Kansas City

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Fetal Surgery for Prenatal Malformations

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for fetal surgery for prenatal malformations when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Vesico-amniotic shunting as a treatment of urinary tract obstruction may be considered **medically necessary** in fetuses under the following conditions:

- Evidence of hydronephrosis due to bilateral urinary tract obstruction; AND
- Progressive oligohydramnios; AND
- Adequate renal function; AND
- No other lethal abnormalities or chromosomal defects.

Open in utero resection of malformed pulmonary tissue or placement of a thoraco-amniotic shunt may be considered **medically necessary** under the following conditions:

- Congenital cystic adenomatoid malformation or bronchopulmonary sequestration is identified; AND
- The fetus is at 32 weeks' gestation or less; AND
- There is evidence of fetal hydrops, placentomegaly, and/or the beginnings of severe pre-eclampsia (i.e., the maternal mirror syndrome) in the mother.

In utero removal of sacrococcygeal teratoma may be considered **medically necessary** under the following conditions:

- The fetus is at 32 weeks' gestation or less; AND
- There is evidence of fetal hydrops, placentomegaly, and/or the beginnings of severe pre-eclampsia (i.e., maternal mirror syndrome) in the mother.

In utero repair of myelomeningocele may be considered **medically necessary** under the following conditions:

- The fetus is at less than 26 weeks' gestation; AND
- Myelomeningocele is present with an upper boundary located between T1 and S1 with evidence of hindbrain herniation.

When Policy Topic is not covered

In utero repair of myelomeningocele is considered **investigational** in the following situations:

- Fetal anomaly unrelated to myelomeningocele; OR
- Severe kyphosis; OR
- Risk of preterm birth (e.g., short cervix or previous preterm birth); OR
- Maternal body mass index of 35 or more.

Other applications of fetal surgery are **investigational**, including but not limited to, temporary tracheal occlusion as a treatment of congenital diaphragmatic hernia or treatment of congenital heart defects.

Considerations

After 32 weeks' gestation, fetal lung maturity is adequate to permit Cesarean section and management of the condition postnatally.

Description of Procedure or Service

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

Most fetal anatomic malformations are best managed after birth. However, advances in methods of prenatal diagnosis, particularly prenatal ultrasound, have led to a new understanding of the natural history and physiologic outcomes of certain congenital anomalies. Fetal surgery is the logical extension of these diagnostic advances, related in part to technical advancement in anesthesia, tocolysis, and hysterotomy.

This policy will pertain to fetal surgery performed for the following clinical conditions:

1. Fetal Urinary Tract Obstruction
   Although few cases of prenatally diagnosed urinary tract obstruction require prenatal intervention, bilateral obstruction can lead to distention of the urinary bladder and is often associated with serious disease such as pulmonary hypoplasia secondary to oligohydramnios. Therefore, fetuses with bilateral obstruction, oligohydramnios, adequate renal function reserve, and no other lethal or chromosomal abnormalities may be candidates for fetal surgery. The most common surgical approach is decompression through percutaneous placement of a shunt or stent. Vesico-amniotic shunting bypasses the obstructed urinary tract, permitting fetal urine to flow into the amniotic space. The goals of shunting are to protect the kidneys from increased pressure in the collecting system and to assure adequate amniotic fluid volume for lung development.

2. Congenital Diaphragmatic Hernia (CDH)
   CDH results from abnormal development of the diaphragm, which permits abdominal viscera to enter the chest, frequently resulting in hypoplasia of the lungs. CDH can vary widely in severity, depending on the size of the hernia and the timing of herniation. For example, late herniation after 25 weeks of gestation may be adequately managed postnatally. In contrast, liver herniation into the chest prior to 25 weeks of gestation is associated with a poor prognosis, and these fetuses have been considered candidates for fetal surgery. Temporary tracheal occlusion using a balloon is being evaluated for the treatment of CDH. Occluding the trachea of a fetus prevents the normal efflux of fetal lung fluid, which results in a build-up of secretions in the pulmonary tree and increases the size of the lungs, gradually pushing abdominal viscera out of the chest cavity and back into the abdominal cavity. It is believed that this, in turn, will promote better lung maturation. Advances in imaging have resulted in the ability to detect less severe lesions, which has resulted in a decrease in mortality rates for defects detected during pregnancy. Due to these changes over time, concurrent controls are needed to adequately compare pre- and postnatal approaches.

3. Congenital Cystic Adenomatoid Malformation (CCAM) or Broncopulmonary Sequestration (BPS)
   CCAM and BPS are the two most common congenital cystic lung lesions, and share the characteristic of a segment of lung being replaced by abnormally developing tissue. CCAMs can have connections to the pulmonary tree and contain air, while BPS does not connect to the airway and has blood flow from the aorta rather than the pulmonary circulation. In more severe cases, the malformations can compress adjacent normal lung tissue and distort thoracic structure. CCAM lesions typically increase in size in mid-trimester and then in the third trimester either involute or compress the fetal thorax, resulting in hydrops in the infant and sometimes mirror syndrome (a severe form of pre-eclampsia) in the mother. Mortality is close to 100% when lesions are associated with fetal hydrops (abnormal accumulation of fluid in two or more fetal compartments). These

patients may be candidates for prenatal surgical resection of a large mass or placement of a thoraco-amniotic shunt to decompress the lesion.

4. Sacrococcygeal Teratoma
   Sacroccoccygeal teratoma (SCT) is both a neoplasm with the power of autonomous growth and a malformation made up of multiple tissues foreign to the region of origin and lacking organ specificity. It is the most common tumor of the newborn and generally carries a good prognosis in infants born at term. However, in utero fetal mortality approaches 100% with large or vascular tumors, which may become larger than the rest of the fetus. In this small subset, SCT is associated with fetal hydrops, which is related to high output heart failure secondary to arteriovenous shunting. In some cases, mothers of fetuses with hydrops can develop mirror syndrome.

5. Myelomeningocele
   Myelomeningocele is a neural tube defect in which the spinal cord forms abnormally and is left open, exposing the meninges and neural tube to the intrauterine environment. Myelomeningocele is the most common cause of spina bifida, and depending on the location results in varying degrees of neurologic impairment to the legs and bowel and bladder function, brain malformation (i.e., hindbrain herniation), cognitive impairment, and disorders of cerebrospinal fluid circulation, i.e., hydrocephalus requiring placement of a ventriculoperitoneal shunt. Traditional treatment consists of surgical repair after term delivery, primarily to prevent infection and further neurologic dysfunction. Fetal surgical repair to cover the exposed spinal canal has been proposed as a means of preventing the deleterious exposure to the intrauterine environment with the hope of improving neurologic function and decreasing the incidence of other problems related to the condition.

6. Cardiac Malformations
   In utero interventions are being investigated for severe narrowing in one of the cardiac outflow tracts (aortic valve or pulmonary valve) that cause progressive damage to the heart in utero. In utero intervention has been proposed for the following lethal cardiac conditions: critical pulmonary stenosis, critical aortic stenosis, and hypoplastic left heart syndrome (HLHS). Critical pulmonary stenosis or atresia with intact ventricular septum is characterized by a very narrow pulmonary valve without a connection between the right and left ventricles. Critical aortic stenosis with impending HLHS is a very narrow aortic valve that develops early during gestation that may result in HLHS. In utero aortic balloon valvuloplasty has been suggested as a way to relieve aortic stenosis in an attempt to preserve left ventricular growth and halt the progression to HLHS. HLHS with intact atrial septum describes the absence of a connection between the left and right atrium. A subset of fetuses with HLHS will present with severe cyanosis and require immediate postnatal intervention to survive. In utero septostomy has been performed in an attempt to improve postnatal survival for this condition.

Rationale

This policy was originally based on 1998 and 1999 TEC Assessments (1, 2) and updated periodically with literature searches of the MEDLINE database. The most recent update was with a review of the literature through December 13, 2013. The Agency for Healthcare Research and Quality (AHRQ) posted a draft technology assessment on fetal surgery in 2009; the final document was published April 2011. (3)

1. Fetal Urinary Tract Obstruction

The 2011 AHRQ assessment identified 26 publications representing 25 unduplicated reports on fetal interventions for obstructive uropathy. From the 3 prospective cohorts and 8 retrospective cohorts identified, 24 fetuses had placements of shunts, 11 had other treatments for posterior urethral valves, 14 had no fetal intervention, and 13 pregnancies were terminated due to poor prognosis. Overall, 53% to 66% of infants who had shunt placement survived short term. However, more than half of otherwise normal infants who have only isolated bladder outlet tract obstruction and do not have multiple anomalies or syndromes, do not recover normal renal function in childhood, and the majority require dialysis and renal transplantation. In addition, a proportion of affected infants have clusters of

syndromic features that are not readily diagnosed prenatally, increasing morbidity among survivors. For example, in a follow-up of 18 male children who had survived prenatal vesicoamniotic shunting (follow-up ranged from 1–14 years), one-third of the children required dialysis or transplantation, and one-half exhibited respiratory, growth and development, or musculoskeletal abnormalities. In spite of this, parents and physicians reported the children to be neurodevelopmentally normal, with the majority having acceptable renal and bladder function and satisfactory self-reported quality of life. (4) There is a need to better identify appropriate surgical candidates and clarify health outcomes in children who do and do not receive fetal intervention to inform decision making. At the time of the AHRQ assessment, one publication described the design of a multicenter randomized trial of percutaneous shunting for lower urinary tract obstruction (PLUTO) that will assess whether intrauterine vesicoamniotic shunting improves pre- and perinatal health outcomes in comparison with conservative, noninterventional care. (5)

Since the publication of the 2011 AHRQ assessment, Morris and colleagues published the results of the PLUTO trial.(6) The study was a randomized, unblinded, controlled trial that included 31 women with male singleton pregnancies complicated by an isolated lower urinary tract obstruction recruited from centers in the United Kingdom, Ireland, and the Netherlands. Inclusion criteria were an ultrasound diagnosis of LUTO (diagnosed on the basis of the visualization of an enlarged bladder and dilated proximal urethra, bilateral or unilateral hydronephrosis, and cystic parenchymal renal disease) about whom the treating physician was uncertain as to the optimum management. Women pregnant with fetuses with other major structural or chromosomal abnormalities were excluded. Women were randomly allocated to either prenatal intervention, consisting of placement of a vesicoamniotic shunt, or control, consisting of usual care. The primary outcome measure was survival to 28 days after birth, with secondary outcomes of survival at 1 and 2 years, and renal function at 28 days, 1 year, and 2 years (measured by serum creatinine, renal ultrasound appearance, and evidence of renal impairment based on need for medical treatment, dialysis, or transplantation). The original planned sample size for the trial of 75 pregnancies in each study group was based on calculations from a meta-analysis reported by the study authors in 2010 (7) and was designed to detect a relative risk of survival with vesicoamniotic shunting of 1.55 with 80% power and an alpha level of 0.05. The study was terminated early due to poor enrollment. Concurrent with the RCT, study authors enrolled eligible subjects who elected not to participate due to either patient or physician preference in an observational registry. There was a high degree of crossover between groups: 3/16 women randomized to receive vesicoamniotic shunting did not receive it, and 2/15 women randomized to the control group received a vesicoamniotic shunt. Analyses were conducted on both an intent-to-treat and per-protocol basis. For the study's primary outcome of 28 day survival, there was no significant difference between the groups: of the 16 pregnancies randomly assigned to vesicoamniotic shunting, eight neonates survived to 28 days, compared with four from the 15 pregnancies assigned to the control group (relative risk [RR] 1.88, 95% CI 0·71–4·96; p=0.27). Analysis based on treatment received showed a stronger association between shunting and survival (RR 3.2, 95% CI 1.06–9.62; p=0.03). The authors conducted a Bayesian analysis, combining data from their trial with elicited priors from experts, and found an 86% probability that vesicoamniotic shunting increased survival at 28 days. Overall, the authors concluded that "survival seemed higher in the fetuses receiving vesicoamniotic shunting, but the size and direction of the effect remained uncertain." While strengths of this study included its randomized, controlled design, and tracking of longer (2 year) outcomes, it was limited by its failure to reach enrollment targets and the significant crossover between treatment and control groups. As such, it is difficult to conclude that the lack of significant association between shunting and survival was not due to underpowering.

2. Congenital Diaphragmatic Hernia (CDH)

In 1999, the TEC Assessment concluded that temporary tracheal obstruction met the TEC criteria as a treatment of congenital diaphragmatic hernia, based in part on a case series. (8) However, in 2003, Harrison and colleagues, the same authors who reported on the original case series, reported the results of a randomized trial of fetoscopic tracheal occlusion compared with standard postnatal care. (9) Enrollment was stopped at 24 women due to the unexpectedly high 90-day infant survival rate with standard care, and thus the safety monitoring board concluded that further recruitment would not result in a significant difference between the groups. In addition, the fetal surgery group had higher rates of

prematurity and lower birth weights. Based on the results of this randomized trial, the policy statement was revised to indicate that tracheal occlusion is considered investigational. The survival rate in the standard treatment group was 73%, considerably higher than the estimated survival rate of 37% based on historical controls. The survival of infants with a lung-to-head ratio (LHR) greater than 1.0 was 100% in both groups. In other publications, survival has been reported to be approximately 10% for children with isolated congenital diaphragmatic hernia who have left-sided lesions, liver herniation, and an LHR of less than 1.0 during mid-gestation. (10) In this subgroup, temporary placement of a detachable balloon to occlude the trachea was reported to result in a survival rate of 55% (35 cases), compared with 8% survival in a group of contemporary controls treated by postnatal therapy.

The 2011 AHRQ technology assessment identified 25 publications with 21 unduplicated populations from 10 U.S. sites, 9 European sites, 3 multinational sites, and 5 other countries, for a total of 335 cases. The single randomized controlled trial (RCT) was by Harrison et al. (reference 7, described above), with follow-up reported by Cortes et al. in 2005. (11) Growth failure occurred in 56% of controls and 86% of infants who had occlusion. No neurodevelopmental differences were observed between groups with follow-up at 1 or 2 years of age. This randomized study reinforces the importance of a concomitant control group, as the survival for CDH with postnatal repair also improved over time. Also noted were results of the Fetal Endoscopic Tracheal Occlusion (FETO) Task Group in Europe, which is using a control group of 86 fetuses with left-sided CDH and liver herniation, managed expectantly and live born after 30 weeks of gestation. In this control group, the survival rate increased from 0% for LHR of 0.4 to 0.7 to approximately 15% survival for LHR of 0.8 to 0.9, 65% for LHR of 1.0 to 1.5, and 83% survival for LHR of 1.6 or more. This ongoing series currently has an 11% survival for LHR less than 1, which can be used as a reference value for Europe, but not for the United States.

In 2012, Ruano and colleagues reported a small randomized trial that compared percutaneous FETO with postnatal management in 41 patients whose fetuses had severe congenital diaphragmatic hernia (LHR less than 1.0 and at least one third of the fetal liver herniated into the thoracic cavity). (12) All fetuses in the FETO group were delivered by *ex-utero* intrapartum therapy in order to remove the tracheal balloon; controls were delivered by Cesarean section at a maximum gestational age of 38 weeks. The primary outcome, survival to 6 months of age by intent-to-treat analysis, was 50% (10/20) in the fetal surgery group and 4.8% (1/21) in controls (relative risk [RR]: 10.5). Mean delivery was about 2 weeks earlier in the fetal surgery group compared to controls (35.6 weeks vs. 37.4). There was a trend for a higher frequency of premature delivery (<37 weeks, 50% FETO vs. 28.6% controls) and extreme premature delivery (<32 weeks, 15% FETO and 0% controls) in the FETO group. For the 10 survivors in the FETO group, the mean age at hospital discharge was 34.7 days.

Results of this small randomized controlled trial are promising. However, given the inconclusive results in the randomized trial by Harrison et al., additional study is needed to determine the survival benefit with greater certainty. Longer follow-up is also needed to evaluate morbidity (e.g., neurologic and pulmonary outcomes) in survivors.

3. Congenital Cystic Adenomatoid Malformation (CCAM) or Bronchopulmonary Sequestration (BPS)

The 2011 AHRQ assessment identified 17 publications describing 6 distinct cohorts and 4 case series from 7 academic centers in the United States, South America, Europe, and Asia. Of approximately 401 infants believed to have CCAMs, 54 had thoracoamniotic shunting and 3 had open procedures, with the goal of decompressing the lung lesion. An additional 13 fetuses with BPS were described. In the cohorts, 44% to 100% of infants who had thoracoamniotic shunts survived to birth or through neonatal hospitalization; there was an overall survival rate of 54% in the literature. For fetuses with hydrops, survival was 20% to 30% following surgical treatment compared with 5.7% for untreated hydrops. Since some infants with large CCAMs respond to in utero medical treatment with steroids, failure to respond to steroids may be an entry criterion for future surgical interventions.

4. Sacrococcygeal Teratoma (SCT)

At the time of the 1999 TEC Assessment, the published literature included only 4 cases of fetal surgery for SCT. However, in utero surgery resulted in prenatal resolution of hydrops, healthy long-term

survival, and normal development in some children. These results were impressive given the near-certain fetal mortality if fetal hydrops is left untreated. For example, in a 2004 report of 4 cases of open surgical resection of SCT, Hedrick and colleagues reported 1 neonatal death and 3 survivals with a follow-up range of 20 months to 6 years. (13) Complications other than the fetal death included 1 embolic event, 1 chronic lung disease, and 1 tumor recurrence. The 2011 AHRQ assessment identified a total of 7 retrospective cohorts and case series from 3 academic fetal surgery groups in the U.S. and U.K. The 17 fetuses reported to be treated with open surgery were compared with 94 cases with other interventions or no intervention; however, the expectant management cases were less severe. Other ablation methods included alcohol sclerosis (all 3 cases died), radiofrequency ablation (RFA) (4 of 7 survived), and laser ablation (all 4 died). For open surgical procedures, the survival rates were 33% to 75%. All fetal and neonatal deaths occurred among patients with hydrops or with prodromal cardiovascular changes concerning for developing hydrops. Challenges in this area are the early and reliable detection of development of hydrops and the timing of the fetal intervention. (3)

5. Myelomeningocele

The endoscopic approach has been abandoned due to high mortality, however, more than 200 fetuses with myelomeningocele have undergone open surgical repair in the United States. (3) All of the 25 reports on open surgery that were identified in the 2011 AHRQ assessment were based on 4 series of patients from 4 academic medical centers in the United States. Two of the studies had concurrent comparisons. (14, 15) One of these analyzed the first 29 cases of open myelomeningocele repair at Vanderbilt University Medical Center, finding significant reductions in the need for postnatal shunt placement (51% vs. 91%) and reduced hindbrain herniation (38% vs. 95%). However, both prospective studies found that in utero repair was associated with greater rates of oligohydramnios (48% vs. 4%), lower gestational ages (33 vs. 37 weeks), and no difference in lower extremity function.

In 2011, results of the National Institutes of Health (NIH)-sponsored RCT, the Management of Myelomeningocele Study (MOMS) comparing prenatal repair with standard postnatal repair were published. (16) The trial began in 2003 and was expected to enroll 200 women ages 18 years or older who were pregnant with fetuses with myelomeningocele. Women assigned to have prenatal surgery were scheduled for surgery within 1 to 3 days after they were randomized and stayed near the MOMS center until they delivered by C-section. Women in the postnatal group traveled back to their assigned MOMS center to deliver, also by C-section, around the 37th week of their pregnancies. Follow-up on the children was scheduled to be performed at 1 year and 2 ½ years of age to evaluate motor function, developmental progress, and bladder, kidney, and brain development. There was a voluntary moratorium in the United States on conducting in utero repair of myelomeningocele outside of this trial. (3)

The inclusion criteria for MOMS included singleton pregnancy, myelomeningocele with the upper boundary located between T1 and S1, evidence of hindbrain herniation, gestational age of 19.0 to 25.9 weeks at randomization, normal karyotype, U.S. residency, and maternal age at least 18 years. Major exclusion criteria were fetal anomaly unrelated to myelomeningocele, severe kyphosis, risk of preterm birth, placental abruption, body-mass index of 35 or greater, contradiction to surgery including previous hysterotomy in the active uterine segment. Surgeons had performed at least 15 cases before this randomized study. Primary outcomes were a composite of fetal or neonatal death or the need for a cerebrospinal fluid shunt (shunt placement or meeting criteria for shunt) at 12 months and a composite score of the Mental Development Index of the Bayley Scales of Infant Development II and the child's motor function at 30 months adjusted by level of lesion. Secondary outcomes were surgical and pregnancy complications and neonatal morbidity and mortality. Women were randomized to treatment group in 1:1 ratio.

Recruitment for the trial, planned to include 200 subjects, was stopped at 183 subjects when a clear advantage of prenatal intervention was apparent. The report includes 158 woman randomized before July 1, 2009. Outcomes up to 30 months are based on 138 women randomized before December 1, 2007. Groups were similar other than that there were more female fetuses and the lesion level was more severe in the prenatal surgery group. Two perinatal deaths occurred in each treatment group.

Both deaths in the prenatal surgery group occurred on the fifth postoperative day, a still birth at 26 weeks and a neonatal death due to prematurity at 23 weeks' gestation. Two neonates in the postnatal surgery group died with severe symptoms of the Chiari II malformation. Fetal or neonatal death or the need for shunt occurred in 68% of infants in the prenatal-surgery group and in 98% of the postnatal-surgery group (relative risk [RR]: 0.70; 97.7% confidence interval [CI]: 0.58 to 0.84; p<0.001). Shunts were placed in 40% of the prenatal-surgery and in 82% of postnatal-surgery groups (p<0.001). At 12 months, 4% of infants in the prenatal-surgery group had no evidence of hindbrain herniation versus 36% in the postnatal-surgery group. There was one death in each group between 12 and 30 months (coxsackie septicemia in a child who received prenatal surgery and complications of chemotherapy for choroid plexus carcinoma in a child who received postnatal surgery). The composite of score of Bayley Scales and motor function adjusted by lesion level at 30 months was significantly better in the prenatal surgery group: mean 148.6 +/- standard deviation (SD): 57.5 in the prenatal surgery group (n=64) versus mean 122.6 +/- SD: 57.2 in the postnatal surgery group (n=70) (p=0.007).

Maternal morbidity and complications related to prenatal surgery included oligohydramnios, chorioamniotic separation, placental abruption, and spontaneous membrane rupture. At delivery, an area of dehiscence or a very thin prenatal uterine surgery scar was seen at delivery in one third of mothers who had prenatal fetal surgery (all subsequent pregnancies should be delivered by cesarean before the onset of labor). The average gestational age of babies in the prenatal surgery group was 34.1 weeks, and 13% were delivered before 30 weeks of gestation. One-fifth of infants in the prenatal surgery group had evidence of respiratory distress syndrome, which was likely related to prematurity. The authors observed that "in the case of infants with low lumbar and sacral sessions, in whom less impairment in lower-limb function may be predicted, the normalization of hindbrain position and the minimization of the need for postnatal placement of cerebral spinal shunt may be the primary indication for surgery." They caution that the potential benefits of fetal surgery must be balanced against the risks of premature delivery and maternal morbidity and that continued assessment is required to learn if early benefits of prenatal surgery are sustained and the effects of fetal surgery on bowel and bladder continence, sexual function, and mental capacity. They warn that results of this trial should not be generalized to centers with less experience or to patients who do not meet eligibility criteria.

Uncontrolled Series

A 2004 report by Bruner et al. described minimum 12-month follow-up of 116 fetuses after intrauterine repair of spina bifida (myelomeningocele or myeloschisis). (17) Sixty-one fetuses (54%) required ventriculoperitoneal shunt placement for hydrocephalus. Statistical analysis revealed that fetuses were less likely to require ventriculoperitoneal shunt placement when surgery was performed at 25 weeks or earlier, when ventricular size was less than 14 mm at the time of surgery, and when the defects were located at L4 or below. Johnson and colleagues reported on the results of a series of 50 fetuses who underwent open fetal closure of a myelomeningocele between 20 and 24 weeks' gestation. (18) Fetal selection criteria included the presence of hindbrain herniation and sonographic evidence of intact neurologic function, i.e., movement of the lower extremities and absence of clubfoot deformities. Perinatal survival was 94%, with a mean age at delivery of 34 weeks. All fetuses demonstrated reversal of hindbrain herniation; 43% required ventriculoperitoneal shunting compared to 68–100% in historical controls, depending on the location of the myelomeningocele. Another study reporting leg function at longer follow-up showed no difference between patients treated with fetal surgery at 20 to 28 weeks versus traditional surgery. (14)

In three papers, investigators at the University of Pennsylvania reported outcomes of myelomeningocele repair in 54 patients treated before the voluntary moratorium. (19-21) At median follow-up of 66 months (range 36-54 months), 37/54 (69%) walk independently, 13/54 (24%) are assisted walkers, and 4/54 (7%) are wheelchair dependent. The strongest factors predicting a lower likelihood to walk independently were higher level lesion (>L4) and the development of clubfoot deformity after fetal intervention. The majority of independent ambulators, and all children who require assistive devices to walk, experience significant deficits in lower extremity coordination. (20) Thirty children returned at 5 years of age for neurocognitive examination. In this highly selected group, most children had average preschool neurodevelopmental scores, and children who did not require shunt

placement were more likely to have better scores. (21) A survey of 48 families focused on hindbrain herniation (HH)-associated brainstem dysfunction, e.g., apnea, neurogenic dysphagia, gastro-esophageal reflux disease, neuro-ophthalmologic disturbances. (19) Half of the children required shunting. At a median age of 72 months, 15 non-shunted and 10 shunted children were free of HH symptoms. There were no HH-related deaths, and no children developed severe persistent cyanotic apnea. Most children had no or only mild brainstem dysfunction. The authors conclude that reversal of HH after fetal surgery may help reduce the incidence and severity of brainstem dysfunction.

Investigators at a German center performed a retrospective analysis of expectantly managed patients who received surgical intervention within 2 days of birth at their institution and compared them with reports of outcomes after fetal surgery from other centers including those noted above and to data from historical controls. (22) Patients were born between 1979 and 2009 and are now 13.3 +/- 8.9 (mean +/- standard deviation [SD]) years old. Gestational age at birth in the expectantly managed group was 37.8 weeks, significantly higher than in the prenatal surgery patients. In the expectantly managed group, shunt placement was required in 69.8% at mean age of 16.0 +/- 10.7 days, which is less than for historical controls and comparable to data reported on patients who received fetal surgery. The authors suggest that inconsistency in clinical criteria for shunting used in studies might contribute to differences in this outcome. Among their expectantly managed patients, 56.4% were assisted walkers and 64.1% attended regular classes, both comparable to historical controls. Noting the discrepancy in the rate of assisted walkers and wheelchair users between expectantly managed patients/historical controls and patients who received surgery, the authors observe that the mean age of the study population was 21.7 years for historical controls, 13.3 years for their population, and only 67.0 months after fetal surgery. They cite earlier papers reporting mobility decreases from early childhood to the early teens including one reporting that “the percentage of patients ambulating the majority of time decreased from 76% at 0-5 years to 46% at 20-25 years, with a flattening beyond 10 years”. (23)

6. Cardiac Malformations

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

- Two case series (n=10) were identified on fetal surgery for pulmonary atresia and intact ventricular septum. The literature was described as scant, reflecting the early formative period of development of procedures for this rare condition.
- Eight prospective case series (n=90) were identified on balloon dilation for critical aortic stenosis. One center in the United Kingdom, 2 centers in Germany, 2 in Brazil, and 1 in the United States performed this procedure. Seventy patients are from Boston. The 2011 technology assessment concluded that it is difficult to determine whether the procedure changes long-term outcomes, since it appears to increase the risk of fetal loss but potentially prevents neonatal deaths. However, it did appear that technical success improves over time within a dedicated team and center. For example, the North American center improved their success rate from 25% to 90% over a period of several years. Overall, the literature was considered to be very early in development.
- Three case series from one U.S. institution with a cumulative total of 24 patients were identified on creation in utero of an atrial septal defect for an intact atrial septum. There were no reports of this procedure being performed outside of the U.S. The procedure appears to have technical success; however, mortality remains high, and no controlled trials were available to compare outcomes in patients treated prenatally with those treated postnatally.

The AHRQ report concluded that overall, procedures for severe fetal cardiac anomalies are in an early stage. Preliminary work is being reported in a few highly specialized centers that are establishing the groundwork for feasibility and future directions for outcomes research in this area. The authors concluded that the most pressing challenge in this area is the ability to identify the “right” patient whose care would be compromised by waiting to do a postnatal repair.

McElhinney et al. analyzed their experience with 70 prenatal balloon aortic valvuloplasties attempted in midgestational fetuses between March 2000 and October 2008 for critical aortic stenosis with evolving hypoplastic left heart syndrome to identify factors associated with procedural and postnatal outcomes.

(24) Median gestational age was 23.2 weeks (range, 20-31 weeks). Technical success was achieved in 52 fetuses. Compared to 21 untreated comparison fetuses, subsequent prenatal growth of the aortic and mitral valves, but not the left ventricle, was improved after intervention. Nine pregnancies did not reach viable term or preterm birth. Seventeen patients had a biventricular circulation postnatally, 15 of them from birth. Two of these patients had no neonatal intervention. Sixteen were alive at a median age of 2.1 years (range, 4 months-7 years). The other patient died of unrelated causes. Guidelines for assessing the potential for a biventricular circulation changed over the period of the study and became more selective. Larger left heart structures and higher left ventricular pressure at the time of intervention were associated with biventricular outcome. The authors conclude that further investigation is required before it is possible to predict whether fetal intervention will result in improved left heart growth and postnatal survival with a biventricular circulation, and "the potential befits of fetal intervention must be weighed against the risk of technical failure, fetal demise, aortic regurgitation, and potential long-term adverse events that have yet to be identified".

In 2013, Marantz et al. reported results from a case series of 5 prenatal balloon aortic valvuloplastics for fetuses with aortic stenosis and risk of progression to hypoplastic left heart syndrome. (25) The procedure was technically successful in all cases with no maternal complications or fetal demise. One pregnancy was terminated after the procedure; of the remaining cases, one progressed to hypoplastic left heart syndrome and three did not. Rates of longer term survival and complications are not provided. The authors conclude that fetal aortic valvuloplasty is safe and feasible.

7. Other

The use of fetal surgery for other defects is expanding; recent case reports include prenatal correction of cleft lip and palate and decompression of the fetal trachea. (26, 27)

A review of 187 maternal-fetal surgeries performed at the University of California San Francisco Fetal Treatment Center found significant short-term maternal morbidity but no maternal deaths. (28) Post-surgical complications included increased rates of cesarean birth, treatment in intensive care, prolonged hospitalization, and blood transfusion.

No new studies of fetal surgery for other applications were identified in the 2011 literature update.

Ongoing Trials

A search of the online site ClinicalTrials.gov on November 25, 2013 using each surgery type as a text phrase returned a total of 6 ongoing trials with recent (after 2011) updates. Most of the surgical procedures are in the early stages of evaluation.

For Lower Urinary Tract Obstruction:

- Fetal Cystoscopy Versus Vesico-amniotic Shunting in Severe Lower Urinary Tract Obstructions (CYSTUO) (NCT01552824). This is a phase 2, randomized, unblinded trial to assess whether vesico-amniotic shunting improves outcomes compared with fetal cystoscopy for severe lower urinary tract obstructions. The primary outcome measures are perinatal survival rate and neonatal renal function. Estimated study enrollment is 60 patients and study completion date is listed as May 2015 with follow up to July 2017.

For Congenital Diaphragmatic Hernia:

- Early FETO for Severe Congenital Diaphragmatic Hernia (NCT01731509). This is a phase 2, randomized, open-label, interventional trial to assess whether early fetal endoscopic tracheal occlusion improves outcomes compared with standard FETO at 26 0/7 weeks-28 6/7 weeks gestation. The primary outcome measures are neonatal (30 day) survival rate and infant (6 month) survival rate. Estimated study enrollment is 70 patients and study completion date is listed as December 2019.

For Myelomeningocele:

- Prenatal Surgical Repair of Myelomeningocele PRIUM) (NCT 01983345). This is a non-randomized, open-label, interventional trial to compare open surgical repair of myelomeningocele in the fetus before 26 weeks gestation to standard care. The primary outcome measure is presence of Arnold-Chiari malformation at birth. Estimated study enrollment is 50 patients and study completion date is listed as September 2019.

For Evolving Hypoplastic Left Heart Syndrome:

- Fetal Intervention for Aortic Stenosis and Evolving Hypoplastic Left Heart Syndrome (NCT01736956). This is a phase 1 and phase 2 non-randomized safety/efficacy study to assess whether fetal balloon aortic valvuloplasty compared with standard care for evolving HLH is associated with improved fetal mitral and left ventricular growth. The primary outcome measure is improved fetal mitral valve and left ventricular growth. Estimated study enrollment is 30 patients and study completion date is listed as October 2017.

Summary

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

Due to a number of factors, including the rarity of the conditions and the small number of centers specializing in fetal interventions, the evidence on fetal surgery remains limited. Fetal surgery for many congenital conditions, including diaphragmatic hernia and heart defects, has not been shown to improve health outcomes in comparison with postnatal treatment. The available evidence is insufficient to demonstrate that fetal tracheal occlusion and aortic valvuloplasty provides improved health outcomes. For these and other applications of fetal surgery that are currently considered investigational, additional studies are needed to identify appropriate candidates and to evaluate longer term outcomes compared with postnatal management.

For conditions leading to fetal hydrops (certain cases of congenital cystic adenomatoid malformation, bronchopulmonary sequestration, or sacrococcygeal teratoma), for which mortality approaches 100%, fetal surgery may be considered medically necessary. For bilateral urinary tract obstruction, evidence from retrospective and prospective cohort studies summarized in the 2011 Agency for Healthcare Research and Quality technology assessment on fetal surgery suggests that vesicoamniotic shunting improves survival, at least in the short term, although longer term follow up of patients treated with shunting and direct evaluation through RCTs is needed. As such, vesicoamniotic shunting for bilateral urinary tract obstruction may also be considered medically necessary to minimize the effects of this condition on kidney and lung development. A recent small, randomized, controlled trial evaluating the use of vesicoamniotic shunting found limited benefit from the procedure when data were analyzed by intent-to-treat analysis. However, the study's significant limitations, including low enrollment leading to early cessation of the study and significant cross-over between treatment and control groups, make it difficult to generalize its finding of no significant benefit from treatment. Additional studies for these surgeries are needed to better define the appropriate surgical candidates, the most effective timing of the interventions, and the long-term health outcomes in surviving children.

Data from the MOMS trial show that prenatal repair of myelomeningocele reduces the need for shunting in the first 12 months after delivery and improves a composite measure of mental and motor function, with adjustment for lesion level, at 30 months of age. Prenatal surgery also improves the degree of hindbrain herniation and the likelihood of being able to walk independently when compared with postnatal surgery. The long-term impact on function needs to be evaluated, and benefits must be balanced against risks to mother and child. Thus, fetal surgery may be considered medically necessary following informed decision making for cases of prenatal myelomeningocele that meet the criteria of the MOMS study.

Practice Guidelines and Position Statements
The Eunice Kennedy Shriver National Institute of Child Health and Human Development convened the fetal myelomeningocele Maternal-Fetal Management Task Force with representatives from the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American Institute of Ultrasound in Medicine, the American Pediatric Surgical Association, the American Society of Anesthesiologists, the American Society of Pediatric Neurosurgeons, the International Fetal Medicine and Surgery Society, the American Association of Neurological Surgeons/Congress of Neurological Surgeons, the North American Fetal Therapy Network, the Society for Maternal-Fetal Medicine, the Society of Pediatric Anesthesia, and the Spina Bifida Association. The Task Force provided recommendations about optimal practice criteria for maternal fetal surgery for myelomeningocele repair.(29) Recommendations are related to 6 key considerations for teams providing in utero myelomeningocele repair:

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

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

The American College of Obstetricians and Gynecologists (ACOG) Committee on Ethics and the American Academy of Pediatrics Committee on Bioethics issued a committee opinion on maternal-fetal intervention and fetal care centers in 2011. (30) The committee recommended that:

- Fetal intervention cannot be performed without the explicit informed consent of the pregnant woman.
- Distinctions should be made to prospective parents between which protocols are standard or evidence-based therapies and which are innovative or experimental interventions.
- The informed consent process should involve thorough discussion of the risks and benefits for both the fetus and the pregnant woman.
- Safeguards should be in place to protect women considering fetal research.
- Access to support services such as social services, palliative care and perinatal hospice services, genetic counseling, and ethics consultation should be provided, when appropriate.
- The organization and governance of centers providing fetal interventions should involve a diverse group of professionals, including members without direct ties to the center involved.
- Cooperation between fetal care centers should be encouraged to establish collaborative research networks and to support multicenter trials to accumulate more robust short- and long-term maternal and fetal outcome data on all categories of fetal intervention. In addition, the establishment of centers of excellence for those procedures that are particularly challenging and rare may help to optimize fetal and maternal outcomes.

A consensus, endorsed by the International Fetal Medicine and Surgery Society proposes the following criteria for fetal surgery (10):

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

Medicare National Coverage
None identified.

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Billing Coding/Physician Documentation Information

S2400 Repair, congenital diaphragmatic hernia in the fetus using temporary tracheal occlusion, procedure performed in utero
S2401 Repair, urinary tract obstruction in the fetus, procedure performed in utero
S2402 Repair, congenital cystic adenomatoid malformation in the fetus, procedure performed in utero
S2403 Repair, extralobar pulmonary sequestration in the fetus, procedure performed in utero
S2404 Repair, myelomeningocele in the fetus, procedure performed in utero
S2405 Repair of sacrococcygeal teratoma in the fetus, procedure performed in utero
S2409 Repair, congenital malformation of fetus, procedure performed in utero, not otherwise classified
59076 Fetal shunt placement, including ultrasound guidance
59897 Unlisted fetal invasive procedure, including ultrasound guidance

Additional Policy Key Words

N/A

Policy Implementation/Update Information

2/1/99 New policy. Added to surgery section. May be medically necessary for fetal urinary tract obstruction, congenital diaphragmatic hernia, congenital cystic adenomatoid malformation, extralobar pulmonary sequestration, or sacrococcygeal teratoma.
2/1/00 No policy statement changes.
2/1/01 No policy statement changes.
2/1/02 Policy statement revised to include other applications of fetal surgery are considered investigational, including but not limited to fetal surgery for myelomeningocele or aqueductal stenosis.
2/1/03 No policy statement changes.
2/1/04 No policy statement changes. Added new s-codes to policy.
2/1/05 Policy statement revised to remove congenital diaphragmatic hernia as medically necessary. Investigational statement revised to read as follows: Other applications of fetal surgery are investigational, including but not limited to, temporary tracheal occlusion as a treatment of congenital diaphragmatic hernia or fetal surgery for myelomeningocele.
2/1/06 No policy statement changes.
2/1/07 No policy statement changes.
2/1/08 Policy statement revised to include treatment of congenital heart defects in the list of other applications considered investigational.
2/1/09 No policy statement changes.

2/1/10	No policy statement changes.
2/1/11	Criteria added to policy statements that were previously listed in the Considerations section. No change to the intent of the policy.
7/1/11	Policy statement revised to indicate prenatal repair of myelomeningocele may be considered medically necessary under specified conditions. This change is effective retroactively to March 10, 2011.
2/1/12	No policy statement changes.
2/1/13	No policy statement changes.
2/1/14	No policy statement changes.
