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The ethics of maternal–fetal surgery

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A B S T R A C T

Maternal–fetal surgery is performed on two patients, the pregnant patient and the fetal patient. Ethics is therefore an essential dimension of maternal–fetal surgery. From its beginnings in only a few centers, various procedures have become available in highly specialized centers in developed countries. Innovation and research have played an indispensable role in the development of maternal–fetal surgery and will continue to do so. In this article we present ethically justified criteria, based on the ethical concept of the fetus as a patient, for clinical innovation and research of maternal–fetal surgery and for the professionally responsible transition from innovation and research into clinical practice. These criteria are designed to be used by clinical innovators, clinical investigators, and by oversight committees.

1. Introduction

Maternal–fetal surgery is performed on two patients, the pregnant patient and the fetal patient [1]. Because there are biopsychosocial benefits and risks to both patients, ethics is an essential dimension of maternal–fetal surgery [2]. From its beginnings in only a few centers, various procedures have become available in highly specialized centers in many developed countries. These centers go by various names, such as “Fetal Center” [1,3]. In response to developments in the USA, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics published joint recommendations for fetal centers. These include ethically significant topics such as informed consent, the oversight of fetal centers, and the need to gather data on outcomes [4].

Innovation and research have played an indispensable role in the development of maternal–fetal surgery and will continue to do so. In this paper we present ethically justified criteria, based on the ethical concept of the fetus as a patient, for such clinical innovation and research and their professionally responsible transition to clinical practice.

2. Fetal surgery as maternal–fetal surgery

In the early stages of the field, surgery for fetal benefit was often characterized by “fetal surgery.” In time, this nomenclature came to be understood as problematic, because surgery for fetal benefit is necessarily also surgery on the pregnant woman for fetal benefit. “Maternal–fetal surgery” is now the preferred nomenclature [2,4,5], which is reflected in the title of this article. It is worth noting that medical intervention for fetal benefit should be understood as maternal–fetal intervention, because medications for fetal benefit must be administered through the pregnant woman's body. Medical maternal–fetal intervention occurs when the pregnant woman is given medication that can cross the placenta and thus affect fetal physiology. For example, medications can be given to the pregnant woman to manage fetal arrhythmias. Maternal–fetal surgery, or surgical maternal–fetal intervention, occurs when the pregnant woman undergoes a surgical procedure to correct abnormal fetal anatomy. The expected outcomes are eliminating or mitigating pathological anatomy and improving fetal physiology. Maternal–fetal surgery is now undertaken to manage life-threatening conditions, such as severe sacrococcygeal teratoma and severe congenital diaphragmatic hernia. Maternal–fetal surgery is also undertaken to prevent childhood disability, notably in utero repair of meningomyelocele. Maternal–fetal surgery is also undertaken to prevent further development of pathology, e.g., stent placement to prevent development of hypoplastic left-heart syndrome. These types of maternal–fetal surgery involve differing, complex trade-offs among short-term and long-term fetal and neonatal benefits

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and risks, on the one hand, and short-term and long-term maternal risks, on the other. Our goal is to provide ethically justified criteria for innovation and research that are adequate to manage this ethical complexity in a professionally responsible way.

3. Innovation and human subjects research in maternal–fetal surgery

3.1. The role of animal models

When there are appropriate animal models, maternal–fetal surgery should be initiated as animal research, with the review and approval of the investigators' Institutional Animal Care and Use Committee. When such research is promising or when there is no appropriate animal model, clinical innovation with patients and clinical research with human subjects may be undertaken, to create an evidence base for the professionally responsible introduction of new techniques of maternal–fetal surgery into clinical practice.

3.2. Innovation and research defined

Innovation and research have the common feature of being forms of experimentation [5]. An experiment occurs when a clinical intervention is used but its outcomes cannot be reliably predicted. Clinical innovation is defined as an experiment performed on a patient for the clinical benefit of that individual patient. More precisely, innovation in maternal–fetal surgery is performed on both the pregnant and fetal patients for the benefit of the fetal patient. Clinical research is an experiment performed on a human research subject who is also a patient with the goal of creating generalizable knowledge that is intended to benefit future patients. It is a mistake to equate human experimentation with human subjects research, because human experimentation also includes clinical innovation. To prevent confusion, in this paper we will use “innovation” and “research” as defined above.

3.3. Innovation, research, and hypothesis formation and testing

Clinical innovation cannot produce generalizable knowledge because clinical success from a clinical innovation on a single pregnant patient–fetal patient pair or on a small series of such pairs produces only data points. Such data points are never sufficient in scientific methodology to test a hypothesis. Clinical innovation can establish the initial feasibility of hypotheses about the fetal and neonatal benefits and maternal risks of a form of maternal–fetal surgery, which may warrant the formulation of a hypothesis. A feasible hypothesis should then be tested in early phase research for efficacy and safety. To maintain clarity about the scientific and ethical relationship between clinical innovation and clinical research, innovation should be organized as pre-research for the potential fetal and neonatal benefit and to generate hypotheses to be investigated in subsequent phases of human subjects research.

3.4. Guidance on surgical innovation

In the USA the Society of University Surgeons has proposed that the era of surgical innovation without peer review should come to an end, because of its mixed record of success and failure. Instead, clinical innovation in surgery should become accountable for its scientific, clinical, and ethical integrity, rather than follow the haphazard approach of the past. Surgical departments should provide oversight of all clinical innovation through prospective review and approval by a Surgical Innovation Committee [6]. In the present context, we propose that this committee should be constituted as a Perinatal Innovation Review Committee [2]. Physicians considering a planned maternal–fetal surgical innovation for fetal and neonatal benefit should prepare a proposal that describes the scientific and clinical justification for the innovation, its prior use in animal models (when feasible) and in cases reported in the peer-reviewed literature (when they exist), the clinical benefit intended for the patient (including reduction of the risks of mortality, morbidity, and disability), the short-term and long-term risks of mortality, morbidity, and disability for both the pregnant and fetal patients, the informed consent process, and what will be considered successful outcomes and their measurement. The informed consent process should make clear to the pregnant woman and those involved in the decision with her that the proposed clinical innovation is an experiment: its outcomes for both the fetal and pregnant patients cannot be reliably predicted and are therefore unknown. The physician leading the informed consent process should emphasize that the proposed clinical innovation is not accepted clinical practice and therefore it should not be expected by the pregnant woman to result in certain fetal and neonatal benefit. The informed consent process should emphasize that the short-term and long-term outcomes for the fetal, neonatal, and pregnant patients are unknown. The pregnant woman should be informed that she therefore has no ethical obligation to her fetus or future child to undergo the risks to her of the proposed innovative maternal–fetal surgery.

3.5. Regulatory requirements for human subjects research

When maternal–fetal surgery is proposed as research, it must receive prospective review and approval by an institutional review board (IRB) or, in other countries, a research ethics Committee [2]. The protocol must address the nature of the maternal–fetal surgery; why (on the basis of previous animal models and case reports of clinical innovation) it should be considered to have scientific and clinical merit and therefore an acceptable benefit:risk ratio for the pregnant patient in this and subsequent pregnancies, as well as for the fetal and neonatal patient; and the informed consent process. The informed consent process should make clear to the pregnant woman that the proposed clinical research is an experiment: its outcome for both the fetal and pregnant patients cannot be reliably predicted. The physician leading the informed consent process should emphasize that the proposed clinical research is not accepted clinical practice. The pregnant woman should be informed that she therefore has no ethical obligation to her fetus or future child to undergo the proposed maternal–fetal surgical research. The pregnant woman, we have argued, is ethically obligated to take only reasonable risk to herself for fetal benefit. Because research is an experiment, fetal benefit is unknown. The pregnant woman has no ethical obligation therefore to take risk to herself, although she is free to do so. This should serve as an important consideration for those pregnant women who say that they would be willing to do anything that will help their baby. The current version of the Common Rule (45 CFR 46) required paternal consent when maternal–fetal research is undertaken with “the prospect of direct benefit solely to the fetus” (45 CFR 46.204(e)). We have argued that this requirement lacks ethical justification but IRBs must nonetheless enforce it [2].

Due to the rarity of the conditions for which maternal–fetal surgery is being developed, multicenter cooperative trials will be essential for the advancement of the field. Such trials could also help to address variation from center to center or even from surgeon to surgeon within large centers in how maternal–fetal surgeries is performed. This variation can affect outcomes. The antidote is multicenter research in which there are comparative trials of potentially clinically significant variable surgical techniques.

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