Fetal Surgery for Myelomeningocele

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BACKGROUND

Myelomeningocele (MMC) is a congenital neural tube defect that occurs in approximately 1 in 2900 live births in the United States.\textsuperscript{1,2} This neurologic anomaly arises from incomplete neural tube closure during early development, resulting in an open spinal canal with exposed neural elements in the form of a flat neural placode. The neural placode then undergoes further traumatic injury in utero. These events form the basis of the two-hit hypothesis of neurologic injury in MMC, with the first hit being the developmental defect itself and the second hit being the additional injury to the exposed neural elements of the spinal cord. In utero intervention to repair the spinal cord does not address the developmental defect, but can ameliorate the subsequent trauma associated with the second hit.

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KEYWORDS

- Fetal surgery
- Hydrocephalus
- Myelomeningocele
- Neural tube defect
- Shunt
- Spina bifida
- Ventriculomegaly

KEY POINTS

- Fetal surgery for myelomeningocele is the most common open fetal surgery currently performed, and has been tested in a randomized controlled trial.
- Prenatal repair of myelomeningocele can improve hindbrain herniation and reduce postnatal shunt requirement.
- Distal neurologic function may also be improved in some patients after prenatal repair.
- Fetoscopic approaches to myelomeningocele repair remain a challenge and are an active area of research.

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The exact etiology of MMC is unknown, but its origin is likely multifactorial. Nutritional, environmental, and genetic factors have all been implicated in the pathogenesis of MMC. Folate deficiency in mothers is associated with an increased incidence of neural tube defects. Folate supplementation can decrease the risk of MMC in the pregnancy by as much as 50%, but it has not eradicated the anomaly. Environmental exposure to toxins and drugs has been implicated in the development of neural tube defects. In addition, genetic abnormalities may have a role in some patients, as seen in patients with PAX3 mutation in Waardenburg syndrome for example.

Patients with MMC can display a broad array of clinical findings depending on the severity of their neurologic defect. Most infants survive the neonatal period without significant morbidity; however, up to 30% of patients die before adulthood because of respiratory, urinary, or central nervous system complications. Long-term morbidity and mortality is related both to neurologic damage from the spinal cord lesion itself and to brain abnormalities from leakage of cerebrospinal fluid. Continued leakage of cerebrospinal fluid is thought to lead to an intercerebral pressure gradient, resulting in a hindbrain herniation known as Arnold-Chiari II malformation. Virtually all newborns with MMC have a Chiari malformation and more than 90% will develop hydrocephalus, requiring ventriculoperitoneal (VP) shunting. The spinal level of the defect determines the degree of motor and somatosensory deficit. In addition, these patients often have dysfunction of bladder and bowel control, as well as loss of sexual function that manifests in adolescence and early adulthood.

RATIONALE FOR FETAL REPAIR OF MMC

The rationale for fetal repair of MMC targets the second hit of the two-hit hypothesis. By limiting in utero damage to the exposed spinal cord and preventing continued leakage of cerebrospinal fluid, in utero coverage of the spinal defect could potentially normalize the intercerebral gradient and lead to improved neurologic outcomes. Several observations in both humans and animals support the two-hit hypothesis. First, early prenatal ultrasonographic examination of human fetuses with MMC has demonstrated normal hindlimb movement. This finding suggests a later loss of function attributable to in utero injury to the spinal cord. Second, postmortem analysis of stillborn and aborted fetuses with MMC has suggested recent in utero injury to the exposed neural placode. Third, patients with milder forms of neural tube defects whereby abnormal neural elements remain covered with skin or a membrane have more normal neural development than those patients with MMC. Finally, observations in mice with neural tube defects have demonstrated normal early anatomy and function, which is then progressively lost in utero.

ANIMAL MODELS

Animal models were developed to study the natural history of MMC and potential fetal interventions before attempting fetal MMC repair in humans. Surgical models in rodent, rabbit, sheep, and nonhuman primates share a similar phenotype to that found in human MMC: paraplegia, extremity deformity, urinary and bowel dysfunction, hydrocephalus, and the Chiari malformation. Prenatal closure of these surgically created defects has produced improvement in motor function and urinary function, and reversal of the Chiari malformation, with normal or near-normal hindbrain development and morphology. Several animal models have demonstrated that the Chiari malformation occurs with surgically created myelomeningocele and, more importantly, that it can be reversed after in utero repair. Further animal studies have also demonstrated improved distal neurologic function after in utero repair of
surgically created MMC. In a rabbit model of fetal MMC repair, neurologic function was improved after birth, as measured by somatosensory-evoked potentials.\textsuperscript{16} In studies examining anal sphincter development in the sheep model, histologic examination of rectum and anal sphincter muscles revealed preservation of longitudinal muscles in the sphincter complex and the submucosal nerve plexus in lambs that had undergone fetal repair.\textsuperscript{17,18}

**EARLY HUMAN EXPERIENCE**

**Fetoscopic Repair**

Before the advent of prenatal repair for MMC, human fetal surgery had been reserved for situations whereby there would be expected perinatal mortality. This approach was adopted to maximize potential benefit in the fetus while minimizing risk and morbidity to the mother. Fetal diseases for which prenatal intervention was considered included severe obstructive uropathies, congenital diaphragmatic hernia, placental anomalies such as twin-twin transfusion syndrome, and nonimmune hydrops secondary to an anatomic defect (eg, sacrococcygeal teratoma, congenital cystic adenoid malformation). MMC was the first nonlethal fetal malformation treated with human in utero surgery.

In an attempt to minimize maternal morbidity, early human fetal MMC repairs were approached fetoscopically.\textsuperscript{19–21} This technique was independently attempted at the Vanderbilt University Medical Center and at the University of California, San Francisco (UCSF). The Vanderbilt group reported 4 fetoscopic repairs via maternal laparotomy and a 3-port technique for in utero access. The amniotic fluid was replaced with carbon dioxide and the defects were covered with a maternal skin graft. Two of 4 fetuses survived to birth; both survivors required reoperation postnatally because no evidence of the skin graft was found at birth.

The UCSF group reported 3 attempts at fetoscopic MMC repair, only 1 of which was successfully closed fetoscopically. In this patient the MMC defect was closed with a decellularized dermal matrix patch; however, at birth the repair was incomplete and required an additional operation to close the defect. The 2 other attempts at fetoscopic repair were converted to open fetal repair because of technical difficulties. Fetoscopic repair would eventually be largely abandoned in favor of open fetal repair, which was technically easier to complete despite its increased maternal morbidity.

**Open Repair**

After these early attempts at minimally invasive repair, fetal surgeons began performing open fetal MMC repair (Fig. 1). The Vanderbilt group was the first to report its results in 1999, and concluded that the open repair method was superior to the fetoscopic method. This group also found that hindbrain herniation was improved in MMC patients who had undergone fetal surgical repair and that the need for VP shunting was significantly lower in these patients: 59\% versus 91\% in historical controls.\textsuperscript{22} These data were limited by their small sample size and the lack of a standardized protocol for postnatal VP shunt placement. A follow-up study with subset analysis demonstrated that repair earlier in gestation, lower-level lesions, and smaller ventricles before repair were all associated with a lower VP shunt rate.\textsuperscript{23,24}

Concurrently, the group at the Children’s Hospital of Philadelphia (CHOP) confirmed the findings of reversal of hindbrain herniation and improvement in the Chiari malformation in patients who had undergone open fetal repair.\textsuperscript{25} These findings were corroborated with studies of head biometry in prenatal and postnatal magnetic resonance imaging scans.\textsuperscript{26} Decreased shunt rates and less ventriculomegaly were also reported, further reinforcing the findings at Vanderbilt.\textsuperscript{27}
Neurologic Function

At all 3 centers, immediate results did not reveal significant improvement in neurologic function or hindlimb movement with fetal repair. Follow-up data were mixed. At UCSF, only 2 of 9 survivors had functional improvement greater than 2 spinal levels above the MMC lesion. Neurologic function correlated well with the level of the spinal lesion in the remainder of patients.21 The Vanderbilt group initially compared the neurologic outcomes of 26 patients who had undergone fetal MMC repair with historical controls and found no improvement.28 Their cohort was later compared with matched controls at the University of Alabama, Birmingham, and again they found no improvement in neurologic function.29 By contrast, the CHOP group examined 54 patients who had fetal MMC repair and found that 57% had neurologic function better than what was predicted from the level of their spinal defect.30 Their median follow-up was 66 months and ranged from 36 to 133 months. Factors that were associated with a lower likelihood of independent ambulation included higher-level lesions and presence of a clubfoot deformity.

Maternal Morbidity

Open fetal surgery places the healthy mother at risk for significant operative and postoperative complications. Two early studies suggested that maternal morbidity was low and that fertility after fetal surgery was preserved.31,32 However, the Vanderbilt data revealed more serious maternal morbidity: intraoperative placenta abruption, uterine dehiscence, and small bowel obstruction.33 Uterine dehiscence and rupture are particularly notable because these risks remain present for any subsequent pregnancies.

Prematurity

Two reports were published from the Vanderbilt group regarding prematurity in neonates who underwent fetal repair of MMC. The first report analyzed whether repair before 25 weeks’ gestation affected gestational age at birth, and found that the degree of prematurity was independent of the gestational age at fetal repair.34 A follow-up study compared the complication rate of premature infants who had fetal repair of MMC with that of controls matched for gestational age, sex, birth weight, antenatal steroid use, and mode of delivery, and found no significant difference in the incidence of morbidity associated with prematurity.35

Urologic Function

Studies of urologic outcome in infants who underwent prenatal closure of MMC have to date demonstrated no improvement in urologic function. The Vanderbilt group...
examined 16 patients with a mean age of 6.5 months and compared urodynamic studies with those from historical controls. Similar results between the two groups were found. The UCSF group examined 6 patients who had fetal MMC repair and also found no significant urologic improvement.

THE MANAGEMENT OF MYELOMENINGOCELE STUDY

From these early reported case series, it was unclear whether prenatal repair of MMC was beneficial when compared with standard postnatal therapy, as no controlled comparisons had been made. To address this question, in 2003 CHOP, Vanderbilt, and UCSF began collaboration on a National Institutes of Health–sponsored prospective randomized controlled trial (Management of Myelomeningocele Study, or MOMS) comparing prenatal MMC repair with postnatal repair. Inclusion and exclusion criteria for the trial are listed in Box 1.

There were 2 primary research questions in this trial. The first was whether fetal surgery for MMC improved outcomes as measured by death or the need for a VP shunt within the first year of life. The second question was whether prenatal repair of MMC improved neurologic function at 30 months of age as predicted by the spinal level of the lesion. Secondary research questions included whether the Chiari malformation was improved, whether neuromotor outcome was improved at 12 and 30 months of age, and the long-term psychological and reproductive consequences for the parents.

**Outcomes**

In 2011, enrollment in the MOMS trial was stopped early because of statistical evidence of benefit in the prenatal surgery group after the enrollment of 183 of a planned 200 patients. Initial analysis of the first 158 patients confirmed that fetal surgery for MMC had decreased the need for postnatal VP shunting in approximately one-third of infants by 12 months (Table 1). The proportion of infants who had no evidence of hindbrain herniation was significantly higher in the prenatal surgery group, and the proportion of infants who had moderate or severe hindbrain herniation was significantly reduced. The second primary outcome, neurologic function as assessed by a score derived from mental and motor development at 30 months, was also significantly improved in the prenatal surgery group. In addition, several secondary outcomes were improved. Most notably, the percentage of patients able to independently ambulate at 30 months increased from 21% to 42% after prenatal repair compared with postnatal surgery, supporting the theory that distal neurologic function can also be improved by in utero closure.

There were no maternal deaths and 2 perinatal deaths in each group, suggesting that mortality was comparable between groups. Prenatal surgery was associated with higher rates of preterm birth, intraoperative complications, uterine-scar defects, and higher rates of maternal transfusion at delivery, all of which are known complications of open fetal surgery. Although enrollment into the MOMS trial has ended, long-term follow-up and analysis is ongoing. In addition, a new study (MOMS II) will follow up the neurologic outcome of these patients into later childhood.

NEW DIRECTIONS

To augment the still limited neurologic function recovered by fetal MMC repair, novel regenerative medicine techniques are being actively studied in research laboratories. One study of murine neural stem cells applied to the MMC defect during fetal repair in sheep showed qualitative improvements in hindlimb movement in the animals that
received stem cells. The neural stem cells survived and engrafted, and they appeared to be more concentrated at areas of greatest damage, suggesting that they may “home in” on the most injured areas. On further histologic analysis, the engrafted neural stem cells were found to remain in a largely undifferentiated state, possibly suggesting a neurotrophic secretory or chaperone-like role for these cells. Other groups are exploring the use of biomaterials such as gelatin microspheres and nanofibrous scaffolds as a means to maximize the unique benefits of prenatal MMC closure. This research is preliminary, but supports further study on the benefits of a multifaceted approach to MMC repair. Because of the maternal morbidity of open fetal surgery, less invasive methods of fetal MMC treatment continue to be investigated. In addition, surgical experiments in fetal sheep have demonstrated

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<th>Box 1</th>
<th>Inclusion and exclusion criteria for the Management of Myelomeningocele Study</th>
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<td><strong>Inclusion Criteria:</strong></td>
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<tr>
<td>1. Myelomeningocele at level T1 through S1 with hindbrain herniation</td>
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<td>2. Maternal age 18 years or older</td>
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<td>3. Gestational age at randomization of 19 to 25 weeks</td>
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<td>4. Normal karyotype</td>
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<td><strong>Exclusion Criteria:</strong></td>
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<tr>
<td>1. Nonresident of the United States</td>
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<td>2. Nonsingleton pregnancy</td>
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<td>3. Insulin-dependent pregestational diabetes</td>
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<td>4. Fetal anomaly not related to MMC</td>
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<td>5. Kyphosis in the fetus of 30° or greater</td>
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<td>6. Current or planned cerclage or documented history of incompetent cervix</td>
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<td>7. Short cervix (&lt;20 mm)</td>
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<td>8. Placenta previa or placental abruption</td>
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<td>9. Body mass index 35 kg/m² or greater</td>
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<td>10. Previous spontaneous delivery before 37 weeks' gestation</td>
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<td>11. Maternal-fetal Rh isoimmunization, Kell sensitization, or neonatal alloimmune thrombocytopenia</td>
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<td>12. Maternal human immunodeficiency virus or hepatitis B status positive</td>
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<td>13. Known hepatitis C positivity</td>
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<td>14. Uterine anomaly such as large or multiple fibroids or Müllerian duct abnormality</td>
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<td>15. Other maternal medical condition that is a contraindication to surgery or general anesthesia</td>
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<td>16. Patient does not have a support person</td>
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<td>17. Inability to comply with travel and follow-up requirements</td>
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<td>18. Patient does not meet other psychosocial criteria to handle the implications of the trial</td>
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<td>19. Participation in another intervention study that influences maternal and fetal morbidity and mortality or participation in this trial during a previous pregnancy</td>
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<td>20. Maternal hypertension that would increase the risk of preeclampsia or preterm delivery</td>
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the feasibility of robot-assisted closure of MMC defects. Given the push toward fetoscopic closure, it is likely that a less invasive fetal MMC technique will become accepted in the near future.

SUMMARY

Myelomeningocele is a devastating disability with significant morbidity and mortality within the first few decades of life. MMC was the first nonlethal disease to be considered and studied for fetal surgery. The recently completed MOMS trial has shown that fetal repair for MMC can improve hydrocephalus and hindbrain herniation associated with the Arnold-Chiari II malformation, can reduce the need for VP shunting, and may improve distal neurologic function in some patients. Potential improvements in outcome must be balanced with the safety and well-being of the mother in addition to that of the unborn patient. Further follow-up will determine the long-term benefit of fetal MMC repair.

REFERENCES


