In utero Repair of Myelomeningocele: Rationale, Initial Clinical Experience and a Randomized Controlled Prospective Clinical Trial

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Abstract
Myelomeningocele (MMC), one of the most common congenital malformations, can result in severe lifelong disabilities, including paraplegia, hydrocephalus, Arnold-Chiari II malformation, incontinence, sexual dysfunction, skeletal deformations, and mental impairment. MMC was the first non-lethal anomaly to be treated by fetal surgery. Studies in animals provide compelling evidence that the primary cause of the neurological deficit associated with MMC is not simply incomplete neurulation but rather chronic mechanical injury and amniotic-fluid-induced chemical trauma that progressively damage the exposed neural tissue during gestation. Initial results suggest that the surgical repair of MMC before 25 weeks of gestation may preserve neurological function, reverse the hindbrain herniation of the Arnold-Chiari II malformation, and obviate the need for postnatal placement of a ventriculoperitoneal shunt. As it is currently unknown whether fetal surgery for MMC is truly beneficial compared to standard postnatal care, a randomized, controlled clinical trial has been initiated within the United States.

Introduction
Myelomeningocele (MMC) is a devastating congenital defect with sequelae that effect both the central and peripheral nervous system. The lesion is characterized by the protrusion of the spinal cord and meninges from the spinal canal with an abnormality in the overlying vertebral arches, muscle, and skin. In most cases, MMC leads to lifelong severe physical and developmental disabilities including impaired mental development, bladder and bowel incontinence, sexual dysfunction, various skeletal deformities, and paraplegia [1]. In addition to motor and sensory deficits caused by the spinal cord lesion, significant problems in MMC arise from hydrocephalus, the Arnold-Chiari II malformation, and spinal cord tethering at the site of surgical repair. Approximately 85% of patients with thoracolumbar, lumbar, and lumbosacral MMC eventually develop hydrocephalus, requiring ventriculoperitoneal shunt placement to prevent the neurological and intellectual compromise that accompanies significant ventriculomegaly [2, 3]. In addition, virtually all children with MMC also have the Arnold-Chiari II malformation, characterized by descent of the medulla, cerebellar tonsils and vermis through the foramen magnum, a small posterior fossa, ‘beaking’ of the midbrain tectum, enlarged massa intermedia of the thalamus, par-
deficiency in folic acid, an essential cofactor for enzymes.

MMC as Multifactorial Disorder

The etiology of MMC remains poorly understood and is believed to be multifactorial. The list of variables that have been implicated as risk factors for MMC is long and varied from exposure to viruses, chemicals and drugs to vitamin and mineral deficiencies, as well as maternal diseases (i.e. diabetes mellitus) [1, 9–11]. The most widely recognized trigger for MMC is a maternal and/or fetal deficiency in folic acid, an essential cofactor for enzymes involved in DNA and RNA synthesis and as a methyl donor in the methylation cycle [12]. The etiologic role of folic acid was further demonstrated by two randomized clinical trials showing that periconceptional folic acid supplementation (4 mg of folic acid daily) reduces the occurrence and recurrence of MMC and other neural tube defects by approximately 70% [13, 14]. In addition to environmental factors, genetic and/or inherited features are implicated in the etiology of MMC [1, 9, 10, 15–18]. Several lines of evidence support the existence of a genetic predisposition for MMC including the variable incidence among ethnic groups and geographical locations, familial recurrence, genetic syndromes associated with MMC, and numerous murine models with at least 80 mutant gene loci that are associated with MMC and other neural tube defects. However, clinical genetic studies have failed to identify any single gene responsible for human MMC [19].

Epidemiology

MMC affects nearly 1 in 2,000 live births in the United States [20, 21]. Not included in this figure are the estimated 23% of MMC pregnancies in which the fetus is aborted [22, 23]. Mothers who choose to continue the pregnancy must prepare for a child with significant care needs and tremendous medical expense. 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 symptomatic brainstem dysfunction secondary to the Arnold-Chiari II malformation [24]. The Center for Disease Control (CDC) estimates that MMC and its associated abnormalities consume approximately USD 200 million in health care cost annually (in 1985 dollars) [25]. Hence MMC remains, at present, a major public health problem.

Prenatal Diagnosis

Maternal serum α-fetoprotein and ultrasound are routinely used to identify fetuses that have or are likely to have neural tube defects [26]. Positive findings from either of these two screens are generally followed by detailed sonography, to confirm the presence of an open defect and amniocentesis, for evaluation of amniotic fluid α-fetoprotein and acetylcholinesterase, as well as examination of fetal karyotype to rule out chromosomal anomalies [27, 28]. In affected fetuses, ultrasound is used...
Multiple studies have assessed the quality, frequency and presence of fetal leg movements during fetal development, only to report inconsistency between pre- and postnatal function [34–36]. Korenromp et al. [34] observed that fetuses with MMC exhibited leg movement at 16–17 weeks of gestation. They suggested that these affected fetuses had good function at that point in gestation. No follow-up could be reported in this series because pregnancies were interrupted. Furthermore, Sival et al. [35] compared the leg movements of 13 fetuses with MMC pre- and postnatally. Only 1 of the 13 had abnormal leg movement before birth, but 11 demonstrated abnormal leg movements postnatally. Two possible explanations for this observation exist. First, the prenatal leg movements could be secondary to spinal cord reflex rather than of cerebral origin, thus permitting motion without electrical impulses conducted through the damaged spinal cord tissue. Second, leg movement early in pregnancy could be due to cerebral function conducted through an exposed spinal cord that is not yet damaged. Most newborns with MMC show neurological impairment of the lower extremities at birth, suggesting that the neurological injury might occur later in gestation or even during delivery. Indeed, vaginal delivery has been associated with trauma to the placode and poorer function as compared with infants delivered by cesarean section. Although other studies have indicated that cesarean section for MMC may not affect neurological outcome, no group has compared vaginal delivery with elective cesarean section of vertex fetuses before onset of labor or rupture of membranes in a randomized, controlled fashion [37–40]. However, it should be noted that patients with lipo- meningomyelocele, in which the neural tissue is covered and protected by skin, have almost normal lower leg and continence function, despite a neurulation abnormality that is nearly identical to that present in newborns with MMC.

Experimental Support for Fetal MMC Repair

In addition to the multiple genetic [15, 16, 41–44] and teratogenic [45–47] models of MMC and other neural tube defects, several models of mechanical disruption of spina bifida have been described. The first was a primate model [48] in which a fetal lumbar laminectomy (L3–L5) was performed late in gestation. One group of animals was repaired immediately with allogeneic bone paste while a control group had no repair. The unrepairsed fetuses showed cystic MMC-like lesions at birth and showed...
severe neurological impairment including paraplegia, incontinence, and somatosensory loss, whereas the repaired group was neurologically normal at birth. Unfortunately, the experiment did not include a period of exposure to the intrauterine environment prior to closure [48]. Heffez et al. [49] reported similar findings in fetal pigs and fetal rats. In both studies, late gestation fetuses underwent surgical creation of an MMC-like defect with immediate or delayed (24 h later) surgical closure resulting in preservation of neurological function compared to the untreated group. Notably, in some of the animals dehiscence of their skin closure occurred resulting in neurological deficit [49, 50]. Histological examination of the exposed neural tissue revealed erosion and necrosis, findings similar to those described in children with MMC.

These studies show that exposure of the fetal spinal cord to the intrauterine environment results in significant acquired neural tissue damage with corresponding neurological deficit at birth. In addition, these studies demonstrate that closure of a surgically created MMC-like lesion is feasible and improves neurological function at birth. The surgical model that is most similar to simulating the human disease is the fetal lamb model of MMC introduced by Meuli et al. [51] in 1994. The MMC-like defect was surgically created at 75 days of gestation (term 145–150 days) by a lumbosacral laminectomy. At 100 days of gestation a reversed latissimus dorsi flap was used to cover the exposed spinal cord and the animals were delivered by cesarean section just prior term [52, 53]. As in the primate, rat, and porcine models, the untreated fetuses showed MMC-like lesions at birth with similar neurological deficit: complete sensorimotor paraplegia, incontinence of stool and urine, and lack of sensory function of the hind limbs. In contrast, animals that underwent closure of the defect had healed skin wounds and near-normal neurological function. Despite mild paraparesis, they were able to stand, walk, perform demanding motor test and demonstrated no signs of incontinence. Furthermore, sensory function of the hind limbs was present clinically and confirmed electrophysiologically [52, 53]. Subsequent findings in sheep studies have shown that this model when combined with a lumbar myelotomy leads to the hindbrain herniation characteristic of the Arnold-Chiari II malformation and that in utero repair restores normal hindbrain anatomy [54, 55].

One of the criticisms of surgical models of MMC is that the lesion is artificially created late in gestation and is therefore unable to replicate the primary defect in neuralization, limiting their experimental relevance to the ‘secondary’ injuries of mechanical or chemical trauma. Therefore we recently developed and characterized a novel short-gestational animal model of isolated MMC in fetal rats by maternal administration of all-trans retinoic acid [56]. Exposure to retinoic acid at the time of posterior neuropore closure (E10 in rats) leads to a pathology that has striking morphological and clinical similarity to human MMC in approximately 60% of the fetal rats [56]. With respect to fetal surgical intervention, this animal model may facilitate investigations in the very early developmental abnormalities of spina bifida, as prenatal administration of retinoic acid induces a primary defect during the neural tube formation and allows subsequent evaluation of role of the intrauterine environment in secondary neural tissue destruction [56–58]. Furthermore, the fetal rat is large enough for surgical manipulation and has minimal propensity for preterm labor after fetal surgery, allowing the potential use of this model to study various approaches for prenatal coverage of MMC and the subsequent effect on postnatal neurological outcome.

**Fetal Surgical Intervention for MMC**

The overriding concern in any fetal operation is maternal safety [60]. Secondary goals are avoiding preterm labor and accomplishing the goals of the fetal intervention. Technical difficulties associated with the small size of the fetus and fragility of the fetal tissue generally limit prenatal intervention before 18 weeks of gestation, and after 32 weeks the risks of preterm labor increases dramatically, so that after 32 weeks it is more reasonable to deliver the fetus first and operate on the abnormality during the neonatal period. Fetal intervention for MMC requires the coordinated effort of many specialties, including perinatologists, radiologists, pediatric surgeons and neurosurgeons, neonatologists, geneticists, an experienced operating-room team, social workers and financial counselors. The issues associated with a serious congenital malformation such as MMC are complex and emotionally challenging. Ideally at least two preoperative counseling meetings are held with the family to review the findings of diagnostic studies (i.e. ultrasound, MRI) and to provide nondirective informed consent including discussion of maternal risk and the implications of pre-mature delivery.

Anesthetic considerations for fetal surgical intervention include maternal, fetal and uteroplacental factors [60]. Because of physiological alterations associated with pregnancy, the mother is at risk for aspiration pneumo-
nia, hypoxemia, and hypotension. The fetus has an immature cardiovascular system and thus is at risk for fetal asphyxia and cardiovascular collapse. Uterine relaxation is essential to expose the appropriate fetal part, prevent placental separation, and avoid preterm labor. Continuous monitoring of both fetus and mother are required. For the mother, routine monitors include electrocardiography, pulse oximetry, blood pressure cuff before induction, urinary catheter, and peripheral nerve stimulator. Fetal status is monitored by sterile intraoperative echocardiography.

To reduce maternal uterine activity an H2 antagonist the evening before and the morning of the surgery is given. Before induction, an oral antacid is given to reduce the risk of aspiration and an epidural catheter is placed for uterine relaxation and postoperative analgesia. A rapid sequence induction and intubation are accomplished. General anesthesia is maintained with 0.5% expired isoflurane and 50% nitrous oxide. Before uterine incision isoflurane is increased to 2% and titrated to uterine relaxation. In addition to the anesthesia the fetus receives via the placental circulation, the fetus receives an intramuscular injection of a narcotic just prior to the MMC repair. During uterine closure, magnesium sulfate is administered intravenously as a bolus and maintained intravenously for 24 h. The isoflurane is decreased to 0.5% expired. After skin closure, the anesthetic agents are discontinued, and the mother is extubated. Appropriate pain medications are given through the epidural catheter and postoperative tocolytic therapy is maintained using calcium channel blockers.

The uterus is exposed through a low transverse abdominal incision and fetal and placental positions are determined by intraoperative sterile ultrasound. An autostapling device (US Surgical, Norwalk, Conn., USA) is used to create a bloodless 6- to 8-cm hysterotomy incision a minimum of 6 cm away from the placental edge. Every attempt is made to maintain intruterine volume to prevent placental separation, contraction, and expulsion of the fetus. This is accomplished by intermittent infusion of warmed (37°C) lactated Ringers’ solution and by exposing only the portion of the fetus that is necessary. The fetus is positioned with the MMC lesion visible through the uterine incision. The cystic membrane of the MMC is excised carefully, and the attachments of the meninges to the skin and soft tissue are detached. If possible, native dura is closed over the spinal cord as a first layer, followed by closure of the paraspinal myofascial flaps, and then the skin surrounding the lesion is carefully mobilized and closed to complete the repair (fig. 1). After completion of surgery, the uterus is closed with a tight two-layer closure and a transparent dressing is applied to the maternal abdomen to allow postoperative sonographic monitoring. Initially, patients are observed in the high-risk obstetrical unit, subsequently discharged (~4 days postoperatively) and kept on bed rest near the hospital. Infants are delivered by planned cesarean delivery between 36 and 37 weeks after confirmation of fetal lung maturity, unless premature labor results in earlier delivery [64].

### Early Clinical Experience with Fetal MMC Repair

Prior to 1997, fetal surgical intervention was considered only for fetuses with life-threatening anomalies [59, 60]. However, the severe morbidity and significant mortality associated with MMC combined with the promising results of animal research led to consideration of prenatal intervention for this disorder.

The first cases of in utero spina bifida repair were performed in 1994 with an endoscopic technique that proved unsatisfactory and was abandoned [61]. In 1998, in utero repair of MMC was performed by hysteromy at the Vanderbilt University [62] and at the Children’s Hospital of Philadelphia (CHOP) [63]. The selection criteria varied between the two institutions. At Vanderbilt, patients were not excluded based on prenatal ventricular size, late gestational age, spinal level, or presence or absence of fetal leg motion on ultrasound. At the CHOP, the fetus was only considered for surgery if the gestational age at the time of the proposed surgery was 26 weeks or less, if the ventricular diameter was less than 17 mm, if the Arnold-Chiari II malformation was present, if the estimated level of the lesion was S1 or above, and if there was convincing leg and foot motion on ultrasound and an absence of club foot deformity [64].

The initial experience suggested that infants that were treated prenatally had improvement in hindbrain herniation as early as 3 weeks after in utero repair [65] and possibly a diminished need for shunting relative to infants that underwent standard postnatal neurosurgical repair [66]. It might be that fetal repair of MMC reduces the need for shunting by eliminating the leakage of spinal fluid that puts back pressure on the hindbrain; such treatment allows reduction of the hindbrain hernia and relieves the obstruction of the cerebrospinal fluid outflow from the fourth ventricle [8]. In a combined series of fetal surgery patients from the CHOP and Vanderbilt, 104 patients followed for at least 1 year had an overall incidence of shunt-
Any benefit in the lower extremity function or sphincter continence has been very difficult to demonstrate. It has been recently reported that children with postnatally repaired MMC have a level of neurological function that correlates very well with the bony level of the defect [72, 73]. In contrast to the Vanderbilt experience in late gestational fetuses (25–30 weeks) [74], lower extremity neuromotor outcome at birth was significantly improved in newborns that underwent fetal MMC before 26 weeks of gestation at the CHOP [64]. The reason for this difference may reflect patient selection, careful evaluation for evidence of intact neurological function before surgery, and younger gestational age at which the fetal repair occurred. In addition, recent reevaluation of children that underwent fetal MMC repair at the CHOP with a mean age of 40 months showed that the initial improvement in lower extremity function at birth not only persisted into preschool age, but also that fetal MMC repair results in a significant improvement of ambulatory potential (i.e. independent walking) and a reduction in the incidence of club foot deformity [75]. The impact of fetal MMC repair
on bowel and bladder continence remains unknown, but is currently under critical evaluation [Danzer, unpubl. data].

Despite these promising findings, there is already concern that some of the early benefit of fetal MMC repair may be at risk. Virtually all of the postnatal lumbosacral MRI studies of these patients suggest tethering, and recently some of the patients have developed symptomatic epidermoid inclusion cysts which have required repeat surgery [76]. It is unclear at this point whether this is a problem unique to fetal closure or simply that it is being detected during routine surveillance after fetal surgery.

Although long-term follow-up of these patients into adulthood is necessary, the implications of the short-term outcomes after fetal MMC repair are significant, if not without controversy [77]. The potential morbidity and mortality (perinatal mortality at the CHOP due to extreme prematurity is 7%, 4 out of 58) resulting from fetal surgery are real, and it is unclear whether the benefits in terms of shunt avoidance, reversal of hindbrain hernia, and improvement of ambulatory potential will be sustained. The optimal timing of surgery is unclear, as is the optimal type of closure. Most uncertain of all are the appropriate criteria by which patients should be selected for fetal MMC repair. In addition to the above-mentioned risk for the fetus, maternal-fetal surgery has postsurgical and future risks for the maternal patients. Potential maternal risks are surgical bleeding, infection (wound, amniotic cavity), preterm rupture of membranes, preterm labor and delivery, medication side effects (tocolysis), anesthesia complications (general, regional), prolonged hospitalization, impaired fertility, repeat cesarean deliveries, and death [60, 78]. With respect to fetal neurosurgical intervention for MMC no maternal deaths have occurred and no patient experienced hysteroscopy dehiscence or rupture. No data have been presented to suggest diminished fertility in any of the maternal patients that underwent fetal MMC.

Management of MMC Study

Due to the lack of a control group of children with MMC who did not undergo prenatal repair, the initial clinical results of in utero repair of spina bifida lesions have been compared to historical controls. Comparison between infants with spina bifida who were treated in utero and historical controls is however subject to substantial bias. Infants treated prenatally represent a highly selected subset of affected individuals. Additionally, the medical management of such infants might differ from that of historical controls for reasons unrelated to the in utero repair. Taken together, it is currently unknown whether fetal surgery for MMC is truly beneficial compared to standard postnatal care. For these reasons, a National Institute of Health-sponsored multicenter, prospective, randomized, clinical trial, comparing outcome after in utero and postnatal surgery for MMC is currently underway. The study centers are the CHOP, the University of California – San Francisco, and Vanderbilt University Medical Center, along with an independent Data and Study Coordinating Center at George Washington University Biostatistics Center. The name of the trial is the Management of Myelomeningocele Study (MOMS).

Briefly, pregnant women who receive a prenatal diagnosis of MMC between 16 and 25 weeks’ gestation will be referred to a central screening center. The eligibility and exclusion criteria for the MOMS trial are summarized in table 1. Eligible patients who consent to participate in the

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<td>Maternal age ≥18 years</td>
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<td>Gestational age at randomization 19 weeks, 0 days to 25 weeks, 6 days</td>
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<td>Normal karyotype</td>
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<td>S1 level lesion or higher</td>
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<td>Confirmed Arnold-Chiari II malformation on prenatal US and MRI</td>
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<td>Nonresident of the United States</td>
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<td>Multifactorial pregnancy</td>
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<td>Insulin-dependent pregestational diabetes</td>
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<td>Additional fetal anomalies unrelated to MMC</td>
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<td>Fetal kyphosis ≥30°</td>
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<td>History of incompetent cervix and/or short cervix &lt;20 mm by ultrasound scan</td>
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<td>Placenta previa</td>
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<td>Other serious maternal medical condition</td>
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<td>Obesity defined by body mass index of 35 or greater</td>
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<td>Previous spontaneous singleton delivery at &lt;37 weeks’ gestation</td>
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<td>Maternal-fetal Rh isoimmunization</td>
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<td>Positive maternal human immunodeficiency virus or hepatitis B or known hepatitis C positivity</td>
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<td>No support person to stay with the pregnant women at the center</td>
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<td>Uterine anomaly</td>
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<td>Psychosocial limitations</td>
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<td>Inability to comply with travel and follow-up protocols</td>
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Table 1. Inclusion and exclusion selection criteria for MOMS trial patients
Fetal MMC repair. Other objectives of the study are to determine if fetal MMC repair improves the degree of the Arnold-Chiari II malformation and neurological outcome as tested by neuroimaging, neuromotor function analysis, cognitive testing, and neurodevelopmental status at 12 and 30 months of life. Neonatal morbidity and the need for postnatal surgical interventions will be recorded. Finally, the long-term psychological and reproductive consequences for mothers who undergo intrauterine repair of MMC will be compared with those in the postnatal repair group. In summary, the trial should determine whether fetal intervention offers improved outcome with a reasonable quality of life for MMC children. Additional information about this trial can be obtained from the study website (www.spinabifidamoms.com).

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