

Fetal Surgery for Myelomeningocele: Patient Selection, Perioperative Management and Outcomes

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Key Words

Myelomeningocele • Spina bifida • Hydrocephalus • Hindbrain herniation • Prenatal diagnosis • Fetal surgery • Management of Myelomeningocele Study

Abstract

Myelomeningocele (MMC), one of the most common congenital malformations, can result in severe lifelong disabilities, including paraplegia, hydrocephalus, Chiari II malformation (CM-II), incontinence, sexual dysfunction, skeletal deformations and mental impairment. MMC was the first nonlethal anomaly to be treated by fetal surgery. Experimental and clinical evidence suggests that the primary cause of the neurologic deficit associated with MMC is not simply incomplete neurulation but rather chronic mechanical injury and amniotic fluid-induced chemical trauma that progressively damages the exposed neural tissue during gestation. Case series and a prospective, randomized study show that fetal surgery for MMC before 26 weeks' gestation may preserve neurologic function, reverse the hindbrain herniation of the CM-II and obviate the need for postnatal placement of a ventriculoperitoneal shunt. However, these studies also demonstrate that fetal surgery is associated with significant maternal and fetal risks. Consequently, further research is warranted to fur-

ther expand our understanding of the pathophysiology of MMC, to evaluate the long-term impact of in utero intervention and to refine the timing and technique of fetal MMC surgery.

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Introduction

Myelomeningocele (MMC) is one of the most common birth defects for which there is no satisfactory postnatal treatment. It was the first nonfatal anomaly considered for fetal surgical intervention, necessitating a careful analysis of risks and benefits [1]. The lesion is characterized by protrusion of meninges and neural elements through a defect in the vertebral arches with secondary complications of lifelong paralysis and varying degrees of mental retardation, bowel and bladder dysfunction and orthopedic disabilities. In addition to motor and sensory deficits below the anatomic level of the lesion, children born with MMC almost invariably have an associated Chiari II malformation (CM-II), consisting of a small posterior fossa and downward displacement of the cerebellar tonsils below the foramen magnum with elongation and compression of the brain stem and obliteration

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of the cisterna magna [2, 3]. The pathogenesis of hindbrain herniation results from the continuous leakage of cerebrospinal fluid (CSF) through the spinal lesion and consequent loss of hydrostatic pressure. The herniation of the hindbrain is linked to the development of an abnormally small posterior fossa [3]. Clinical presentations of this malformation depend upon the age of the child but typically include dysfunction of the cerebellum, medullary respiratory center and cranial nerves [4, 5]. Despite aggressive medical and surgical management, 15–30% of neonates with MMC die within the first 5 years of life, and the majority of these deaths are attributable to severe CM-II-associated symptoms [5–7]. Further, hindbrain herniation with obstruction of the outflow of CSF from the fourth ventricle is believed to be the primary cause of hydrocephalus. The incidence of clinically significant hydrocephalus ranges from 80 to 90%, and children treated with a CSF shunt are shunt-dependent for life [8, 9]. Hydrocephalus adversely affects neurocognitive outcome and results in later morbidity and mortality caused by shunt malfunction and infection [10, 11].

Advances in prenatal diagnosis now permit detection of MMC as early as the first trimester [12], and extensive research into the etiology and pathophysiology of MMC has elucidated genetic, environmental and micronutrient causes [13–15]. Although substantial progress has been made in preventing this disorder through folic acid supplementation, MMC still affects approximately 1 in 3,000 live births, which translates to 1,500 live-born MMC babies each year in the USA [16]. This figure does not include the estimated rate of up to 50% of MMC pregnancies in which the fetus is electively terminated [17].

Although approximately two thirds of affected individuals have an IQ >80, only one half are able to live independently as adults, and one third continue to require substantial daily care [18]. No recent data are available, but in 1994 the cost of care exceeded USD 500 million per year (in 1992 dollars) in the USA alone. Thus, it is clear that improvements in treatment are desperately needed [19].

This review will not only discuss the pathophysiology of fetal MMC (fMMC) and the rationale for fMMC surgery but also provide a detailed overview of patient selection, perioperative management and the short-term outcomes from initial clinical experience with human fMMC closure as well as the results from the recently completed National Institutes of Health-sponsored multicenter, prospective, randomized clinical trial comparing outcomes after prenatal and postnatal surgery for MMC [20].

Rationale for fMMC Surgery

Embryology and Pathophysiology

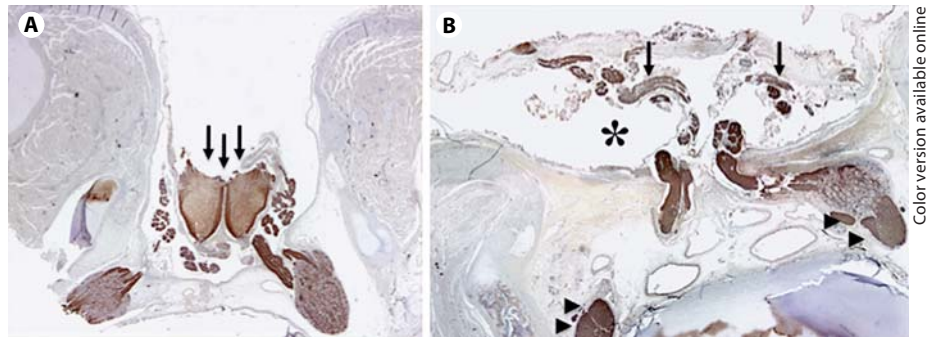
The rationale for fMMC surgery cannot be properly appreciated without understanding the embryology and pathophysiology of this condition. The closure of the neural tube is normally completed within the first 4 weeks of gestation. MMC is generally believed to result from failure of the neural tube to close completely [13, 14]. Secondary destruction of the exposed neural elements by amniotic fluid, direct trauma, hydrodynamic pressure or a combination of these factors may occur throughout gestation (i.e. ‘the two-hit hypothesis’). It is this secondary damage which may be ameliorated by early fetal coverage. There are many observations that support the premise that fetal coverage of the MMC defect might prevent the secondary, acquired injury to the exposed spinal cord. However, the controversy in the context of prenatal therapy arises over how much each of the two hits contributes to the observed neurologic deficits and, from a practical standpoint, at what stage during fetal development the secondary damage occurs.

Examination of human embryos and first-trimester fetuses with MMC shows an open but undamaged spinal cord with almost normal cytoarchitecture [21–23]. In subsequent studies of spinal cords of midgestational human fetuses with MMC, varying degrees of neural tissue loss were observed almost exclusively in the dorsal, protruding portion of the cord, while the neural elements proximal to the defect were normal (fig. 1) [24, 25].

In addition to the traumatic injury, experimental evidence suggests that prolonged exposure of the vulnerable fetal spinal cord to amniotic fluid or chemical components within the amniotic fluid (e.g. urea, creatinine, meconium) might be responsible at least in part for the secondary injury seen in MMC [26–28]. Exposure of the delicate, unprotected neural tissue to meconium significantly increased the spinal cord necrosis in fetal rats with surgically induced MMC [27].

CSF pressure within the subarachnoid space is believed to be the third component of the acquired damage to the exposed spinal cord in MMC [24]. Accumulation of CSF within the ventral subarachnoid space, limited dorsally by the attachment of the meninges to the skin, displaces the neural elements dorsally through the vertebral defect, resulting in tearing of the spinal nerve roots as well as excessive splaying of the cord.

More recently, it has been postulated that ependymal denudation found in human MMC fetuses at as early as 16 weeks of gestation may precede or even trigger the de-



Color version available online

Fig. 1. Representative histomorphological section through the center of an fMMC. **A** MMC in a fetus at 17 weeks' gestation. Early in gestation, a nonneurulated and open spinal cord is seen. The neuroepithelium is directly exposed to the intrauterine environment and not covered by meninges or other tissue. The cytoarchitecture of the spinal cord appears normal, and significant traumatic or degenerative changes, except for the most dorsal part of the lesion, are absent (arrows). **B** The lesion in a fetus at 28 weeks' gestation. Late in gestation, the spinal cord exhibited extreme flattening and erosion. The protruding, fluid-filled (aster-

isk) sac contained the flattened and almost completely destroyed spinal cord tissue (arrows); only the dorsal root ganglia appeared to be preserved (arrowheads). This CSF accumulation leads to a gradual expansion of the arachnoid space, which may have produced overextension, thinning and tearing of the neural tissue and lead to disruption of neural connections and additional neural damage. Immunohistochemical staining using a neurofilament protein antibody was performed as described elsewhere. Original magnification $\times 50$.

velopment of secondary acquired neurological injury to the exposed spinal cord [29–31]. Ependymal differentiation occurs in a fixed temporal and spatial pattern starting at about 4 weeks of gestation and is completed during the second trimester [32]. When ependymal cells are lost (i.e. ependymal denudation has occurred), progenitor cells are lost and functional restoration may be impossible. Ependymal denudation is followed by macrophage invasion into the denuded areas, which subsequently leads to increased inflammation, gliosis and fibrosis in the denuded area [31]. Consequently, worsening of the pathological neurodevelopmental processes associated with MMC may result.

Besides these experimental studies, several sonographic observations of fetuses with MMC further support the two-hit hypothesis. Sequential ultrasonographic images suggest that insults to both the central and peripheral nervous systems may be progressive. Lower extremity function may be lost [33, 34], and hindbrain herniation and hydrocephalus [35–37] may worsen with advancing gestational age.

Although some authors remain unconvinced [38], prevention of secondary neurological injury at the time of delivery by elective cesarean section performed before the onset of labor or rupture of fetal membranes may decrease the acquired trauma to the exposed neural placode and improve functional outcome [39]. In addition to the

expected trauma to the exposed neural elements during passage through the birth canal, another potential cause of late injury in MMC fetuses is abrasion of the spinal cord secondary to repeated contact with the uterine wall. As the fetus grows, especially in the third trimester, the extent of the 'amniotic fluid cushion' decreases, hence leaving the uterine wall in close proximity to the fetus' exposed spinal cord. Indirect support for this hypothesis is provided by Thevenet and Sengel [40], who evaluated the impact of oligohydramnios on wound healing in an avian model and found that with reduction of the amniotic fluid volume the chick embryos develop pressure necrosis, skin erosion and abrasion in prominent areas of the body. Of note, erosions, abrasions and pressure necrosis of the exposed neural elements in human MMC fetuses have been reported [24, 25, 31].

Finally, it should be noted that patients with closed neural tube defects such as myelocystocele or lipomeningomyelocele, 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 [14].

Taken together, these studies indicate that the early stages of MMC development are characterized by non-neurulated but otherwise (near) normal neural elements. There is a consensus that prolonged intrauterine expo-

sure of spinal cord tissue leads to progressive deterioration. Timed in utero coverage for protection of the cord might prevent or ameliorate the secondary component of the acquired damage.

Animal Models for fMMC Surgery

Multiple genetic [41, 42], teratogenic [43, 44] and surgical [27, 45–50] animal models of MMC have been developed not only to study the embryology and pathophysiology of MMC but also to evaluate whether prenatal coverage is feasible and improves neurological function.

The surgical model that is most similar to the human disease is the fetal lamb model of MMC introduced by Meuli et al. [48] in 1995. The MMC-like defect was surgically created at 75 days of gestation (term 145–150 days) by a lumbar (L1–L5) 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 to term [47, 49]. The untreated fetuses showed MMC-like lesions at birth with similar neurological deficits including complete sensorimotor paraplegia and incontinence of stool and urine. In contrast, animals that underwent closure of the defect had healed skin wounds and near-normal neurological function. Furthermore, sensory function of the hind limbs was present clinically and confirmed electrophysiologically [47, 49]. Russell Jennings at the University of California, San Francisco [51], and our group at the Children's Hospital of Philadelphia (CHOP) [52] subsequently showed that this model, when combined with a lumbar spinal cord myelotomy to enhance CSF leakage out through the lumbar laminectomy, leads to the hindbrain herniation characteristic of the CM-II and that in utero surgery restores normal hindbrain anatomy. The observed reversal of hindbrain herniation after fMMC surgery in these animals supports the unified mechanisms of embryogenesis proposed by McLone and colleagues [3, 53], who suggest that the MMC allows excessive drainage of ventricular CSF through the open defect and leads to collapse of the rhombencephalic vesicle and a small posterior fossa volume. Growth of the cerebellum and brain stem within a small posterior fossa results in downward herniation and caudal displacement of the cerebellar vermis and brain stem into the cervical spinal canal. By closing the MMC early in fetal life, it is likely that back pressure is again established in the posterior fossa, which disimpacts the brain from the spinal canal and reestablishes a more normal CSF drainage pathway.

One of the criticisms of surgical models of MMC is that the lesion is artificially created at midgestation and is therefore unable to replicate the primary defect in neurulation, limiting their experimental relevance to the 'secondary' injuries of mechanical or chemical trauma. Therefore, we recently developed and characterized a novel short-gestation animal model of isolated MMC in fetal rats by maternal administration of all-*trans*-retinoic acid (RA) [54]. Fetal rats exposed to RA develop MMC lesions that are confined to the lumbosacral area, and the histopathological features of the lesions are quite similar to those in human MMC [54]. Clinically, fetal rats with MMC develop clubfoot deformity, abnormal bladder function and features of the CM-II identified on postnatal MRI [54–56]. Of note, prenatal administration of RA induces a primary defect during neural tube formation. Therefore, the RA-induced MMC model enables investigation of the evolution of abnormalities in the development of MMC from the point of defective neurulation forward. Consequently, using this animal model we were able to provide clear evidence that most MMC rat fetuses have normal neurological function early in gestation despite the absence of normal primary neurulation [57]. Loss of this initial function is associated with neurodegeneration that is acquired later in gestation.

Fetal Surgical Intervention for MMC

The overriding concern in any fetal operation is maternal safety [58, 59]. Secondary goals are avoiding preterm labor and achieving 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 prior to 18 weeks' gestation.

Preoperative Assessment and Patient Selection

The issues associated with a serious congenital malformation such as MMC are complex and emotionally challenging. Fetal intervention for MMC requires the coordinated effort of many specialties, including maternal-fetal surgeons, perinatologists, neurosurgeons, neonatologists, anesthesiologists, radiologists, geneticists and social workers. In general, our preoperative workup includes a comprehensive anatomic and transvaginal ultrasound to document appropriate cervical length, gestational age based on fetal biometry, lesion level, ventricular diameter, lower extremity movement and foot positioning, as well as the exclusion of any other significant abnormality. Following the ultrasonographic assessment, all potential

fMMC surgery candidates undergo high-resolution ultrafast fetal MRI to evaluate the severity of hindbrain herniation and to screen for non-MMC-associated brain, spine and other abnormalities. Amniocentesis is performed to rule out associated genetic abnormalities. It is of utmost importance to exclude skin-covered dysraphic lesions such as lipomyelomeningocele or myelocystocele [60]. If the sac has a thick wall, no hindbrain herniation is evident and there is no elevation of amniotic fluid α -fetoprotein or acetylcholinesterase, one of these lesions should be suspected rather than an MMC. These forms of occult dysraphism are skin covered and therefore unsuitable for fetal intervention. After completion of a fetal echocardiogram to exclude congenital heart disease, maternal physical examination and clearance for surgery is performed by the perinatologists and anesthesiologists. The physical examination is followed by a comprehensive psychosocial evaluation to identify family dynamics and social issues to ensure that the patient has adequate psychosocial support systems. Subsequently, the results of the maternal and fetal evaluation are discussed in detail with the family. If the mother is a fetal surgery candidate and wishes to proceed, a follow-up family meeting with the entire team occurs, to reiterate the nature of the operation and the attendant risks, benefits and alternatives. A detailed consent form outlining the risks and benefits of fMMC surgery is signed and the patient undergoes fetal intervention usually within the next 24–48 h. Our current patient selection criteria are based on the Management of Myelomeningocele Study (MOMS) inclusion and exclusion criteria (table 1).

Anesthetic Considerations for fMMC Surgery

Anesthetic considerations for fetal surgical intervention include maternal, fetal and uteroplacental factors [61]. Because of physiological alterations associated with pregnancy, the mother is at risk for aspiration pneumonia, hypoxemia and hypotension. The fetus has an immature cardiovascular system and is thus 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 essential. For the mother, routine monitoring includes electrocardiography, pulse oximetry, blood pressure cuff before induction, radial arterial line placement, urinary catheter placement, leg compression boots and a peripheral nerve stimulator. Fetal status is monitored by sterile intraoperative sonography and echocardiography.

Table 1. Our inclusion and exclusion criteria are similar to the requirements of MOMS [5]

Inclusion criteria

Maternal age greater or equal to 18 years
 Gestational age at randomization between 19 weeks, 0 days and 25 weeks, 6 days
 Normal karyotype
 S1-level lesion or higher
 Confirmed Arnold-Chiari II malformation on prenatal US 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 as body mass index of 35 or greater
 Previous spontaneous singleton delivery at 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 woman at the center
 Uterine anomaly
 Psychosocial limitations
 Inability to comply with travel and follow-up

Cephazolin (1,000 mg i.v.) and indomethacin (50 mg p.r. or p.o.) are given preoperatively. Before induction, an oral antacid is given to reduce the risks of aspiration, and an indwelling epidural catheter is placed to facilitate postoperative analgesia. A rapid sequence induction and intubation are performed. General anesthesia is maintained with 0.5% volatile anesthetic agents (e.g. isoflurane) and 50% nitrous oxide. Before the uterine incision, isoflurane is increased to 2% and titrated to complete uterine relaxation. In addition to the anesthesia the fetus receives via the placental circulation, the fetus also receives an intramuscular injection of a narcotic and muscle relaxant just prior to the start of the fetal portion of the operation (see below).

fMMC Surgery Procedure

The gravid uterus is exposed via a low transverse incision. A vertical skin incision may be needed in patients with a BMI >30 or those with a previous vertical skin scar. The fetal position, the MMC defect and the placenta

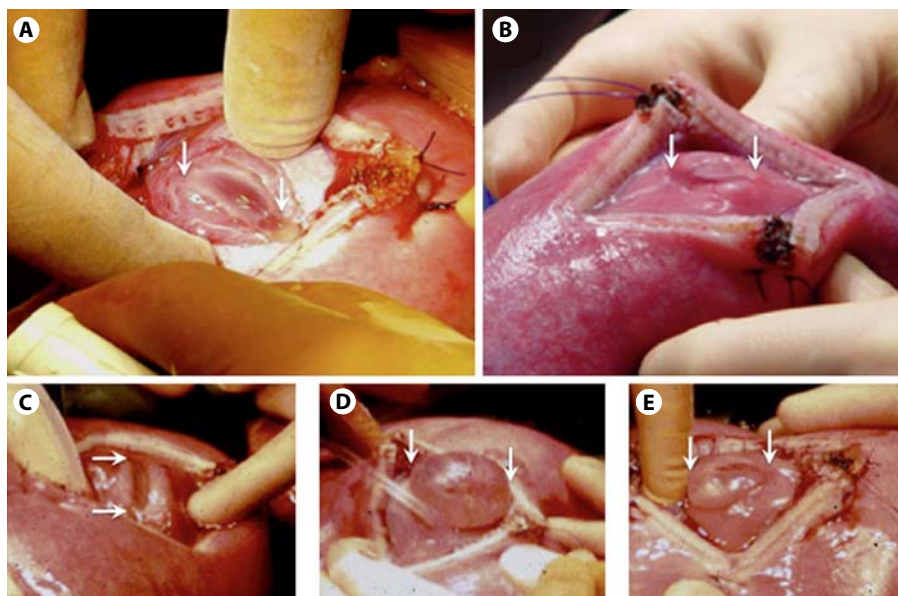


Fig. 2. Midgestational exposure of fetuses through hysterotomy showing various types and sizes of MMC defects encountered during prenatal intervention, ranging from small flat lesions (**A, B**) to defects without a sac (**C**), to lesions with large bulging MMC sacs (**D, E**). The arrows identify the cranial and caudal borders of the exposed neural placode.

are located by intraoperative sterile ultrasound, and the hysterotomy location is chosen by the primary surgeon to be at least 6 cm away from the placental edge. In case of an anterior placenta, a fundal or posterior hysterotomy will be required. In case of a posterior placenta, the uterine incision is made anteriorly. Under sonographic guidance, two monofilament traction sutures are placed through the full-thickness uterine wall, and the initial uterine incision is accomplished using a Bovie cautery between the uterine traction sutures, followed by the passage into the uterine cavity of the uterine stapling device loaded with absorbable polyglycolic acid staples (Covidien Auto Suture, Norwalk, Conn., USA). A spear-like device that snaps onto the lower limb of the uterine stapler facilitates uterine entry. Ultrasonography and manual palpation of the stapling device is used to exclude the presence of fetal tissue between the stapler and the uterine wall. The stapler is used to create a 6–8 cm uterine incision large enough to expose the fMMC (fig. 2). Prior to beginning the operation on the fetus, the fetus is given an intramuscular injection of fentanyl (20 $\mu\text{g}/\text{kg}$) and vecuronium (0.2 mg/kg). In order to minimize the risks of placental separation, uterine contractions and expulsion of the fetus, intrauterine volume is maintained by infusion of warmed (37°C) lactated Ringer's solution using a Level I infusion device (H-1200, Fast Flow Fluid Warmer, Smiths Medical ASD Incorporated, St. Paul, Minn., USA).

Fetal surgery for MMC is facilitated by surgical loupe magnification. An incision is made at the fetal skin-

arachnoid membrane junction, the MMC sac (if present) is excised and the neural placode is positioned within the spinal canal. The dura is closed over the placode using a fine running monofilament suture. Myofascial flaps are created and closed over the dura. Skin flaps are then mobilized and closed to complete the watertight fMMC closure. If it is not possible to obtain primary skin closure, an Alloderm (LifeCell, Branchburg, N.J., USA) patch is used. After completion of the fetal surgery, the uterus is closed in two layers. The first running full-thickness layer incorporates the absorbable staples and uterine membranes. Before completion of the first layer, warmed Ringer's lactate mixed with antibiotics (2 g of oxacillin or 900 mg of clindamycin) is added to the uterus until the amniotic fluid index is normal. A second layer of full-thickness sutures are placed first, and these sutures are then tied once the first layer is complete. To help achieve a watertight hysterotomy closure, the uterine wound is covered with an omental patch. Finally, the abdominal wall is closed in layers, a subcuticular skin closure is performed and a clear plastic dressing is placed.

Post-fMMC Surgery Care

During uterine closure, magnesium sulfate (6-gram loading dose, then 2–4 g/h) is administered intravenously as a bolus and maintained intravenously for the first 18–24 h following surgery. Postoperative pain medications are initially given through the epidural catheter. Cephazolin (1 g every 6 h for a total of 4 doses) is contin-

ued postoperatively. Indomethacin (50 mg) is given per rectum or orally every 6 h for the first 24 h following surgery, and then 25 mg is administered every 6 h on the second day. During the 2 days on indomethacin, a fetal echocardiogram is performed daily to evaluate cardiac function and assess potential constriction of the fetal ductus arteriosus. Since prenatal surgery patients are at increased risk of preterm labor, maintenance tocolytic therapy consists of oral nifedipine (10–20 mg every 4–6 h) until gestation has reached 36 weeks and 6 days. In the case of palpable, uncomfortable contractions occurring preterm for longer than 1 h and at a frequency of greater than or equal to 4 per 20 min, magnesium sulfate should be reinitiated as first-line tocolytic therapy. The patients are observed in our Special Delivery Unit and discharged once they are on a regular diet, have normal bowel function, are able to ambulate to the bathroom without assistance and demonstrate good tocolytic and pain control with oral medications. The average hospital stay is 4 days. In general, all patients are kept on modified bed rest for the first 2 weeks after surgery. Subsequently, we allow our mothers to gradually increase activity if the uterus remains quiescent. Most postoperative mothers remain close to our fetal center to permit standardized postoperative management, weekly ultrasound evaluation and delivery. Others may be transferred back to the outpatient care of their referring physician if the clinical circumstances are good and stable.

Outpatient follow-up is scheduled every week. In addition to the usual content of a prenatal visit, maternal assessment includes the degree of postoperative discomfort, wound healing and premature labor/delivery risks. A brief ‘targeted’ ultrasound is performed to assess amniotic fluid volume and membrane status, since oligohydramnios and chorioamniotic membrane separation are the most frequent complications following maternal-fetal surgery and their presence may directly impact pregnancy management. Fetal well-being is determined at every visit after 25 weeks by means of a biophysical profile. Comprehensive ultrasonography is performed monthly to measure the following: biparietal diameter, head circumference, ventricular size, femur length, abdominal circumference, status of the chorion, amniotic fluid index and maximum vertical pocket.

If our patients experience preterm labor and are unresponsive to tocolytic therapy and the likelihood of preterm labor is high, then a single course of corticosteroids is used to minimize complications of respiratory distress syndrome. In the case of chorioamnionitis, placental abruption or a nonreassuring fetal status, the fetus is de-

livered via cesarean section; otherwise, all fetuses are delivered via cesarean section at 37 weeks of gestation. Although the same abdominal incision is used for the cesarean as for the fMMC surgery, the fetus is preferably delivered via a lower uterine segment incision, and the fetal surgery hysterotomy closure is inspected and revised if there is any evidence of wound dehiscence.

Clinical Outcome following fMMC Surgery

Nonrandomized Results

The first case of fMMC surgery was performed in 1994 at Vanderbilt University using an endoscopic technique [62]. This approach proved disastrous (2 of 4 fetuses died) and was abandoned. Percutaneous fetoscopic patch coverage has been tried more recently in a small series of patients and has also proven enormously problematic [63, 64]. Investigators from the University of California, San Francisco [64], reported 3 patients who underwent fetoscopic fMMC surgery. Fetoscopic coverage was successfully completed in 1 patient. However, the patch partially detached after fetal surgery 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 1 month of age. The third fetus required conversion to an open approach secondary to an anterior placenta and difficulties to appropriately position the fetus. In the case series by Kohl et al. [63], endoscopic coverage of the MMC defect in 3 fetuses resulted in fetal patch detachment in 1 fetus, successful completion of the operation in the second and fetal death in the third. Premature rupture of membranes is a substantial problem with the multiple-port site fetoscopic approach.

The first successful (i.e. improved postnatal neurologic function) open fMMC surgery in an early-gestation human fetus was performed by our group at CHOP in 1998 [65]. A fetus at 23 weeks’ gestation with a T11-S1 lesion, hindbrain herniation and normal lower extremity movements assessed by preoperative high-resolution ultrasonography underwent open surgical coverage of the dysraphic defect. Surgery and recovery were uneventful, and the fetus was delivered by cesarean section at 30 weeks of gestation after the onset of preterm labor. Postnatally, the infant had a right clubfoot deformity and neuromotor function at the L4 level on the right and L5 level

on the left. Whereas hindbrain herniation was documented preoperatively, postnatal MRI confirmed complete resolution of hindbrain herniation and absence of ventriculomegaly, and as a consequence a ventriculoperitoneal shunt was not required.

Subsequent studies from CHOP and Vanderbilt University suggest that infants who were treated prenatally had improvement in hindbrain herniation as early as 3 weeks after fMMC surgery and appeared to have a diminished need for shunting relative to infants who underwent standard postnatal neurosurgical repair [66, 67]. Compared to historical controls, it was estimated that fMMC surgery may reduce the need for ventriculoperitoneal shunt placement from 80–90 to 40% [9]. The functional significance of the more normal position of the hindbrain, reduced shunt rate and restoration of near-normal CSF hydrodynamics [68, 69] is that the vast majority of fMMC children demonstrated absent to mild brain stem dysfunction symptoms at 6 years of follow-up [70, 71].

Recent evaluation of children who underwent fMMC surgery at CHOP not only showed that the initial improvement in lower extremity function at birth persisted into preschool age but also revealed that 69% of fMMC children were independent walkers at a mean follow-up age of 66 months [72]. However, toddlers and preschool children often continue to demonstrate coordinative deficits and gait disturbances that are characteristic of children with MMC. Despite these promising findings, recently a few of the patients have developed clinical symptomatic spinal cord tethering in association with dermoid inclusion cysts at the fetal closure site and have required repeat surgery, usually with restoration of function [73]. A possible late decline in neuromotor function due to tethering with or without a dermoid inclusion cyst underscores the importance of investigating better coverage materials and techniques for fMMC surgery as well as careful continued long-term neurologic surveillance of these children.

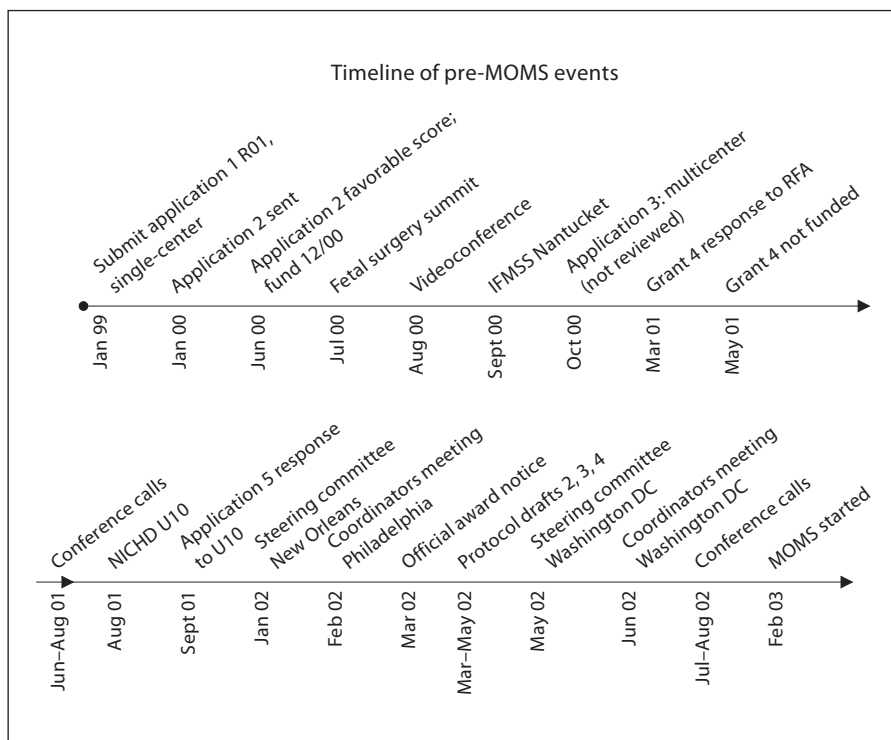
Regarding preschool neurocognitive outcome, 30 of the initial 54 fMMC survivors (56%) at our institution underwent standardized preschool neurodevelopmental assessment [74]. At a mean follow-up age of 61 months, the majority of fMMC children had neurocognitive scores in the average to high-average range and were at an age-appropriate point in schooling. Although fMMC children who did not require ventriculoperitoneal shunt placement were more likely to have better scores, for the entire cohort there was a pattern of consistently higher scores in the verbal areas compared to scores for visual-

motor or nonverbal learning skills, suggesting the possibility of later learning difficulties [74]. More recently, we evaluated the impact of prenatal intervention on daily life functional status in children who underwent fMMC surgery at our institution prior to the randomized trial [75]. Our results showed that although the majority of fMMC children achieve neurocognitive and neurofunctional independence, nearly one third continue to require maximal assistance when carrying out self-care tasks (e.g. toileting, bladder and bowel management). These functional studies confirm previous findings by other centers that show only minimal impact of prenatal MMC surgery on continence function [76, 77].

MOMS: A Prospective, Randomized Trial

Comparisons of infants with spina bifida who were treated in utero to previously reported postnatally repaired controls are subject to substantial bias. Additionally, the medical management of such infants might differ from that of historical controls for reasons unrelated to fetal surgery. For these reasons, the National Institutes of Health sponsored a multicenter, prospective, randomized clinical trial comparing outcome after in utero and postnatal surgery for MMC (fig. 3). The study was performed by three fetal surgery units (CHOP, Vanderbilt and University of California, San Francisco), the Data Study and Coordinating Center at George Washington University and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. MOMS was initiated in 2003, and in December 2010 enrollment was stopped because the efficacy of prenatal surgery was demonstrated after recruitment and randomization of 183 of a planned sample of 200 patients [20]. The objective of the trial was to determine if intrauterine surgery for MMC between 19 and 25 weeks of gestation improves outcomes compared with standard postnatal neurosurgical repair. One primary outcome was a composite of fetal or neonatal death or the need for placement of a CSF shunt by the age of 12 months, and another primary outcome at 30 months of age was a composite of mental development and motor function. A variety of secondary neonatal and maternal outcome measures were also examined. Similar to the earlier, nonrandomized results from patients who underwent fMMC surgery, MOMS showed a significant reduction in ventriculoperitoneal shunt placement at 1 year of age following fMMC surgery (prenatal group 40% vs. postnatal group 82%; $p < 0.001$) [20]. 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

Fig. 3. Timeline summary of the tremendous groundwork necessary to start MOMS in February 2003. Starting in January 1999, a single-center grant proposal was submitted to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), requiring multiple revisions and expansion to a multicenter trial. After considerable discussions of the trial design, the definition of patient selection criteria and the standardization of the fMMC surgery technique and patient care management at various steering committee meetings, the International Fetal Medicine and Surgery Society (IFMSS) meeting in 2000 and multiple phone conferences, the trial was approved by the sponsoring institution, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, in March 2002. Following Institutional Review Board approval at each of the three fetal surgery centers involved and additional steering committee meetings and conference calls, MOMS began in February 2003. RFA = Request for applications.



42% of fMMC children were walking independently compared to only 21% in the postnatal group ($p < 0.01$). Finally, there was much less hindbrain herniation in the fMMC surgery group than in the postnatal surgery group (no hindbrain herniation in 36 and 4% of the infants, respectively, and severe herniation in 6 and 22%, respectively; $p < 0.001$) [20]. The impact on mental capacity, bladder and bowel continence and sexual function remains to be elicited as these infants advance in age and development.

Despite these promising results, MOMS also revealed that fMMC 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 fMMC children who were born before 30 weeks of gestation [20]. The average gestational age at delivery in the prenatal surgery group was 34.1 weeks' gestation compared to 37.3 weeks' gestation in the postnatal surgery group ($p < 0.001$). Also, at the time of delivery, approximately 25% of mothers in the fMMC surgery group showed evidence of thinning of the uterine wound, and 10% demonstrated variable degrees of dehiscence at the hysterotomy site, but none had a hysterotomy rupture.

Conclusion

Until recently, fetal surgical interventions have been limited to fetal anomalies perceived to be lethal because of the potential risk of such a major surgical procedure to an otherwise healthy mother. Fetal surgery for MMC – a nonlethal but highly morbid disorder – has extended the original criteria for fetal surgery to a disorder causing irreversible organ damage before birth with associated quality-of-life morbidities after birth. We have traveled a long road in our effort to improve the outcome of MMC fetuses. The idea of reducing or preventing the significant MMC-associated neurological morbidities by fetal surgery was born over 20 years ago and was followed by many years of experimental studies in multiple animal models to demonstrate the potential benefit and feasibility of such intervention. The initial clinical efforts succeeded based on careful and cautious application in a highly selected patient cohort and were recently confirmed in a properly controlled randomized clinical trial which has provided a definitive answer regarding the efficacy of fMMC surgery. Despite the success, possible fetal benefits must be balanced against the risks of fetal surgery including the substantial risks of prematurity and maternal morbidity. For all children who underwent

fMMC surgery either as part of the trial or prior to the randomized study, continued follow-up is imperative to determine whether the early benefits are durable and to evaluate the impact of fMMC surgery on future bowel and bladder continence, sexual function and mental capacity. It is difficult to speculate about potential technical

refinements that may develop to decrease maternal and fetal risk and improve outcome. However, we have recently developed a novel tissue engineering approach in our laboratory [78] which would potentially allow for earlier intervention and less invasive surgery to cover the MMC defect – a compelling vision.

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