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Responsible surgical innovation and research in maternal–fetal surgery

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A B S T R A C T

The field of maternal–fetal intervention is rapidly evolving with new technologies and innovations. This raises complex ethical and medico-legal challenges related to what constitutes innovative treatment versus human experimentation, with or without the umbrella of "medical research." There exists a gray zone between these black and white classifications, but there are also clear guidelines that should be responsibly negotiated when making the essential transition between an innovative treatment and a validated therapy. This review attempts to define some of the current and future ethical challenges in maternal–fetal research, and to offer constructive insight into how they might be addressed.

1. Introduction

The field of maternal–fetal surgery has rapidly developed over the past 30 years. Advances in prenatal imaging as well as genetic testing have allowed clinicians to diagnose congenital and genetic anomalies very early in gestation. Physicians have long recognized that some of these conditions that result in neonatal death or significant morbidity could be treated or ameliorated if intervened upon before birth. This has led to the development of fetal therapies and maternal–fetal surgery. Research on pregnant women and their fetuses poses significant ethical challenges for investigators and institutional review boards. The evolution of maternal–fetal surgery has not been without criticism, especially for being offered as therapeutic, when it was still experimental.

There continues to exist considerable confusion about how to distinguish innovative therapy from research and how to transition from innovation to formal research to clinical practice [1]. Thus, the goal of this article is threefold. We start by distinguishing innovation from research and outline a responsible process of transitioning from innovation to research. Second, we review the development of prenatal surgery for spina bifida as an example of such a transition. Finally, we discuss three current ethical challenges for the future of prenatal surgery: introducing minimally invasive techniques, expanding patient selection criteria, and controlling the growth of maternal–fetal surgery centers. We reference multiple historical examples of surgical and medical innovation more generally to illustrate how innovation has been successfully and unsuccessfully managed and transitioned to research.

2. Distinguishing research from therapy

Clinical research is generally understood as an activity designed to evaluate the effectiveness of a treatment modality. The Belmont Report defines research as "an activity to test a hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge" [2]. This is in contrast to medical therapy which aims to relieve or cure disease for an individual patient. This is not to say that clinical research never benefits individual patients; however, this is not the primary goal of clinical research. What distinguishes research from therapy is not how innovative it is – the "newness" of the treatment – but rather the difference is based on the goal of the treatment [3]. Therefore, according to these usual definitions, a surgeon could offer patients an innovative operation with no intention to evaluate its effectiveness, and it would not be considered research. In contrast, it would be considered research to study an old and safe surgical technique.

Critics of these definitions of "therapy versus experiment" argue that the lines are less well defined than these definitions imply. Innovation is not simply a dichotomy – individual therapy versus the pursuit of generalizable knowledge – but rather a dynamic process progressing from hypotheses to animal experiments to

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clinical trials [4,5]. Thus, it is crucial to properly and responsibly transition from innovation to research to clinical care. Surgeons always make individual choices about how to perform particular operations – where to make the incision, how large the incision, what type of suture or instrument to use for a particular task. This latitude is appropriate and well accepted. What becomes problematic is when a surgeon offers a new procedure that is a significant deviation from the conventional approach without evaluating its effectiveness. Yet how much deviation should be considered significant?

We would argue that surgeons have the ethical obligation to responsibly assess innovation – for both new techniques as well as modifications to conventional approaches. The moral core of medicine is the fiduciary relationship between a patient and physician [6]. Patients need to be able to trust that their health and wellbeing is the only consideration when their physician makes a recommendation. Research naturally alters this relationship. The clinician-investigator has multiple goals, not simply the wellbeing of the individual patient being treated. There is also personal motivation to see the research succeed. Furthermore, patients are extremely susceptible to therapeutic misconception – misunderstanding research decisions to be based on judgments of clinical benefit [7]. And patients may have the misconception that newer therapy is better simply by the virtue that it is new.

3. Responsibly managing innovation and transitioning to research

Chervenak and McCullough argue that innovation, properly speaking, should be understood as “pre-research” [8]. Innovation, or pre-research, usually involves a case report of a single or a few cases where, serendipitously, observations are made that generate hypotheses. The dynamic process then continues with more formal research – perhaps developing appropriate animal models to begin to gage potential benefit as well as iatrogenic morbidity and mortality. Next, the feasibility, safety, and efficacy of the innovation should be determined through a larger case series. If clinical equipoise (uncertainty about the merits of an intervention compared to the standard of care) is achieved the innovation should be studied through a randomized controlled trial (RCT). Chervenak and McCullough argue that at least three criteria must be satisfied to support equipoise in maternal–fetal research prior to beginning an RCT: (1) the case series demonstrates that the intervention is life-saving or decreases serious morbidity; (2) among alternatives, the intervention involves the least number of risks to the fetus; and (3) the mortality and morbidity risks to the pregnant woman are low. Finally, trials should have clear endpoints and measures to adequately assess them. And the outcomes should be subject to academic scrutiny before becoming a standard of care. There will be rare circumstances in which this pathway is unethical: for example, conditions for which there is a 100% mortality rate and no alternative therapies available. An example of this is prenatal resection of congenital cystic adenomatoid malformation in selected patients with hydrops fetalis [9].

4. A brief history of prenatal surgery for spina bifida

Maternal–fetal surgery was pioneered in the late 1970s and early 1980s to correct anomalies that otherwise would lead to fetal or neonatal death despite optimal postnatal treatment. Myelomeningocele (MMC), or open spina bifida, represents the first application of maternal–fetal surgery to a non-lethal anomaly. MMC is caused by a failure of the neural tube to close during the first four weeks of embryonic development and is characterized by protrusion of the spinal cord through the open vertebrae. The malformation is compatible with long-term survival; however, it is associated with significant lifelong disability including motor and sensory deficits, urinary and fecal incontinence, hindbrain herniation, hydrocephalus, and cognitive deficits [10]. Most children will require a shunt to divert cerebral spinal fluid. Pathologic examination of the spinal cords of stillborn fetuses [11] and sonographic examination of fetuses with MMC [12,13] suggested a “two-hit” hypothesis in which the damage to the spinal cord is first due to failed neurulation at the time of defect formation and second from chronic chemical and mechanical in-utero insults. Intrauterine surgery aims to mitigate damage from the latter.

Several animal models were developed to test the feasibility of intrauterine surgery to cover the defect, thus preventing further damage to the spinal cord. In 1995, researchers at the University of California, San Francisco, developed a fetal sheep model where they created a spina-bifida-like lesion at 75 days gestation and then after an additional 25 days gestation repaired the lesion in utero [14]. The animals had near-normal neurological function after in-utero repair. Shortly thereafter, Vanderbilt University reported on the first two cases of endoscopic MMC repair in human fetuses [15]. One of the two fetuses was delivered one week after the operation and died in the delivery room. This minimally invasive approach was initially abandoned. In 1998, the Children's Hospital of Philadelphia and Vanderbilt University both reported successful open MMC repair ($n = 1$ and $n = 4$) [16,17] with subsequent larger series published by both groups the following year ($n = 10$ and $n = 29$) [18,19]. These early results showed reversal of hindbrain herniation and a decreased incidence of shunting for hydrocephalus.

Despite these encouraging results, the surgery was associated with serious neonatal and maternal complications, and the long-term consequences remained unknown. At the time, a survey of members of the Society for Maternal–Fetal Medicine showed that the majority of high-risk obstetricians (56%) did not feel that prenatal MMC repair had been validated [20]. Following a multidisciplinary conference at the National Institute of Health (NIH) in the summer of 2000, many experts, including the American College of Obstetrics and Gynecology, proposed that a moratorium be placed on the surgery until an RCT could be performed [21–23].

In February 2003, the Management of Myelomeningocele Study (MOMS), a National Institutes of Health (NIH)-sponsored multicenter RCT, began at the Children's Hospital of Philadelphia, Vanderbilt University, and the University of California, San Francisco (UCSF) [24]. During the trial, all other US fetal care centers voluntarily agreed to not offer prenatal repair. The trial was closed in December 2010 for efficacy of prenatal repair. Prenatal repair resulted in a reduced need for shunting and improved motor outcomes at 30 months of age. However, not all fetuses benefited, and the potential benefit must be weighed against both the maternal and fetal risks, including preterm rupture of membranes, increased incidence of dehiscence at the uterine scar, and fetal prematurity. This cohort is continuing to be studied in the NIH-sponsored MOMSII study to assess long-term outcomes. However, prenatal closure of MMC is now a standard of care for select women.

5. Three current challenges

5.1. The transition from open to minimally invasive approaches

It is generally accepted that minimally invasive surgery is better for patients than conventional open approaches. Minimally invasive techniques require much smaller incisions resulting in less postoperative pain, shorter hospital length of stay, and better cosmesis. But minimally invasive surgery is not merely a slight modification of an open technique, it is in reality a new technique that can be accompanied with unanticipated challenges and

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