Fetal Surgery In Utero

Number: 0449

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.*

Aetna considers in utero fetal surgery medically necessary for any of the following indications:

I. Ablation of anastomotic vessels in acardiac twins;
II. Insertion of pleuro-amniotic shunt for fetal pleural effusion;
III. Laser ablation or occlusion of anastomotic vessels in early, severe twin-twin transfusion syndrome;
IV. Removal of sacrococcygeal teratoma;
V. Repair of myelomeningocele;
VI. Resection of malformed pulmonary tissue, or placement of a thoraco-amniotic shunt as a treatment of either of the following:
   A. Congenital cystic adenomatoid malformation; or
   B. Extralobar pulmonary sequestration;
VII. Thoracoamniotic shunt for pleural effusions;
VIII. Twin reversed arterial perfusion (TRAP);
IX. Vesico-amniotic shunting as a treatment of urinary tract obstruction.

Policy History

Last Review
07/08/2019
Effective: 10/04/2000
Next Review: 04/24/2020

Definitions

Additional Information

Clinical Policy Bulletin
Notes
Aetna considers the following applications of in utero fetal surgery experimental and investigational because its effectiveness for these indications has not been established:

- Fetal aortic valvuloplasty;
- Fetal tracheal occlusion for congenital diaphragmatic hernia;
- Fetoscopic laser ablation for type 2 vasa previa;
- Shunting for the treatment of fetal cerebral ventriculomegaly;
- Treatment of amniotic band syndrome;
- Treatment of aqueductal stenosis (i.e., hydrocephalus);
- Treatment of cleft lip and/or cleft palate;
- Treatment of congenital heart disease (e.g., mitral valve dysplasia);
- Treatment of fetal hydronephrosis;
- Treatment of gastroschisis.

Aetna considers in utero stem cell transplantation, in utero gene therapy, and other applications of in utero surgery experimental and investigational because their effectiveness has not been established.

Aetna considers serial amnioreduction for twin-to-twin transfusion syndrome medically necessary when criteria are met:

- Women after 26 weeks of gestation; and
- Evidence of abnormal blood flow documented by Doppler studies in one or both fetuses; and
- Evidence of polyhydramnios in the recipient fetus; and
- Donor fetus is oligohydramniotic.

**Background**
Intrauterine fetal surgery involves accessing the fetus through the uterine wall using either an open or a minimally invasive, endoscopic technique, surgically correcting the fetal abnormality and closing the uterus to permit completion of gestational development until delivery. The purpose of intrauterine fetal surgery is to correct fetal malformations that interfere with organ development and fetal survival. Fetal surgery in-utero has been attempted for various congenital anomalies including congenital diaphragmatic hernia (CDH), spina bifida and urinary tract abnormalities.

Congenital diaphragmatic hernia is a defect in the diaphragm of a developing fetus, which results in abdominal viscera protrusion into the chest, displacing the lungs and heart in the thoracic cavity. Congenital diaphragmatic hernias are usually repaired after delivery; however, 2 primary methods for treating CDH in-utero have emerged in an attempt to overcome pulmonary hypoplasia and persistent pulmonary hypertension in infants who are more severely affected: (i) surgical repair of the herniated diaphragm, and (ii) ligation of the fetal trachea, with subsequent stimulation of lung growth.

Surgical treatment of spina bifida usually occurs within 24 hours of birth; however, in-utero repair has been used as a method to decrease nerve damage and improve outcomes at birth. Lower urinary tract obstruction has a significant impact on neonatal and child health. Pulmonary hyperplasia and renal impairment could be direct or indirect consequences of this condition leading to significant morbidity and mortality. Vesico-amniotic fetal shunting, open fetal surgery and more recently endoscopic fetal surgery for this condition are available as possible options of fetal intervention. Vesico-amniotic shunting has the advantage of bypassing the obstruction, however it is often associated with complications. Open fetal surgery is not usually recommended because of the complications and high fetal loss rate. Endoscopic surgery to
visualize and treat the cause of lower urinary tract obstruction has been tried. Fetal endoscopic surgery is in its infancy and endoscopic procedures are limited to a few groups.

Twin-twin transfusion syndrome is the most common complication of monochorionic pregnancies affecting between 5 and 15% of such pregnancies and accounts for 15 to 77% of perinatal mortality in twins. Twin-twin transfusion syndrome is believed to occur as the result of uncompensated arteriovenous anastomoses in a monochorionic placenta, which lead to greater net blood flow going to one twin at the expense of the other. No single therapy is associated with a uniformly improved outcome for the involved twins and success is primarily related to gestational age and severity at diagnosis. A variety of therapies have been attempted, but serial therapeutic amniocenteses of the recipient twin's amniotic sac is most frequently used (ACOG, 2005). This therapy is believed to work by favorably changing intraamniotic pressure and, thus, placental intravascular pressure, allowing redistribution of placental blood flow and normalization of amniotic fluid volumes in each sac. More aggressive therapies, which usually are considered only for very early, severe cases, include abolishing the placental anastomoses by endoscopic laser coagulation or selective feticide by umbilical cord occlusion (ACOG, 2005). Clinical studies have shown that, in very early (less than 26 weeks gestation), severe cases of twin-twin transfusion syndrome, selective laser coagulation, when compared to serial amniocentesis, results in improved survival rates in at least one twin, less neurologic morbidity in survivors, and improved gestational age at time of delivery (Senat et al, 2004).

Rossi and D'Addario (2008) reviewed current controversy on laser therapy (LT) versus serial amnioreduction (SA) performed for twin-twin transfusion syndrome (TTTS). A search in PubMed from 1997 to 2007 was performed. Inclusion criteria were diamniotic monochorionic pregnancy, TTTS diagnosed with standard parameters, and peri- and neo-
Natal outcomes well-defined. Triplets and investigations on other topics of TTTS rather than perinatal outcomes were excluded. A meta-analysis was performed by fixed-effect model (heterogeneity less than 25%). A total of 10 articles provided 611 cases of TTTS (LT: 70%; SA: 30%) and included 4 studies comparing the 2 treatments (395 cases: LT, 58%; SA, 42%). Fetuses undergoing LT were more likely to survive than fetuses undergoing SA (overall survival rate: p < 0.0001; odds ratio [OR], 2.04; 95% confidence interval [CI]: 1.52 to 2.76; neonatal death: p < 0.0001; OR, 0.24; 95% CI: 0.15 to 0.40; neurologic morbidity: p < 0.0001; OR, 0.20; 95% CI: 0.12 to 0.33). The authors concluded that this meta-analysis showed that LT is associated with better outcomes than SA.

Szaflik et al (2013) noted that TTTS occurs in 15% of monochorionic twin pregnancies. Untreated, TTTS has been reported to have a mortality of nearly 100%. Two main therapies include SA and fetoscopic laser coagulation for the vascular anastomoses. The authors stated that comparison of the 2 treatments showed better outcomes with higher survival rates and minor neurological defects in cases treated with laser coagulation.

An UpToDate review on “Management of twin-twin transfusion syndrome” (Moise and Johnson, 2013) states that “The clinical threshold to begin serial amnioreductions is subjective. Serial amniocentesis to remove excess amniotic fluid in the recipient twin’s amniotic cavity results in higher survival rates than expectant management, but not as high as laser photocoagulation. Disadvantages of amnioreduction are that multiple procedures are usually required and complications from the procedure may preclude subsequent treatment by laser photocoagulation of the vascular communications. No more than 5 liters of amniotic fluid should be removed at the time of amnioreduction, and we suggest removing lesser amounts in severe TTTS …. For women with severe (Quintero stage II-IV) TTTS under 26 weeks of gestation, we suggest
laser ablation of placental anastomoses rather than serial amnioreduction …. For women with TTTS after 26 weeks of gestation, we suggest serial amnioreduction or septostomy rather than laser therapy (Grade 2C). The upper gestational age limit is due to Food and Drug Administration restrictions on the use of current fetoscopes, as well as technical issues that make laser therapy difficult in the third trimester.

Twin reversed-arterial-perfusion (TRAP) sequence is a serious complication of monozygotic twin pregnancies, affecting 1% of monozygotic twins, or 1 in 35,000 births (James, 1997). It has been hypothesized that in the presence of artery-to-artery anastomoses in a monozygotic placenta, blood is perfused by the hemodynamically advantaged twin (“donor” or “pump” twin) to the other twin (“recipient” twin) by means of reversed arterial flow (Quintero et al, 1994; van Allen et al, 1984). Inadequate perfusion of the recipient twin is responsible for the development of a characteristic and invariably lethal set of anomalies, including the acardius fetal malformation (acardiac twins) and acephalus. Typically, the pump twin is structurally normal, but it is at risk for in-utero cardiac failure and without treatment dies in 50 to 75% of cases, particularly if the recipient twin weighs more than half as much as the pump twin (Quintero et al, 1994).

Acardiac twinning is usually recognized by early fetal echocardiography. One approach to management is interruption of the vascular anastomosis between the donor and recipient twin. This is accomplished using endoscopic laser coagulation in pregnancies 24 weeks gestation or ligation of the umbilical cord using endoscopic or sonographic guidance at a greater gestational age (Arias et al, 1998). In a 1998 study of 7 pregnancies treated with laser therapy, the rate of death in the normal twin was 13.6%, compared to an expected death rate reported in the literature of 50% in the pump twin when the pregnancy is managed expectantly.
Another approach is the use of radiofrequency ablation to obliterate the blood supply of the acardiac twin. Tsao et al (2002) reported on the results of selective reduction of the abnormal twin in 13 consecutive cases of monochorionic twin gestation with TRAP sequence. The radiofrequency ablation needle was percutaneously inserted through the maternal abdominal wall into the intrauterine fetal abdomen at the level of the cord insertion site of the acardiac twin. The investigators reported that all 13 pump fetuses had been delivered, and that 12 of 13 infants are alive and well. One infant was delivered at 24.4 weeks gestation and subsequently died from complications of prematurity. The investigators reported that the average gestational age at delivery was 36.2 weeks.

Another approach to acardiac twins is expectant management. Although death rates of 50% in the pump twin have been reported with expectant management of acardiac twins, Sullivan et al (2003) found that outcomes in expectantly managed cases may be better than reported due to increased antenatal diagnosis. Sullivan et al ascertained all cases of antenatally diagnosed acardiac twins delivered in the Salt Lake community between 1994 and 2001. All were managed expectantly. Of the 10 cases were identified, 9 women delivered a healthy pump twin. There was 1 neonatal death. The mean gestational age at delivery was 34.2 weeks. The mean weights of the pump and acardiac twins were 2,279 g and 1,372 g, respectively.

Other congenital anomalies that are amenable to in-utero treatment include myelomeningocele, cystadenomatoid malformation of the lung and saccrococcygeal teratoma, shunts for uropathies and thoracic fluids.

In-utero hematopoietic stem cell transplantation is a promising approach for the treatment of a potentially large number of fetuses affected by congenital hematological disorders. Expansion of clinical application will depend on improved
understanding of the biological barriers to engraftment in the fetus as well as on the development of effective clinical strategies based on the hematopoietic biology of individual disorders (Hayashi and Flake, 2001).

Findings of recent studies indicated that the effectiveness of in-utero approach in treating CDH has not been established. Downard and Wilson (2003) noted that antenatal maternal steroid administration and fetal surgery are not proven interventions for CDH. Adzick and Kitano (2003) stated that fetuses diagnosed with left CDH before 26 weeks' gestation with associated liver herniation and a low right lung to head circumference ratio have a reduced prognosis with conventional therapy after birth, but in-utero therapeutic approaches have yet to show a comparative survival benefit. Adzik and Kitano stated that a prospective randomized trial is required to critically evaluate the efficacy of fetal tracheal occlusion for severe diaphragmatic hernia. Heerma et al (2003) reported on comparative autopsy in 16 cases of congenital diaphragmatic hernia with fetal intervention (12 cases tracheal occlusion; 4 cases hernia repair) with 19 cases of congenital diaphragmatic hernia without fetal intervention. The investigators concluded that tracheal occlusion did not prevent development of lung pathology associated with pulmonary hypoplasia.

A prospective randomized controlled trial (RCT) of fetal tracheal occlusion for CDH found no differences in outcomes between subjects assigned to fetal endoscopic tracheal occlusion or standard care (Harrison et al, 2003). Enrollment was stopped after 24 women carrying fetuses with severe CDH had been enrolled because of the unexpectedly high survival rate with standard care and the conclusion of the data safety monitoring board that further recruitment would not result in significant differences between the groups. Eight of 11 fetuses (73 % in the tracheal-occlusion group and 10 of 13 (77 %) in the group that received standard care survived to 90 days of age. The authors concluded that tracheal occlusion
did not improve survival or morbidity rates in this cohort of fetuses with CDH. In an accompanying editorial, Wenstrom (2003) argued that there are several reasons why antenatal tracheal occlusion may not result in a better outcome than conventional therapy. Wenstrom reasoned that, with new diagnostic technologies, congenital diaphragmatic defects of varying degrees of severity, from mild to severe, are now routinely identified antenatally, and affected neonates receive care at tertiary centers that offer highly specialized treatments for respiratory disease, including extracorporeal membrane oxygenation, high-frequency oscillatory ventilation, inhaled nitric oxide, exogenous surfactant, and others. As a result, the current survival rate for all cases of isolated CDH -- from mild to severe -- approaches 70% without fetal surgery, and neonates who do not require extracorporeal life support (approximately 50% of those with isolated CDH) have a survival rate of at least 80%. Wenstrom argued that another reason why antenatal intervention may not result in a better outcome than conventional therapy is that any potential benefit may be negated by the substantial fetal morbidity associated with the surgical procedure itself. Most pregnancies subjected to antenatal fetal surgery end in preterm delivery. Wenstrom noted that, in the study by Harrison et al, premature rupture of the membranes and preterm delivery occurred in 100% of those receiving antenatal treatment. The mean age at delivery was 30.8 weeks in the treated group, an age at which morbidity related to prematurity is likely. In addition, because birth occurred, on average, just 6 weeks after the procedure, appropriate catch-up lung growth may not yet have occurred. Wenstrom concluded that “[t]he study by Harrison et al also illustrates the critical importance of randomized clinical trials in evaluating new therapies – even heroic procedures performed in only a small fraction of neonates – before they are adopted as part of standard practice.”
In a RCT, Keller et al (2004) concluded fetal tracheal occlusion for severe CDH resulted in modest improvements in neonatal pulmonary function that, according to the investigators, were of questionable clinical significance.

There is considerable scientific and clinical interest in the potential use of hematopoietic stem cells before birth to treat congenital disease. In theory, stem cell transplantation in utero offers a number of possible advantages. First, intervention in utero will permit "correction" of a disorder before clinical manifestations have developed. Second, because the fetal immune system has not yet developed, it will not reject foreign cells. Unlike bone marrow transplantation after birth, there is no need to match donor cells. The fetus will become "tolerant" to the foreign cells allowing for further treatment after birth, again without the risk of rejection.

Current evidence for in-utero stem cell transplantation comes from animal models and from a small number reported cases of in utero transplantations of unmodified bone marrow progenitor cells in human fetuses involving such disorders as X-linked severe combined immunodeficiency and hemoglobinopathies (e.g., alpha thalassemia, sickle cell anemia and beta thalassemia). Although there is some evidence for success of in-utero stem cell transplantation in X-linked severe combined immunodeficiency syndrome, there is no proven clear advantage over post-natal stem cell transplantation for this indication. Regarding other potential uses, thus far, in utero stem cell transplantation has been unsuccessful in target disorders such as hemoglobinopathies where there is not a selective advantage for donor cells (Muench and Barcena, 2004; Flake, 2004).

Nijagal et al (2012) stated that in utero hematopoietic cell transplantation is a promising strategy for the treatment of common hematopoietic disorders and for inducing immune tolerance in the fetus. Although the effectiveness of in utero
hematopoietic cell transplantation has been demonstrated in multiple small and large animal models, the clinical application of this technique in humans has had limited success.

In-utero gene therapy (i.e., the genetic modification of somatic cells in utero) has been proposed as most appropriate in disorders which result in irreversible illness or death in the pre- or post-natal period. Examples may include Gaucher’s disease, Krabbe’s disease, Hurler’s disease, etc. Currently evidence is limited to animal models that certain genetic conditions can be corrected in-utero using gene therapy using virus vectors. In addition to the need for evidence of the effectiveness of gene therapy in-utero in humans, it has been argued that 2 key issues need to be addressed before such an intervention is considered; that there must be a clear advantage over post-natal gene therapy; and that there must be an advantage over therapy with unmodified cells.

Strumper et al (2005) noted that chronically compromised uterine perfusion may lead to placental insufficiency and subsequent intra-uterine growth restriction (IUGR). Various interventions such as the use of vasodilators/low-dose aspirin, intravenous glucose infusion, as well as hemodilution are often of limited effectiveness. The use of local anesthetics has been demonstrated to improve placental blood flow in pre-eclamptic women. In a pilot study (n = 10), these researchers examined whether epidural administration of local anesthetics might improve outcome in IUGR independent of the underlying cause. Women presenting with oligohydramnios and IUGR were included in the study. In addition to the standard protocol (magnesium, glucose, betamethasone), each patient received an epidural catheter (T10/T12) with continuous infusion of bupivacaine 0.175 % at a rate of 5 ml/hour. Uteroplacental circulation was monitored by Doppler sonography and the amount of amniotic fluid was estimated daily. Epidural insertion and infusion was performed without complications. Four patients continued to deteriorate rapidly, amniotic fluid volume did not change and uterine artery pulsatility index (PI)
tended to increase. In the remaining 6 patients the clinical status stabilized, amniotic fluid volume tended to increase and uterine artery PI tended to decrease during treatment. This improvement was associated with a prolonged interval to cesarean section and increased infant birth weight. The authors concluded that even if the underlying cause of IUGR is not pre-eclampsia, epidural infusion of local anesthetic might improve placental blood flow and be beneficial in a subgroup of patients. They stated that a clinical trial to test this hypothesis appears warranted.

Gardiner (2008) noted that the concept of fetal therapy is well-established for many disorders diagnosed before birth; but practical issues regarding its introduction into clinical practice are more difficult. Cardiac malformations are common, with major lesions affecting about 3.5 per 1,000 pregnancies; however, only a small proportion of these is likely to benefit from an intra-uterine intervention. In addition, there are no good animal models of human cardiac disease and knowledge of the underlying mechanisms is at best sketchy. This combination of factors has resulted in slow progress in developing effective therapies for the intra-uterine management of cardiac disease. The author stated that recent research and clinical developments have included percutaneous valvuloplasty for severe aortic and pulmonary stenosis, perforation of the closed or restrictive inter-atrial septum and pacing for complete heart block. Progress in these endeavours has been variable; but overall shows promise for treatment of the human fetus.

McElhinney et al (2009) stated that aortic stenosis in the mid-gestation fetus with a normal-sized or dilated left ventricle predictably progresses to hypoplastic left heart syndrome when associated with certain physiological findings. Pre-natal balloon aortic valvuloplasty may improve left heart growth and function, possibly preventing evolution to hypoplastic left heart syndrome. Between March 2000 and October 2008, 70 fetuses underwent attempted aortic valvuloplasty for critical
aortic stenosis with evolving hypoplastic left heart syndrome. These investigators analyzed this experience to determine factors associated with procedural and postnatal outcome. The median gestational age at intervention was 23 weeks. The procedure was technically successful in 52 fetuses (74%). Relative to 21 untreated comparison fetuses, subsequent pre-natal 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 a biventricular circulation post-natally, 15 from birth. Larger left heart structures and higher left ventricular pressure at the time of intervention were associated with biventricular outcome. A multi-variable threshold scoring system was able to discriminate fetuses with a biventricular outcome with 100% sensitivity and modest positive-predictive value. The authors concluded that technically successful aortic valvuloplasty alters left heart valvar growth in fetuses with aortic stenosis and evolving hypoplastic left heart syndrome and, in a subset of cases, appeared to contribute to a biventricular outcome after birth. Fetal aortic valvuloplasty carries a risk of fetal demise. Fetuses undergoing in-utero aortic valvuloplasty with an unfavorable multi-variable threshold score at the time of intervention are very unlikely to achieve a biventricular circulation post-natally.

Friedman et al (2011) noted that fetal aortic balloon valvuloplasty (FAV) has shown promise in altering in-utero progression of aortic stenosis to hypoplastic left heart syndrome. In patients who achieve a biventricular circulation after FAV, left ventricular (LV) compliance may be impaired. Echocardiographic indexes of diastolic function were compared between patients with biventricular circulation after FAV, congenital aortic stenosis (AS), and age-matched controls. In the neonatal period, patients with FAV had similar LV, aortic, and mitral valve dimensions but more evidence of endocardial fibroelastosis than patients with AS. Patients with FAV underwent more post-natal cardiac interventions than patients with AS ($p = 0.007$). Mitral annular early diastolic
tissue velocity (E') was lower in patients with FAV and those with AS and controls in the neonatal period and over follow-up (p < 0.001). Septal E' was similar among all 3 groups in the neonatal period. In follow-up patients, with FAV had lower septal E' than patients with AS or controls (p < 0.001). Early mitral inflow velocity/E' was higher in patients with FAV as neonates and at follow-up (p < 0.001). Mitral inflow pulse-wave Doppler-derived indexes of diastolic function were similar between groups. The authors concluded that echocardiographic evidence of LV diastolic dysfunction is common in patients with biventricular circulation after FAV and persists in short-term follow-up. LV diastolic dysfunction in this unique population may have important implications on long-term risk of left atrial and subsequent pulmonary hypertension.

Rogers et al (2011) stated that mitral valve dysplasia syndrome is a unique form of left-sided heart disease characterized by aortic outflow hypoplasia, dilated left ventricle, dysplastic/incompetent mitral valve, and a restrictive/intact atrial septum. Patients with this constellation of abnormalities have been managed in a variety of ways with overall poor outcomes. These investigators performed a retrospective review of all patients with mitral valve dysplasia syndrome to identify fetal echocardiographic markers predictive of outcomes. Mitral valve dysplasia syndrome was identified in 10 fetuses. Fetal left heart dilation and abnormal pulmonary venous flow were associated with increased mortality. Seven fetuses had abnormal pulmonary venous Doppler patterns; 3 had a unique "double-reversal" flow pattern. Severe fetal left heart dilation (left heart/right heart area ratio greater than 1.5) was present in 5. Pre-natal intervention was performed on 3 fetuses: balloon aortic valvuloplasty (n = 2) and balloon atrial septostomy (n = 1). Of the 3, 1 died in-utero and neither survivor underwent a 2-ventricle repair. Five patients required an immediate post-natal intervention to open the atrial septum. The overall mortality was 50%. The authors concluded that mitral valve
dysplasia syndrome is a unique form of congenital heart disease with severe aortic stenosis but normal or enlarged left ventricle secondary to primary mitral valve disease. Increased left heart size and pulmonary vein Doppler patterns are predictive of post-natal outcome. Despite the presence of a dilated left ventricle, post-natal management with staged single ventricle palliation may be the most effective strategy.

An assessment prepared for the Agency for Healthcare Research and Quality (AHRQ) (Walsh, et al., 2011) evaluated the evidence for prenatal aortic valvuloplasty for aortic stenosis. Eight prospective case series were identified on balloon dilation for critical aortic stenosis. One center in the United Kingdom, two centers in Germany, two in Brazil, and one in the U.S. performed this procedure. The 2011 technology assessment concluded that it is difficult to determine whether the procedure changes long-term outcomes, since it appears that it may also increase risk of fetal loss. They concluded that, overall, the literature was considered to be very early in development. An earlier assessment by the National Institute for Health and Clinical Excellence (NICE, 2006) reached similar conclusions.

A phase I/II clinical trial “Fetal Intervention for Aortic Stenosis and Evolving Hypoplastic Left Heart Syndrome” is underway to examine whether in-utero balloon aortic valvuloplasty may improve fetal growth of left heart structures and thus improve potential for biventricular repair strategies after birth.

Adzick (2010) stated that myelomeningocele (MMC) is a common birth defect that is associated with significant lifelong morbidity. Little progress has been made in the post-natal surgical management of the child with spina bifida. Post-natal surgery is aimed at covering the exposed spinal cord, preventing infection, and treating hydrocephalus with a ventricular shunt. In-utero repair of open spina bifida is now performed in selected patients and presents an additional therapeutic alternative for expectant mothers carrying a fetus.
with MMC. It is estimated that about 400 fetal operations have now been performed for MMC worldwide. Despite this large experience, the technique remains of unproven benefit. Preliminary results suggested that fetal surgery results in reversal of hind-brain herniation (the Chiari II malformation), a decrease in shunt-dependent hydrocephalus, and possibly improvement in leg function, but these findings might be explained by selection bias and changing management indications. A prospective, randomized study (the MOMS trial) is currently being conducted by 3 centers in the United States, and is estimated to be completed in 2010. The author stated that further research is needed to better understand the pathophysiology of MMC, the ideal timing and technique of repair, and the long-term impact of in-utero intervention.

Jani and colleagues (2009) examined operative and peri-natal aspects of fetal endoscopic tracheal occlusion (FETO) in CDH. It was a multi-center study of singleton pregnancies with CDH treated by FETO. The entry criteria for FETO were severe CDH on the basis of sonographic evidence of intra-thoracic herniation of the liver and low lung area to head circumference ratio (LHR) defined as the observed to the expected normal mean for gestation (o/e LHR) equivalent to an LHR of 1 or less. Fetal endoscopic tracheal occlusion was carried out in 210 cases, including 175 cases with left-sided, 34 right-sided and one with bilateral CDH. In 188 cases, the CDH was isolated and in 22 there was an associated defect. Fetal endoscopic tracheal occlusion was performed at a median gestational age of 27.1 (range of 23.0 to 33.3) weeks. The first 8 cases were done under general anesthesia, but subsequently either regional or local anesthesia was used. The median duration of FETO was 10 (range of 3 to 93) mins. Successful placement of the balloon at the first procedure was achieved in 203 (96.7 %) cases. Spontaneous preterm prelabor rupture of membranes (PPROM) occurred in 99 (47.1 %) cases at 3 to 83 (median of 30) days after FETO and within 3 weeks of the procedure in 35 (16.7 %) cases. Removal of the balloon was pre-natal either by fetoscopy or ultrasound-
guided puncture, intra-partum by ex-utero intra-partum
treatment, or post-natal either by tracheoscopy or
percutaneous puncture. Delivery was at 25.7 to 41.0 (median
of 35.3) weeks and before 34 weeks in 65 (30.9 %) cases. In
204 (97.1 %) cases, the babies were live born and 98 (48.0 %)
were discharged from the hospital alive. There were 10
defects directly related to difficulties with removal of the
balloon. Significant prediction of survival was provided by the
o/e LHR and gestational age at delivery. On the basis of the
relationship between survival and o/e LHR in expectantly
managed fetuses with CDH, as reported in the ante-natal CDH
registry, these researchers estimated that in fetuses with left
CDH treated with FETO the survival rate increased from 24.1
% to 49.1 %, and in right CDH survival increased from 0 % to
35.3 % (p < 0.001). The authors concluded that FETO in
severe CDH is associated with a high incidence of PPROM
and preterm delivery but a substantial improvement in
survival. They also stated that these findings need to be
tested in a RCT.

Gastroschisis is associated with inflammatory changes in the
exposed bowel that leads to intestinal dysmotility following post-
natal repair. In a retrospective study, Heinig et al (2008)
followed a case-series of fetuses with isolated gastroschisis to
evaluate if small-bowel dilatation may be indicative for
emerging obstetric complications. The secondary objective of
the study was to establish preliminary normative curves for the
external diameter and wall thickness of eventerated fetal small
bowel in gastroschisis during the 2nd and 3rd trimester of
pregnancy. A total of 14 fetuses with isolated gastroschisis
were followed at a single center. Repeated ultrasound
examinations for fetal surveillance with measurement of fetal
small-bowel diameter and wall thickness over the course of
pregnancy until delivery were performed. Longitudinal data
analysis showed significantly increasing bowel diameter and
wall thickness of eventerated small bowel with advancing
gestation. Dilatation of small bowel more than 25 mm in the
3rd trimester of pregnancy was associated with an increased
risk of short-term pre-natal complications as fetal distress or intra-uterine fetal death (positive predictive value 100%; 95% confidence interval [CI]: 29.2 % to 100 %, negative predictive value 100 %; 95 % CI: 71.5 % to 100%). The authors concluded that dilatation of the extra-abdominal fetal small bowel in the 3rd trimester may allow identifying fetuses with increased risk of fetal distress requiring closer monitoring of fetal well-being or delivery in a short interval to prevent impending fetal death.

Cohen-Overbeek et al (2008) studied in infants with gastroschisis whether outcome is different when comparing a pre-natal diagnosis with a diagnosis only at birth with the intention to develop a pre-natal surveillance protocol. Intestinal atresia established after birth and preterm versus term delivery were studied as risk factors. A total of 24 fetuses and 9 infants diagnosed with gastroschisis and were studied retrospectively. The infants of the pre-natal subset were delivered at the authors' tertiary center and 18 survived. There were 2 pregnancy terminations, 3 intra-uterine deaths at 19, 33 and 36 weeks, respectively, and 1 neonatal death. All 9 infants in the post-natal subset survived — 8 were out-born and 1 was delivered at the authors' tertiary center. Pre-natal bowel dilatation did not correlate with outcome. Between the pre-natal and post-natal subset, no significant difference in outcome of live-born infants was established. For 4 infants with intestinal atresia a significant difference was demonstrated for induction of preterm labor (p < 0.05), duration of parenteral nutrition (p < 0.01), number of additional surgical procedures (p < 0.001) and length of hospital stay (p < 0.01). The 15 infants born prior to 37 weeks of gestation spent a significantly longer period in hospital compared to those delivered at term. When the cases with bowel atresia were excluded this difference was no longer present. Five of the 33 cases were diagnosed with associated anomalies which mainly involved the urinary tract. The authors concluded that neonatal outcome of live born infants following a pre-natal diagnosis of gastroschisis is not different from a diagnosis at
birth. The presence of intestinal atresia is the most important prognostic factor for morbidity. The supplemental value of prenatal diagnosis to the outcome of infants with gastroschisis may be in the prevention of unnecessary intra-uterine death and detection of intestinal complications. A proposed surveillance protocol for fetuses with gastroschisis focused on intra-uterine signs of pending distress such as a dilated stomach, intra-abdominal bowel dilatation with peristalsis, notches in the umbilical artery Doppler signal, development of polyhydramnios and an abnormal cardiotocography registration may improve outcome. Currently, in-utero repair of gastroschisis is being studied in the sheep model (Stephenson et al, 2010). Thus, this approach is not ready for clinical use.

Adzick et al (2011) compared outcomes of in-utero repair for myelomeningocele with standard postnatal repair. These investigators randomly assigned eligible women to undergo either prenatal surgery before 26 weeks of gestation or standard postnatal repair. One primary outcome was a composite of fetal or neonatal death or the need for placement of a cerebrospinal fluid shunt by the age of 12 months. Another primary outcome at 30 months was a composite of mental development and motor function. Inclusion criteria were a singleton pregnancy, myelomeningocele with the upper boundary located between T1 and S1, evidence of hind-brain herniation, a gestational age of 19.0 to 25.9 weeks at randomization, a normal karyotype, U.S. residency, and maternal age of at least 18 years. Major exclusion criteria were a fetal anomaly unrelated to myelomeningocele, severe kyphosis, risk of preterm birth (including short cervix and previous preterm birth), placental abruption, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 35 or more, and contraindication to surgery, including previous hysterotomy in the active uterine segment. The trial was stopped for efficacy of pre-natal surgery after the recruitment of 183 of a planned 200 patients. This report was based on results in 158 patients whose children were evaluated at 12 months. The first primary
outcome occurred in 68% of the infants in the prenatal-surgery group and in 98% of those in the postnatal-surgery group (relative risk, 0.70; 97.7% CI: 0.58 to 0.84; p < 0.001).

Actual rates of shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group (relative risk, 0.48; 97.7% CI: 0.36 to 0.64; p < 0.001).

Prenatal surgery also resulted in improvement in the composite score for mental development and motor function at 30 months (p = 0.007) and in improvement in several secondary outcomes, including hind-brain herniation by 12 months and ambulation by 30 months. However, prenatal surgery was associated with an increased risk of preterm delivery and uterine dehiscence at delivery. The authors concluded that prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks.

In an editorial that accompanied the afore-mentioned study, Simpson and Greene (2010) stated that "[t]o what extent can these results be generalized? Caution is necessary here. For the decade of this trial, all cases nationwide were funneled to the 3 study centers, which by now should have developed near-optimal prowess. With the trial complete, other U.S. centers are likely to initiate their own programs, diluting experience and necessitating individual center-specific learning curves. Fetal results may not be as good as those in MOMS, and maternal complications could be increased. In addition, most women who expressed interest in the trial were either ineligible or declined to participate, with only 15% participation of those who were screened. This percentage may or may not increase as access extends beyond the 3 centers. Earlier diagnosis of myelomeningocele and the performance of open fetal surgery earlier than that performed in MOMS might further improve outcomes, but the potential benefits of even earlier intervention must be weighed against the greater likelihood of maternal complications and possibly increased difficulty of fetal repair. More work is also needed to determine whether baseline characteristics could predict which
fetuses would be more or less likely to benefit from prenatal surgery. But surely the greatest benefit would derive from a less traumatic approach. Our job as physicians is to communicate options and available data to patients as lucidly as possible while assiduously adhering to the principles of non-directive genetic counseling. For many women, the 20% absolute improvement in ambulation at the age of 3 years and the decreased need for shunting may be perceived as sufficient to justify the increased risk of maternal complications, but it should be recognized that outcomes after prenatal surgery were less than perfect in MOMS. Couples who do not elect to terminate a pregnancy unavoidably feel pressured “to do everything possible” and hence may be inclined to interpret even marginal benefit favorably. It is also human nature to over-estimate the likely benefit for one’s own fetus and to under-estimate the associated risks. Counseling should involve not only precise quantitative statements comparing outcomes of prenatal versus postnatal surgery on the basis of this report but also the provision of information on center-specific experience. The degree to which intrauterine repair will transform outcomes for fetuses with myelomeningocele remains unclear. The study by Adzick et al is a major step in the right direction, but the still suboptimal rates of poor neonatal outcome and high maternal risk necessitate the use of less invasive approaches if such procedures are to be widely implemented”.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2006) concluded that current evidence on the safety and efficacy of pleuro-amniotic shunts to drain fetal pleural effusions appears adequate. The guidance noted, however, that there are uncertainties about the natural history of fetal pleural effusion and about patient selection. Therefore, this procedure should not be used without special arrangements for consent and for audit or research.

Bacha (2011) stated that fetal cardiac interventions performed by interventional cardiologists are currently in a clinical
experimental phase. The 3 most frequent interventions are: (i) aortic balloon valvuloplasty for critical aortic stenosis with a small left ventricle or with a normal size left ventricle but poor function; (ii) atrial septostomy for highly restrictive or intact atrial septum in hypoplastic left heart syndrome; and (iii) pulmonary valvuloplasty for pulmonary atresia and hypoplastic right ventricle.

Rogers et al (2011) stated that mitral valve dysplasia syndrome is a unique form of left-sided heart disease characterized by aortic outflow hypoplasia, dilated left ventricle, dysplastic/incompetent mitral valve, and a restrictive/intact atrial septum. Patients with this constellation of abnormalities have been managed in a variety of ways with overall poor outcomes. These investigators performed a retrospective review of all patients with mitral valve dysplasia syndrome to identify fetal echocardiographic markers predictive of outcomes. Mitral valve dysplasia syndrome was identified in 10 fetuses. Fetal left heart dilation and abnormal pulmonary venous flow were associated with increased mortality; 7 fetuses had abnormal pulmonary venous Doppler patterns; 3 had a unique "double-reversal" flow pattern. Severe fetal left heart dilation (left heart/right heart area ratio greater than 1.5) was present in 5. Pre-natal intervention was performed on 3 fetuses: balloon aortic valvuloplasty (n = 2) and balloon atrial septostomy (n = 1). Of the 3, 1 died in utero and neither survivor underwent a 2-ventricle repair. Five patients required an immediate post-natal intervention to open the atrial septum. The overall mortality was 50%. The authors concluded that mitral valve dysplasia syndrome is a unique form of congenital heart disease with severe aortic stenosis but normal or enlarged left ventricle secondary to primary mitral valve disease. Increased left heart size and pulmonary vein Doppler patterns are predictive of postnatal outcome. Despite the presence of a dilated left ventricle, post-natal management with staged single ventricle palliation may be the most effective strategy.
An UpToDate review on “Amniotic band sequence” (Bodamer, 2013) states that “Amniotic band sequence refers to a highly variable spectrum of congenital anomalies that occur in association with amniotic bands. It is called a sequence because the pattern of congenital anomalies results from a single defect that can be produced by a variety of different etiologies. In contrast, a syndrome refers to a pattern of congenital anomalies that are known, or at least assumed, to result from only a single etiology …. There is no in utero treatment. Postnatally, surgical correction and limb prostheses may be needed”.

Javadian et al (2013) presented 2 successful cases of fetoscopic release of amniotic bands with umbilical cord involvement, and provided a review of the literature on fetal intervention for amniotic band syndrome (ABS). These 2 case reviews, as well as a review of the literature were performed. A total of 14 patients with an ABS underwent fetoscopic intervention between 1965 and 2012. Two of the authors, independently completed literature searches in PubMed, Ovid and MEDLINE for articles related to ABS. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed. Among 14 published cases of ABS, 57 % and 7 % of cases were complicated by PPROM and spontaneous preterm birth (SPTB), respectively. Over all, the procedure resulted in a functional limb in 50 % (7/14) of cases. There were 3 cases with intra-operative complications including intra-amniotic bleeding, uterine wall bleeding, and inability to complete the cases due to ineffective equipment. The authors concluded that fetoscopic release of amniotic bands with minimally invasive surgery may allow for preservation of life and/or limb function, in cases of ABS. They stated that the acceptable functional outcome in 50 % of the cases is reassuring, although more experience and further studies are needed in order to hone in on the appropriate selection criteria that will justify the risk of this invasive in-utero therapy for ABS.
Ville et al (1994) stated that in monozygotic twin pregnancies with reversed arterial perfusion (TRAP) sequence, the donor twin is at high-risk of perinatal death. These investigators described the use of endoscopic surgery in the management of this condition. In 4 cases of TRAP sequence presenting at 17, 20, 26 and 28 weeks' gestation, respectively, an endoscope was introduced into the uterus under local anesthesia and a Nd-YAG laser was used to coagulate the umbilical cord vessels of the acardiac twin. Laser coagulation was successful in arresting blood flow to the acardiac fetus in the cases treated at 17 and 20 weeks, and healthy infants were delivered at term. In the pregnancies treated at 26 and 28 weeks, the umbilical cords were very edematous and laser coagulation failed to arrest blood flow; healthy infants were delivered after spontaneous labor at 29 weeks. The authors concluded that these findings suggested that, during mid-gestation, endoscopic laser coagulation of the umbilical cord vessels of the acardiac twin is an effective method of treating TRAP sequence. In later pregnancy, alternative methods of treatment are needed.

Weisz et al (2004) described their management of pregnancies complicated by TRAP sequence. This was a retrospective study involving all cases of TRAP sequence referred to our fetal medicine unit in a 3-year period (2000 to 2002). Patients were routinely managed by repeat sonographic surveillance with sonographic anatomical evaluation and detailed echocardiography. Cases with signs of impending cardiac failure were treated by in-utero YAG-laser coagulation of the umbilical vessels of the acardiac twin. A total of 6 cases were studied; 3 patients in whom there were no signs of deterioration in the status of the pump twin, and in whom the acardiac twin was smaller than the pump twin, were managed conservatively. However, 1 of these with monoamniotic twins ended in intrauterine fetal death of the pump twin. The other 2 cases presented with spontaneous cessation of blood flow in the umbilical artery of the acardiac twin. Both delivered at term normal neonates whose follow-up
revealed no signs of neurological sequelae. One case of quadruplet pregnancy (with TRAP sequence and 2 dichorionic twins) was treated by selective termination of the monochorionic twins. Two cases with signs of impending cardiac failure were treated by in-utero YAG-laser occlusion of the vessels in the acardiac mass. Both interventions had a favorable outcome. The authors concluded that conservative treatment is suitable for milder cases of TRAP sequence in which the pump twin is the larger one. Cases in which the acardiac twin is larger have a poorer prognosis and should be treated by invasive intervention and cord occlusion.

In a prospective, multi-center study, Hecher et al (2006) evaluated the feasibility and outcome of fetoscopic laser coagulation in pregnancies with TRAP sequence. Percutaneous fetoscopic laser coagulation of placental anastomoses (n = 18) or the umbilical cord of the acardiac twin (n = 42) was performed in 60 consecutive pregnancies at a median gestational age of 18.3 (range of 14.3 to 24.7) weeks under local or loco-regional anesthesia. Vascular coagulation with arrest of blood flow was achieved in 82% (49/60) of cases by laser alone and in a further 15% (9/60) by laser coagulation in combination with bipolar forceps. The overall survival rate of the pump twin was 80% (48/60). Median gestational age at delivery was 37.4 (range of 23.7 to 41.4) weeks and the median interval between the procedure and delivery was 18.2 (range of 1.1 to 25.7) weeks. Median birth weight was 2,720 (range of 540 to 3,840) g. Preterm premature rupture of membranes before 34 weeks' gestation occurred in 18% (11/60) at a median of 62 (range of 1 to 102) days after the procedure. However, only 2 (3%) women delivered within 28 days of the procedure. The authors concluded that fetoscopic laser coagulation of placental vascular anastomoses or the umbilical cord of the acardiac twin is an effective treatment of TRAP sequence, with a survival rate of 80%, and 67% of pregnancies with surviving pump twins going beyond 36 weeks' gestation without further complications.
Wegrzyn et al (2012) noted that TRAP sequence complicates about 1% of all monochorionic twin pregnancies and about 1 to 35,000 of all pregnancies. It involves an acardiac twin whose structural defects are incompatible with life, and an otherwise normal “pump” co-twin. As the blood flow in the acardiac twin is reversed, it keeps on growing owing to the oxygenated blood from the co-twin. These investigators reported a case of monochorionic, diamniotic twin pregnancy after ICS/ET complicated with TRAP sequence, diagnosed at 11 weeks of pregnancy. The unusual finding in this case was the residual heart in the so called acardiac twin. Gradually the normal twin developed signs of hemodynamic compromise. Reversed a-wave in ductus venosus was observed. The acardiac twin showed subcutaneous edema. On November 24, 2011 a successful interstitial ultrasound-guided laser coagulation was performed at 16 weeks of gestation; 17-G needle and 0.6 mm laser fiber were used. The needle was introduced into the pelvic region of the acardiac twin through the abdominal wall. A series of laser bursts lasting 5 to 10 seconds were fired, until cessation of blood flow in the pelvic vessels and umbilical cord of the acardiac twin was confirmed using color Doppler. The course of the intervention was uneventful. Routine steroid therapy was administered at 27 weeks of gestation. At 32 weeks the patient was hospitalized and oral antibiotics were administered due to premature rupture of the membranes and suspicion of intrauterine growth retardation of the pump twin. The patient delivered spontaneously at completed 33 weeks of pregnancy (weight 1,805 g, Apgar 10). After the delivery, a stage 2 intraventricular hemorrhage and jaundice were observed in the neonate. Phototherapy was administered and the mother and the child were eventually discharged from the hospital, both in good general condition. Since then, 2 more successful interstitial laser coagulations in TRAP sequence were performed in the authors’ institution. The essence of the treatment of TRAP sequence is cessation of the blood flow from the pump to the acardiac twin. Fetoscopic cord ligation or coagulation, and laser or radiofrequency ablations of the
acardiac twin vessels, are the possible methods of intervention. The interstitial laser coagulation of the acardiac twin is less invasive than fetoscopic umbilical cord coagulation, as the outer diameter of the 17-G needle is much smaller. A meticulous comparison of these methods would require a randomized study but at 16 weeks of MCDA twin pregnancy interstitial laser coagulation seems to be the method of choice.

An UpToDate review on “Diagnosis and management of twin reversed arterial perfusion (TRAP) sequence” (Holland et al, 2014) states that “In utero therapy -- For continuing pregnancies with one or more poor prognostic criteria, antenatal intervention, delivery, and expectant management are options. As the acardiac twin is nonviable, treatment for TRAP sequence is focused on improving the outcome for the pump twin. Historically, intervention in pregnancies with TRAP sequence was limited to amnioreduction to reduce hydramnios or relief for the pump twin by selective delivery of the acardiac twin via hysterotomy or administration of sclerosing agents (e.g., alcohol) into the umbilical cord of the acardiac twin. For pregnancies between 18 and 27 weeks of gestation, current treatment modalities target occlusion of the umbilical cord of the acardiac twin and include laser ablation, bipolar cord coagulation, and radiofrequency ablation (RFA), which are performed with local anesthesia and conscious sedation. Fetoscopic cord ligation is an alternative, but is less common”.

Lissauer et al (2007) noted that fetal lower urinary tract obstruction (LUTO) affects 2.2 per 10,000 births. It is a consequence of a range of pathological processes, most commonly posterior urethral valves (64 %) or urethral atresia (39 %). It is a condition of high mortality and morbidity associated with progressive renal dysfunction and oligohydramnios, and hence fetal pulmonary hypoplasia. Accurate detection is possible via ultrasound, but the underlying pathology is often unknown. In future, magnetic resonance imaging (MRI) may be increasingly used alongside ultrasound in the diagnosis and assessment of fetuses with
LUTO. Fetal urine analysis may provide improvements in prenatal determination of renal prognosis, but the optimum criteria to be used remain unclear. It is now possible to decompress the obstruction in utero via percutaneous vesico-amniotic shunting or cystoscopic techniques. In appropriately selected fetuses intervention may improve perinatal survival, but long-term renal morbidity amongst survivors remains problematic.

Ethun and associates (2013) examined the outcomes of patients with LUTO treated with vesico-amniotic shunt (VAS) to improve the quality of prenatal consultation and therapy. The medical records of all patients diagnosed with LUTO at the authors’ center between January 2004 and March 2012 were reviewed retrospectively. Of 14 male fetuses with LUTO, all with characteristic ultrasound findings, 11 underwent intervention. One patient received vesicocentesis alone, while 10 had VAS. Two fetuses additionally underwent cystoscopy (1 with attempted valve ablation), and 2 had peritoneo-amniotic shunts. Of 16 total VAS, 13 were placed successfully, 8 dislodged (median of 7 days), and 1 obstructed (84 days). Two fetuses suffered in utero demise, and 2 have unknown outcomes. Lower urinary tract obstruction was confirmed in 6 of 8 live-born fetuses. One patient died in the neonatal period, while 7 survived. All 6 available at follow-up (median of 3.7 years), had significant genitourinary morbidity. Five patients had chronic kidney disease, but only 1 has required dialysis and transplant; 3 had respiratory insufficiency, and 1 required a tracheostomy. The authors concluded that despite significant perinatal and long-term morbidity, VAS offers patients faced with a poor prognosis an improved chance of survival. Moreover, they stated that these results underscore the need for further research into the diagnosis and treatment of LUTO.

Furthermore, an UpToDate review on “Overview of antenatal hydronephrosis” (Baskin and Ozcan, 2014) states that “Fetal surgery -- Although there have been several prospective and
retrospective studies of antenatal surgery in fetuses with sonographic findings consistent with lower urinary tract obstruction, there is no good evidence that this intervention improves renal outcome. These procedures increase the amount of amniotic fluid, thus potentially improving lung development and survival rate. However, there remains a high rate of chronic renal disease in the survivors, necessitating renal replacement therapy in almost two-thirds of the cases”.

Ruano et al (2013) evaluated the effect of early fetoscopic tracheal occlusion (FETO) (22 to 24 weeks’ gestation) on pulmonary response and neonatal survival in cases of extremely severe isolated congenital diaphragmatic hernia (CDH). This was a multi-center study involving fetuses with extremely severe CDH (lung-to-head ratio less than 0.70, liver herniation into the thoracic cavity and no other detectable anomalies). Between August 2010 and December 2011, a total of 8 fetuses underwent early FETO. Data were compared with 9 fetuses that underwent standard FETO and 10 without fetoscopic procedure from January 2006 to July 2010. FETO was performed under maternal epidural anesthesia, supplemented with fetal intramuscular anesthesia. Fetal lung size and vascularity were evaluated by ultrasound before and every 2 weeks after FETO. Post-natal therapy was equivalent for both treated fetuses and controls. Primary outcome was infant survival to 180 days and secondary outcome was fetal pulmonary response. Maternal and fetal demographic characteristics and obstetric complications were similar in the 3 groups (p > 0.05). Infant survival rate was significantly higher in the early FETO group (62.5%) compared with the standard group (11.1%) and with controls (0%) (p < 0.01). Early FETO resulted in a significant improvement in fetal lung size and pulmonary vascularity when compared with standard FETO (p < 0.01). The authors concluded that early FETO may improve infant survival by further increases of lung size and pulmonary vascularity in cases with extremely severe
pulmonary hypoplasia in isolated CDH. They stated that the findings of this study supports formal testing of the hypothesis with a randomized controlled trial.

Ruano et al (2014) reviewed the indications, technical aspects, preliminary results, risks, and clinical implications of FETO for severe CDH performed outside the United States and its potential future directions in this country and globally.

Congenital diaphragmatic hernia occurs in approximately 1 in 2,500 live births and results in high neonatal morbidity and mortality, largely associated with the severity of pulmonary hypoplasia and pulmonary arterial hypertension. With the advent of prenatal imaging, CDH can be diagnosed before birth, and in-utero treatment is now available in some centers. The prognosis of CDH can be evaluated by assessing the fetal lung size, the degree of liver herniation, and the fetal pulmonary vasculature in isolated forms of CDH. These parameters help classify fetuses as having mild, moderate, severe, or extremely severe isolated CDH. Severe and extremely severe diaphragmatic hernias have poor outcomes and thus are candidates for innovative therapies such as FETO. Fetal endoscopic tracheal occlusion is usually performed between 26 and 30 weeks' gestation. In-utero, an endoscope is passed through the fetal mouth and down to the carina; the balloon is deployed just above the carina. After the procedure, ultrasound surveillance every 2 weeks ensures the balloon's structural integrity and measures the fetal pulmonary response. At approximately 34 weeks' gestation, the balloon is deflated and removed. Fetal endoscopic tracheal occlusion is thought to improve outcomes by decreasing mortality and allowing more rapid neonatal stabilization. Ultimately, the goal of FETO is to minimize pulmonary hypoplasia and pulmonary arterial hypertension. Following delivery, neonates still require diaphragm repair.
Furthermore, an UpToDate review on “Congenital diaphragmatic hernia: Prenatal diagnosis and management” (Hedrick and Adzick, 2015) states that “In utero therapy is an investigational procedure with limited geographic availability”.

Sizarov and Boudjemline (2017) noted that efficient use of fetal echocardiography has enabled early detection of congenital heart disease and of its often irreversible complications, such as ventricular hypoplasia in case of severe stenosis of the semilunar valves. Experience of the past 25 years has proved that balloon dilatation of the severely stenotic or atretic valve in fetuses as early as the 23rd week of gestation is technically feasible with a learning curve. Reported results regarding the ultimate bi-ventricular circulation outcome after fetal valve intervention are at best controversial, with the desired improvements in the quality of life (QOL) and cost-benefits of the post-natal treatment being as yet unconfirmed. Despite acute hemodynamic success with a relatively low rate of fetal complications, the number of suitable candidates for the fetal valve intervention remains low. High valvular tissue plasticity in the fetus and difficulties of assessing the point of no return of the myocardial damage often makes the success of fetal valve intervention short-lived and unpredictable. The authors concluded that future refinements of the equipment, imaging, and biodegradable tissue regeneration materials will lead to better results of the fetal valve interventions beyond their technical success.

Fetal Aortic Valvuloplasty

A recent American Heart Association’s Scientific Statement (Donofrio et al, 2014) assigned a IIb classification (procedure/treatment may be considered; additional studies with broad objectives needed; additional registry data would be helpful) to fetal aortic valvuloplasty (FAV) for evolving hypoplastic left heart syndrome (HLHS), based upon a B level of evidence (recommendations usefulness/efficacy less well-
established; greater conflicting evidence from single randomized trial or non-randomized studies). The authors stated that “Because fetal AS with evolving HLHS is relatively uncommon and probably more often than not goes undetected prenatally, clinical experience with fetal intervention for this lesion is limited. Given the morbidity and mortality associated with palliative surgery for HLHS, aortic valve dilation may be considered in fetuses with AS in whom the selection criteria are met. Before the procedure, extensive family counseling should detail the risks of the procedure to mother and fetus and lay out the expected clinical course for those who undergo intervention to those who choose more standard management .... Although it is important to appreciate the potential benefits and promise of fetal cardiac catheter intervention for critical AS evolving into HLHS by possibly creating a postnatal 2-ventricle system, the long-term benefits and outcomes of this procedure are unknown. Although outcomes for HLHS after the Fontan operation and the limitations of this strategy are relatively clear, the fetus undergoing a cardiac catheter intervention for AS may be at future risk for multiple operations, valve replacements, ventricular dysfunction, and possibly pulmonary hypertension within the context of a borderline-size small left ventricle. Families should be counseled about these concerns and about the lack of data on long-term outcomes. Comparative analysis of these alternative strategies through careful investigational efforts is warranted.”

Freud et al (2014) stated that FAV can be performed for severe mid-gestation aortic stenosis in an attempt to prevent progression to HLHS. A subset of patients has achieved a bi-ventricular (BV) circulation FAV. The post-natal outcomes and survival of the BV patients, in comparison with those managed as HLHS, have not been reported. This study included 100 patients who underwent FAV for severe mid-gestation aortic stenosis with evolving HLHS from March 2000 to January 2013. Patients were categorized based on post-natal management as BV or HLHS. Clinical records were reviewed. A total of 88 fetuses were live-born, and 38 had a BV
circulation (31 from birth, 7 converted after initial uni-
ventricular [UV] palliation). Left-sided structures, namely aortic
and mitral valve sizes and left ventricular volume, were
significantly larger in the BV group at the time of birth (\(p < 0.01\)). After a median follow-up of 5.4 years, freedom from
cardiac death among all BV patients was 96 ± 4 % at 5 years
and 84 ± 12 % at 10 years, which was better than HLHS
patients (log-rank \(p = 0.04\)). There was no cardiac mortality in
patients with a BV circulation from birth. All but 1 of the BV
patients required post-natal intervention; 42 % underwent
aortic or mitral valve replacement. On the most recent
echocardiogram (ECG), the median left ventricular end-
diastolic volume z score was +1.7 (range of -1.3 to +8.2), and
80 % had normal ejection fraction (EF). The authors
concluded that short- and intermediate-term survival among
patients who underwent FAV and achieved a BV circulation
post-natally is encouraging. However, morbidity still exists,
and ongoing assessment is warranted.

In an editorial that accompanied the afore-mention study by
Freud et al, Rychik (2014) stated that "Despite abundant
enthusiasm for this approach, much more work is necessary,
with many more questions to be answered before we know the
optimal strategy for management of HLHS in the rapidly
advancing era of fetal diagnosis and treatment”.

Mellander and Gardiner (2014) noted that the update course in
fetal cardiology held by the Fetal Working Group of the
Association for European Pediatric and Congenital Cardiology
in Istanbul in May 2012 included a session on fetal cardiac
therapy. In the introductory overview to this symposium, these
investigators examined the level of evidence supporting or
refuting proposed fetal cardiac therapies including trans-
placental treatment of fetal tachyarrhythmias, steroid treatment
in fetal atrioventricular block, and FAV. The authors
concluded that the evidence for the safety and effectiveness of
currently available fetal cardiac therapies is low, with no
therapy based on a RCT. Trans-placental treatment of fetal
tachycardia is generally accepted as effective and safe, based on extensive and widespread clinical experience; however, there is no consensus on which drugs are the most effective in different electrophysiological situations. Randomized studies may be able to resolve this, but this is complicated because tachyarrhythmias are relatively rare conditions, the fetus is not accessible for direct treatment, and it is the healthy mother who accepts treatment she does not need on behalf of her fetus. The indications for steroid treatment in fetal atrioventricular block and for FAV are even more controversial. The authors stated that although randomized trials would be desirable, the practical issues of recruiting sufficient sample sizes and controlling for variation in practice across multiple sites is not to be underestimated. They stated that multi-center registries, analyzed free of bias, may be an alternative way to improve the evidence base of fetal cardiac therapy.

Moon-Grady et al (2015) described initial report of the International Fetal Cardiac Intervention Registry (IFCIR), which collected data for maternal/fetal dyads and newborns who were referred and evaluated as possible candidates for fetal cardiac intervention. Exploratory analysis of the data was performed to compare outcomes of the intervention group versus those of patients who met criteria but who had no intervention or had an unsuccessful one. Fetal survival to live-birth was 80.0% in the intervention group and 85.2% in the non-intervention group; survival to discharge was 57.5% and 59.3%, respectively. In the subgroup of fetuses with aortic stenoses and evolving HLHS, 42.9% of live-born infants were discharged with a BV circulation after successful fetal intervention versus 19.4% of those who had no fetal intervention or the intervention was unsuccessful. When fetal deaths were counted as intervention failures, the percentage of patients discharged with a BV circulation after successful intervention was 31.3% versus 18.5% with no intervention. The authors concluded that present post-natal data suggested
potential benefit to fetal therapy among pregnancies considered for possible intervention and support proposals for additional work.

An accompanying commentary (Donofrio, 2015) identified the limitations of this registry data in reaching conclusions and drawing definitive recommendations: “There are inherent limitations of using registry data to draw overarching conclusions and make definitive recommendations. First and foremost, the lack of randomization precludes a true control group to determine whether those who receive intervention have outcomes similar to those who do not. Although this issue is addressed by using fetuses with unsuccessful interventions as control subjects, this is not ideal and not truly representative of the affected population. Second, there is no uniformly accepted strategy for determining post-natal surgical care for these patients, including accepted criteria for biventricular repair. It is important to note that post-natal management is essential to treating newborns with aortic stenoses and a borderline left ventricle. Key factors, including access to specialized interventional catheterization procedures and innovative surgical techniques, must be considered. Different care strategies from individual practices may introduce center bias, making it difficult to ascertain whether fetal intervention or specialized post-natal care determines success. Also, although most practitioners believe it is more beneficial for a patient to have biventricular repair than single-ventricle palliation, the long-term benefits of strategies that begin with fetal intervention remain unknown. Comparative analysis of long-term outcomes of fetal intervention as an alternate strategy through detailed follow-up is imperative. Finally, alterations in brain development and brain injury in fetuses with aortic stenosis versus those with HLHS will need to be addressed. Data suggest that lack of antegrade aortic flow may have an impact on brain maturation in the third trimester. Careful assessment of brain development and injury in fetuses with aortic stenosis post-fetal intervention will need to be investigated.”
Marantz and Grinenco (2015) stated that FAV is intended to alter the natural history of aortic stenosis evolving to HLHS. These investigators reviewed the most recently reported data and advances on this procedure. The highlights of the latest experience were the advances in further understanding of the pre-natal and post-natal natural history of this disease, and the way in which FAV impacts on it, the identification of new predictors of BV outcome, and the report of post-natal survival of intervened patients. These researchers noted that recently reported short-term and middle-term results are encouraging. Experimental research on procedural aspects is ongoing, with no definite results; multi-center studies are also ongoing. The authors concluded that in recent years, there have been advances in the understanding of the pre-natal and post-natal process of aortic stenosis evolving to HLHS and the effects of FAV, as well as the need of adequate post-natal therapeutic strategies for these patients. Procedural aspects are being studied with animal models, but still need far more experience before human application. Moreover, long-term results are still to be discovered, and multi-center studies may provide a new perspective. The authors stated that continuing research is mandatory so that ultimately fetal heart intervention finds its place among the therapeutic resources for congenital heart disease (CHD).

In a systematic review and meta-analysis, Araujo Junior and colleagues (2016) evaluated perinatal outcomes and intra-uterine complications following fetal interventions for CHDs. A systematic review and meta-analysis was performed following electronic search of the PubMed and SCOPUS databases (last searched August 2015). Perinatal outcomes included fetal death, live birth, preterm birth less than 37 weeks and neonatal death. Intra-uterine complications included Bradycardia requiring treatment and hemo-pericardium requiring drainage. The estimated proportions were reported as mean with 95 % CI. Electronic search retrieved 2,279 records, and 29 studies (11 retrospective cohort and 18 case reports) were considered eligible. The number of studies and
proportions (95 % CI) of neonatal death were 3 and 65 % (95 % CI: 26 to 88) for FAV; 1 and 25 % (95 % CI: 10 to 49) for pulmonary valvuloplasty; 1 and 14 % (95 % CI: 6 to 28) for septoplasty; 24 and 29 % (95 % CI: 18 to 41) for pericardiocentesis and/or pericardio-amniotic shunt. The number of studies and proportion (CI 95 %) for bradycardia requiring treatment was 2 and 52 % (95 % CI: 16 to 87) following FAV; 1 and 44 % (95 % CI: 23 to 67) for pulmonary valvuloplasty; 1 and 27 % (95 % CI: 15 to 43) for septoplasty. The authors concluded that the current evidence on the effectiveness of prenatal interventions for CHDs comes mostly from case reports and a few larger series; none of the studies was randomized. They stated that although their results are encouraging in terms of perinatal survival, they should be interpreted with caution when compared with procedures performed after birth.

Gardiner et al (2016) described the natural history of fetal aortic stenosis and tested previously published criteria designed to identify cases of evolving HLHS with the potential for a BV outcome following FAV. These investigators reported the natural history of 107 fetuses in continuing pregnancies that did not undergo FAV from a retrospective multi-center study in Europe of 214 fetuses with aortic stenosis (2005 to 2012). They examined longitudinal changes in Z-scores of aortic and mitral valve and left ventricular dimensions, and documented direction of flow across foramen ovale and aortic arch, and mitral valve inflow pattern and any changes to determine those fetuses satisfying the Boston criteria for emerging HLHS and to estimate the proportion of these that would also have been considered ideal FAV candidates. These researchers applied the threshold score where a score of 1 was awarded to fetuses for each Z-score meeting the following: left ventricular length and width greater than 0; mitral valve width greater than -2 and aortic valve width greater than -3.5 and also where the pressure gradient across either the mitral or aortic valve was greater than 20 mmHg and compared the predicted circulation with known survival and
final post-natal circulation (BV; post-natal UV or conversion from BV to UV). In the 107 ongoing pregnancies there were 8 spontaneous fetal deaths, resulting in 99 live-born children; 5 were lost during follow-up; 5 had comfort care and 4 had mild aortic stenosis not requiring intervention. There was an intention-to-treat in the remaining 85, but 5 of them died before surgery before the circulation could be determined. Thus, a total of 80 underwent post-natal procedures with 44 BV, 29 UV and 7 BV-UV outcomes; 70/85 children (82 %) with an intention-to-treat had greater than or equal to 30 day survival. Survival was superior in BV circulation at a median of 6 years (p = 0.041). Aortic valve size was significantly smaller at presentation in fetuses with UV outcomes (p = 0.004), but its growth velocity was similar in both circulatory outcomes. In contrast, the mitral valve (p = 0.008) and left ventricular inlet length (p = 0.0042) and width (p = 0.0017) were significantly reduced by term in fetuses with UV compared to BV outcomes. Fetal data from 70 treated neonates, recorded before 30 completed gestational weeks was evaluated for emerging HLHS; 44 had moderate or severe left ventricular depression and 38 of these had retrograde flow in the aortic arch with a further 2 having left-to-right flow at atrial level and a-wave reversal in the pulmonary veins. Thus, 40 of the 70 satisfied the criteria associated with emerging HLHS and a BV circulation was documented in 13 (33 %); 12 of the 40 fetuses (30 %) had a threshold score of 4 or 5, with a BV circulation in 5 (42 %) of them without fetal intervention. The authors concluded that their natural history cohort of children diagnosed with aortic stenosis with known outcomes showed that a substantial proportion of fetuses meeting the criteria for emerging HLHS, with or without favorable selection criteria for FAV, had a sustained BV circulation without fetal intervention. They stated that these findings indicated that further work is needed to refine selection criteria to offer appropriate therapy to fetuses with aortic stenosis.
Freud and Tworetzky (2016) discussed the rationale, patient selection, technical aspects, and outcomes of percutaneous, ultrasound-guided fetal cardiac intervention (FCI) for structural congenital heart disease. These investigators stated that FCI is most commonly performed for 3 forms of congenital heart disease: severe aortic stenosis with evolving hypoplastic left heart syndrome (HLHS), pulmonary atresia with intact ventricular septum and evolving hypoplastic right heart syndrome, and HLHS with intact or highly restrictive atrial septum. For severe aortic stenosis and pulmonary atresia with intact ventricular septum, the goal of intervention is to alter the natural history such that a biventricular circulation may be achieved post-natally. A growing number of patients have achieved a bi-ventricular circulation; however, patient selection and post-natal management strategy are essential for success; HLHS with intact or highly restrictive atrial septum is one of the most lethal forms of congenital heart disease, and the goal of FCI is to improve survival. Although the creation of an atrial communication in-utero is technically feasible and may permit greater stability in the immediate post-natal period, significant improvements in survival have not yet been reported. The authors concluded that FCI is an evolving form of treatment for congenital heart disease that holds promise for select patients; critical evaluation of both short and long-term outcomes is needed.

Yuan and Humuruola (2016) stated that fetal cardiac interventions for congenital heart diseases may alleviate heart dysfunction, prevent them evolving into hypoplastic left heart syndrome, achieve bi-ventricular outcome and improve fetal survival. Candidates for clinical fetal cardiac interventions are now restricted to cases of critical aortic valve stenosis with evolving hypoplastic left heart syndrome, pulmonary atresia with an intact ventricular septum and evolving hypoplastic right heart syndrome, and hypoplastic left heart syndrome with an intact or highly restrictive atrial septum as well as fetal heart block. The therapeutic options are advocated as pre-natal aortic valvuloplasty, pulmonary valvuloplasty, creation of inter-
atrial communication and fetal cardiac pacing. Experimental research on fetal cardiac intervention involves technical modifications of catheter-based cardiac clinical interventions and open fetal cardiac bypass that cannot be applied in human fetuses for the time being. Clinical fetal cardiac interventions are plausible for mid-gestation fetuses with the above-mentioned congenital heart defects. The technical success, bi-ventricular outcome and fetal survival are continuously being improved in the conditions of the sophisticated multi-disciplinary team, equipment, techniques and post-natal care. Experimental research is laying the foundations and may open new fields for catheter-based clinical techniques. The authors stated that attempts to make substantial improvements of fetal cardiac bypass outcomes are underway with regard to technical modifications and candidate selection. In spite of the reproducibility of experimental fetal cardiac bypass, fetal hypoxia and demise subsequent to cytokine-mediated injury and placental dysfunction following bypass significantly impede the technical application in human fetuses. They noted that future directions of fetal cardiac interventions are a combination of non-surgical cardiac therapy with minimally invasive surgical techniques (e.g., robot-guided fetal cardiac intervention, fetoscopic fetal cardiac surgery and open cardiac surgery); more and more advantageous techniques and better outcomes are anticipated.

Laraja and associates (2017) characterized neurodevelopmental outcomes after fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome and examined the risk factors for adverse neurodevelopment. Questionnaires were mailed to families of children who underwent fetal aortic valvuloplasty from 2000 to 2012, and medical records were reviewed retrospectively. The primary outcome was the General Adaptive Composite score of the Adaptive Behavior Assessment System Questionnaire-Second Edition. Other questionnaires included the Behavior Assessment System for Children, Behavior Rating Inventory of Executive Function, Ages and Stages, and Pediatric Quality of Life Inventory.
Among 69 eligible subjects, 52 (75%) completed questionnaires at median age of 5.5 (range of 1.3 to 12) years; 30 (58%) had biventricular status circulation. The General Adaptive Composite mean score (92 ± 17) was lower than population norms (p < 0.001) and similar to published reports in patients with hypoplastic left heart syndrome without fetal intervention; scores in the uni-ventricular versus bi-ventricular group were 97 ± 19 versus 89 ± 14, respectively (p = 0.10). On multi-variable analysis, independent predictors of a lower General Adaptive Composite score were total hospital duration of stay in the first year of life (p = 0.001) and, when forced into the model, bi-ventricular status (p = 0.02). For all other neurodevelopmental questionnaires (Behavior Assessment System for Children, Behavior Rating Inventory of Executive Function, Ages and Stages, Pediatric Quality of Life Inventory), most subscale scores for patients with bi-ventricular and uni-ventricular status were similar. The authors concluded that the children who underwent fetal aortic valvuloplasty have neurodevelopmental delay, similar to patients with hypoplastic left heart syndrome without fetal intervention. Achievement of bi-ventricular circulation was not associated with better outcomes. These investigators inferred that innate patient factors and morbidity during infancy have the greatest effect on neurodevelopmental outcomes.

Furthermore, an UpToDate review on “Fetal cardiac abnormalities: Screening, evaluation, and pregnancy management” (Copel, 2017) states that “In some cases, prenatal diagnosis also provides an opportunity for in utero treatment. Transplacental medical therapy improves the prognosis of some fetal arrhythmias, particularly tachycardias. Invasive in utero cardiac intervention (e.g., aortic or pulmonary balloon valvuloplasty, atrial needle septoplasty) may improve the prognosis of some lesions, such as HLHS or severe valvular abnormalities (e.g., severe mitral regurgitation, aortic stenosis, pulmonary atresia); however, these interventions are performed at only a few fetal surgery centers and are considered investigational”.
In Utero Shunting for the Treatment of Fetal Cerebral Ventriculomegaly

Pisapia and colleagues (2017) stated that fetal ventriculomegaly (VM) refers to the enlargement of the cerebral ventricles in utero. It is associated with the post-natal diagnosis of hydrocephalus. Fetal VM is clinically diagnosed on ultrasound (US) and is defined as an atrial diameter greater than 10 mm. Because of the anatomic detailed seen with advanced imaging, VM is often further characterized by fetal MRI. Fetal VM is a heterogeneous condition with various etiologies and a wide range of neurodevelopmental outcomes. These outcomes are heavily dependent on the presence or absence of associated anomalies and the direct cause of the ventriculomegaly rather than on the absolute degree of VM. The authors discussed diagnosis, work-up, counseling, and management strategies as they relate to fetal VM. They described imaging-based research efforts aimed at using pre-natal data to predict post-natal outcome. They also reviewed the early experience with fetal therapy such as in utero shunting, as well as the advances in pre-natal diagnosis and fetal surgery that may begin to address the limitations of previous therapeutic efforts.

Furthermore, an UpToDate review on “Fetal cerebral ventriculomegaly” (Norton, 2018) does not mention in utero fetal surgery as a therapeutic option.

Thoracoamniotic Shunt for Fetal Pleural Effusions

Peranteau and co-workers (2015) stated that hydrops and pulmonary hypoplasia are associated with significant morbidity and mortality in the setting of a congenital lung lesion or pleural effusion (PE). These researchers reviewed their experience using in-utero thoraco-amniotic shunt (TAS) to manage fetuses with these diagnoses. They performed a retrospective review of fetuses diagnosed with a congenital lung lesion or PE who underwent TAS placement from 1998 to
2013. A total of 97 shunts were placed in 75 fetuses. Average gestational age (± SD) at shunt placement and birth was 25 ± 3 and 34 ± 5 weeks. Shunt placement resulted in a 55 ± 21 % decrease in macro-cystic lung lesion volume and complete or partial drainage of the PE in 29 % and 71 % of fetuses; 69 % of fetuses presented with hydrops, which resolved following shunt placement in 83 %. Survival was 68 %, which correlated with gestational age at birth, % reduction in lesion size, unilateral PEs, and hydrops resolution. Surviving infants had prolonged neonatal intensive care unit (NICU) courses and often needed either surgical resection or tube thoracostomy in the peri-natal period. The authors concluded that TAS provided a therapeutic option for select fetuses with large macro-cystic lung lesions or PEs at risk for hydrops and/or pulmonary hypoplasia; survival following shunting depended on gestational age at birth, reduction in mass size, and hydrops resolution.

In a retrospective, single-center study, Suyama and colleagues (2018) examined the role of lung size and abnormal Doppler findings in the umbilical artery (UA) in determining the outcomes of fetuses with primary fetal hydrothorax (FHT) associated with hydrops who underwent TASs. These researchers included cases of primary FHT with hydrops who underwent TAS at the authors' hospital between 2004 and 2016. They evaluated the relationship between mortality until 28 days after birth and US findings, including absent or reversed end-diastolic velocity (AREDV) in the UA and the lung-to-thorax transverse area ratio (LTR), before and after TAS. A total of 41 cases of primary FHT with hydrops underwent TAS. The median (range) gestational age at TAS was 28.5 (19.3 to 33.8) weeks. Bilateral PE was observed in 39 cases (95.1 %). Among the 41 cases, 19 (46.4 %) survived, 11 (26.8 %) died in-utero, and 11 (26.8 %) died in the neonatal period. AREDV in the UA before and after TAS were not associated with mortality (p = 0.32 and 0.47, respectively). The OR for mortality in LTR 0.2 to 0.3 before TAS was 0.62 (versus LTR of less than 0.2, p = 0.45) and that
in LTR 0.2 to 0.3 and greater than 0.3 after TAS were 0.27 and 0.06, respectively (versus LTR less than 0.2, p for trend < 0.01). The authors concluded that a larger LTR following TAS was significantly associated with a better prognosis in hydropic primary FHT. The fetal lung size after the procedure may be a prognostic factor of primary FHT.

Hidaka and associates (2018) stated that although the efficacy of TAS for FHT is well-recognized, the coexistence of hydrops fetalis is still a clinical challenge. The pre-operative determinants of shunting efficacy are not fully understood. In this study, these investigators examined the perinatal and postnatal outcomes of hydrops fetalis with PE treated by TAS using a double-basket catheter, and discussed the pre-operative factors predictive of patients who will benefit from TAS. These researchers conducted a retrospective study in hydropic fetuses with PE treated by TAS between 2007 and 2015. They extracted information regarding post-natal survival and pre-therapeutic US findings, including skin-edema thickness, PE pocket size, and Doppler readings. A total of 12 subjects underwent TAS at a median gestational age of 29 + 5 weeks (range of 25 + 5 to 33 + 2 weeks). Skin edema disappeared or regressed in 7; 3 experienced early neonatal death and the other 9 ultimately survived after a live-birth at a median gestational age of 33 + 4 weeks (range of 29 + 1 to 38 + 2 weeks). All surviving children, except for 1, had a pre-therapeutic PE pocket greater than the precordial-edema thickness. All 3 children who died had precordial-edema thickness equal to or greater than the size of the PE pocket. The authors achieved a high survival rate (75%) using the double-basket technique. These investigators noted that a greater pre-therapeutic width of skin edema compared with the PE pocket was possibly suggestive of a treatment-resistant condition and subsequent poor post-natal outcome.

Dorsi and co-workers (2018) stated that congenital chylothorax is a rare disease and prognostic factors are key element in properly informing parents. These investigators determined
the pre-natal factors associated with neonatal survival in a cohort of live-born infants with congenital chylothorax. Observational monocentric cohort study including all live-born neonates consecutively admitted for congenital chylothorax were included in this study. Neonatal mortality was 32% (16/50). Prematurity (or birth-weight), persistence of hydrops at birth, and the absence of TAS procedure were significantly associated with mortality, whereas pre-natal diagnosis of PE, side of PE, hydrops fetalis and amnio-drainage were not. In case of prenatal diagnosis of hydrops fetalis, the reversal in-utero of hydrops fetalis was significantly associated with survival (p = 0.001). In case of TAS, the interval between TAS intervention and delivery was significantly longer for patients who survived (p = 0.03). The authors concluded that TAS and reversal of hydrops significantly improved survival, whereas prematurity worsened outcome of live-born infants with congenital chylothorax. These researchers stated that these findings also suggested that the interval between TAS and birth appeared to be crucial; the longer the interval, the more likely was the reversal of ante-natal hydrops and neonatal survival.

Chon and colleagues (2019) noted that congenital PE is a rare condition with an incidence of approximately 1 per 15,000 pregnancies. The development of secondary hydrops is a poor prognostic indicator and such cases can be managed with a TAS. These investigators described post-natal outcomes in survivors after TAS placement for congenital PEs. They carried out a retrospective review of all cases with fetal PEs treated between 2006 and 2016. Patients with dominant unilateral or bilateral PEs complicated by secondary hydrops fetalis received TAS placement. The results were reported as median (range). A total of 29 patients with PE with secondary hydrops underwent TAS placement. The gestational age at the initial TAS placement was 27.6 (20.3 to 36.9) weeks. Before delivery, hydrops resolved in 17 (58.6%) patients. The delivery gestational age was 35.7 (25.4 to 41.0) weeks; and the overall survival (OS) rate was 72.4%. Among
the 21 survivors, 19 (90.5 %) required admission to the NICU for 15 (5 to 64) days. All 21 survivors had post-natal resolution of the PEs. All 21 children were long-term survivors, with a median age of survivorship of 3 years and 3 months (9 months to 7 years and 6 months) at the time of last reported follow-up. The authors concluded that TAS in fetuses with a dominant PE(s) and secondary hydrops resulted in a 72 % survival rate. Nearly all survivors required admission to the NICU; however, a majority did not have significant long-term morbidity.

Fetoscopic Laser Ablation for Type 2 Vasa Previa

Chmait and colleagues (2010) stated that vasa previa is associated with increased perinatal morbidity and mortality because of fetal exsanguination at time of membrane rupture. These investigators reported their experience in the treatment of type II vasa previa via in-utero laser ablation in the 3rd trimester. Two cases of type II vasa previa were identified via endo-vaginal US in the 2nd trimester and treated via 3rd trimester fetoscopic laser ablation. In case 1, fetoscopic laser ablation of the vasa previa was performed without complication at 28 3/7 weeks' gestation as a prophylactic measure. The patient delivered at 33 3/7 weeks' gestation after rupture of membranes without sequelae with good perinatal outcome. In case 2, expectant management of twins with a vasa previa was planned. However, significant cervical shortening and funneling was documented at 30 5/7 weeks, and the risk of membrane rupture was deemed relatively high. As a therapeutic alternative to outright preterm delivery, the patient underwent uncomplicated laser ablation of the vasa previa. Delivery occurred at 34 3/7 weeks after rupture of membranes, and the twins did well. The authors suggested that type II vasa previa could be definitively treated in-utero by laser photo-coagulation in the 3rd trimester. Ablation of the vasa previa may be performed prophylactically or as a therapeutic measure to delay delivery if symptoms of preterm labor and/or cervical shortening develop.
Johnston and associates (2014) noted that unrecognized vasa previa carries a significant risk of fetal mortality. Advances in US have improved detection of vasa previa and led to a dramatic reduction in fetal morbidity and mortality. However, current management strategies require prolonged hospitalized surveillance, preterm delivery prior to the onset of labor or rupture of membranes, and a Cesarean delivery. Fetoscopic laser ablation of type II vasa previa allows for the possibility of term vaginal delivery. These researchers presented a patient who underwent successful laser photo-coagulation of a type II vasa previa at 32(5)/7 weeks' gestation. She subsequently delivered vaginally at term without complications. The authors concluded that the potential benefits of definitive in-utero treatment of non-type I vasa previa, such as vaginal delivery at term, must be weighed against the procedure-related risks of operative fetoscopy.

Furthermore, an UpToDate review on "Velamentous umbilical cord insertion and vasa previa" (Lockwood and Russo-Stieglitz, 2019) states that "Case reports have described use of fetoscopic laser ablation for treatment of type 2 vasa previa, with variable outcomes. This procedure should be considered investigational".

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>59001</td>
<td>Amniocentesis; therapeutic amniotic fluid reduction (includes ultrasound guidance)</td>
</tr>
<tr>
<td>59072</td>
<td>Fetal umbilical cord occlusion, including ultrasound guidance</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
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<tr>
<td>--------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>59076</td>
<td>Fetal shunt placement, including ultrasound guidance</td>
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</tbody>
</table>

Other CPT codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>59074</td>
<td>Fetal fluid drainage (eg, vesicocentesis, thoracocentesis, paracentesis), including ultrasound guidance</td>
</tr>
<tr>
<td>59897</td>
<td>Unlisted fetal invasive procedure, including ultrasound guidance</td>
</tr>
</tbody>
</table>

HCPCS codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2401</td>
<td>Repair, urinary tract obstruction in the fetus, procedure performed in utero</td>
</tr>
<tr>
<td>S2402</td>
<td>Repair, congenital cystic adenomatoid malformation in the fetus, procedure performed in utero</td>
</tr>
<tr>
<td>S2403</td>
<td>Repair, extralobar pulmonary sequestration in the fetus, performed in utero</td>
</tr>
<tr>
<td>S2404</td>
<td>Repair, myelomeningocele in the fetus, procedure performed in utero</td>
</tr>
<tr>
<td>S2405</td>
<td>Repair of sacrococcygeal teratoma in the fetus, procedure performed in utero</td>
</tr>
<tr>
<td>S2409</td>
<td>Repair, congenital malformation of fetus, procedure performed in utero, not otherwise classified</td>
</tr>
<tr>
<td>S2411</td>
<td>Fetoscopic laser therapy for treatment of twin-to-twin transfusion syndrome</td>
</tr>
</tbody>
</table>

HCPCS codes not covered for indications listed in the CPB:

Fetoscopic laser ablation for type 2 vasa previa - no specific code:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2400</td>
<td>Repair, congenital diaphragmatic hernia in the fetus using temporary tracheal occlusion, procedure performed in utero</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- **D48.0** Neoplasm of uncertain behavior of bone and articular cartilage
- **O30.021-O30.029** Conjoined twin pregnancy [twin reversed arterial perfusion (TRAP)]
- **O33.7xx+** Maternal care for disproportion due to other fetal deformities
- **O36.891-O36.899** Maternal care for other specified fetal problems
- **O43.021-O43.029** Fetus-to-fetus placental transfusion syndrome [severe]
- **P02.3** Newborn (suspected to be) affected by placental transfusion syndrome [twin-twin transfusion syndrome]
- **P28.89** Other specified respiratory conditions of newborn [pleural effusion]
- **Q05.0-Q05.9** Spina bifida
- **Q07.00-Q07.09** Arnold-Chiari syndrome
- **Q33.0** Congenital cystic lung
- **Q33.2-Q33.3** Sequestration and agenesis of lung
- **Q33.6** Congenital hypoplasia and dysplasia of lung
- **Q62.31-Q62.39** Other obstructive defects of renal pelvis and ureter [not covered for fetal hydronephrosis]
<table>
<thead>
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<th>Code</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>Q64.2</td>
<td>Congenital posterior urethral valves</td>
</tr>
<tr>
<td>Q64.31 - Q64.39</td>
<td>Other atresia and stenosis of urethra and bladder neck</td>
</tr>
<tr>
<td>Q89.4</td>
<td>Conjoined twins [twin reversed arterial perfusion (TRAP)]</td>
</tr>
<tr>
<td>Q89.8</td>
<td>Other specified congenital malformations [acardia] [twin reversed arterial perfusion (TRAP)]</td>
</tr>
<tr>
<td>R89.7</td>
<td>Abnormal histological findings in specimens from other organs, systems and tissues</td>
</tr>
</tbody>
</table>

ICD-10 codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>O35.0xx0 - O35.0xx9</td>
<td>Maternal care for (suspected) central nervous system malformation in fetus [acqueductal stenosis (hydrocephalus)]</td>
</tr>
<tr>
<td>O35.1xx0 - O35.1xx9</td>
<td>Maternal care for (suspected) chromosomal abnormality in fetus</td>
</tr>
<tr>
<td>O35.8xx1</td>
<td>Maternal care for other (suspected) fetal abnormality and damage, fetus 1 [fetal aortic valvuloplasty]</td>
</tr>
<tr>
<td>O35.9xx0 - O35.9xx9</td>
<td>Maternal care for (suspected) fetal abnormality and damage, unspecified</td>
</tr>
<tr>
<td>O69.4xx0 - O69.4xx9</td>
<td>Labor and delivery complicated by vasa previa [type 2 vasa previa]</td>
</tr>
<tr>
<td>P02.8</td>
<td>Newborn (suspected to be) affected by other abnormalities of membranes [amniotic band syndrome]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>P60</td>
<td>Disseminated intravascular coagulation of newborn</td>
</tr>
<tr>
<td>P61.0 - P61.9</td>
<td>Other perinatal hematological disorders</td>
</tr>
<tr>
<td>Q03.0 - Q03.9</td>
<td>Congenital hydrocephalus</td>
</tr>
<tr>
<td>Q04.8</td>
<td>Other specified congenital malformations of brain [fetal cerebral ventriculomegaly]</td>
</tr>
<tr>
<td>Q06.0 - Q06.9</td>
<td>Other congenital malformations of spinal cord</td>
</tr>
<tr>
<td>Q20.0 - Q24.9</td>
<td>Congenital malformations of the heart</td>
</tr>
<tr>
<td>Q35.1 - Q37.9</td>
<td>Cleft palate and cleft lip</td>
</tr>
<tr>
<td>Q79.0 - Q79.1</td>
<td>Congenital malformations of diaphragm</td>
</tr>
<tr>
<td>Q79.3</td>
<td>Gastrochisis</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


69. Comite d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT). Feotoscopic placental laser therapy in the twin-twin transfusion syndrome. CEDIT
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104. Ville Y, Hyett JA, Vandenbussche FP, Nicolaides KH. Endoscopic laser coagulation of umbilical cord vessels
in twin reversed arterial perfusion sequence.


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praevid: diagnosis and management. Green-top

142. Society of Maternal-Fetal (SMFM) Publications
Committee, Sinkey RG, Odibo AO, Dalse J. #37:
Diagnosis and management of vasa previa. Am J
AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0449 Fetal Surgery In Utero

There are no amendments for Medicaid.