Fetal Surgery for Myelomeningocele

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Myelomeningocele (MMC), a nonlethal neural tube defect, occurs in approximately 1 in 2000 live births in the United States. Developmentally, it arises early in gestation at about the third week and results in an open spinal canal with exposed neural elements in the form of a flat neural placode. The neural placode can undergo further injury in utero, and thus gives rise to the "two-hit" hypothesis of neurologic injury in MMC, with the first "hit" being the original defect and the second one being additional injury to the exposed neural elements of the spinal cord. Fetal intervention and repair would potentially ameliorate this second injury. This concept is the foundation for the rationale for prenatal repair of these neural tube defects.

Although the exact cause of MMC is unknown, its origin is believed to be multifactorial. Folate deficiency in mothers is associated with an increased incidence of MMC. Folate supplements in pregnant women have decreased the rate of MMC by as much as 70% and are now considered a standard regimen for expectant mothers. In addition, environmental exposure to toxins and drugs has been implicated in the development of MMC. Finally, genetic abnormalities, such as mutations in the PAX3 gene, may have a role in the development of MMC, as seen in Waardenburg's syndrome.

Patients who have MMC have significant clinical findings and morbidity. Most infants who have MMC are born alive and healthy; however, up to 30% of patients die before adulthood because of respiratory, urinary, or central nervous system complications. Virtually all newborns who have MMC have the Chiari hindbrain malformation and most 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 and loss of sexual function.

FETAL SURGERY

Rationale

As stated previously, the main rationale behind fetal surgery for MMC is based on the two-hit hypothesis. The first hit is the original developmental defect that causes the...
open neural tube defect. The second hit is postulated to be direct neural injury from exposure to amniotic fluid and by means of direct trauma to the exposed neural elements.\textsuperscript{1,2} This theory is supported by several observations. First, early ultrasound examinations of fetuses that have MMC can demonstrate normal hind limb movement, suggesting a later loss of function, correlating with in utero injury to the spinal cord.\textsuperscript{3} Second, postmortem analysis of stillborn and aborted fetuses that have MMC demonstrates significant recent injury to the exposed neural placode.\textsuperscript{1} Finally, patients who have milder forms of neural tube defects in which the abnormal neural elements remain covered with skin or a membrane have more normal neural development than those patients who have MMC.\textsuperscript{4} More recently, observations with curly-tailed mice (which develop a primary defect of neural tube formation) have demonstrated normal anatomic and functional correlation with normal mice; however, the mice then develop progressive neurologic degeneration during gestation, also suggesting this second hit.\textsuperscript{5}

**Animal Models**

Before undertaking fetal MMC repair in humans, animal models were developed for the study of MMC and potential fetal interventions. Surgical models in rodents, rabbits, sheep, and nonhuman primates have all shown similar findings as in human disease: paraplegia, extremity deformity, urinary and bowel dysfunction, hydrocephalus, and the Chiari malformation. Prenatal closure of these surgically created defects has shown improvement in motor function, urinary function, and reversal of the Chiari malformation, with normal or near-normal hindbrain development and morphology. Several different animal models have demonstrated that the Chiari malformation occurs with surgically created MMC and that it can be reversed with in utero repair.\textsuperscript{6–10} Further animal studies demonstrating improved neurologic function after in utero repair of surgically created MMC have also been published. Julia and colleagues\textsuperscript{11} demonstrated improved neurologic function in the rabbit model using somatosensory evoked potentials after birth. Another study examining anal sphincter development after fetal MMC repair in the sheep model was published by Yoshizawa and colleagues.\textsuperscript{12,13} In those experiments, rectum and anal sphincter muscles were histologically examined. Findings in unrepaired animals included hypoplastic longitudinal muscles in the sphincter complex and an underdeveloped submucosal nerve plexus. These structures were preserved in animals that underwent in utero repair.

**Human Experience**

Before MMC, fetal surgery had been reserved for specific situations in which there would be significant perinatal morbidity or mortality. This approach was adopted to minimize maternal risk and morbidity and to maximize potential benefit in the fetus. Previously treated diseases included obstructive uropathy; congenital diaphragmatic hernia; twin-twin transfusion syndrome; and nonimmune hydrops attributable to massive shunting within a mass, as seen in sacrococcygeal teratoma, or mediastinal shift, as seen in cystic adenoid malformation. MMC is the first nonlethal fetal malformation treated with in utero surgery. To minimize maternal morbidity, the first attempts at human fetal MMC repair were done fetoscopically. This technique was independently attempted at the Vanderbilt University Medical Center (VUMC) in Nashville, Tennessee, and at the University of California, San Francisco (UCSF).\textsuperscript{14–16} The VUMC group reported four fetoscopic repairs in which a maternal laparotomy was performed and a three-port access technique was used. The amniotic fluid was replaced with carbon dioxide, and the defects were covered with a maternal skin graft.
Two of the four fetuses survived; at birth, no evidence of the skin graft was found and the patients required reoperation for postnatal repair.\textsuperscript{14,15}

The UCSF group reported three cases, but only one was successfully closed fetoscopically. In that 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 MMC, and a VP shunt was also placed. The two other patients were converted to open repairs. There were two deaths in this series: one from a spontaneous abortion and the other from postnatal urosepsis.\textsuperscript{16}

\section*{Outcomes}

\subsection*{Hydrocephalus}

After these largely failed attempts at minimally invasive repair, the VUMC group began performing open fetal MMC repair (\textit{Fig. 1}). After 2 years, they reported their results, stating that the open repair method is superior to the fetoscopic method. The VUMC group also found that hindbrain herniation was improved in the patients who had undergone fetal surgical repair of their MMCs and, additionally, that the need for VP shunting was significantly lower in those patients: 59\% versus 91\% in historic controls.\textsuperscript{17} These data were limited in the small number of treated patients, in addition to the lack of standardization of criteria leading to VP shunt placement. Subsequent follow-up data from the VUMC group with subset analysis suggest that repair earlier in gestation, lower lesions, and smaller ventricles before repair are all associated with a lower VP shunt rate.\textsuperscript{18,19}

Concurrently, the group at the Children’s Hospital of Philadelphia (CHOP) performed open fetal surgical repair of MMC defects and confirmed the findings of

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\caption{Open fetal repair of myelomeningocele. (A) Myelomeningocele defect before repair. (B) Closure of defect with decellularized dermal matrix patch. (C) Primary closure of defect.}
\end{figure}
reversal of hindbrain herniation and improvement in the Arnold-Chiari II malformation in patients who had undergone fetal repair. These findings were also corroborated by studies of head biometry in pre- and postnatal MRI scans in prenatally repaired MMC and postnatal repair. Furthermore, decreased shunt rates and less ventriculomegaly were also noted in the patients who had undergone fetal MMC repair, further mirroring the findings at the VUMC.

**Neurologic function**

At all three centers, the initial findings after fetal MMC repair did not demonstrate any significant improvement in neurologic function or hind limb movement. Follow-up data have been mixed. At the UCSF, only two of nine survivors had functional improvement greater than two spinal levels above the MMC lesion. The remaining patients’ neurologic function correlated well with the level of the spinal lesion. The VUMC group initially compared the neurologic outcomes of the patients who had undergone fetal MMC repair with historical controls and found no improvement. In a later study, the outcomes of those patients were compared with matched controls at the University of Alabama, Birmingham. Again, no improvement in neurologic function was found. In contradistinction, Danzer and colleagues from the CHOP group examined 54 patients who had fetal MMC repair and found that 57% of patients had neurologic function better than what was predicted from the level of their spinal defect. 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 and prematurity**

An important finding in the VUMC data was the occurrence of significant maternal morbidity: intraoperative placenta abruption, uterine dehiscence, and small bowel obstruction. Recently, more data have been published regarding outcomes of the mothers and fetuses undergoing fetal interventions for MMC. To date, there have been no specific studies examining maternal outcomes after MMC repair. Two limited studies suggest that maternal morbidity is low and that fertility after fetal surgery is preserved, however.

Two reports have been published from the VUMC group regarding prematurity in neonates who underwent fetal repair of MMC. In the first report, Hamdan and colleagues compared whether repair before 25 weeks of gestation affected gestational age at birth. Those data suggested that the degree of prematurity was independent of the gestational age at fetal repair. In a follow-up study, Hamdan and colleagues compared the complication rate of premature infants who had fetal repair of MMC at the VUMC. Using controls matched for gestational age, gender, birth weight, antenatal steroid use, and mode of delivery, they found no significant difference in the incidence of morbidity associated with prematurity.

**Urologic function**

Studies of urologic outcome in infants who underwent prenatal closure of MMC have uniformly demonstrated no improvement in urologic function. The VUMC group examined 16 patients with a mean age of 6.5 months and compared urodynamic studies with those from historic controls. They found similar results between the two groups. The UCSF group examined 6 patients who had fetal MMC repair and corroborated the findings of the VUMC group.
CLINICAL TRIAL

From the preliminary data discussed previously, it is not clear whether or not prenatal repair of MMC is truly beneficial when compared with standard postnatal therapy. As a result, a prospective, randomized, National Institutes of Health-funded, multicenter trial for fetal surgery for MMC was proposed and is currently underway at the VUMC, UCSF, and CHOP. There are two primary research questions in this trial. First is whether or not fetal surgery for MMC improves outcome as measured by death or the need for a VP shunt within the first year of life as compared with postnatal surgery. The second question is whether or not prenatal repair of MMC improves neurologic function at 30 months of age as predicted by the spinal level of the lesion. Secondary research objectives include whether the Chiari II malformation is improved, whether neuromotor outcome is improved at 12 and 30 months of age, and what are the long-term psychological and reproductive consequences for the parents. Inclusion and exclusion criteria for the trial are listed in Box 1. Operative procedures are

| Inclusion criteria for the ongoing myelomeningocele clinical trial in the United States |

**Inclusion criteria**

1. MMC at level T1 through S1 with hindbrain herniation
2. Maternal age of 18 years or older
3. Gestational age at randomization of 19 weeks to 25 weeks and 6 days
4. Normal karyotype

**Exclusion criteria**

1. Nonresident of the United States
2. Nonsingleton pregnancy
3. Insulin-dependent pregestational diabetes
4. Fetal anomaly not related to MMC
5. Kyphosis in the fetus of 30° or greater
6. Current or planned cerclage or documented history of incompetent cervix
7. Short cervix (<20 mm)
8. Placenta previa or placental abruption
9. Body mass index of 35 or greater
10. Previous spontaneous delivery before 37 weeks of gestation
11. Maternal-fetal Rh isoimmunization, Kell sensitization, or neonatal alloimmune thrombocytopenia
12. Maternal HIV- or hepatitis B-positive status
13. Known hepatitis C positivity
14. Uterine anomaly, such as large or multiple fibroids or müllerian duct abnormality
15. Other maternal medical condition that is a contraindication to surgery or general anesthesia
16. Patient does not have a support person
17. Inability to comply with travel and follow-up requirements
standardized in this trial, in addition to follow-up. A team neurosurgeon as part of the trial is designated to help guide the physicians caring for the infant to ensure uniformity in the decision to place a VP shunt. This prospective randomized trial is in its sixth year, and as of February 1, 2009, it has enrolled 150 of a planned 200 patients.

NEW DIRECTIONS

In an attempt to improve on nerve repair and regeneration in MMC, Fauza and colleagues recently published a study in a sheep model in which murine neural stem cells were applied to the defect during fetal repair. Neurologic outcomes in the animals treated with stem cells were comparable to those in animals that underwent standard fetal repair. There were qualitative improvements in hind limb movement in the animals that received stem cells, however. In addition, after histologic analysis, the neural stem cells showed survival and engraftment and seemed to be more concentrated at areas of greatest damage, suggesting that they may “home in” on the most injured areas. Finally, on further histochemical 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 stem cells. These data are largely preliminary but may support further study into a multifaceted approach to MMC repair.

Newer less invasive methods of fetal MMC treatment have been investigated in animals as well. Recent surgical experiments in fetal sheep have demonstrated the feasibility of robot-assisted closure of MMC defects. In an attempt to revisit the feasibility for minimally invasive repair, further attempts at refining those techniques have shown promise in the ovine model. Furthermore, prenatal steroid treatment in a rabbit model of MMC has been shown to reduce inflammation in the neural placode at delivery. In addition, in that study, preterm delivery was associated with less hindbrain herniation. These findings might suggest that anti-inflammatory medications may be beneficial in protecting the exposed neural elements in MMC from intrauterine injury.

SUMMARY

MMC can be a devastating disease with significant morbidity and mortality within the first few decades of life. Fetal intervention for MMC may improve hydrocephalus and hindbrain herniation associated with the Arnold-Chiari II malformation and may reduce the need for VP shunting. As of now, there is little evidence that prenatal repair of MMC improves neurologic function—sensory, motor, or urologic. MMC is the first nonlethal disease under consideration and study for fetal surgery. As a result, potential improvements in outcome must be balanced with maternal safety and well-being, in addition to that of the unborn patient. The current multicenter trial should provide answers regarding the benefit of fetal surgery for MMC. In addition, other significant insights should be gleaned from the trial regarding optimal treatment of patients who have MMC and maternal safety in open fetal surgery.

REFERENCES


