuloplasty in one study, with a rate of 25%; after septoplasty in one study, with a rate of 14%; and after pericardiocentesis and/or pericardioamniotic shunt placement in 24 studies, with a rate of 29%. Bradycardia requiring treatment was reported after aortic valvuloplasty in two studies, with a rate of 52%; after pulmonary valvuloplasty in one study, with a rate of 44%; and after septoplasty in one study, with a rate of 27%. The authors concluded that current evidence on the effectiveness of prenatal intervention for CHD derives mostly from case reports and a few larger series; no study was randomized. Although the results of the meta-analysis are encouraging in terms of perinatal survival, they should be interpreted with caution when comparing with procedures performed after delivery (2016).

Pedra et al. (2014) reported results of a small case series of fetal cardiac procedures for various cardiac conditions (21 fetuses; 22 procedures). The procedures included atrial septostomy, fetal aortic valvuloplasty (FAV), pulmonary valvuloplasty, or a combination of aortic septostomy and FAV. The fetal clinical conditions consisted of critical aortic stenosis (AS) (n = 13), hypoplastic left heart syndrome (HLHS) and intact interatrial septum or small patent foramen ovale (n = 4), pulmonary atresia with intact ventricular septum (n = 1), and critical pulmonary stenosis (n = 3). A total of 91% of procedures (20 of 22) were considered successful. Two procedures, FAV and pulmonary valvuloplasty, failed. One fetus died and no maternal complications were reported. Long-term morbidity was frequent, and 12 fetal deaths eventually occurred.

A retrospective review was conducted of 100 patients who underwent FAV for severe mid-gestation AS with evolving HLHS from March 2000 to January 2013. The median gestational age at intervention was 23.8 weeks. Patients were categorized based on postnatal management as biventricular (BV) or HLHS. Eighty-eight fetuses were live-born, and 38 had a BV circulation (31 from birth, seven converted after initial univentricular palliation). Left-sided structures, namely aortic and mitral valve sizes and left ventricular (LV) volume, were significantly larger in the BV group at the time of birth. After a median follow-up of 5.4 years, freedom from cardiac death among all BV patients was 96 ± 4% at 5 years and 84 ± 12% at 10 years, which was better than HLHS patients. There was no cardiac mortality in patients with a BV circulation from birth. All but one of the BV patients 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 patients who underwent FAV and achieved a BV circulation postnatally is encouraging. However, morbidity still exists, and on-going assessment is warranted (Freud et al., 2014).

A total of 70 fetuses underwent attempted FAV for critical AS with evolving HLHS. The procedure was technically successful (increased flow across the valve) in 52 fetuses (74%). Forty-five of these resulted in a viable live birth. Relative to 21 untreated comparison fetuses, subsequent prenatal growth of the aortic and mitral valves, but not the left ventricle, was improved after intervention. Nine pregnancies (13%) did not reach a viable term or preterm birth. Seventeen patients had BV circulation postnatally, 15 from birth. Larger left heart structures and higher left ventricular pressure at the time of intervention were associated with BV outcome. Technically successful FAV alters left heart valvar growth in fetuses with AS and evolving HLHS and, in a subset of cases, appeared to contribute to a BV outcome after birth. The authors note that FAV carries a risk of fetal demise. Further studies from well-designed clinical trials are needed to confirm these results (McElhinney et al., 2009).

Vida et al. (2007) retrospectively identified 32 neonates with a diagnosis of HLHS and intact or highly restrictive atrial septum who underwent left atrial decompression in utero or postnatally before surgery. Fourteen patients (44%) underwent fetal intervention, either atrial septoplasty (n = 9) or FAV (n = 5). The investigators concluded that prenatal decompression of the left atrium may be associated with greater hospital survival. Proposed effects of fetal intervention on lung pathology and longer-term survival require further study.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The fetal interventions described in this policy are surgical procedures and are not subject to FDA approval.

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Policy History/Revision Information

Date	Summary of Changes

12/01/2021	**Coverage Rationale**
	• Added language to indicate fetoscopic endoluminal tracheal occlusion (FETO) is proven and medically necessary for the intrauterine treatment of congenital diaphragmatic hernia (CDH) when the following criteria are met:
	  ○ Diagnosis of CDH before 30 weeks of gestation
	  ○ Severe pulmonary hypoplasia defined as a quotient of the observed-to-expected lung-to-head ratios of less than 25.0%
	  ○ No other major structural or chromosomal defects are present
	• Replaced language indicating:
	  ○ "Intrauterine fetal surgery (IUFS) is proven and medically necessary for treating Twin-Twin Transfusion Syndrome (TTTS): Fetoscopic laser surgery" with "intrauterine fetal surgery (IUFS) is proven and medically necessary for treating Twin-Twin Transfusion Syndrome (TTTS): Fetoscopic laser surgery *(Stages II, III, IV in pregnancies at < 26 weeks of gestation)*"
	  ○ "Intrauterine fetal surgery (IUFS) is unproven and not medically necessary *for CDH*" with "intrauterine fetal surgery (IUFS) is unproven and not medically necessary *when the FETO criteria above are not met or for other approaches to intrauterine CDH surgery*"
	Supporting Information
	• Updated *Clinical Evidence* and *References* sections to reflect the most current information
	• Archived previous policy version CS062KY.01

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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