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# Fetal Surgery for Spina Bifida: Past, Present, Future

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## Abstract

Open spina bifida or myelomeningocele (MMC) is a common birth defect that is associated with significant lifelong morbidity. Little progress has been made in the postnatal surgical management of the child with spina bifida. Postnatal surgery is aimed at covering the exposed spinal cord, preventing infection, and treating hydrocephalus with a ventricular shunt. Experimental and clinical evidence suggest that the primary cause of the neurologic defects associated with MMC is not simply incomplete neurulation, but rather chronic mechanical and amniotic-fluid induced chemical trauma that progressively damages the exposed neural tissue during gestation. The cerebrospinal fluid leak through the MMC leads to hindbrain herniation and hydrocephalus. *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. In the past, studies in animal models and clinical case series laid the groundwork for a clinical trial to test the safety and efficacy of fetal MMC repair. In the present, a prospective, randomized study (the MOMS trial) has shown that fetal surgery for MMC before 26 weeks' gestation may preserve neurologic function, reverse the hindbrain herniation of the Chiari II malformation, and obviate the need for postnatal placement of a ventriculoperitoneal shunt. However, this study also demonstrates that fetal surgery is associated with significant risks related to the uterine scar and premature birth. In the future, research will expand our understanding of the pathophysiology of MMC, evaluate the long-term impact of *in-utero* intervention, and to refine timing and technique of fetal MMC surgery using tissue engineering technology.

### Keywords

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

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

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arches leading to lifelong paralysis. In addition, MMC patients are often limited by various degrees of mental retardation, bowel and bladder dysfunction, and orthopedic disabilities. While the etiology of MMC remains poorly understood, primary failure of either neural tube or mesenchymal closure at the caudal neuropore in the embryonic period results in exposure of the developing spinal cord to the uterine environment.[1, 2] 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. 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 challenges.

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.[3] While substantial progress could be made in preventing this disorder through folic acid supplementation, the impact of this preventative approach have leveled off.[4, 5] Consequently, spina bifida affects 1 in 3000 live births.[6–8] Not included in this figure are the estimated 25–40% of MMC pregnancies in which the fetus is aborted.[9, 10] Mothers who choose to continue the pregnancy must prepare for a child with significant care needs and high medical expenses. Despite aggressive intervention, 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.[11] While 70% of patients have an I.Q. above 80, only half are able to live independently as adults, even with adapted accommodations.[12] The emotional and financial impact on the family and community are enormous. No recent data are available, but in 1994 the cost of care exceeded $500 million per year (in 1992 dollars) in the United States alone.[13]

In addition to motor and sensory deficits due to the spinal cord lesion, significant complications in MMC come from hydrocephalus, the Arnold-Chiari II malformation, and spinal cord tethering at the site of surgical repair. Hydrocephalus, defined as any enlargement of the cerebral ventricles, occurs in more than 85% of patients with MMC.[14] 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 within the first year of placement.[15, 16] Almost all patients with MMC also have the Arnold-Chiari II malformation, 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.[17] Descent of the hindbrain through the foramen magnum can lead to brain stem compression, the leading cause of mortality in children with MMC.[18] 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, though some patients ultimately require laminectomy and decompression of the cranio-cervical junction.[19,20] Tethering is fixation of the spinal cord secondary to adhesions between the previously exposed neural elements and the surrounding tissues, leading to tension on the neural axis. The diagnosis is confirmed radiographically, usually after a patient develops progressive worsening of neurologic function. While surgical release can limit further damage in some patients, the functional decline may be irreversible in others.[21,22] Therapeutic interventions aimed at preventing these complications could significantly impact the quality of life of children with MMC. *In utero* intervention may hold the key for reversing the hindbrain herniation, limiting the need for ventriculoperitoneal shunting due to hydrocephalus, and preventing late loss of function due to tethering.

## Rationale for *In Utero* Intervention

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.[23] 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 fetuses produced similar findings.[24]

Additional support for the two-hit hypothesis of spinal cord damage comes from sonographic observation of fetuses with MMC. Multiple studies have assessed the quality, frequency, and presence of fetal leg movements during fetal development, only to report inconsistency between prenatal and postnatal function. Korenromp used sonography to document normal flexion and extension at the hips and knees as early as 16–17 weeks in MMC fetuses.[25] Sival studied the leg movements of 13 fetuses with MMC and compared the results to postnatal function.[26] Only one of the 13 had abnormal leg movements prenatally, but 11 had abnormal postnatal leg movements. The leg movements seen prenatally could be secondary to spinal arc reflexes rather than of cerebral origin, thus permitting motion without electrical impulses through damaged segments of spinal cord. Alternately, the leg motions could come from the cerebrum through an intact spinal cord that is damaged secondarily throughout gestation, in labor and/or at delivery. As is illustrated by these studies, accurate neurologic assessment *in utero* of the fetus with MMC remains a challenge.

Further support for the theory of acute neurologic damage comes from studies demonstrating improved neurologic outcomes following cesarean section *prior* to the onset of labor. Luthy reported 160 infants with MMC and compared outcomes based on vaginal delivery, cesarean section prior to the onset of labor, and cesarean section after the onset of labor. Delivery by cesarean section before the onset of labor resulted in better motor function at two years of age than with vaginal delivery or delivery by cesarean section after a period of labor.[27] In a subsequent report by this same group, the cesarean section groups were further stratified into patients with or without preoperative rupture of the amniotic membranes.[28] They noted improved outcomes, as measured by the difference in the mean between anatomic level and motor level, in those who had cesarean section after onset of labor but before rupture of membranes, as compared to those who underwent cesarean section after onset of labor with rupture of membranes. They concluded that labor prior to membrane rupture causes minimal injury to the protruding nervous tissue while loss of amniotic fluid with labor after membrane rupture may lead to traumatic injury.

While other studies have indicated that cesarean section for MMC may not impact neurologic outcome, no group has compared vaginal delivery with elective cesarean section of vertex fetuses prior to onset of labor or rupture of membranes in a randomized, controlled fashion.[29,30] Until such a study is performed, it is common obstetrical practice that fetuses with MMC are delivered by cesarean section prior to the onset of labor or rupture of membranes to minimize potential trauma to the spinal cord.

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.[31] 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.[32] In hemimyelocele, half of the dysrhaphic 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.[33] In contrast, the opposing limb varied in innervation and function.

## Animal Models

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.[34] 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.[35,36] 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.[37,38] 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.[39] 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 were conducted by Martin Meuli, Scott Adzick, and colleagues which demonstrated the similarities between a surgically created large animal model and human MMC and documented neurologic improvement following *in utero* repair.[40,41] 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.[41,42] 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.[43]

## Early Clinical Experience

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 magnetic resonance imaging (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.[44] 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.[45,46] 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.[47] By careful correlation of imaging results with known clinical outcomes, we have improved prenatal counseling of parents and planning of therapeutic interventions.

Because of the significant risks inherent in prenatal intervention, fetal surgery was initially offered only to those mothers in which the fetus had a large thoracolumbar defect, the Arnold-Chiari malformation, mild or moderate ventriculomegaly, normal leg movements, no apparent clubbing of the feet, normal karyotype, and absence of concomitant severe anomalies. Encouraging results with the first few patients led to surgical repair of smaller spinal defects, provided the other criteria are met. By limiting interventions to those with the Arnold-Chiari malformation, we target those most likely to suffer from hydrocephalus or life-threatening brainstem symptoms which require frequent postnatal surgical intervention.

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.[40] 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.[48]

The intraoperative and postoperative management algorithm for fetal MMC surgery has been extensively described in the recent MOMS trial publication in the *New England Journal of*

*Medicine*.[49] After maternal laparotomy followed by hysterotomy using a uterine stapling device, the fetus is positioned with the MMC lesion visible through the uterine incision. We have shown that intraoperative fetal echocardiographic monitoring is imperative.[50] 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.

Follow-up after hospital discharge included twice weekly ultrasounds to assess for fetal well being, ventriculomegaly, and evidence of fetal leg movement or clubbed feet. Ultrafast fetal MRI was performed every 3 weeks postoperatively in the first case series to further evaluate brain and spinal cord development. At 36 weeks, an amniocentesis was performed to confirm lung maturity and, if mature, the fetus was delivered by cesarean section. Physical examination, neurologic testing, and magnetic resonance imaging were performed on the neonate and at regular intervals thereafter.

The first report of *in utero* coverage of MMC came in 1997 from Tulipan and Bruner who described endoscopic placement of a maternal split-thickness skin graft over the fetal neural placode.[51] Of the two patients reported, one died shortly after surgery and the other showed no improvement in neurologic function. After abandoning the endoscopic technique, they subsequently reported four fetuses that underwent late gestation (28–30 weeks) open repair. Interestingly, all four patients demonstrated absence of hindbrain herniation at birth, but two required postnatal placement of a ventricular shunt and the neurologic outcome was not described.[52]

We subsequently reported evidence of improved neurologic function following in utero open fetal surgical repair **earlier** in gestation at the Children's Hospital of Philadelphia (CHOP).[53] A 23-week gestation fetus with a T11-S1 dysrhaphic lesion and Arnold-Chiari malformation underwent open surgical repair. Seven weeks later at delivery the infant had a right club foot, but excellent flexion and extension at the knee and hip on that leg. The left leg had normal function except for absent plantar flexion of the foot. Whereas hindbrain herniation was documented preoperatively, postnatal MRI confirmed resolution of hindbrain herniation and absence of hydrocephalus. A ventriculoperitoneal shunt has never been required. Unfortunately, this first patient developed severe tethering of the spinal cord at the repair site after 6 months of age leading to loss of lower extremity function and requiring operative release. This late decline in function due to tethering underscored the importance of investigating better coverage materials and techniques for fetal MMC repair.

In 1999, we reported the findings of our first ten patients who underwent fetal MMC closure at 22–25 weeks gestation.[54] 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 hypothesize that fetal closure leads to more normal CSF pressure gradients with consequent ascent of the hindbrain, re-expansion of the cisterna magna, and improved CSF circulation.

At the same time, Bruner and colleagues reported decreased hindbrain herniation in 29 patients following MMC repair between 24 and 30 weeks gestation.[55] Only 11 (38%) demonstrated any degree of postoperative cerebellar herniation, with moderate herniation present in two infants. In a comparison group of patients repaired postnatally, herniation was present in 95%. Likewise, 17 of the 29 patients (59%) required ventriculoperitoneal shunt placement and required it at a later postnatal age than the control group which had a 91% shunt placement rate (minimum follow up of 6 months). While improved leg function was not found in this group, exclusion of fetuses with preoperative evidence of decreased lower extremity function was not a component of their study. Additionally, the later gestational ages at time of repair may have contributed to the absence of improved neurologic function due to *in utero* biochemical or traumatic damage. This fact was part of the rationale for fetal MMC repair before 26 weeks gestation in the subsequent MOMS trial.

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.[56] 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. The overall head size has been shown to be small in myelomeningocele patients, and to increase towards normal after fetal surgery due to normalization of extra-axial CSF spaces.[57] 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 [58]. The ventriculoperitoneal shunt rate was 46%, which is much lower that the predicted overall shunt rate of 84% based upon 297 historical controls followed at the CHOP Spina Bifida Clinic between 1983 and 2000.[59] In assessing motor skills, fetal surgery in this population resulted in better than predicted lower extremity function at birth, and ambulatory status at followup revealed that 66% were independent walkers.[60] Followup neuroanatomic imaging is important since we have seen postoperative intradural dermoid cysts develop at the fetal closure site.[61] Twenty-eight of the children underwent neurodevelopmental evaluation at 5 years of age. The majority (83%) have 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.[62,63]

The ramifications of these observations and outcomes are potentially significant. After fetal MMC repair, ascent of the hindbrain and improved CSF hydrodynamics may reduce hydrocephalus and avert the need and morbidity of ventricular shunts. With a more normal anatomic location of the hindbrain, the symptomatic sequelae of the Arnold-Chiari

malformation and need for subsequent surgery should be reduced. In the case of lower lumbar and sacral lesions where less impairment in lower extremity function may be predicted, normalizing hindbrain position and minimizing the need for postnatal ventriculoperitoneal shunt placement may be the primary indication for surgery. Persistence of improved lower extremity function, especially in patients with lesions at higher spinal levels, should permit greater independence and potentially improved quality of life. A reduction in the incidence of club feet and other orthopedic anomalies should limit the need for surgical intervention and enhance the possibility of future ambulation. The impact of prenatal intervention on bowel and bladder continence, sexual function, and mental capacity remains to be elicited as these infants advance in age and development. Two followup studies of women who underwent open fetal surgery at CHOP demonstrated no impairment of future reproductive capacity, and the hysterotomy risks were comparable to those of a classic cesarean section.[64,65] The latter finding mandates cesarean delivery for the fetal surgery pregnancy and all subsequent pregnancies.

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

Due to the lack of a control group of children with MMC who did not undergo prenatal surgery, the initial clinical results of fetal MMC surgery have been compared to previously published cohorts. Infants treated prenatally represent a highly-selected subset of affected individuals. Comparison between MMC patients who were treated prenatally and previously reported controls are subject to bias. For these reasons the National Institutes of Health (NIH) sponsored a multicenter, prospective, randomized clinical trial comparing outcome after prenatal and postnatal surgery for MMC beginning in 2003.[49] 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. The study was performed by three fetal surgery units including CHOP, Vanderbilt University, and University of California San Francisco (UCSF); the Data Study and Coordinating Center at George Washington University: and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Prior to the beginning of the trial, all other U.S. centers voluntarily agreed not to offer fetal surgery for MMC outside of the trial, essentially closing a “back door” to the intervention until the trial was completed.

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 1.

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 “SWAT” medical team of pediatricians and psychologists.

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 ($P<0.01$). 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.

An analysis of the full delivery cohort from the MOMS study was presented by Mark Johnson at the Society for Maternal-Fetal Medicine meeting in February 2012.[66] This study evaluated the risk factors for preterm delivery prior to 34 weeks gestation after fetal myelomeningocele repair. It appears that short fetal surgical time serves as proxy for technical expertise of the operative team because longer fetal surgical time was associated with the development of spontaneous rupture of membranes, oligohydramnios, and subsequent early delivery. Pregnancies that develop chorioamniotic membrane separation during the first month after surgery are also at increased risk for delivery at less than 34 weeks gestation. Nulliparous patient should be counseled that they may be at higher risk for hysterotomy complications following prenatal MMC repair.

## 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 1), and if the family chooses fetal surgery.

Between March 2011 and September 2012, 299 mothers with a prenatal diagnosis of spina bifida were referred to CHOP, and 181 patients underwent on-site evaluation in Philadelphia. Forty-eight patients (27%) underwent fetal MMC repair, 85 patients underwent postnatal MMC repair, 42 had TOP, one had an intrauterine fetal demise, three had an anatomically normal fetus, and one decided to have fetal surgery at a center closer to home. 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 1). In particular, there were 19 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.

## Experience with Fetoscopic Approaches for Myelomeningocele Repair

Although fetoscopic techniques that involve making multiple puncture wounds in the uterus are theoretically appealing to potentially mitigate maternal morbidity, clinical reports on their use are limited and the results have been disappointing, primarily because of uterine membrane problems leading to premature birth 3 to 6 weeks after the procedure and delivery before 30 weeks gestation. The first cases of fetal MMC surgery were reported in 1997 using an endoscopic approach at Vanderbilt University. This technique proved disastrous (two of four fetuses died) and was abandoned.[51] In 2003, Farmer and colleagues from UCSF reported three patients that underwent fetoscopic MMC surgery.[67] Fetoscopic coverage was successfully completed in one patient, but the patch partially detached after fetal intervention and the newborn required standard repair and shunt placement postnatally. Due to technical difficulties, the MMC defect in the second fetus was never completely covered and the fetus was delivered prematurely at 31 weeks of gestation. Postnatally the newborn required neurosurgical repair of the lesion and ventriculoperitoneal shunt placement and subsequently died of urosepsis at one month of age. The third fetus required conversion to an open approach secondary to an anterior placenta and difficulties in appropriately positioning the fetus.

Fetoscopic patch coverage has also been tried in Europe in a small series of patients, and has also proven very problematic.[68,69] Complete coverage of the defect was only achieved in 11 of 16 (69%) fetuses. In four fetuses the surgery was terminated prior to completion of the procedure secondary to bleeding at the trocar sites. Mean age at delivery was 28 weeks which is considerably earlier than the reported mean gestational age at delivery of 34–35 weeks for the open approach.[49,56] Oligohydramnios developed in 9 (56%) pregnancies. Overall survival was only 81% (the 3 deaths were due to severe prematurity, intraoperative demise, and termination of pregnancy after fetal surgery). As compared with the open fetal surgery technique, fetoscopic repair of MMC has resulted in higher rates of fetal death, premature rupture of the membranes, chorioamnionitis, premature delivery, and persistent

hindbrain herniation. If the problems of membrane rupture associated with multiple-port fetoscopy can be solved, this minimally invasive approach to repairing MMC before birth should be tested clinically.

## Future Studies

Future improvements in fetal MMC surgery will depend on a number of factors delineated in the Isabella Forshall Lecture at the 2012 meeting of the British Association of Paediatric Surgeons. [70] First, 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? The improved outcomes with fetal MMC repair make it less costly over a lifetime than surgery after delivery in a study that used MOMS data and a financial model to show that health care savings of $3,135,557 would occur for every 100 cases of fetal MMC repair performed [71]. 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 NIH has funded a followup study of the MOMS trial patients at 6–9 years of age (MOMS II).

Second, the results of our studies cannot be generalized to patients that either undergo fetal MMC surgery at less experienced centers or have fetal surgery outside the eligibility criteria set forth by the MOMS trial (Table 1). Outcomes may be less favorable than those in the trial, and maternal and fetal complications may be greater as part of the recognized “learning curve” at new centers. For patient safety and optimal outcome, fetal MMC surgery should be limited to high-volume fetal surgery centers with a committed multidisciplinary team of experts following a standardized patient care protocol. The NICHD has sponsored a Maternal-Fetal MMC Repair Task Force that will soon publish a consensus statement regarding this issue with input and approval from multiple medical societies whose specialists might participate in fetal MMC surgery. A REDCap data registry to collate the outcomes for fetal MMC repair patients is planned by the North American Fetal Therapy Network (www.NAFTNet.org).

Third, what is our approach to help centers in the U.S. and internationally to start a fetal MMC repair program? We believe that at least three conditions are essential: 1) the visiting team should refer patients to CHOP who are candidates for fetal MMC repair in order that the team can watch and learn about the entire process from counseling to followup; 2) the

visiting team should reflect a truly multidisciplinary effort and therefore the visiting team should include specialists in pediatric surgery, pediatric neurosurgery, maternal-fetal medicine, anesthesiology, and a coordinator. The process cannot be learned by a single specialist showing up to “watch a case”; 3) the center must demonstrate a commitment to following their patients (mother and child) for long-term outcomes, and be committed to research in this area (clinical, basic, or ideally both), all if which requires a substantial institutional commitment. Our approach has successfully catalyzed the development of several fetal MMC repair centers in the U.S. and in Europe.

Finally, 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 RA-induced MMC and demonstrated that these scaffolds adhere to the MMC and subsequently promote tissue coverage over the defect.[63] 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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## Table 1

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