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Original Article

Professionally responsible maternal-fetal surgery: from innovation to research

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Abstract: Fetal surgery has developed from concept, through innovation and research with pregnant and fetal patients, to introduction into clinical practice during the past several decades. This technological and clinical transformation has been facilitated by such factors as the introduction of advanced perinatal technology and the increasing integration of obstetrics and pediatrics in perinatal medicine. Fetal surgery has now become available in additional specialized perinatal centers. We explain why fetal surgery should be understood as maternal-fetal surgery. We then explain the concepts of innovation and research. An approach to ethics of maternal-fetal surgery is then described that provides a clinically comprehensive focus on clinical innovation, clinical research, and the professionally responsible transition to clinical practice, appealing to the ethical concepts of the pregnant woman and fetus as patients.

Keywords: Ethical concept of being a patient, ethics, fetal therapy, maternal-fetal surgery

Introduction

Maternal-fetal surgery has become available in highly specialized centers in developed countries, known as "fetal centers" and by other names [1, 2]. To provide guidance, the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics published joint recommendations about informed consent, the oversight of fetal centers, and the need to gather data on outcomes [3]. Professionally responsible investigation of maternal-fetal surgery should proceed in an orderly fashion, starting with animal models, when feasible, and then proceeding through innovation as a form of pre-research to Phase 1 and later-Phase research. This paper provides an ethical framework for doing so.

Fetal surgery as maternal-fetal surgery

Medical and surgical intervention for fetal benefit should in all cases be understood as maternal-fetal intervention, because medications or surgical techniques 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. Surgical maternal-fetal intervention occurs when the pregnant woman undergoes a surgical procedure to correct abnormal fetal anatomy with the goal of eliminating or mitigating pathological anatomy and thereby improving fetal physiology. Both medical and surgical maternal-fetal interventions are designed and intended to manage life-threatening pathophysiology aiming for the outcomes of preventing in utero fetal demise and increasing the probability of live birth. Medical and surgical maternal-fetal interventions are also undertaken to manage diseases and disabling conditions aiming at the outcomes of mitigating their effects during gestation and therefore their effects on the future child.

From innovation to research and the transition into clinical practice

Maternal-fetal surgery should be initiated as clinical innovation and clinical research, to provide the evidence base for the professionally

responsible introduction of these surgical techniques into clinical practice. Innovation and research are both forms of experimentation, because they are forms of clinical management the outcomes of which cannot be reliably predicted. Clinical innovation is an experiment performed on a patient for the clinical benefit of that individual patient. 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 research subject who is also a patient with the goal of creating generalizable knowledge that is intended to benefit future patients. Clinical innovation cannot produce generalizable knowledge because clinical success from a clinical innovation on a single pregnant patient-fetal patient pair is not sufficient in scientific methodology to test a hypothesis. Clinical innovation can establish the initial feasibility of a form of maternal-fetal surgery and may warrant the formulation of a hypothesis of fetal benefit and acceptable maternal and fetal risk, which 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 clinical benefit of an individual fetal patient and to generate hypotheses to be investigated in subsequent clinical research.

In the United States the Society of University Surgeons has proposed that clinical innovation in surgery should become accountable for its scientific, clinical, and ethical integrity, rather than a haphazard approach as in the past. Surgical departments should provide oversight of all clinical innovation through prospective review and approval by a Surgical Innovation Committee [4]. In the present context, this committee should be constituted as a Perinatal Innovation Review Committee [5]. Physicians considering a planned maternal-fetal innovation for fetal 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, 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 patient, the informed consent process, and what will be considered a successful outcome. 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 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 innovation is not accepted clinical practice. The pregnant woman should be informed that she therefore no ethical obligation to her fetus or future child to undergo the proposed innovative maternal-fetal surgery.

When maternal-fetal surgery is proposed as research, it must receive prospective review and approval by an Institutional Review Board (IRB). The protocol must address such matters as 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 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 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 no ethical obligation to her fetus or future child to undergo the proposed-maternal-fetal surgical research.

Maternal-fetal clinical intervention that has been developed through the process of pre-research or innovation followed by research may be introduced into clinical practice when the outcomes of research support the clinical ethical judgment that the intervention is reliably expected to result in net clinical benefit for the fetal patient and acceptable risk to the pregnant patient. Such clinical intervention should be considered medically reasonable. In the informed consent process the physician has the professional responsibility to present all medically reasonable alternatives to the patient, or the surrogate decision maker for a patient not able to participate in the informed consent process or not permitted by law to pro-

vide consent. The physician should attempt to ascertain that the patient understands this information and that the patient's decision-making process is voluntary, i.e., free of controlling internal or external influences.

Maternal-fetal surgery for spina bifida illustrates how the transition from research to clinical practice should occur. This surgery was shown in a randomized controlled clinical trial, known as the MOMS Trial, to be clinically beneficial for children and acceptably risky for the fetal and pregnant patients in a population defined by inclusion and exclusion criteria [6]. This form of in utero surgery decreased rates of disability and the need for shunting for hydrocephalus in children when compared to expectant obstetric management followed by neonatal surgical repair, with acceptable rates of maternal morbidity and fetal mortality and morbidity. It follows that in utero repair for spina bifida for pregnant patients who meet the MOMS Trial criteria is medically reasonable. All pregnant women whose fetus has been diagnosed to have spina bifida and who meet the MOMS Trial criteria should therefore be offered both in utero repair and expectant obstetric management followed by neonatal repair. The physician should attempt to ascertain that the pregnant woman understands that in utero repair is maternal-fetal surgery, the nature of the procedure, its morbidity risks for the pregnant woman in her current and future pregnancies, and the mortality and morbidity risks for the fetal patient and future child. The physician should also make a reasonable effort to ensure that the pregnant woman's decision-making process is free of internal or external controlling influences.

We have offered a comprehensive ethical framework that addresses clinical ethical judgment about the initiation of innovation, early phase research, randomized controlled clinical trials, and the responsible transition to clinical practice [7]. The distinctive feature of this approach is that it appeals explicitly to the ethical concept of the fetus as a patient, beneficence-based obligations of the pregnant woman to the fetal patient, and the pregnant woman's beneficence-based ethical obligation to take only reasonable risks to herself for fetal benefit. Beneficence is an ethical principle that obligates the physician to act in a way that produces a greater balance of clinical goods over harms for the patient, as judged from a rigorous clinical perspective. These beneficence-based obligations support criteria to address potential benefit and risk to the fetal patient, as well as potential benefit and risk to the pregnant woman in the current and future pregnancies. Their approach identifies risks of mortality, morbidity, and disability. Because their approach includes an account of the moral status of the fetus as a patient, their approach is clinically applicable to maternal-fetal surgery to prevent imminent fetal and neonatal mortality, mortality, and disability.

We have set forth ethical criteria for clinical innovation, clinical research, and the professionally responsible transition from research to clinical practice.

Clinical ethical criteria for clinical innovation and early-phase clinical research for efficacy and safety: The clinical ethical justification for clinical innovation and early-phase clinical should be based on beneficence-based criteria that focus on minimizing the risks of mortality and the risks of morbidity, injury, and disability to both the pregnant and fetal patient.

1. The proposed fetal intervention is reliably expected on the basis of previous animal studies either to be lifesaving or to prevent serious and irreversible disease, injury, or disability for the fetal patient; 2. Among possible alternative designs, the intervention is designed in such a way as to involve the least risk of mortality and morbidity to the fetal patient; 3. On the basis of animal studies and analysis of theoretical risks both for the current and future pregnancies, the mortality risk to the pregnant woman is reliably expected to be low and the risk of disease, injury, or disability to the pregnant woman is reliably expected to be low or manageable for current and future pregnancies [7].

Clinical ethical criteria for randomized controlled clinical trials (RCTs): When feasible, the initiation of a randomized controlled clinical trial requires equipoise: evidence-based evaluation of the outcomes of early-phase requires the scientifically rigorous clinician to become uncertain about the relative clinical benefit of the maternal-fetal surgery versus expectant obstetric management and neonatal intervention. The beneficence-based criteria focus on continued minimization of the risks of mortality

and the risks of morbidity, injury, and disability to both the pregnant and fetal patient.

1. The initial case series indicates that the proposed fetal intervention is reliably expected either to be lifesaving or to prevent serious and irreversible disease, injury, or disability for the fetal patient; 2. Among possible alternative designs, the intervention continues to involve the least risk of morbidity and mortality to the fetal patient; 3. The case series indicates that the mortality risk to the pregnant woman is reliably expected to be low and the risk of disease, injury, or disability to the pregnant woman, including for future pregnancies, is reliably expected to be low or manageable [7].

Clinical ethical criteria for the professionally responsible transition to clinical practice: The beneficence-based criteria focus on the clinical ethical judgment that the outcomes of either early-phase research (when an RCT is infeasible) or of an RCT support an expectation of significant fetal benefit and acceptable risks of mortality, morbidity, injury, and disability for both the pregnant and fetal patient.

1. The maternal or fetal intervention has positive results, i.e., it has a significant probability of being life saving or preventing serious or irreversible disease, injury, or disability for the pregnant woman or fetal patient; 2. The maternal or fetal intervention involves low mortality and low or manageable risk of serious and irreversible disease, injury, or disability to the fetal patient; 3. The mortality risk to the pregnant woman is low and the risk of disease, injury or disability is low or manageable, including for future pregnancies [7].

Conclusion

As a result of innovation and organized research, maternal-fetal surgery has now reached a high degree of scientific, clinical, and ethical sophistication in highly specialized centers in developed countries. Innovation and research will continue and most likely accelerate. Such clinical innovation and research should be undertaken in a professionally responsible manner. Clinically comprehensive ethical criteria, justified by appeal to the ethical principle of beneficence, have been proposed to guide professionally responsible maternal-fetal surgery. Professional associations of physicians have also provided ethical guidance. The resulting use of ethics as a tool of professionally responsible self-regulation by physicians serves as a model that can be adapted to other clinical areas.

Disclosure of conflict of interest

None.

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