

Fetal Repair of Open Neural Tube Defects: Ethical, Legal, and Social Issues

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Abstract: Open neural tube defects or myelomeningoceles are a common congenital condition caused by failure of closure of the neural tube early in gestation, leading to a number of neurologic sequelae including paralysis, hindbrain herniation, hydrocephalus and neurogenic bowel and bladder dysfunction. Traditionally, the condition was treated by closure of the defect postnatally but a recently completed randomized controlled trial of prenatal versus postnatal closure demonstrated improved neurologic outcomes in the prenatal closure group. Fetal surgery, or more precisely maternal-fetal surgery, raises a number of ethical issues that we address including who the patient is, informed consent, surgical innovation and equipoise as well maternal assumption of risk. As the procedure becomes more widely adopted into practice, we suggest close monitoring of new fetal surgery centers, in order to ensure that the positive results of the trial are maintained without increased risk to both the mother and fetus.

Keywords: myelomeningocele; fetal surgery; surgical innovation

Introduction

Most of the literature on fetal repair of open neural tube defects, commonly known as myelomeningocele (MMC), has focused on technical aspects of the procedure and clinical outcomes, which, in our opinion, is not enough emphasis on the ethical issues that arise from an intervention that significantly impacts on both fetus and mother. These include what the definition of patient is, ethical issues in research and surgical innovation, and the ethics of adopting a novel treatment into practice. This paper is the first to focus on the fundamental ethical issues arising from a novel neurosurgical intervention whose use is continuing to expand.

History of fetal surgery and fetal myelomeningocele repair

The first maternal-fetal surgery was carried out in 1963 by A William Liley, who performed a blood transfusion into the peritoneal cavity of a fetus to treat anemia from Rh incompatibility.¹ By the 1980s, the use of maternal-fetal surgeries to treat life threatening fetal anomalies, such as urinary tract obstruction, congenital diaphragmatic hernia, and sacral teratoma were pioneered.² Though these experimental procedures showed promise in improving fetal outcomes in highly selected conditions, it became apparent that there were significant risks associated with these interventions, both for the fetus and the pregnant woman—including preterm labor, uterine dehiscence and the need for cesarean section for subsequent pregnancies.³

Despite these risks, indications for prenatal surgery expanded and began to be considered as a treatment possibility for both disabling as well as life threatening fetal conditions, for which it had been previously reserved. There were attempts in the 1980s to treat fetal hydrocephalus prenatally with ventriculo-amniotic

fluid shunting.⁴ Outcomes were poor, with unacceptably high rates of procedure related deaths and long term disability in children after they were born.⁵ The treatment was therefore largely abandoned for this indication, but the concept of using prenatal surgery to reduce the risk and magnitude of future disability in affected children remained. Attention began to turn to the idea of prenatal closure of MMC, usually referred to in layman terms as spina bifida, a relatively common (1 in 3000 live births) disabling condition affecting the central nervous system, which is usually diagnosed in the second trimester through maternal serum alpha-fetoprotein screening and prenatal ultrasound.⁶

The first human cases of prenatal closure of fetal MMC were carried out at Vanderbilt University in Nashville, Tennessee in the 1990s.⁷ Early published case series suggested improved outcomes, including a reduction in hindbrain herniation and the need for cerebrospinal fluid (CSF) shunting, both significant causes of long term disability in children with MMC. Questions were raised, however, over the clinical significance of the improvement in outcome and whether it was offset by the risks of the surgery to both mother and fetus.

The Management of Myelomeningocele Study (MOMS) trial,⁸ a randomized controlled trial comparing prenatal with postnatal repair of MMC, was designed and completed in order to definitively answer the question of whether prenatal repair improved neurological outcomes and reduced the need for CSF shunting compared with postnatal repair, as well as to compare the risks of both interventions. To ensure adequate enrolment in the trial and to answer the primary research question, access to prenatal surgery in North America was restricted solely to trial participants, and confined to three centers with experience in performing the procedure—Vanderbilt University Medical Center, University of California San Francisco Medical Center, and Children's Hospital of Philadelphia (CHOP)—for the nearly 8-year duration of the trial.

The trial was halted early for efficacy favoring the prenatal surgery arm. In particular, 68 percent of 78 children who had prenatal surgery had the primary outcome of death or CSF shunt at 12 months of age compared with 98 percent of 80 children who had postnatal surgery ($p < 0.001$). The chance of receiving a CSF shunt by 12 months of age was 40 percent in the prenatal surgery group and 82 percent in the postnatal surgery group. Also, by 30 months of age, 42 percent of 64 children in the prenatal surgery arm were able to walk independently, compared with 21 percent of 70 children who had postnatal surgery. There were no significant differences in the need for treatment of symptomatic hindbrain herniation (known as a Chiari Type II malformation) or in cognitive outcomes between the treatment arms.

Long-term outcomes and subgroup analyses from the MOMS trial have been insightful as well. Subgroup analysis has shown that there is no reduction in the long-term need for CSF shunting in those who underwent fetal repair and had enlarged ventricles prenatally, suggesting fetal surgery may not be beneficial for the purpose of preventing hydrocephalus in this subpopulation.⁹ Long-term outcome assessment of urological function has also shown that there is no significant reduction in the need for clean intermittent catheterization, a surrogate for bladder dysfunction, in children who underwent prenatal surgery, compared with postnatal closure.¹⁰ New techniques are currently being developed as well, such as minimally invasive endoscopic and fetoscopic approaches,¹¹ in order to reduce the risks of prenatal surgery to the pregnant women.

Since the end of the trial, the number of centers offering fetal surgery has increased significantly. The North American Fetal Therapy Network (NAFTNet) was formed as an association of medical centers performing fetal therapy, including but not limited to prenatal closure of MMC. It is not a regulatory body, but rather has the goal of fostering cooperation and research between centers.¹² NAFTNet currently consists of 24 member centers, but there are an unknown number of centers performing fetal surgery outside of NAFTNet. There is currently no standardized monitoring or regulation of prenatal maternal-fetal MMC surgery in North America, though at least one center has independently published their outcome data for the purpose of proving their outcomes match those of the MOMS trial. NAFTNet would be an ideal organization to establish a database to monitor all referrals for fetal surgery assessments, as well as outcomes of those who receive maternal-fetal surgery and those who do not. Such a database could be the basis of performing multicenter clinical research studies, and is ethically essential if deviations from the MOMS trial protocol are to be attempted, in order to protect the safety of participants.

From Scalpel to Society: Current ethical, legal and social issues in Fetal MMC repair

Who is the patient?

There are few topics so controversial as the debate over the personhood status of the fetus. In Canadian law, a fetus becomes a person with legal rights only after birth.¹³ Certain religious faiths alternatively argue that a fetus/embryo is a person from conception, while others argue that the fetus becomes a person once it reaches the age of viability—when it can survive outside the mother with technological support.¹⁴ The age of viability is an evolving cutoff that depends on the capabilities of neonatal support services available, but generally occurs at around 24 weeks gestation in most developed countries. Still others argue that the fetus becomes a person when a particular organ system begins to function, such as when the fetal heart starts to beat or when the fetal brain produces its first electrical signals.¹⁵

Regardless of the personhood status of the fetus, there is no doubt that the pregnant woman is a person. Fetal surgery may be better termed maternal-fetal surgery, as the pregnant woman must also receive an operation in order to access the fetus. Depending on which definition of fetal personhood is used, it could be that the mother is the patient receiving medical treatment, or the mother and the fetus are both patients, or that a unique entity termed ‘the pregnant woman’ is the patient.¹⁶ Some have argued that the fetus alone is the patient, while the mother is a healthy altruistic volunteer, similar to a healthy parent volunteering to surgically donate a part of their liver or a kidney to their sick child.¹⁷

Some degree of self imposed and/or societally imposed parental obligation is likely present from a mother to her child from the moment a woman learns she is pregnant until the end of her or her child’s life, unless the pregnancy is terminated or the child is adopted. A certain degree of this obligation is based around principles of nonmaleficence—the ethical duty of the mother to do nothing that is likely to harm her child during pregnancy and afterwards. An example of nonmaleficent

behavior is the abstention from illegal drugs or heavy alcohol consumption. Beneficence drives mothers as well, to do what they can to optimize their child's health outcomes for the child's best interests, and is very likely the motivation behind a mother seeking fetal MMC closure. The somewhat less-recognized fact remains, however, that it is generally also in the pregnant woman's best interest, not just her future child's, to optimize her fetus' health outcomes. A child that is healthier requires fewer resources and less work, and places a smaller financial and social-emotional burden on the mother and family.¹⁸

Given the significant burden of care placed on caregivers of children with MMCs,¹⁹ a pregnant woman may be motivated through a combination of self interest, as well as altruism toward her future child, in minimizing her parenting workload by doing what she can to optimize functional and health outcomes of her child, even if that means taking on an upfront high personal risk.

Ultimately, given that pregnant women and their fetuses are irrevocably intertwined until miscarriage, abortion or birth, and since both are receiving surgery and are affected by the possible complications and benefits of maternal-fetal surgery, both should be considered patients for the purposes of clinical care, research study design, equipoise and informed consent.

Informed Consent

Informed consent is an essential component of ethical health care delivery as well as ethically conducted research.²⁰ The pregnant woman is clearly able to provide informed consent for herself, but it is less clear whether she is the only person required to provide informed consent for her fetus. Although the father typically is also expected to have a moral interest in the health of the fetus, the pregnant woman's wishes should supersede those of the father when consenting to participate in fetal research and/or surgery. US federal regulations in the past have been distinctive for requiring the father's consent as well as the mother's in order for a pregnant woman to undergo fetal research and/or maternal-fetal surgery.²¹ Despite this, in order to preserve her right to bodily integrity and autonomy, the pregnant woman should have the ultimate right to decide what is done to her fetus through her own body, regardless of the wishes of the father. The American College of Obstetricians and Gynecologists Committee on Ethics and the American Academy of Pediatrics Committee on Bioethics have provided their support for this position in a joint committee opinion paper.²² Although historically, there have been cases where the right to bodily integrity of a pregnant woman has been revoked in the name of nonmaleficence or beneficence toward the fetus,^{23,24} in the context of fetal surgery, consent of the pregnant mother must be obtained.

Given the potential pressures on pregnant women to sacrifice or put themselves at risk for their children, informed consent in maternal-fetal surgery interventions should always use noncoercive language. When participating in a research trial of a novel procedure, the interventions should not be called treatment or therapy, but rather experimental interventions, emphasizing the fact that the intervention may not have efficacy and indeed, may cause harm to both the mother and fetus. Even the terms mother, father and baby carry with them a strong emotional context and some have suggested that they not be used during the consent process for fetal surgery.²⁵

Equipoise in maternal-fetal surgery research

Equipoise is achieved when two clinical management options are thought to be largely equivalent in terms of perceived benefits and risks to patients.²⁶ Equipoise is considered to be an ethical prerequisite to the design and implementation of randomized controlled trials. How is equipoise achieved when there are two patients involved, as in comparing a maternal-fetal prenatal surgical procedure with postnatal surgery as in the MOMS trial? Strictly speaking, the mother will receive no medical benefit from the fetal intervention and is exposed only to potential harm. There are physical risks to the mother in a prenatal intervention that are not present when the intervention is undertaken postnatally, so how can there be equipoise for her as a patient? In the MOMS trial, it would seem that clinical equipoise was achieved by weighing the potential risks and benefits to the fetus in order to justify offering the trial and its associated risks to pregnant women. A pregnant woman may then determine whether the possible benefits for her fetus are worth the risks to themselves, as well as to their fetus.

In fetal surgery trials, Lyerly has suggested that the pregnant woman is usually treated more like a volunteer/innocent bystander than a research subject,²⁷ and argues that considerations regarding the presence of clinical equipoise are preferentially centered on the fetus as the mother herself will not medically benefit. Thus, the mother is allowed to expose herself to risk provided there is equipoise for the fetus. Although this can be an autonomous decision on the part of the mother, during the consent process it must be ensured that there are no coercive or paternalistic undertones in the discussion. The risk that both potential patients/research subjects are exposed to during a fetal intervention adds a unique nuance to the concept of equipoise and informed consent.

As an example, until the safety of prenatal surgery can be improved for both pregnant women and fetuses, there is wide-spread consensus in the medical community that maternal-fetal surgery should not be undertaken for cosmetic reasons,²⁸ such as repair of fetal cleft lip to reduce postnatal scarring even if some women would desire taking on the risk.

Chervenak has proposed the following criteria as necessary for obtaining normative equipoise in maternal-fetal surgery research:

1. The initial case series indicates that the proposed fetal intervention is reliably expected to be life saving or to prevent serious and irreversible disease, injury or disability.
2. Among possible alternative designs, the intervention continues to involve the least risk for morbidity and mortality to the fetus.
3. The case series indicates that the mortality risk to the pregnant woman is reliably expected to be low and the risk for disease, injury, or disability to the pregnant woman, including for future pregnancies, is reliably expected to be low or manageable.²⁹

Though these criteria involve a degree of subjectivity in determining what is an acceptably low risk to the pregnant woman, they provide an acceptable balance between the risks and benefits to both the fetus and pregnant woman with appropriate deference to the woman's right to autonomous decision-making.

Surgical Innovation vs. Surgical Research

The Society of University Surgeons defines innovation as “a new or modified surgical procedure that differs from currently accepted local practice, the outcomes of which have not been described, and which may entail risk to the patient.”³⁰ Innovation can involve modifying a device or procedure, or adding new equipment such as laparoscopy, or changing the system of care delivery.³¹ Innovation in surgery is regulated differently than research, and typically entails significantly reduced oversight with many surgical innovations not requiring an ethics review board approval before being explored and implemented.³²

The line between innovation and research can be blurry. As an example, in an effort to reduce the complication risk of open prenatal myelomeningocele closure, minimally invasive endoscopic and fetoscopic surgical techniques have been developed and performed on pregnant women following the MOMS trial. The results to date have been less than satisfactory, with increased risk of preterm labor, increased length of surgery, and increased CSF leak rates.^{33,34}

Given the risks involved to healthy pregnant women, ongoing innovations in prenatal surgery should be considered as research, with rigorous ethical oversight and adequate monitoring, in order to assess and evaluate outcomes on an ongoing basis. The IDEAL recommendations for evaluating surgical innovation, published in the *Lancet* in 2009,³⁵ provides an ethical framework on how innovations in maternal-fetal surgery might be evaluated and monitored. Among other recommendations, they call for public registration of protocols and cases (anonymously if necessary in cases with adverse outcomes), prospective databases to monitor early and late outcomes, and the use of randomized trials whenever possible.

Ethics of performing prenatal surgery for nonlethal, disabling conditions.

There is some debate over whether it is ethical to offer risky prenatal surgery to prevent a nonlethal but disabling condition.³⁶ We may be sending a message of intolerance to people with disabilities when we offer surgery that entails significant risk to both the pregnant women and the fetus in an effort to reduce the degree of disability the future child may live with. This is particularly relevant in MMC, where children with postnatally closed MMCs have been shown to have a similar psychosocial quality of life compared with unaffected children.³⁷ Though they have a reduced motor quality of life, it is the psychosocial quality of life that seems to matter most to life satisfaction.³⁸ Factors that are associated with a lower health related quality of life include shunted hydrocephalus and a symptomatic Chiari II malformation. Both of these are risks that are reduced, but not eliminated by prenatal surgery for MMC. Nonetheless, physicians must remember and counsel that prenatal surgery is not a cure for MMC related disability.

Ethical issues related to the MOMS trial and generalizability

The MOMs trial was plagued by low enrollment rates, taking nearly 8 years to enroll 183 pregnant women before the trial was stopped. Assuming that the cases were spread out evenly over time between the three involved centers, each center would have completed approximately seven cases per year based on referrals from across North America. Since publication of the positive trial results, there has been

a proliferation of centers in the United States that now perform fetal closure for MMC. This raises two concerns: first, will the increased number of centers offering the procedure result in dilution in the number of cases performed at each individual center, resulting in diminished expertise and results that fail to replicate the improved neurologic outcome demonstrated in the MOMs cohort and second, will the strict inclusion and exclusion criteria within the trial be loosened, resulting in the procedure being done for a patient population in which the results are not necessarily generalizable?

One center offering fetal MMC closure has already loosened inclusion criteria to allow for the procedure to be done in women with a body mass index of up to 40.³⁹ These women would not have been eligible for the therapy during the MOMs trial because of concerns of increased risk in this patient population. Local IRB approval for this deviation from MOMs criteria has been received, but it remains to be seen whether this results in acceptable outcomes.

When new fetal MMC closure centers deviate from the strict inclusion and exclusion criteria used in the MOMs trial, it is unclear whether the results of the trial can be generalized to prospective patients during the informed consent process. The risks of preterm labor and uterine dehiscence may be unacceptably higher, or the likelihood of an improved outcome in the fetus may be unacceptably lower, with expanded indications and less centralized centers of excellence. This has been shown to be the case for prenatal surgery on fetuses with MMC who have enlarged ventricles prenatally, as they do not have the significant reduction in the need for CSF shunting seen in the MOMS trial.⁴⁰ Since the need for CSF shunting was one of the primary outcome measures in the MOMS trial, this means that the potential benefit of surgery is significantly reduced for this patient population. Clearly, given the risks to the healthy volunteer (the pregnant woman), providing the maternal-fetal surgery, outside of the MOMS trial's inclusion and exclusion criteria, should be treated as research. It is essential to provide prospective patients with adequate disclosure of the experimental nature of the surgery in situations that are outside of the trial's inclusion/exclusion criteria and protocol, in order to obtain true informed consent. This also underscores the need for rigorous monitoring and follow up of results, to ensure centers are able to, at least, duplicate the results seen in the MOMs trial.

Furthermore, there is evidence to suggest that outcomes for any intervention may be better in the context of a research trial; the so called Trial Effect⁴¹ where the benefits seen in a trial are not reproduced when an intervention is accepted into wide spread use. As another example of deviation from MOMS trial protocols, some new fetal surgery centers keep pregnant patients in close proximity to the center for two or three weeks after prenatal surgery for observation, but they are then allowed to return home to deliver by cesarean section away from the fetal surgery center, unlike in the MOMS trial where the women were obligated to remain at the trial center to deliver.⁴² Hospitals outside of the trial centers may not provide high-risk obstetrical services and neonatal intensive care unit (NICU) services with the clinical experience present in the trial centers; both essential components of maintaining an acceptably low risk profile for the maternal-fetal surgery. Given the modest improvement in some outcomes seen in the MOMS trial, it is uncertain whether these results can be maintained outside of the research study protocol and centers, especially with expanding inclusion criteria, deviations from the trial protocol, and potential dilution of clinical expertise. Ongoing monitoring

and evaluation is essential, and centers should take care to conform to the MOMS study protocol until outcomes can be proven to be equivalent to those in the trial.

The principle of justice is also relevant in the context of prenatal surgery for MMC. Generally, it is important for evidence-based medical care to be readily available to all people who need it. The opening of new fetal care centers may be an important means of providing improved access to maternal-fetal surgery for many pregnant women who otherwise could not afford to travel to one of the three MOMS trial centers, especially if the new centers can provide care to at least an equivalent standard. This is particularly relevant for women pregnant with fetuses with MMC, as these women are less likely to have access to adequate prenatal care, and are more likely to have a lower socioeconomic status than women pregnant with fetuses without a MMC diagnosis.^{43,44} They may also not be as easily able to afford the long-term costs associated with the increased risk that will accompany all future pregnancies which will require mandatory cesarean sections because of the hysterotomy associated with open fetal repair. As a result of this, issues of justice and uniform access to care need to be taken into consideration when determining standards for opening new centers. Care should also be taken in minimizing the risk to patients from the learning curve inherent in setting up a new program. We strongly recommended mandatory mentoring of new centers by those with more experience, as well as rigorous quality assurance initiatives to ensure results which are at least equal to those seen in the MOMS trial.

Economic implications of fetal MMC closure

There may be a politico-economic drive for medical centers to offer fetal surgery to elevate their reputation for being a cutting edge program and to attract prospective patients, especially in a for profit health care environment. Given the small numbers of available prospective patients, and the increasing number of centers, this may result in significant competition for patients, and with this, the potential for exaggerated claims of competency, and indeed, exaggerated claims of benefit from the procedure. There is an essential need to enforce recognized standards for centers to offer fetal surgery services in general and MMC prenatal surgery services in particular. At a minimum, the center must have a well-trained multidisciplinary team including high-risk obstetrics and a tertiary care neonatal intensive care unit, as well as a multidisciplinary MMC care team that manages children with this disorder after birth.

The fetal MMC Maternal-Fetal Medicine Management Task Force has developed optimal practice criteria for new fetal care centers, and for centers performing prenatal MMC closure surgery⁴⁵ which include (1) adequate volume of cases to maintain competency, (2) the initial 5 cases must be undertaken under the training of a competent surgeon from an established center, (3) precise adherence to the protocol followed in the MOMs trial, (4) any modifications to the protocol should be studied in the context of a cooperative trial, and (5) a national registry monitoring outcome should be established.

Although there is no mechanism for mandatory adherence, these criteria form a reasonable safety net, balancing the push for innovation and desire for increased access to this prenatal surgery, with the need to minimize the risks to pregnant women and their affected fetuses. Ongoing monitoring and research is currently being conducted in an unregulated fashion by some centers⁴⁶ and by NAFTA⁴⁷

this should be expanded to be a more comprehensive regulation and monitoring in line with the above recommendations.

Ethical, legal and social issues in Fetal MMC repair- what does the future hold?

Few novel surgical interventions have been held to the rigor of the randomized controlled MOMS trial. In addition, a moratorium on fetal MMC repair in North America ensured that no patients were treated outside the trial and no modifications of the MOMS protocol undertaken or developed while the trial was ongoing. As fetal repair has become widely accepted as a treatment option, and centers offering the therapy have proliferated, modifications to the therapy are inevitable. This, coupled with advances in technologies potentially transferrable to fetal MMC repair underscores the need for continued vigilance and rigor in the evaluation of proposed new interventions. Potential advances likely to undergo further study include fetoscopic repair, robotic-assisted repair and the use of placental stem cells to assist in MMC closure.

Minimally invasive surgical techniques such as fetoscopic MMC repair are already used in some centers.^{48,49} The short- and long-term efficacy of these techniques, as well as the risk profile for fetal and mother, compared to the open repair utilized in the MOMS trial, remains unclear

Robotic-assisted surgery is well established for the treatment of prostate cancer,⁵⁰ cardiac disease,⁵¹ and increasingly, neurosurgical disorders.⁵² Although robotic fetal surgery has not been attempted in humans, there are promising animal models that utilize robotic techniques on fetal tissue—techniques that may be transferrable to fetal MMC repair.^{53,54}

Finally, as in many spheres of medicine, the use of stem cells holds promise in fetal surgery. Animal models utilizing fetal or placental derived stem cells to assist in the closure of open neural defects already exist.^{55,56}

For all these potential modifications and advances, it is critical that similar rigor be used to evaluate open fetal MMC repair in the MOMS trial, with attention to the short- and long-term effects on fetal and maternal health being utilized. We strongly advocate that the steps outlined in the IDEAL recommendations⁵⁷ serve as a framework for evaluation of these potential therapies.

Conclusions

MMC is a complex disorder frequently causing long-term disability in affected children and, in turn, placing a significant burden on affected families and caregivers. Prenatal closure of MMC is a new treatment option available to select affected pregnant women that may improve motor outcomes and reduce the need for CSF shunting in the affected children. There are significant ethical issues to be considered when developing surgical innovations for pregnant women and their fetuses—spanning informed consent, equipoise and the definition of who the patient/research subject is. There are also issues of justice in determining how to safely make the treatment more widely available as a management option to affected pregnant women and their fetuses. The development of new fetal care centers, however, should strictly follow existing recommendations to ensure competent delivery of care, following the MOMS trial protocol standards. Deviations from

the protocol should be considered research in surgical innovation, and studied using the IDEAL guidelines for evaluating surgical innovation.⁵⁸ The NAFTA Net collaborative research network is best situated to build and maintain a strong prospective database so that outcomes and innovations may be monitored and evaluated in a rigorous fashion. In this way, much desired improvements in outcomes for patients with MMC can continue to be sought in an ethical manner.

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