Intrauterine Fetal Surgery (for Louisiana Only)

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Instructions for Use

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Application

This Medical Policy only applies to the state of Louisiana.

Coverage Rationale

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

- Congenital cystic adenomatoid malformation (CCAM)/congenital pulmonary airway malformation (CPAM) 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 federal, state, or contractual requirements 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

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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

Codes labeled with an asterisk (*) are not on the State of Louisiana Medicaid Fee Schedule and therefore are not covered by the State of Louisiana Medicaid Program.

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)/Congenital Pulmonary Airway Malformation (CPAM) and Extralobar Pulmonary Sequestration (EPS)

In a long term, single center study of fetuses that underwent thoracoamniotic shunt (TAS) insertion for congenital lung malformation (CLM), Muntean et al. (2023) reported a success rate on first attempt in 30 of 31 fetuses (97%) with six cases requiring a 2nd shunt between 2-10 weeks following the first insertion due to shunt displacement (n = 2), TAS blockage (n = 2), or residual/recurrent macrocystic component (n = 2). Of the 31 fetuses that underwent TAS, 28 survived to be born with 16 delivered at a gestational age of 39 (36-41) weeks. Median interval from shunting to delivery was 13 (15-17) weeks. At delivery, seven infants did not require any respiratory support, 5 required intubation, 1 required continuous positive airway pressure and 3 received oxygen via nasal canula. All infants underwent surgical resection at age of 2 (0–535) days [emergency surgery (n = 9); expedited intervention (n = 4) or as an elective procedure (n = 3)], and five infants developed a total of eight complications in the early postoperative period consisting of wound infections (n = 2), grade IIIa pneumothorax after drain removal requiring reinsertion (n = 5) and grade Iva aspiration pneumonia that required reintubation (n = 1). The infants were followed for a period of 10.7 (0.4-20.4) years with a total of 15 complications noted in 9 children that consisted of chest wall deformities including scoliosis (n = 5), pectus excavatum (n = 4), mild chest wall asymmetry (n = 4), winging of the scapula (n = 1) and raised left diapragm (n = 1). The authors reported that histopathology showed that more than 90% of cases were congenital pulmoary airway malformation (CPAM) type I. Limitations noted by the authors include its single-center, retrospective design, the small sample size and the collection of data by chart review. The authors concluded that TAS insertion was associated with high perinatal survival and excellent long-term outcomes.

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 10 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 non-hydropic 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 non-hydropic 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

Kelly et al. (2021) conducted a single-center, retrospective, cohort analysis of 132 fetuses diagnosed with hydrothorax (FHT) who underwent thoracoamniotic shunting in utero to assess short- and long-term outcomes and to examine the antenatal predictors of survival and of survival with normal neurodevelopmental outcomes beyond 18 months. Their selection criteria for fetal thoracoamniotic shunt insertion included non-immune hydrops fetalis in which the pleural effusion was suspected to be the primary etiology, an isolated pleural effusion, without hydrops, occupying > 50% of the thoracic cavity and causing marked mediastinal deviation or which was rapidly increasing in size, and the absence of any other obvious associated major anomaly. The mean gestational age at diagnosis of FHT was 25.6 weeks with 61% of cases being hydropic at diagnosis, 69% had bilateral effusions and 55% had bilateral shunts placed. There were other diagnoses present in 24% of cases, of which, two-thirds were only discovered postnatally. There were 16 (12.1%) intrauterine fetal deaths, all of which were hydropic at diagnosis of FHT with worsening of the hydrops despite shunting in 11 of the cases. The authors also reported 30 (22.7%) neonatal deaths with almost a third having pulmonary hypoplasia as a significant contributor. The overall perinatal mortality rate reported by the authors was 34.8%, leaving 86 (65.2%) survivors. At delivery, the mean gestational age of liveborn infants was 35.4 weeks (range 26.9-41.6 weeks), with 76% preterm (n = 88). The authors reported that 75% of the 87 babies delivered at their facility had respiratory and/or cardiovascular morbidity after birth that resulted in lenghty hospital stays of an average of 36 days. They also reported that, overall, 84% of survivors were developmentally normal beyond 18 months with better outcomes noted when pleural effusions were isolated and that 92% of these infants were neurodevelopmentally normal. While gestational age at delivery was the only factor independently predictive of both survival and survival with normal neurodevelopmental outcome, no trend in survival or neurodevelopmental outcome over time was found. Most (89%) of the 55 survivors with relevant follow-up had no long-term pulmonary complications despite the presence of FHT and neonatal respiratory issues. Limitations of the study include the single-center design, the potential for changes in practice that may have occurred during the long-term follow-up period, and that a large number of the fetuses were delivered at other institutions with potentially different neonatal management. The authors concluded that FHT is associated with other pathologies in a quarter of cases and carries a significant risk of prematurity, mortality and neonatal morbidity and that the outcome is best in survivors who only experienced isolated pleural effusions.

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 mos. (9 mos.-7 years 6 mos.). 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, 7 were related to pulmonary hypoplasia, 5 to genetic syndromes, 2 to aneuploidy and 1 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 5 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)

A retrospective, single-center cohort analysis by Katsoufis et al. (2022) assessed the impact of vesicoamniotic shunting (VAS) on a 16 male infants with severe congenital lower urinary tract obstruction (cLUTO) to delineate the postnatal course and infant kidney function following definitive intrauterine urinary diversion. All infants were all born with mechanically functional shunts at the time of birth that had been inserted at a median of 20 weeks of gestational age and all were born prematurely at a median of 34 weeks with low birth weight (median 2340 grams). The authors reported that, of the 16 with various primary diagnoses, 6 (38%) had a lax abdomen phenotype. Four of the 6 had the constellation of findings consistent with Eagle-Barrett syndrome, while an additional two were variants without the full triad that includes undescended testicles. Biochemical markers collected in the study period included serum creatinine (SCr) at its neonatal peak or maximum rise after birth, at discharge from the intensive care unit at a time deemed appropriate by the medical care team, and at 1 to 3-month intervals throughout the first year of life to determine the nadir SCr or lowest recorded level. Serum cystatin C (CysC) was assayed during the neonatal hospitalization within 3 weeks of birth, and at 3-month intervals throughout the first year of life. Patients were categorized into two subgroups according to their stage of CKD at 1 year of life. Infants with chronic kidney disease (CKD) stages 1–3 had an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m2 by 12 months of age while infants with advanced CKD, CKD stages 4–5, had an eGFR < 30 ml/min/1.73 m2 by 12 months of age. The authors found that the majority of infants (n = 10, 62%) developed advanced CKD stage 4–5 in the first year of life. Three patients died in the neonatal period, with 1 receiving kidney replacement therapy (KRT). Three additional patients required KRT before 12 months of age. Limitations of the study included the small sample size, the retrospective, single-center design and the limited availability of fetal urine analytes. The authors concluded that, even with definitive VAS for cLUTO, postnatal morbidity and mortality remain high in spite of urinary diversion, emphasizing the role of renal dysplasia in postnatal kidney dysfunction and they recommend future studies with larger sample size and with multiple treatment sites.

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 9 studies (4 retrospective cohort, 1 combined prospective and retrospective cohort, 1 randomized trial, and 2 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 6-month or 12-month survival (OR, 1.77 (95% CI, 0.25–12.71)) or 2-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 1–2-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)

After completing a retrospective cohort study of women with TTTS that underwent fetoscopic laser photocoagulation (FLC) at two high-volume fetal centers to identify risk factors for donor demise and recipient demise, Mustafa et al. (2022) conducted a systematic review and meta-analysis to better characterize these factors. In their cohort study that included 514 pregnancies with TTFS managed with FLC, there were 67 participants with stage I, 161 participants with stage II, 247 participants with stage III, and 39 participants with stage IV. The authors reported that the fetal demise rate was 25% (n = 126) for the donor and a 12% (n = 62) rate of demise for recipients. Significant factors noted by the authors included selective fetal growth restriction and umbilical artery blood flow with absent or reversed end-diastolic velocity for donor demise while a significant factor for recipient demise was absent or reversed a-wave in the ductus venosus of the recipient. The systematic review and meta-analysis included data from 23 studies (21 retrospective and 2 prospective) on pregnancies with TTTS managed with FLC, including their own cohort study, with analysis of data on 4892 pregnancies with TTTS for risk factors for donor demise, and 4594 pregnancies with TTTS for risk factors for recipient demise. Twenty of the studies (91%) were assessed to be of high quality. The authors reported that the incidence rates for fetal demise in the studies included in the systematic review were up to 35.8 percentile for donor demise and 24.5 percentile for recipient demise and they noted that the incidence was variable across years, across centers, with different sample sizes, and with different definitions used for fetal demise. The authors noted that perinatal survival was found to decrease with advanced stages of TTTS in some studies, whereas the survival rate of at least 1 twin was independent of the stage of the disease in other studies and that these differences may reflect a major limitation of the current TTTS staging system. A double staging system was proposed by the authors with the donors' staging system including fetal growth restriction and fetal anemia while the recipients' staging system includes cardiac hypertrophy and hydrops. Limitations of this study included the heterogeneity of the studies included in the systematic review, the retrospective, nonrandomized study design, and the lack of standardized criteria for antenatal surveillance, management and timing of delivery. The authors concluded that both preoperative and operative factors were associated with fetal demise in TTTS after FLC and that there was a significant association of TTTS stage III with donor demise and TTTS stage IV with recipient demise. They stated that predictive models for fetal demise may not be possible due to the differences in surgical techniques, skills and clinical scenarios.

In a single-center, retrospective observational study, Chang et al. (2022) investigated the fetal growth pattern after FLC in maternity patients with TTTS and the effect FLC had on placental perfusion and intrauterine growth restriction (IUGR). The study included 76 TTTS cases (128 liveborn neonates) with a live delivery of both twins at least 28 days after FLP and with a neontal follow-up at least 60 days after delivery. The median gestational age at time of FLC was 20.8 weeks. The authors noted that the method of FLC changed during the study from a selective approach to the Solomon approach; however there were no differences noted between the two groups. The incidence of intrauterine fetal death (IUFD) was 20 (26.3%) and were predominantly single fetal deaths, most of which were donor fetus, and most of which occurred shortly after the FLC procedure with a median latency time from FLA to IUFD of 1 day. The authors analyzed body weight discordance (BWD) between the twins and total weight percentile (TWP) of both twins combined that was collected before FLC, upon birth and at neonatal follow-up and found that the BWD decreased from prior to FLC to birth and when compared to neonatal follow-up weight. The authors also reported that the TWPs decreased between FLC and birth and increased between birth and their neonatal follow-up. The IUGR incidences in donor twins were significantly lower after FLC and further decreased after delivery although no significant difference was observed in recipient twins' IUGR. The authors reported that data showed that the donor twin had catch- up growth in body weight, height, and head circumference after delivery, while the recipient twin had catch-up growth in only body height after delivery. Limitations of the study include the small sample size, the small size, the single center, retrospective study design, and the limited data due to care being provided outside of the study center. The authors concluded that FLC decreased placental perfusion and also improved the TTTS prognosis because of reduced BWD and donor twin IUGR incidence.

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 6 months without severe neurologic morbidity. Severe complications of prematurity and maternal morbidity were secondary outcomes. The trial was stopped at 117 of 200 planned inclusions for slow accrual rate over 7 years: 58 women were allocated to expectant management and 59 to immediate laser treatment. Intact survival was seen in 84 of 109 (77%) expectant cases and in 89 of 114 (78%) (p = 0.88) immediate surgery cases, and severe neurologic morbidity occurred in 5 of 109 (4.6%) and 3 of 114 (2.6%) (p = 0.49) cases in the expectant and immediate surgery groups, 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 non-significantly (78% and 71% following immediate and rescue surgery, respectively). The authors concluded that it is unlikely that early fetal surgery is of benefit for stage 1 twin-twin transfusion syndrome in asymptomatic pregnant women with a long cervix and that although expectant management is reasonable for these cases, 60% of the cases will progress and require rapid transfer to a surgical center.

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 6 months and at 3 years of age. There were 9 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 3 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 1 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 4 studies comparing the 2 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 2 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)

In a retrospective, single-center study of 28 pump fetuses in TRAP sequence (TRAPs) and 28 normal control twins, Zhang et al. (2022) evaluated the alterations in fetal Doppler parameters before and 24 hours after radiofrequency ablation surgery (RFA). The authors hypothesized that the pump fetus may have an underlying hemodynamic disorder and that the alleviation of the hemodynamic burden following RFA may elicit a hemodynamic response that could be assessed via changes in fetal Doppler

parameters. They further suggested that predicting these hemodynamic responses could provide a theoretical basis for the timing of treatment and understanding of the disease evolution after surgery. The control group was determined by random selection of normal monochorionic diamniotic twin pregnancies matched to those in the TRAPs group for maternal age and gestational age (GA) during the last six months of the study. The fetal Doppler parameters included in this study were the umbilical artery pulsatility index (UA-PI), the middle cerebral artery peak systolic velocity (MCA-PSV), the middle cerebral artery pulsatility index (MCA-PI), and the cerebroplacental ratio (CPR), of the controls, The median time of RFA surgery for the TRAPs group was 19.50 (15–25) weeks with 12 surgeries were performed before 20 weeks, and 16 were performed after 20 weeks. Nine patients had 1 cycle of RFA coagulation, 19 had 2 cycles, and 1 had 3 cycles. There were no differences reported in RFA cycles, duration of coagulation, or total operative time between fetuses with a GA of ≥ 20 weeks and fetuses with a GA of < 20 weeks. The authors reported that there was an increasing trend and further increase in the MCA-PSV, MCA-PI, MCA-PSV Z score, and MCA-PI Z score after surgery in pump fetuses with gestational age (GA) ≥ 20 weeks but that these changes were not observed in pump fetuses with a GA of < 20 weeks. They also found that the UA-PI and CPR before and after surgery were not different between control and pump fetuses, whether the GA was ≥ 20 or < 20 weeks. The authors also noted that there was a lower cesarean section rate, a later delivery GA, and a higher neonatal birth weight in the pump fetuses in the TRAPs group than in the twin fetuses in the control group. Limitations of this study include the risk of selection bias because of the retrospective design, the small sample size, the variable follow up as some patients were referred to the center only for the procedure and were followed elsewhere, possible operator bias, and the variability of fetal Dopper due to gestational age, The authors concluded that the pump fetus might experience high cardiac output rather than hypoxemia before surgery, and congestive heart failure or hemodilutional anemia after surgery if the RFA is done in the middle second trimester. The authors stated that this may provide some theoretical evidence in favor of early intervention to avoid unnecessary hemodynamic alterations and they recommend additional studies on the cerebrovascular response to altered hemodynamic conditions to further understand the cerebral autoregulatory capacity of the pump fetus.

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 2 consecutive examinations or if there were cardiac or hydropic changes in the pump twin at the first examination. A total of 18 cases of TRAP were referred during this period and all were counselled regarding fetal therapy if the situation were to deteriorate: 5 couples (27.7%) opted for termination of pregnancy; of the remaining 13, 7 (53.8%) agreed to perform intervention following confirmation of a normal karyotype. Six (85.7%) and 1 (14.3%) lasers were performed in the second and third trimesters, respectively; all 7 had a normal outcome of the pump twin. There were 6/13 (46.2%) in the expectant group who continued the pregnancy with no intervention, with 2 term live births (33.3%). The authors concluded that there is a high risk of spontaneous loss in untreated pregnancies with TRAP, primarily due to polyhydramnios and fetal hydrops and in the pregnancies that underwent interstitial laser, there was a more favorable outcome. They also stated that interstitial laser is minimally invasive, safe, and feasible in experienced hands.

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 3 patients refusing any therapy and excluded from the analysis. Among the stage IIb cases, 1 underwent RFA and 1 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 7 patients underwent intrafetal ablation of the acardiac twin with RFA. Median gestational age at the intervention was 17 weeks. A total of 5 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, 6 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)

Paslaru et al. (2021) performed a systematic review of outcomes in prenatal versus postnatal surgical repair of MMC over 10 years following the Management of Myelomeningocele Study (MOMS) trial (see Adzik, 2011 below) to provide a review of the changes and updates in spina bifida repair that have been developed. In their review, 27 articles were identified that met the inclusion criteria of being RCTs or observational studies published between 2011 and 2021, written in English and reporting singleton fetuses with isolated spina bifida who underwent either a prenatal fetoscopic or open repair or postnatal surgical closure with a minimum of 30 days follow-up; however, no RCTs met the inclusion criteria. Maternal outcomes after prenatal interventions showed a higher placental abruption in one study where fewer than 30 patients had been treated whereas studies including more than 30 patients reported an average rate of placental abruption of 5.9%. The authors noted that there was a placental abruption rate of 9.41% in fetoscopic series and of 3.69% in series using open techniques. The average rate of preterm premature rupture of membranes (PPROM) in studies using fetoscopic techniques was 63.23% while the average rate in open surgeries was 30.71%. In looking at fetal, neonatal and infant outcomes, the authors reported an average hydrocephalus rate of 45.65% in prenatal series and 66.57% in those reporting a postnatal treatment, an ability to walk of 68.78% in the prenatal series compared to 60.24% in the postnatal treatment group, a urinary continence average rate of 40.97% in the prenatal series compared to 8.94% with postnatal series, and a reversal of the hindbrain herniation of 63.41% in prenatal versus 33.71% in the postnatal group. When comparing fetal outcomes in the fetoscopic series versus the open technique series, the authors noted a higher average hydrocephalus rate in the fetoscopic surgery groups of 54.98% compared to an average of 36.31% in the open surgery groups; however, hindbrain herniation reversal was achieved in 93.85% in fetoscopic surgery series compared to 51.25% in open surgery series. The ability of the authors to perform a substantial statistical analysis of the prognosis associated with different treatment approaches was limited by the heterogeneity of the study designs (treatment approaches, outcome measures, follow-up period) of the included studies, The authors concluded that the outcome of spina bifida-associated conditions could be improved and the risks to both the mother and fetus reduced with growing experience and with the improvement of prenatal open and fetoscopic techniques. The authors recommended continuous follow-up of treated infants and additional RCTs to study complications, advantages and disadvantages of any given treatment strategy.

A 2022 update to the 2018 Hayes health technology assessment identified 11 newly published studies, including 2 long-term follow-up, 3 subset analyses of a randomized controlled trial, and 6 comparative studies pertaining to fetal surgery for MMC. While the review consisted of study abstracts only, the literature showed that the evidence on patient selection criteria remains unchanged and that there was no new evidence with longer-term follow-up since the 2018 publication. The report continues to suggest 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, 5 reported outcomes using fetoscopic MMC repair (n = 179) and 6 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 5 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 1-year evaluation. In terms of bladder function, all 5 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 1-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 5 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, reaffirmed 2021).

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; reaffirmed 2022).

Congenital Diaphragmatic Hernia (CDH)

In a systematic review and meta-analysis on survival and the postnatal care setting following fetoscopic tracheal occlusion (FETO) for treatment of severe CDH, Sferra et al. (2022) evaluated the impact of an integrated prenatal and postnatal care setting on survival outcomes. The meta-analysis included five studies (4 prospective controlled and one RCT) that reported on FETO and an expectant management control group, while nine studies (including the Ruano 2012 study previously included in this policy) provided individual FETO participant data for analysis. Following completion of the data extraction, 192 CDH patients were included in the meta-analysis with 109 managed in an integrated program and 83 managed in a nonintegrated care setting. The individual participant analysis included 150 FETO patients, with 58 patients in the integrated cohort and 92 patients in the nonintegrated cohort. The authors reported that the meta-analysis revealed a significant increased in hospital survival after FETO when compared to patients with similar disease severity who underwent expectant fetal management

(50.4% vs. 4.7%) and that a subgroup analysis showed a significant survival benefit for FETO patients managed in an integrated care setting but not for those managed in a nonintegrated setting with an in-hospital survival rate following FETO in an integrated care setting of 70.7% compared to an in hospital survival rate of 45.7% in nonintegrated settings. Multi-level logistic regression identified increased availability of extracorporeal membrane oxygenation (ECMO) as the strongest determinant of postnatal survival, while gestational age at preterm premature rupture of membranes (PPROM) and higher 5 minutes Apgar scores were also independent and significant cofactors for increased survival. This systematic review was limited by the small sizes of the included studies, the study designs, the heterogeneity of the healthcare settings, the expanded length of time between studies and the inability of the authors to account for all possible patient-specific markers. The authors concluded that integration of a multi-disciplinary care model, with coordinated involvement of neonatal and surgical teams working closely with maternal fetal medicine specialists and other fetal surgeons was associated with the highest overall survival in children with severe 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.

In their 2022 update to their 2018 Health Technology Report, Hayes identified 8 newly published studies that may meet the inclusion criteria for this report consisting of 2 RCTs (the two Deprest studies discussed above), 1 pooled analysis of 2 RCTs, and 5 comparison studies; however, their update was based on a review of study abstracts only. In this update, Hayes noted that there is new evidence regarding efficacy and safety in these studies and that there is no new evidence related to the patient selection criteria or on longer-term follow-up. The report remains unchanged with their conclusion 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 3 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 1 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.

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 2 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 1-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)

In a systematic review and meta-analysis to investigate the type of postnatal circulation achieved following fetal aortic valvuloplasty (FAV), Vorisek et al. (2022) found that biventricular circulation (BVC) was achieved in 46%, which increased to 52% when patients underwent technically successful FAV for aortic stenosis. The systematic review was comprised of seven cohort studies (one prospective and six retrospective and included the Kovacevic (2018), Freud (2014), and Pedra (2014) studies previously summarized in this policy) that investigated the type of postnatal circulation achieved following FAV in patients diagnosed prenatally with aortic stenosis. There were a total of 266 fetuses, with 3 of the studies (n = 29) including hydrops. The median follow-up was from 12 months to 13.2 years. The pooled prevalence of BVC among liveborn patients was 45.8%, while the pooled prevalence of univentricular circulation (UVC) among liveborn patients was 43.6%. The pooled prevalence of technically successful FAV procedure was 82.1%, fetal death had a pooled prevalence of 16.0% (n = 39), termination of pregnancy (TOP) was 5.7% (n-11), neonatal death (NND) was 8.7% (n = 14), palliative care was 4.0% (n = 5), infant death was 10.3% (n = 16), and live birth was 78.8% (n = 214). Of 266 fetuses undergoing FAV, 82% (n = 219) had a technically successful procedure. Among this cohort, 182 infants were born alive. Four of the studies were assessed to be of good quality in that they had higher number of participants, long follow-up and precise definition of postnatal circulation outcome. Limitations included the lack of RCTs, small sample sizes, incomplete follow-up, heterogeneity in inclusion criteria and surgical techniques, and lack of well-defined postnatal circulation outcomes. The authors concluded that the study showed a BVC rate of 46% among liveborn patients with aortic stenisis who underwent FAV. They cautioned that the results should be interpreted carefully due to the lack of RCTs and that the current data did not suggest a true benefit of FAV for achieving BVC. The authors recommend well-designed international collaborative RCTs with standardized selection criteria and evaluation of outcomes beyond the neonatal period to conclusively determine the postnatal circuation outcome following FAV.

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 2279 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 3 studies, with a rate of 31%; after pulmonary valvuloplasty in 1 study, with a rate of 25%; after septoplasty in 1 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 2 studies, with a rate of 52%; after pulmonary valvuloplasty in 1 study, with a rate of 44%; and after septoplasty in 1 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).

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.

References

Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993-1004.

American College of Obstetricians and Gynecologists (ACOG). ACOG committee opinion #501: Maternal-fetal intervention and fetal care centers. Obstet Gynecol. 2011 Aug;118(2 Pt 1):405-10. Reaffirmed 2020. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/08/maternal-fetal-intervention-and-fetal-care-centers. Accessed March 1, 2023.

American College of Obstetricians and Gynecologists (ACOG). ACOG committee opinion #720: Maternal-fetal surgery for myelomeningocele. Obstet Gynecol. 2017 Sep;130(3):672-673. Reaffirmed 2022. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/09/maternal-fetal-surgery-for-myelomeningocele. Accessed March 1, 2023.

Araujo Júnior E, Tonni G, Chung M, et al. Perinatal outcomes and intrauterine complications following fetal intervention for congenital heart disease: systematic review and meta-analysis of observational studies. Ultrasound Obstet Gynecol. 2016 Oct;48(4):426-433.

Cabassa P, Fichera A, Prefumo F, et al. The use of radiofrequency in the treatment of twin reversed arterial perfusion sequence: a case series and review of the literature. Eur J Obstet Gynecol Reprod Biol. 2013; Feb;166(2):127-32.

Chang YL, Hsu CC, Chao AS, Chang SD, Cheng PJ, Li WF. Effect of Fetoscopic Laser Photocoagulation on Fetal Growth and Placental Perfusion in Twin-Twin Transfusion Syndrome. J Clin Med. 2022 Jul 28;11(15):4404. doi: 10.3390/jcm11154404. PMID: 35956021; PMCID: PMC9368961.

Chon AH, Chmait HR, Korst LM, et al. Long-term outcomes after thoracoamniotic shunt for pleural effusions with secondary hydrops. J Surg Res. 2019;233:304–309.

Cohen AR, Couto J, Cummings JJ, et al. Position statement on fetal myelomeningocele repair. Am J Obstet Gynecol. 2014; 210(2):107-11.

Committee on Obstetric Practice, Society for Maternal–Fetal Medicine. Committee opinion No. 720: Maternal-fetal surgery for myelomeningocele. Obstet Gynecol. 2017 Sep;130(3):e164-e167. Reaffirmed 2021.

Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 187: Neural tube defects. Obstet Gynecol. 2017 Dec;130(6):e279-e290.

Crombleholme TM, Shera D, Lee H, et al. A prospective, randomized, multicenter trial of amnioreduction vs selective fetoscopic laser photocoagulation for the treatment of severe twin-twin transfusion syndrome. Am J Obstet Gynecol 2007;197:396.e1-396.e9.

Danzer E, Adzick NS, Rintoul NE, et al. Intradural inclusion cysts following in utero closure of myelomeningocele: clinical implications and follow-up findings. J Neurosurg Pediatr. 2008; Dec;2(6):406-13.

Danzer E, Gerdes M, Bebbington MW, et al. Lower extremity neuromotor function and short-term ambulatory potential following in utero myelomeningocele surgery. Fetal Diagn Ther. 2009; Jan 28;25(1):47-53.

Deprest JA, Benachi A, Gratacos E, et al.; TOTAL Trial for moderate hypoplasia investigators. Randomized trial of fetal surgery for moderate left diaphragmatic hernia. N Engl J Med. 2021b Jul 8;385(2):119-129.

Deprest JA, Nicolaides KH, Benachi A, et al.; TOTAL Trial for severe hypoplasia investigators. Randomized trial of fetal surgery for severe left diaphragmatic hernia. N Engl J Med. 2021a Jul 8;385(2):107-118. Deprest J, Jani J, Van Schoubroeck D, et al. Current consequences of prenatal diagnosis of congenital diaphragmatic hernia. J Pediatr Surg. 2006 Feb;41(2):423-30.

Freud LR, McElhinney DB, Marshall AC, et al. Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: postnatal outcomes of the first 100 patients. Circulation. 2014 Aug 19;130(8):638-45.

Graef C, Ellenrieder B, Hecher K, et al. Long-term neurodevelopmental outcome of 167 children after intrauterine laser treatment for severe twin-twin transfusion syndrome. Am J Obstet Gynecol. 2006 Feb;194(2):303-08.

Grivell RM, Andersen C, Dodd JM. Prenatal interventions for congenital diaphragmatic hernia for improving outcomes. Cochrane Database Syst Rev. 2015 Nov 27;(11):CD008925.

Hayes, Inc. Health Technology Assessment. Fetal surgery for congenital diaphragmatic hernia. Hayes, Inc.; July 20, 2018, updated August 16, 2022.

Hayes, Inc. Health Technology Assessment. Fetal Surgery for Myelomemingocele. Hayes, Inc.; July 23, 2018, updated July 26, 2022

Hedrick HL, Flake AW, Crombleholme TM, et al. Sacrococcygeal teratoma: prenatal assessment, fetal intervention, and outcome. J Pediatr Surg. 2004;39(3):430-438.

Hirose S, Farmer DL, Lee H, et al. The ex utero intrapartum treatment procedure: Looking back at the EXIT. J Pediatr Surg. 2004 Mar;39(3):375-80.

Jeong BD, Won HS, Lee MY, et al. Perinatal outcomes of fetal pleural effusion following thoracoamniotic shunting. Prenat Diagn. 2015 Dec;35(13):1365-70.

Kabagambe SK, Jensen GW, Chen YJ, et al. Fetal surgery for myelomeningocele: a systematic review and meta-analysis of outcomes in fetoscopic versus open repair. Fetal Diagn Ther. 2018;43(3):161-174.

Katsoufis CP, DeFreitas M, Leuchter J, et al. Predictors of advanced chronic kidney disease in infancy after definitive vesicoamniotic shunting for congenital lower urinary tract obstruction. Front Pediatr. 2022 Oct 14;10:977717.

Kelly EN, Seaward G, Ye XY, et al. Short- and long-term outcome following thoracoamniotic shunting for fetal hydrothorax. Ultrasound Obstet Gynecol. 2021 Apr;57(4):624-630.

Kim R, Lee MY, Won HS, et al. Perinatal outcomes and factors affecting the survival rate of fetuses with twin-to-twin transfusion syndrome treated with fetoscopic laser coagulation: a single-center seven-year experience. J Matern Fetal Neonatal Med. 2021 Apr 20:1-12.

Knox EM, Kilby MD, Martin WL, et al. In-utero pulmonary drainage in the management of primary hydrothorax and congenital cystic lung lesion: a systematic review. Ultrasound Obstet Gynecol. 2006 Oct;28(5):726-34.

Koh CJ, DeFilippo RE, Borer JG, et al. Bladder and external urethral sphincter function after prenatal closure of myelomeningocele. J Urol. 2006;176(5):2232-2236.

Kovacevic A, Öhman A, Tulzer G, et al. Fetal Working Group of the AEPC. Fetal hemodynamic response to aortic valvuloplasty and postnatal outcome: a European multicenter study. Ultrasound Obstet Gynecol. 2018 Aug;52(2):221-229.

Kunisaki SM, Barnewolt CE, Estroff JA, et al. Ex utero intrapartum treatment with extracorporeal membrane oxygenation for severe congenital diaphragmatic hernia. J Pediatr Surg. 2007 Jan;42(1):98-104.

Lee H, Bebbington M, Crombleholme TM; North American Fetal Therapy Network. The North American Fetal Therapy Network Registry data on outcomes of radiofrequency ablation for twin-reversed arterial perfusion sequence. Fetal Diagn Ther. 2013;33(4):224-9.

Litwińska M, Litwińska E, Janiak K, et al. Thoracoamniotic Shunts in Macrocystic Lung Lesions: Case Series and Review of the Literature. Fetal Diagn Ther. 2017;41(3):179-183.

McElhinney DB, Marshall AC, Wilkins-Haug LE, et al. Predictors of technical success and postnatal biventricular outcome after in utero aortic valvuloplasty for aortic stenosis with evolving hypoplastic left heart syndrome. Circulation. 2009; Oct 13;120(15):1482-90.

Muntean A, Cazacu R, Ade-Ajayi N, et al. The long-term outcome following thoraco-amniotic shunting for congenital lung malformations. J Pediatr Surg. 2023 Feb;58(2):213-217.

Mustafa HJ, Javinani A, Goetzinger K, et al. Single fetal demise following fetoscopic ablation for twin-to-twin transfusion syndrome-cohort study, systematic review, and meta-analysis. Am J Obstet Gynecol. 2022 Jun;226(6):843.e1-843.e28.

Moise KJ Jr, Dorman K, Lamvu G, et al. A randomized trial of amnioreduction versus septostomy in the treatment of twin-twin transfusion syndrome. Am J Obstet Gynecol. 2005;193(3 Pt 1):701–707.

Nassr AA, Shazly SAM, Abdelmagied AM, et al. Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: an updated systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017 Jun;49(6):696-703.

National Institute for Health and Care Excellence (NICE) Interventional procedures guidance [IPG198]. Intrauterine laser ablation of placental vessels for the treatment of twin-to-twin transfusion syndrome. Published date: December 2006.

National Institute for Health and Care Excellence (NICE) Interventional procedures guidance [IPG613]. Percutaneous balloon valvuloplasty for fetal critical aortic stenosis. Published date: May 2018.

Ozawa K, Sugibayashi R, Wada S, et al. Fetoscopic laser photocoagulation for amniotic fluid discordance bordering on twin-twin transfusion syndrome: Feasibility, perinatal and long-term outcomes. J Obstet Gynaecol Res. 2017 Aug;43(8):1256-1262.

Pagani G, D'Antonio F, Khalil A, et al. Intrafetal laser treatment for twin reversed arterial perfusion sequence: cohort study and meta-analysis. Ultrasound Obstet Gynecol. 2013 Jul;42(1):6-14.

Paslaru FG, Panaitescu AM, Iancu G, et al. Myelomeningocele surgery over the 10 years following the MOMS trial: A systematic review of outcomes in prenatal versus postnatal surgical repair. Medicina (Kaunas). 2021 Jul 12;57(7):707.

Pedra SR, Peralta CF, Crema L, et al. Fetal interventions for congenital heart disease in Brazil. Pediatr Cardiol. Mar 2014; 35(3):399-405.

Peranteau WH, Adzick NS, Boelig MM, et al. Thoracoamniotic shunts for the management of fetal lung lesions and pleural effusions: a single-institution review and predictors of survival in 75 cases. J Pediatr Surg. 2015 Feb;50(2):301-5.

Roberts D, Gates S, Kilby M, et al. Interventions for twin-twin transfusion syndrome: a Cochrane review. Ultrasound Obstet Gynecol. 2008 Jun;31(6):701-11.

Roberts D, Neilson JP, Kilby MD, et al. Interventions for the treatment of twin-twin transfusion syndrome. Cochrane Database Syst Rev. 2014 Jan 30;1:CD002073.

Rossi AC, D'Addario V. Laser therapy and serial amnioreduction as treatment for twin-twin transfusion syndrome: A metaanalysis and review of literature. Am J Obstet Gynecol. 2008;198(2):147-152.

Ruano R, Duarte SA, Pimenta EJ, et al. Comparison between fetal endoscopic tracheal occlusion using a 1.0-mm fetoscope and prenatal expectant management in severe congenital diaphragmatic hernia. Fetal Diagn Ther. 2011;29(1):64-70.

Ruano R, Yoshisaki CT, da Silva MM, et al. A randomized controlled trial of fetal endoscopic tracheal occlusion versus postnatal management of severe isolated congenital diaphragmatic hernia. Ultrasound Obstet Gynecol. 2012 Jan;39(1):20-7.

Salomon LJ, Ortqvist L, Aegerter P, et al. Long-term developmental follow-up of infants who participated in a randomized clinical trial of amniocentesis vs laser photocoagulation for the treatment of twin-to-twin transfusion syndrome. Am J Obstet Gynecol. 2010 Nov;203(5):444.e1-7.

Sananes N, Javadian P, Schwach Werneck Britto I, et al. Technical aspects and effectiveness of percutaneous fetal therapies for large sacrococcygeal teratomas: cohort study and literature review. Ultrasound Obstet Gynecol. 2016 Jun;47(6):712-9.

Senat MV, Deprest J, Boulvain M, et al. Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. N Engl J Med. 2004; Jul;351(2):136-44.

Sferra SR, Miller JL, Cortes M S, et al. Postnatal care setting and survival after fetoscopic tracheal occlusion for severe congenital diaphragmatic hernia: A systematic review and meta-analysis. J Pediatr Surg. 2022 Dec;57(12):819-825.

Sfakianaki AK, Copel JA. Congenital cystic lesions of the lung: congenital cystic adenomatoid malformation and bronchopulmonary sequestration. Rev Obstet Gynecol. 2012;5(2):85–93.

Shettikeri A, Acharya V, V S, Sahana R, et al. Outcome of pregnancies diagnosed with TRAP sequence prenatally: a single-centre experience. Fetal Diagn Ther. 2020;47(4):301-306.

Simonini C, Strizek B, Berg C, et al. Fetal teratomas - A retrospective observational single-center study. Prenat Diagn. 2021 Feb;41(3):301-307.

Society for Maternal-Fetal Medicine (SMFM), Norton ME, Chauhan SP, et al. Society for maternal-fetal medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. Am J Obstet Gynecol. 2015 Feb;212(2):127-39.

Society for Maternal-Fetal Medicine (SMFM), Simpson LL. Twin-twin transfusion syndrome. Am J Obstet Gynecol. 2013; Jan;208(1):3-18. Updated August 2014 per website. https://www.smfm.org/publications/80-twin-twin-transfusion-syndrome Accessed March 9, 2023.

Stirnemann J, Slaghekke F, Khalek N, et al. Intrauterine fetoscopic laser surgery versus expectant management in stage 1 twin-to-twin transfusion syndrome: an international randomized trial. Am J Obstet Gynecol. 2021 May;224(5):528.e1-528.e12.

Vida VL, Bacha EA, Larrazabal A, et al. Hypoplastic left heart syndrome with intact or highly restrictive atrial septum: surgical experience from a single center. Ann Thorac Surg. 2007; Aug;84(2):581-5.

Vorisek CN, Zurakowski D, Tamayo A, et al. Postnatal circulation in patients with aortic stenosis undergoing fetal aortic valvuloplasty: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2022 May;59(5):576-584.

Walsh WF, Chescheir NC, Gillam-Krakauer M, et al. Technical Brief No. 5: Maternal-fetal Surgical Procedures. (Prepared by the Vanderbilt Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality (AHRQ). April 2011.

Witlox R, S, G, M, Lopriore E, Rijken M, et al: Long-term neurodevelopmental and respiratory outcome after intrauterine therapy for fetal thoracic abnormalities. Fetal Diagn Ther 2019;45:162-167.

Yinon Y, Grisaru-Granovsky S, Chaddha V, et al. Perinatal outcome following fetal chest shunt insertion for pleural effusion. Ultrasound Obstet Gynecol. 2010 Jul;36(1):58-64.

Zhang L, Liu H, Huang S, et al. Alterations in fetal doppler parameters before and twenty-four hours after radiofrequency ablation for twin reversed arterial perfusion sequence. Front Med (Lausanne). 2022 Apr 14;9:802666.

Zhang ZT, Yang T, Liu CX, et al. Treatment of twin reversed arterial perfusion sequence with radiofrequency ablation and expectant management: A single center study in China. Eur J Obstet Gynecol Reprod Biol. 2018 Jun;225:9-12.

Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Coverage Rationale** • Replaced reference to “congenital cystic adenomatoid malformation (CCAM)” with “congenital cystic adenomatoid malformation (CCAM)/ *congenital pulmonary airway malformation (CPAM)*”

Date	Summary of Changes
	Applicable Codes • Added notation to indicate HCPCS code S2411 is not on the State of Louisiana Medicaid Fee Schedule and therefore is not covered by the State of Louisiana Medicaid Program **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version CS062LA.L

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