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Prospects for Fetal Surgery

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Abstract

Until about forty years ago, the womb shielded the fetus from observation and therapy. The rapid changes in the diagnosis and treatment of human fetal anatomical abnormalities is due to improved fetal imaging studies as well as fetal sampling techniques (e.g. amniocentesis, chorionic villus sampling), and a better understanding of fetal pathophysiology derived from laboratory animals. Fetal therapy is the logical culmination of progress in fetal diagnosis. In other words, the fetus is now a patient. The fetal surgical treatment of the most severe form of spina bifida - myelomeningocele (MMC) - will be used as a paradigm to illustrate progress in and future prospects for fetal surgery. This review will focus on the rationale for *in utero* repair in the context of pathologic observations and animal models of MMC, outcomes from human fetal MMC repair including the recently completed Management of Myelomeningocele Study (MOMS trial), and future research directions.

Keywords

fetal surgery; prenatal diagnosis; spina bifida; myelomeningocele; Management of Myelomeningocele Study; MOMS trial

Accurate diagnosis of a fetal anomaly allows the physician and parents to choose the best way to manage the pregnancy. Although most prenatally diagnosed malformations are best managed by maternal transport (transport of the mother to the tertiary medical center for planned delivery), planned delivery near term, and appropriate neonatal therapy, other choices include elective abortion, a change in the timing or mode of delivery, or *in utero* therapy. There are some simple anatomical abnormalities with predictable and life-threatening prenatal pathophysiological consequences that may benefit from surgical correction before birth (Table 1).

In the 1960s, direct fetal exposure and catheterization of fetal vessels for exchange transfusion was unsuccessful and the procedure was abandoned. In the 1970s, experience with increasingly advanced ultrasound technology led to the accurate diagnosis before birth

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of many anatomical defects. In the 1980s, the rationale and feasibility of *in utero* repair for various fetal anomalies was explored. The steps leading from laboratory to bedside can be summarized as follows: the pathophysiology of potentially treatable fetal abnormalities was clarified in fetal laboratory animals, and experimental *in utero* correction was shown to be efficacious; serial sonographic study of human fetuses with anatomical lesions determined the features that affect clinical outcome and helped to devise selection criteria for prenatal intervention; and the surgical, anesthetic, and tocolytic techniques for hysterotomy and fetal surgery were developed in non-human primates, were shown to be safe for the mother and her future reproductive potential, and were finally introduced clinically. In the 1990s, clinical fetal surgery became more widespread, and ultrafast fetal magnetic resonance imaging (MRI) was introduced to enhance prenatal diagnosis. In the first decade of 21st century, refinements in patient selection and treatment were introduced, and randomized clinical trials elucidated the safety and efficacy of fetal surgical therapy. The indications for fetal surgery were extended to non-life-threatening but serious birth defects such as spina bifida.

The promise of fetal surgery is that the earliest possible intervention for a life-threatening or disabling fetal disorder may produce the best results. Because fetal surgery jeopardizes the pregnancy and may put the mother as well as the fetus at risk, it should be considered only in centers that are committed to a program of continuing research together with circumspect clinical application (Table 2). A fetal treatment center requires the close collaboration of dedicated pediatric surgeons, perinatal obstetricians, radiologists, echocardiographers, neonatologists, geneticists, ethicists, obstetric and neonatal nurses, and a compassionate nurse coordinator. The fetal treatment team should be committed to having this innovative therapy reviewed by uninvolved professional colleagues (institutional review board), to publish all results (bad as well as good), to avoid media reports until cases are peer reviewed, and to test the validity and cost-effectiveness of this approach in properly controlled trials.

The Vexing Challenge of Spina Bifida

Open spina bifida or myelomeningocele (MMC) is a devastating congenital defect of the central nervous system for which there is no cure. The natural history of MMC includes a constellation of findings which correlate with the proximal anatomic extent of the defect. MMC is characterized by protrusion of the meninges and spinal cord through open vertebral arches leading to lifelong paralysis and hydrocephalus (Figure 1). In addition, MMC patients are often limited by various degrees of mental impairment, bowel and bladder dysfunction, and orthopedic disabilities. While the etiology of MMC remains poorly understood, primary failure of neural tube closure at the caudal neuropore in the embryonic period results in exposure of the developing spinal cord to the uterine environment.[1] Without protective tissue coverage, secondary destruction of the exposed neural tissue by trauma or amniotic fluid may occur throughout gestation. Until 15 years ago, treatment of MMC consisted of surgical closure of the spinal canal at birth and lifelong supportive care. Since that time the clinical experience with midgestational human repair has been shown to improve neurologic function and reduce morbidity from hydrocephalus and the Arnold-Chiari II malformation by reversal of the hindbrain herniation component.

Advances in prenatal diagnosis now permit diagnosis of spina bifida as early as the first trimester, and extensive research into the etiology of neural tube defects has elucidated both genetic and micronutrient causes.[2] While substantial progress has been made in preventing this disorder through folic acid supplementation, the impact of this preventative approach have leveled off.[3] Consequently, spina bifida affects 1 in 2000 live births, which translates to about 1500 live births with spina bifida in the United States each year. Not included in these figures are the estimated 25-40% of MMC pregnancies in which the fetus is aborted. Mothers who choose to continue the pregnancy must prepare for a child with significant care needs and high medical expenses. Despite aggressive postnatal treatment, nearly 14% of all spina bifida neonates do not survive past 5 years of age, with the mortality rising to 35% in those with symptoms of brainstem dysfunction secondary to the Arnold-Chiari malformation. While 70% of patients have an I.Q. above 80, only half are able to live independently as adults, even with adapted accommodations. The emotional and financial impact on the family and community are enormous.

In addition to motor and sensory deficits due to the spinal cord lesion, significant complications in MMC come from hydrocephalus and the Arnold-Chiari II malformation. Hydrocephalus, defined as any enlargement of the cerebral ventricles, occurs in more than 85% of patients with MMC. More than 80% of spina bifida patients require placement of shunts to prevent the neurologic and intellectual compromise that accompanies significant ventriculomegaly, and 46% have complications of shunts such as infection and occlusion within the first year of placement.[4] The Arnold-Chiari II malformation is characterized by descent of the cerebellar vermis through the foramen magnum, elongation and kinking of the medulla, caudal displacement of the cervical spinal cord and medulla, and obliteration of the cisterna magna. Descent of the hindbrain through the foramen magnum can lead to brain stem compression, the leading cause of mortality in children with MMC. Clinical presentation of this malformation depends on the age of the child, but typically it includes dysfunction of the cerebellum, medullary respiratory center, and cranial nerves IX and X as well as hydrocephalus. Surgical management for symptomatic hindbrain herniation is beneficial in only selected patients and consists of a ventricular shunt, although some patients ultimately require laminectomy and decompression of the cranio-cervical junction.

The Rationale for Fetal MMC Repair

The neural damage in MMC may be primarily the result of defective spinal cord development, a secondary event resulting from damage to the exposed spinal cord by the intrauterine milieu, or both - the "two-hit hypothesis". The two-hit hypothesis states that primary congenital abnormalities in anatomic development allow a relatively normal spinal cord to become secondarily damaged by amniotic fluid exposure, direct trauma, hydrodynamic pressure, or a combination of these factors. It is this secondary damage which may be ameliorated by early fetal surgical repair.

There are many observations that support this premise. Hutchins and colleagues performed a pathologic examination of the spinal cords of 8 stillborn human fetuses with MMC and carefully described the relationships of the spinal cord, meninges, and dermal-epidermal junction.[5] There were varying degrees of neural tissue loss at the site of the defect, but

normal appearing dorsal and ventral horns were present at the proximal aspect of the lesion. This group was among the first to suggest the two-hit pathophysiology since they attributed these alterations to injuries occurring subsequent to primary neural tube formation. A study of ten additional human fetuses produced similar findings.[6]

Insight into the protection provided by spinal cord coverage also comes from analysis of some of the less severe variants of spinal dysraphism which are interesting “experiments of nature”. In cervical dysraphism, a cystic sac containing neuroglial tissue bulges through open posterior vertebral elements, but remains covered by a thick layer of skin. The neurological examination in these patients is typically normal or near normal. Lipomyelomeningocele involves a spinal dysraphism in which a lipoma covers the neural elements, generally preventing herniation of the cord through the defect. Compared to MMC patients, patients with lipomeningocele typically have more mild neurologic deficits including retained bowel and bladder continence, despite significant dysplasia of the caudal spinal cord. In hemimyelocele, half of the dysraphic spinal cord is devoid of dura and openly exposed to the uterine environment while the remaining half is covered with a dural membrane. In a study of 16 patients with this disorder, Duckworth reported that the dural encapsulated portion of the cord remained in complete continuity and corresponded to a lower extremity with normal or only mildly disturbed function.[7] In contrast, the opposing limb varied in innervation and function.

Animal Models of Fetal MMC Repair

Multiple animal models of MMC have been developed to test the hypothesis that *in utero* intervention can prevent further spinal cord damage and the consequent neurologic deficits. The first was a primate (*Macaca mulatta*) model developed by Michejda in which a fetal L3-5 laminectomy was performed late in gestation.[8] The unrepaired fetuses showed cystic MMC-like lesions at birth and had neurologic deficits. A similar group of monkeys underwent immediate repair of the laminectomy *in utero* using allogeneic bone paste to reconstruct the resected dorsal arches. These fetuses repaired *in utero* were neurologically normal at birth. Unfortunately, the experiment did not include an initial procedure for creation of the defect with a period of exposure to the uterine environment prior to closure. Similar experiments by Heffez in fetal rats and pigs demonstrated increased loss of spinal cord tissue in a group not undergoing immediate repair.[9] Stiefel studied the curly tail mouse model of exposed lumbosacral spina bifida and demonstrated progressive deterioration of neuroanatomic appearance and neurologic function with increasing gestational age.[10] Working in our laboratory, Danzer developed a retinoic acid-induced MMC in fetal rats and histopathology confirmed the entire spectrum of severity observed in human MMC as well as features of the Arnold-Chiari malformation (Figure 2).[11] While these studies support the principle of improved neurologic function with *in utero* coverage of the spinal cord, a large animal model with prolonged periods of time *in utero* after surgical manipulation was needed before extrapolation of these findings to humans.

Beginning in 1993, a series of experiments conducted by Martin Meuli, Scott Adzick, and colleagues demonstrated the similarities between a surgically created large animal model and human MMC and documented neurologic improvement following *in utero* repair.[12] A

sheep model was created in fetal lambs at 75 days gestation (term 145 days) by excision of skin, paraspinal musculature, vertebral arches of lumbar vertebrae 1 through 4, and the exposed dorsal dura mater. The pregnancy was then continued to near term, and cesarean section was performed at 140 days gestation. The lambs developed lumbar cystic sacs with abnormal spinal cord tissue on the dorsal aspect. Histology revealed loss of neural tissue, disruption of neural bundles, and areas of cord necrosis in the exposed segments, strikingly similar to that seen in human MMC. The spinal cord and its coverings proximal to the lesion appeared normal. Clinically, the lambs demonstrated incontinence of urine and stool, flaccid paraplegia, as well as lack of sensation in the hindlimbs, which was confirmed by somatosensory evoked potentials.

Having demonstrated the feasibility of creating a spinal defect resembling human MMC, we then performed *in utero* closure of the spine using this same model. Following creation of a spina bifida-type lesion at 75 days, the fetal lambs were operated on a second time at 100 days gestation.[13] A reversed latissimus dorsi flap was used to cover the exposed spinal cord placode, and the animals were delivered by Cesarean section just prior to term. Compared to the unrepaired group, the repaired group demonstrated near normal motor function, apparent continence of stool and urine, and intact sensation by clinical evaluation and somatosensory evoked potentials. Compared to normal postnatal sheep, the animals had some neurologic delay and hindlimb weakness, but they were able to stand, walk, and climb stairs. Histologically, the spinal cord, nerve roots, and spinal ganglia had well preserved cytoarchitecture in all specimens, with only flattening and mild dilation of the central canal.

This was the first large animal experiment that demonstrated a spinal cord lesion could be created *in utero* and repaired at a later time point with preservation of neurologic function. Unlike the previous animal models, this sheep model more closely resembled that of human MMC in duration of exposure of the cord to the environment, clinical examination, and histology. These findings suggested that the uterine environment plays a significant role in secondary neural tissue destruction, perhaps even more than the primary embryologic abnormality. Furthermore, it suggested that *in utero* repair may permit preservation of neurologic function. Subsequent sheep studies have shown that this model when combined with a lumbar myelotomy leads to hindbrain herniation, and that *in utero* closure results in reversal of hindbrain herniation.[14]

Early Clinical Experience at the Children's Hospital of Philadelphia (CHOP)

Prior to 1997, we considered only fetuses with life-threatening anomalies and very poor predicted outcomes as candidates for fetal surgery. However, the severe morbidity and significant mortality of MMC combined with the promising results of animal research as well as the development of diagnostic ultrafast fetal MRI studies led to consideration of prenatal intervention for this disorder.

Expectant mothers considering *in utero* therapy undergo extensive prenatal evaluation to include obstetrical evaluation, genetic screening, ultrasonography, fetal echocardiography, and ultrafast MRI. Although most cases of MMC are isolated abnormalities, genetic screening permits identification of some of the genetic and chromosomal syndromes

associated with spinal dysraphism. Ultrasonography assesses lower extremity function, identifies club foot anomalies, and estimates the spinal level of the defect by localizing vertebral arch defects. As a rule, fetuses with thoracolumbar defects have the worst functional outcomes, while those with progressively lower lesions tend to do better. Using ultrafast sequencing techniques for fetal MRI, we have been able to further define the presence or absence of the hindbrain herniation component of the Arnold-Chiari malformation, hydrocephalus, and any other brain abnormalities.[15] By careful correlation of imaging results with known clinical outcomes, we have improved prenatal counseling of parents and planning of therapeutic interventions.

Based on our experience with other fetal surgical interventions and observations in animal models, we speculated that the surgical procedure was ideally performed between 19 and 25 weeks gestation. Repair at this age minimizes the length of time during which neuronal damage to the exposed cord may occur. Prior to this age, fetal tissues are quite gelatinous making the procedure technically difficult. Additionally, we believed early repair might limit progression of hydrocephalus, since increasing ventricular size over the course of gestation is characteristic of fetal MMC.

The intraoperative and postoperative management algorithm for fetal MMC surgery has been extensively described in the MOMS trial publication in the *New England Journal of Medicine*. [16] After maternal laparotomy followed by hysterotomy using a uterine stapling device, the fetus is positioned with the MMC lesion visible through the uterine incision (Figure 3). We have shown that intraoperative fetal echocardiographic monitoring is imperative.[17] The cystic membrane of the MMC is excised and the attachments of the meninges to the skin and soft tissues are detached. If possible, native dura is closed over the spinal cord as a first layer, followed by closure of paraspinal myofascial flaps, and then the skin surrounding the lesion is mobilized and closed to complete the repair. When the skin cannot be closed primarily, an acellular human dermis graft is used to complete the closure.

We reported evidence of improved neurologic function following *in utero* surgical repair in a 23 week gestation fetus in 1998.[18] One year later, we reported the findings of our first ten patients who underwent fetal MMC closure at 22-25 weeks gestation.[19] Nine remained *in utero* for an average duration of 10 weeks following surgery, and the remaining fetus delivered prematurely at 25 weeks gestation and died from respiratory insufficiency. At birth, six of the nine patients had leg function at least two or more spinal segment levels better than expected based on prenatal MRI. All nine fetuses demonstrated ascent of the hindbrain and increased cerebrospinal fluid (CSF) volumes around the posterior fossa by ultrafast fetal MRI assessment, consistent with hindbrain herniation reversal while still *in utero*. Four patients (44%) required postnatal placement of a ventriculoperitoneal shunt, one at the time of our report and three patients in subsequent follow up. We hypothesized that fetal closure prevented CSF leakage from the MMC and lead to more normal CSF pressure gradients with consequent ascent of the hindbrain, re-expansion of the cisterna magna, improved CSF circulation, and decreased need for ventricular shunting.

We reported our experience with fifty-eight patients treated with fetal surgery from 1998-2003 prior to the beginning of the MOMS trial in 2003.[20] There were 4 deaths due

to preterm delivery, and the average age at delivery was 34 weeks, 4 days. Comprehensive followup examinations were performed at one, two, three, and five years of age. There was resolution of hindbrain herniation in nearly all patients treated *in utero*, and the ascent of hindbrain structures could be demonstrated within 3 weeks of the fetal closure using serial MRI. Restoration of CSF volume in the posterior fossa after *in utero* repair is indicative of reversal of hindbrain herniation. The functional significance is that the vast majority of children demonstrated no or minimal brainstem dysfunction symptoms at followup [21]. The ventriculoperitoneal shunt rate was 46%, which is much lower than the predicted overall shunt rate of 84% based upon 297 historical controls followed at the CHOP Spina Bifida Clinic between 1983 and 2000.[22] In assessing motor skills, fetal surgery resulted in better than predicted lower extremity function at birth, and ambulatory status at followup revealed that 66% were independent walkers.[23] Neurodevelopmental evaluation at 5 years of age showed that the majority (83%) had overall cognitive functioning in the average to high range. There was a pattern of consistently higher scores in verbal areas compared to scores for visual-motor or non-verbal reasoning, suggesting the possibility of later learning difficulties.[24]

Management of Myelomeningocele Study (MOMS): A Randomized, Prospective Clinical Trial

Comparison between MMC patients who were treated prenatally and previously reported controls were subject to bias. The three major centers performing fetal MMC repair at that time – CHOP, University of California San Francisco (UCSF), and Vanderbilt – agreed that it was the right time to test this fetal therapy with a prospective randomized trial before the surgery became much more widespread without compelling proof of safety and efficacy. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) supported moving forward with treatment protocol standardization, review of multiple grant submissions, and MOMS trial oversight. The Data Study and Coordinating Center at George Washington University was enlisted to collect the data and monitor compliance with the MOMS trial protocol.

Patient randomization in the study began in March, 2003.[16] Potential patients were referred to the closest center based on geographic criteria. Patients willing to accept either procedure were randomized after consent to either prenatal surgery or postnatal surgery at that center. All prenatal and postnatal patient care protocols were standardized among the three centers. Patient inclusion and exclusion criteria for the MOMS trial are shown in Table 3.

The objective of the trial was to evaluate if intrauterine repair of MMC between 19 to 25 weeks gestation improves outcomes compared with standard neurosurgical repair. One primary outcome was a composite of fetal or neonatal death or the need for ventriculoperitoneal shunt placement by the age of 12 months. A second primary outcome was the assessment of mental development and motor function at 30 months. A variety of secondary neonatal and maternal outcome measures were also examined. The long-term psychological and reproductive consequences in mothers who undergo intrauterine repair of

MMC are being compared to those in the postnatal repair group. During the study, the investigators were blinded to the results, since the followup evaluation of the children and mothers was performed by an independent team of pediatricians and psychologists appointed and supervised by the Data Study and Coordinating Center.

Enrollment was stopped by the Data Safety and Monitoring Board in December, 2010 because of the efficacy of fetal surgery after recruitment and randomization of 183 of a planned sample size of 200 patients. Similar to the earlier, non-randomized results of patients who underwent fetal MMC repair, the MOMS trial showed a significant reduction of ventriculoperitoneal shunt placement at one year of age following fetal MMC surgery (prenatal group: 40% vs. postnatal group: 82%, $P<0.001$). The trial also demonstrated a substantial improvement in the overall neuromotor function at 30 months of age by a variety of measures including the finding that 42% in the fetal surgery group were walking independently compared to only 21% in the postnatal surgery group ($P<0.01$). This is despite the fact that on average, there were higher and more severe MMC lesions in the prenatal surgery group just by serendipity. For those with a lesion of L3 or lower on ultrasonography, 68% of the prenatal surgery group were in that less severe class, whereas those lower levels were 84% of the postnatal surgery group. So there was better motor function in the prenatal surgery group, despite the fact that on average, they had higher lesions. Finally, hindbrain herniation was significantly reversed in the fetal surgery group compared to the postnatal surgery group (no hindbrain herniation in 36% and 4% of the infants, respectively, and severe herniation in 6% and 22%, respectively, $P<0.001$).

Despite these promising results, the MOMS trial also revealed that fetal MMC surgery increases the risks for spontaneous rupture of membranes (prenatal surgery: 46% vs. postnatal surgery: 8%, $P<0.001$), oligohydramnios (21% vs. 4%, $P=0.001$), and preterm delivery (79% vs. 15%, $P<0.001$) including 13% of fetal surgery group that were born before 30 weeks of gestation. The average gestational age at delivery in the fetal surgery group was 34.1 weeks gestation compared to 37.3 weeks in the postnatal surgery group. At the time of delivery, approximately one-fourth of mothers in the fetal surgery group demonstrated evidence of thinning of the uterine wound, and 10% showed partial (9%) or complete (1%) degrees of tissue edge separation at the hysterotomy site, but none had a hysterotomy rupture.

Clinical Experience at CHOP after the MOMS Trial Publication

The MOMS Trial elucidated the benefits and risks of fetal MMC repair. The mother carrying a fetus with MMC at less than 24 weeks gestation now has three choices: termination of the pregnancy (TOP), continuation of the pregnancy with near-term cesarean section and postnatal repair, or prenatal surgery. At CHOP, prenatal surgery for MMC is a new standard of care option for these families if the mother and fetus meet the highly specific criteria (Table 3), and if the family chooses fetal surgery.

Between March 2011 and July 2013, 468 mothers with a prenatal diagnosis of spina bifida were referred to CHOP, and 289 patients underwent on-site evaluation in Philadelphia. Eighty-five patients (29%) underwent fetal MMC repair, 117 patients underwent postnatal

MMC repair, and 87 had TOP. The vast majority of patients who chose postnatal repair or TOP had been excluded as fetal surgery candidates because of maternal or fetal exclusion criteria (Table 3). In particular, there were 22 fetuses who proved to have closed spina bifida defects as determined by an absence of hindbrain herniation diagnosed on fetal MRI (but not necessarily diagnosed for this finding by much less sensitive fetal ultrasound) which highlights the importance of fetal MRI in the evaluation process. Of course, fetal surgery is not warranted for a fetus with a closed spina bifida defect and absence of hindbrain herniation.

Research Directions

The results of the non-randomized and randomized studies regarding prenatal therapy for MMC are less than perfect, and it is clear that prenatal surgery is not a cure for MMC. Despite fetal closure, 40% still required shunting, and not all had improved neuromotor function or complete reversal of hindbrain herniation. Because the trial was closed early due to the efficacy of fetal surgery, complete followup of the entire 183 patient MOMS trial cohort at 12 and 30 months of age is important, and prenatal anatomic predictors of outcome need to be delineated. Completion of the MOMS trial data set should help answer many questions. How accurate is prenatal ultrasound compared to postnatal X-ray or MRI in predicting the anatomic level of the MMC? Does fetal ventricular size greater than 15-20 mm increase the likelihood of a postnatal shunt even after prenatal surgery? What impact does prenatally diagnosed bilateral or unilateral talipes have on postnatal motor function at age 2 ½ years? What are the urologic findings in the two groups? What is the effect of prenatal surgery compared to postnatal surgery on health care costs? How does prenatal surgery affect maternal morbidity, future reproductive capacity, and psychology? Long-term follow-up is crucial to assess the durability of the initial benefits, and the National Institutes of Health has funded a followup study of the MOMS trial patients at 6-9 years of age (MOMS II). A REDCap data registry to collate the outcomes for fetal MMC repair patients after the MOMS trial is being coordinated by the North American Fetal Therapy Network (www.NAFTNet.org).

The timing and technique of fetal MMC surgery needs to be optimized. The development of minimally invasive approaches for fetal MMC surgery may not only minimize preterm labor and delivery, but may also permit prenatal coverage of the lesion much earlier in gestation. We evaluated gelatin-hydrogel based scaffolds embedded with growth factors for early gestation prenatal coverage of MMC in fetal rats with retinoic acid-induced MMC and demonstrated that these scaffolds adhere to the MMC and subsequently promote tissue coverage over the defect.[25] This study supports the therapeutic potential of a tissue engineering approach for prenatal MMC coverage, perhaps by introducing these tissue engineered components through a single fetoscopic port or through an amniocentesis needle under ultrasound guidance. Such coverage must be completely “water tight” to prevent the leakage of CSF through the MMC defect that leads to hindbrain herniation, and to prevent amniotic fluid exposure which damages the neural tissues in the MMC defect. Rigorous experimental testing and comparisons with open fetal MMC surgery techniques will be required in an effort to decrease the risks to the mother and fetus and to improve outcomes.

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Fetal Surgery for Myelomeningocele (MMC) – the most severe form of Spina bifida

**Spina bifida
affects about
1,500 babies born
each year in the
United States**

FETUS WITH MYELOMENINGOCELE

1. Part of the spinal cord and spinal nerves, usually encased in a sac, protrude through an opening in the back and are exposed to the amniotic fluid.
2. Arnold-Chiari II Malformation • The brain stem (hindbrain) descends, or herniates, into the spinal canal in the neck and blocks the circulation of cerebrospinal fluid. This can cause a damaging buildup of fluid in the brain called hydrocephalus.

Figure 1.

The neural tube fails to close by 4 – 6 weeks gestation leading to spina bifida.

Figure 2.

Representative photographs of retinoic acid-induced lumbosacral MMC defects in fetal rats at term (embryonic day 22) (A-C). Similar to human fetuses with MMC, a thin fibrous membrane covers the defect. Various degrees of curly or bent tail (black arrows) as well as clubfoot deformities (black arrow head) are noted.

A

B

Figure 3.

A (left-hand panel). Exposure of 22 week gestation human fetus through hysterotomy showing the MMC. B (right-hand panel). After dural closure and myofascial flap closure, the skin is closed.

Table 1

Diseases amenable to fetal surgical intervention in selected cases

Malformation	Effect on development	<i>In Utero</i> Treatment
Cystic adenomatoid malformation or Pulmonary sequestration	Pulmonary hypoplasia, hydrops	Thoracoamniotic shunting, fetal lobectomy, steroids
Sacroccygeal Teratoma	Vascular steal, hydrops	Excision
Urethral Obstruction	Renal dysplasia, pulmonary hypoplasia	Vesicoamniotic shunting, laser ablation of PUV
Laryngeal Atresia	Congenital High Airway Obstruction Syndrome, hydrops	Ex Utero Intrapartum Therapy (EXIT Procedure)
Congenital Diaphragmatic Hernia	Pulmonary hypoplasia, respiratory failure	Tracheal occlusion and release
Hypoplastic left heart syndrome	Inadequate cardiac growth	Increase cardiac chamber blood flow
Twin-Twin Transfusion & TRAP	Vascular steal, hydrops	Laser coagulation of placental vessels or umbilical cord
Amniotic Bands	Limb deformity & functional loss	Lyse bands
Chorioangioma	Vascular steal, hydrops	Laser photocoagulation of placental vessels
Myelomeningocele	Damage to spinal cord, hindbrain herniation, hydrocephalus	Closure of defect

Table 2**Criteria for Fetal Surgery**

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1. Accurate diagnosis possible with exclusion of associated anomalies
 2. Natural history of the disease is documented, and prognosis is 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 protocols and approval of an Institutional Oversight Board with informed consent of the mother or parents
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Table 3

Our current inclusion and exclusion selection criteria at CHOP are the same as for the MOMS trial

Inclusion criteria	· Maternal age greater or equal to 18 years
	· Gestational age at randomization 19 weeks, 0 days to 25 weeks, 6 days
	· Normal karyotype
	· S1-level lesion or higher
	· Confirmed hindbrain herniation on prenatal ultrasound and MRI
Exclusion criteria	· Multiple gestation pregnancy
	· Insulin-dependent pregestational diabetes
	· Additional fetal anomalies unrelated to MMC
	· Fetal kyphosis greater than or equal to 30 degrees
	· History of incompetent cervix and/or short cervix less than 20 mm by ultrasound scan
	· Placenta previa
	· Other serious maternal medical condition
	· Obesity defined by body mass index of 35 or greater
	· Previous spontaneous singleton delivery less than 37 weeks gestation
	· Maternal-fetal Rh isoimmunization
	· Positive maternal human immunodeficiency virus or hepatitis-B or known hepatitis-C positivity
	· No support person to stay with the pregnant women at the center
	· Uterine anomaly
	· Psychosocial limitations
	· Inability to comply with travel and follow-up