Intrauterine closure of myelomeningocele: an update

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Preliminary evidence suggests that intrauterine myelomeningocele repair may benefit patients by reducing the both incidence of hydrocephalus and the severity of the Chiari malformation; however, this benefit remains unproved. Furthermore, the procedure entails substantial risks not associated with conventional therapy. A randomized controlled trial of intrauterine and conventional therapies is underway. This study should definitively establish the procedure-related risks and benefits. Regardless of the outcome, it is clear that the risks of intrauterine intervention need to be reduced before myelomeningocele, or other congenital malformations, can be effectively treated prior to birth. To that end, studies are being conducted to assess the potential advantages of applying state-of-the-art endoscopic techniques to intrauterine therapy. If benefit can be proven and risks reduced, intrauterine myelomeningocele repair has the potential to become the preferred therapy for patients suffering from this debilitating disease.

KEY WORDS • myelomeningocele • fetal surgery • robotic • intrauterine

Although the incidence of myelomeningocele has gradually decreased over the last 10 years, it remains the most common congenital malformation of the central nervous system.5 Each year more than 1000 infants with myelomeningocele are born in the US alone; interest in finding an effective treatment for this disease therefore remains quite high. Until the late 1990s, treatment for myelomeningocele had remained static for more than 20 years. This treatment, consisting of postnatal closure of the defect and subsequent shunt placement in most cases, was largely palliative. Closure of the defect reduced the risk of infection and further spinal cord injury, but in no way reversed preexisting damage. Shunt placement, when successful, reduced the symptoms of hydrocephalus but was fraught with immediate and delayed complications. Thus, any therapy that might reduce the spinal cord dysfunction associated with myelomeningocele or eliminate the need for shunting would be welcomed by the neurosurgical community.

With this in mind a series of experiments were conducted during the 1980s and into the 1990s designed to determine the feasibility of performing myelomeningocele repair in utero.15 The theory underlying these experiments was that exposure of the neural placode to the intrauterine environment might lead to secondary damage, thus compounding the preexisting embryological injury. Early closure might prevent that secondary injury. Results of these experiments generally suggested that early closure would, in fact, reduce the degree of neurological disability associated with myelomeningocele; however, these conclusions had to be tempered by the fact that no true animal model of myelomeningocele exists in a species readily amenable to intrauterine surgery. These experiments were, therefore, only rough approximations of the true clinical situation. Despite this, several centers found these results adequately encouraging to develop protocols for IUMR in humans.

The first of these procedures were performed within weeks of each other at VUMC and CHOP in 1997.2,12 Since that time more than 270 procedures have been performed at four centers in the US, and a handful of additional procedures have been performed in Europe and South America. Preliminary results suggest that IUMR may reduce the incidence of shunt-dependent hydrocephalus (Table 1).14 There is also ample evidence that IUMR reduces the severity of the hindbrain herniation generally associated with the CM II.11,13 Whether the latter results in any palpable improvement in patients’ symptoms remains to be studied. Unfortunately, all of the studies published to date rely on historical controls. No randomized controlled trials of IUMR compared with conventional therapy exist. The existing studies are thus rightfully subject to skepticism and criticism.
This skepticism is further compounded by the fact that IUMR is not without considerable risk. Currently, combined statistics from VUMC and CHOP suggest a 4% mortality rate and an 11% morbidity rate, much of which is directly related to extreme prematurity. When the techniques of fetal surgery were first being developed the procedures were restricted to lethal congenital anomalies. If the alternative to fetal therapy was death then the substantial morbidity and morality rates could be justified. In fact the overall mortality rate for fetal repair of congenital anomalies could be justified. In fact the following table demonstrates that severe premature infants have a better survival rate than babies who are born at term.

### Table 1: Comparison between shunt rates stratified according to level of lesion and gestational age at the time of IUMR

<table>
<thead>
<tr>
<th>Spinal Level</th>
<th>≤25 Wks (no. of patients [%])</th>
<th>&gt;25 Wks (no. of patients [%])</th>
<th>Control (no. of patients [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic</td>
<td>3/4 (75)</td>
<td>1/1 (100)</td>
<td>35/35 (100)</td>
</tr>
<tr>
<td>L-1</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
<td>5/6 (83.3)</td>
</tr>
<tr>
<td>L-2</td>
<td>3/4 (75)</td>
<td>2/2 (100)</td>
<td>13/15 (86.7)</td>
</tr>
<tr>
<td>L-3</td>
<td>2/6 (33.3)</td>
<td>6/7 (85.7)</td>
<td>22/23 (95.7)</td>
</tr>
<tr>
<td>L-4</td>
<td>8/20 (40)</td>
<td>5/6 (83.3)</td>
<td>30/33 (90)</td>
</tr>
<tr>
<td>L-5</td>
<td>9/20 (45)</td>
<td>10/15 (66.7)</td>
<td>30/37 (81.1)</td>
</tr>
<tr>
<td>Total lumbar</td>
<td>24/52 (46.2)</td>
<td>25/32 (78.1)</td>
<td>100/114 (87.7)</td>
</tr>
<tr>
<td>Sacral</td>
<td>3/12 (25)</td>
<td>1/3 (33.3)</td>
<td>27/40 (67.5)</td>
</tr>
<tr>
<td>Total</td>
<td>30/68 (44.1)</td>
<td>27/36 (75)</td>
<td>162/189 (85.7)</td>
</tr>
</tbody>
</table>

Formal follow-up evaluation will be at 12 and 30 months by a group of clinicians specially trained by the NICHD. Primary end points will be the need for shunt placement and/or death. Shunts will be placed according to specified criteria (Table 3). An independent panel of disinterested pediatric neurosurgeons will review all cases to certify that the criteria for shunt placement have been met. Patients without shunts who meet the criteria for shunt placement will still be counted as having received a shunt. In short, every effort will be made to ensure that no unconscious bias against shunting in the IUMR group will skew the results. Other parameters to be tested will include intelligence, leg function, bowel and bladder function, CM-related symptoms, and others. As of this writing, 15 IUMRs have been performed under the NICHD. Qualified candidates will then be assigned to one of the three centers according to geographic criteria. Candidates will undergo an intensive evaluation to ensure that the entry criteria are met. These include verification of the diagnosis as well as exclusion of other chromosomal or structural anomalies (Table 2). After intensive counseling, qualified candidates will then be asked to sign informed consent. Only then will they be randomized to study groups. Those who are randomized to the fetal surgery arm will immediately undergo IUMR and then reside near their assigned center until it is time for them to deliver the child. Those assigned to conventional surgery will be urged return to their assigned center for delivery by cesarean section at approximately 37 weeks' gestation unless preterm labor or other obstetrical issues necessitate urgent delivery elsewhere.

### Table 2: Inclusion criteria for MOMS

- Myelomeningocele (including myeloschisis) at T1–S1 level w/ hindbrain herniation. Lesion level will be confirmed by ultrasound, and hindbrain herniation will be confirmed by MR imaging at the MOMS Center.
- Maternal age ≥18 yrs.
- Gestational age at randomization of 19 to 25 weeks as determined by clinical information & evaluation of first ultrasound. If the patient’s LMP is deemed sure and her cycle is 26–32 days, and if the biometric measurements from the patient’s first ultrasound confirm this LMP w/in the ranges given below, the LMP will be used to determine gestational age. In all other cases (if the LMP is unsure, if she has an irregular cycle or her cycle is outside the 26–32-day window, or if the measurements from her first ultrasound are more than 10 days discrepant from the ultrasound), the ultrasound determination will be used. Once the EDC has been determined for the purposes of the trial, no further revision is made.
- Gestational age at first ultrasound by LMP & ultrasound agreement w/ LMP ≤19 wks ± 7 days, and ≥20 wks ± 14 days, respectively.
- Normal karyotype with written confirmation of culture results. Results by fluorescence in situ hybridization will be acceptable if the patient is at ≥24 wks or more.

* EDC = expected date of confinement; LMP = last menstrual period.

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### Table 3: Criteria for shunt placement (MOMS)

- At least two of the following:
  - an increase in the greatest occipitofrontal circumference adjusted for gestational age defined as crossing percentiles;
  - a bulging fontanelle, or split sutures or sunsetting sign,* increasing hydrocephalus on 2 consecutive imaging studies determined by increase in ratio of biventricular diameter/biparietal diameter according to the method of O’Hayon, et al.;
  - head circumference >95th percentile for gestational age or presence of marked syringomyelia (syrinx w/ expansion of spinal cord) w/ ventriculomegaly (undefined)
  - ventriculomegaly (undefined) and symptoms of CM (stridor, swallowing difficulties, apnea, bradycardia)
  - persistent cerebrospinal fluid leakage from the myelomeningocele wound or bulging at the repair site

* A bulging fontanelle is defined as above the bone as assessed when the baby is in an upright position and not crying.
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As previously mentioned, the second prerequisite to achieving mainstream acceptance of IUMR is reduction of risk. To that end, interest in minimally invasive approaches to fetal therapy has remained high for many years. The theoretical advantage of a minimally invasive approach is that by minimizing trauma to the uterus one might prevent the preterm labor that is the overwhelming source of morbidity after fetal surgery. In the early 1990s a series of experiments was performed in sheep at VUMC to assess the feasibility of performing IUMR by using standard minimally invasive techniques. The results of these experiments were encouraging enough that a limited clinical trial was initiated. A series of four patients underwent IUMR; standard 3- and 5-mm instruments and a five mm camera were used (Fig. 1). Prior to surgery it had been determined that a conventional suture closure would be too difficult to achieve under these conditions. For that reason a technique had been devised to place a small patch of maternal skin over the defect and hold it in place using fibrin glue. Unfortunately, the results of these pilot studies were not encouraging. Unlike in the sheep uterus, the working space within the human uterus was quite limited despite insufflation. The surgeon was further hampered by the bulk of the instruments and other limitations inherent to conventional laparoscopic surgery. These include left-right disorientation (the hand and handle are moved left to move the tip of the instrument right) and loss of depth perception (the conventional camera is two dimensional). An additional difficulty was proper positioning of the fetus. In the end, two patients underwent successful repair, but the skin patch did not appear to survive until the child was born. Of the other two, one died when the mother began labor soon after the surgery, and the other died of amnionitis. Given these difficulties the project was abandoned. Since that time we have reported further technical modifications in experimental models involving the use of conventional laparoscopic techniques.

Given the potential benefits of a minimally invasive approach we, at VUMC, have decided to revisit this option; however, we have elected to abandon conventional laparoscopic techniques and instead to use newer technology that was unavailable 10 years ago. In particular, robotic devices have become commercially available that may enable the neurosurgeon to overcome many of the obstacles that previously prevented successful repair. These devices interpose a computer between the surgeon and the instruments, thus enhancing the surgeon’s skills. Specifically, the computer interface enables complete elimination of physiological tremor. The surgeon’s hand movements can be scaled to produce proportionately finer movements of the instruments. Left–right dissociation can be eliminated such that any movement of the hand is precisely mirrored by the instrument. Advanced instruments have also been developed that incorporate a wristlike articulation that mimics the human hand. Finally, the device incorporates a three-dimensional camera that allows the surgeon virtually to immerse him- or herself in the operative field.

Using this instrument, a series of experiments were performed at VUMC in sheep. The gravid uterus was exposed and three 1-cm ports were inserted. These were then “docked” to the robot. The amniotic fluid was removed, and the uterus was insufflated. A myelomeningocele defect was then simulated by excision of a 1-cm patch of skin. This skin defect was then sutured closed using a 7-0 absorbable suture. It was easily possible to manipulate the instruments and accomplish simple suturing by using this technique. These results encouraged the authors to believe that a minimally invasive robot-assisted IUMR might eventually be accomplished in humans; however, this impression must be tempered by the fact that the previous minimally invasive sheep experiments failed to translate successfully to the clinical setting. This was in large part due to the smaller size and lack of distensibility of the human uterus compared with the sheep. This difference may therefore remain an obstacle.

An additional series of experiments has now been initiated at VUMC with the object of exploring the possibility of performing a robotic-assisted IUMR percutaneously, that is, without surgical exposure of the uterus. This would seem to be the next logical step in the progression toward truly minimally invasive intrauterine intervention. The obvious obstacle to this goal is the fact that both the abdominal and uterine walls must be cannulated. This cannulation must be accomplished without disruption or separation of the amniotic membrane because such disruption leads to premature labor. Only a small number of animals have been studied, but the initial results are encouraging (unpublished data). In the first few animals, difficulty was encountered during the cannulation process.

Fig. 1. Schematic diagram illustrating camera and port placement for endoscopic IUMR.
The amniotic membrane tended to separate from the uterine wall, and once separated it became impossible to achieve insufflation of the true amniotic cavity. In a subsequent animal, the uterine wall was visualized via a mini-laparotomy and the insufflation needle was successfully placed. Once this had been accomplished, the amniotic fluid was removed and the uterus was insufflated. With insufflation, the amniotic membrane was compressed against the uterine wall, and the uterine wall compressed against the abdominal wall, thus facilitating the placement of additional ports. Once placed there was ample room to manipulate the fetus by using robotically controlled instruments even though uterine insufflation was constrained within the abdomen. Therefore, using this technique it appears that there are no obvious obstacles to successful percutaneous IUMR, although many more experiments will be needed to perfect the technique.

Despite the tentative success of these experiments there are still problems to overcome. The first of these involves positioning of the fetus. When the amniotic fluid is removed, the fetus tends to “settle” into the lateral decubitus position. This, for obvious reasons, is suboptimal for purposes of IUMR. It will therefore be necessary to develop techniques to manipulate the fetus within the uterus. This may entail introduction of a device to suspend the fetus in the appropriate position or possibly the insertion of a third instrument that would be used solely for the purpose of “retracting” the fetus into an optimal position. Regardless of how this problem is solved, it is clear that it will be crucial to successful IUMR and almost any other intrauterine procedure that might be envisioned. A second problem is the method for myelomeningocele closure. Despite the advances in technology outlined previously, it will remain quite difficult to perform a conventional layered closure of the myelomeningocele sac when using minimally invasive techniques. The instruments remain a bit too cumbersome for this purpose, and the surgeon’s range of motion is still more constrained than in open surgery. This limitation will become even more obvious if attempts are made to repair the lesion even earlier during the gestational period. At less than 20 weeks’ gestation the skin is poorly epithelialized and has an almost gelatinous consistency. It will therefore not hold a stitch. For that reason, it will be necessary to devise alternative methods to cover the sac and prevent cerebrospinal fluid leakage. It is likely that some sort of patch will need to be sewn into place that performs both of these functions. These are but two of the many potential problems that will need to be overcome as intrauterine techniques mature. There do not, however, appear to be any overwhelming roadblocks to continued progress.

In summary, IUMR has successfully moved from the laboratory to the clinic during the past 20 years. Worldwide, more than 270 procedures have now been performed. Early indications are that the procedure may be of benefit, but this remains to be proven. Future efforts must focus on the betterment of current techniques so that outcomes can be improved and risks can be minimized. The next big step will likely be the application of minimally invasive techniques, perhaps with computer assistance, to this problem. Eventually, it can be hoped that IUMR and other complex fetal interventions will be performed with minimal risk to both the mother and her unborn child.

References

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