42 Ethical considerations

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INTRODUCTION

Ethics is an essential dimension of maternal–fetal medicine (1–3). In this chapter, we develop a framework for clinical judgment and decision-making about the ethical dimensions of clinical practice and research in maternal–fetal medicine. We emphasize a preventive ethics approach that appreciates the potential for ethical conflict and adopts ethically justified strategies to prevent those conflicts from occurring. Preventive ethics helps to build and sustain a strong physician–patient relationship. We first define ethics, medical ethics, and the fundamental ethical principles of medical ethics, beneficence, and respect for autonomy. Second, we show how these two principles should interact in clinical judgment and practice in maternal–fetal medicine, with emphasis on the core concept of the fetus as a patient. Third, we set out an ethical framework for innovation and research in maternal–fetal medicine, with an emphasis on ethically justified criteria to guide the initiation and implementation of research in maternal–fetal medicine.

ETHICS, MEDICAL ETHICS, AND ETHICAL PRINCIPLES

Ethics is the disciplined study of morality. Medical ethics is the disciplined study of morality in medicine and concerns the obligations of physicians and health-care organizations to patients as well as the obligations of patients (4). It is important not to confuse medical ethics with the many sources of morality in a pluralistic society. These include, but are not limited to, law, our political heritage as free people, the world's religions (most of which now exist in our country), ethnic and cultural traditions, families, the traditions and practices of medicine (including medical education and training), and personal experience. Medical ethics since the eighteenth-century European and American Enlightenments has been secular (5). It makes no reference to God or revealed tradition, but to what rational discourse requires and produces. At the same time, secular medical ethics is not intrinsically hostile to religious beliefs. Therefore, ethical principles and virtues should be understood to apply to all physicians, regardless of their personal religious and spiritual beliefs (6).

The traditions and practices of medicine constitute a major source of morality for physicians. They provide an important reference point for medical ethics because they are based on the obligation to protect and promote the health-related interests of the patient. This obligation tells physicians what morality in medicine ought to be, but in very general abstract terms. Providing a more concrete, clinically applicable account of that obligation is the central task of medical ethics, using ethical principles (4).

The *ethical principle of beneficence* in its general meaning and application requires one to act in a way that is expected reliably to produce the greater balance of benefits over harms in the

lives of others (6). To put this principle into clinical practice requires a reliable account of the benefits and harms relevant to the care of the patient, and of how those goods and harms should be reasonably balanced against each other when not all of them can be achieved in a particular clinical situation, such as a request for an elective cesarean delivery (7). In medicine, the principle of beneficence requires the physician to act in a way that is reliably expected to produce the greater balance of clinical benefits clinical over harms for the patient (4).

Beneficence-based clinical judgment has an ancient pedigree, with its first expression found in the Hippocratic Oath and accompanying texts (8). Beneficence-based clinical judgment makes an important claim: to interpret reliably the health-related interests of the patient from medicine's perspective. This perspective is provided by accumulated scientific research, clinical experience, and reasoned responses to uncertainty. As rigorously evidence based (9), beneficence-based judgment is thus not the function of the individual clinical perspective of any particular physician and therefore should not be based merely on the clinical impression or intuition of an individual physician. On the basis of this rigorous clinical perspective, focused on the best available evidence, beneficence-based clinical judgment identifies the clinical benefits that can be achieved for the patient in clinical practice based on the competencies of medicine. The clinical benefits that medicine is competent to seek for patients are the prevention and management of disease, injury, handicap, and unnecessary pain and suffering, and the prevention of premature or unnecessary death. Pain and suffering become unnecessary when they do not result in achieving the other goods of medical care, for example, allowing a woman to labor without effective analgesia (4).

Nonmaleficence means that the physician should prevent causing harm and is best understood as expressing the limits of beneficence. This is also known as *Primum non nocere* or “first do no harm.” This commonly invoked dogma is really a Latinized misinterpretation of the Hippocratic texts, which emphasized beneficence while avoiding harm when approaching the limits of medicine (4). Nonmaleficence should be incorporated into beneficence-based clinical judgment: when the physician approaches the limits of beneficence-based clinical judgment, that is, when the evidence for expected benefit diminishes and the risks of clinical harm increase, then the physician should proceed with great caution. The physician should be especially concerned to prevent serious, far-reaching, and irreversible clinical harm to the patient. It is important to note that there is an inherent risk of paternalism in beneficence-based clinical judgment. By this, we mean that beneficence-based clinical judgment, if it is *mistakenly* considered to be the sole source of moral responsibility and therefore moral authority in medical care, invites the unwary

physician to conclude that beneficence-based judgments can be imposed on the patient in violation of her autonomy. Paternalism is a dehumanizing response to the patient and, therefore, should be avoided in the practice of obstetrics and gynecology.

The preventive ethics response to this inherent paternalism is for the physician to explain the diagnostic, therapeutic, and prognostic reasoning that leads to his or her clinical judgment about what is in the interest of the patient so that the patient can assess that judgment for herself. This general rule can be put into clinical practice in the following way: the physician should disclose and explain to the patient the major factors of this reasoning process, including matters of uncertainty. In neither medical law nor medical ethics does this require that the patient be provided with a complete medical education (10). The physician should then explain how and why other clinicians might reasonably differ from his or her clinical judgment. The physician should then present a well-reasoned response to this critique. The outcome of this process is that beneficence-based clinical judgments take on a rigor that they sometimes lack in maternal–fetal medicine and the process of their formulation includes explaining them to the patient. It should be apparent that beneficence-based clinical judgment will frequently result in the identification of a continuum of clinical strategies that protect and promote the patient's health-related interests, such as indications for cesarean delivery for fetal distress. Awareness of this feature of beneficence-based clinical judgment provides an important preventive ethics antidote to paternalism by increasing the likelihood that one or more of these medically reasonable, evidence-based alternatives will be acceptable to the patient. All beneficence-based clinical alternatives should be identified and explained to all patients, regardless of how the physician is paid, especially those that are well established in evidence-based obstetrics and gynecology.

One advantage for the physician in carrying out this approach to communicating with the patient would be, we believe, to increase the likelihood of compliance (11). This is an especially pertinent consideration in the management of pregnancy, where the pregnant patient often must monitor herself for clinical changes, for example, self-observation for unusual weight gain or bleeding. Another advantage would be to provide the patient with a better-informed opportunity to make a decision about whether to seek a second opinion. The approach outlined above should make such a decision less threatening to her physician, who has already shared with the patient the limitations on clinical judgment.

In contrast to the principle of beneficence, there has been increasing emphasis in the literature of medical ethics on the *ethical principle of respect for autonomy* (6). This principle requires one always to empower the patient in the informed consent process by providing her with information about the beneficence-based alternatives for managing her or the fetus's condition and then implement the value-based preferences of the pregnant patient, unless there is compelling ethical justification for not doing so. The pregnant patient increasingly brings to her medical care her own perspective on what is in her interest. The principle of respect for autonomy translates this fact into autonomy-based clinical judgment. Because each patient's perspective on her interests is a function

of her values and beliefs, it is impossible to specify the benefits and harms of autonomy-based clinical judgment in advance. Indeed, it would be inappropriate for the physician to do so, because the definition of her benefits and harms and their balancing are the prerogative of the patient. Not surprisingly, autonomy-based clinical judgment is strongly antipaternalistic in nature (4).

To understand the demands of this principle in clinical practice, we need an operationalized concept of autonomy to make it relevant to clinical practice. To do this, we identify three sequential autonomy-based behaviors on the part of the patient: (i) absorbing and retaining information about her condition and alternative diagnostic and therapeutic responses to it, (ii) understanding that information (evaluating and rank-ordering those responses and appreciating that she could experience the risks of treatment), and (iii) expressing a value-based preference. The physician has a role to play in each of these. They are, respectively, (i) to recognize the capacity of each patient to deal with medical information (and not to underestimate that capacity), provide information (disclose and explain all beneficence-based alternatives), and recognize the validity of the values and beliefs of the patient; (ii) not to interfere with but, when necessary, to assist the patient in her evaluation and ranking of diagnostic and therapeutic alternatives for managing her condition; and (iii) to elicit and implement the patient's value-based preference (4).

The legal obligations of the physician regarding informed consent were established in a series of cases during the twentieth century. In 1914, *Schloendorff v. The Society of The New York Hospital* established the concept of simple consent, whether the patient says "yes" or "no" to medical intervention (10,12). To this day in the medical and bioethics literature, this decision is quoted: "Every human being of adult years and sound mind has the right to determine what shall be done with his body, and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages" (12). The legal requirement of consent further evolved to include disclosure of information sufficient to enable patients to make informed decisions about whether to say "yes" or "no" to medical intervention (10).

There are two accepted legal standards for such disclosure. The professional community standard defines adequate disclosure in the context of what the relevantly trained and experienced physician tells patients. The reasonable person standard, which has been adopted by most states, goes further and requires the physician to disclose "material" information, what any patient in the patient's condition needs to know and the layperson of average sophistication should not be expected to know. Patients need to know what the physician thinks is clinically salient, that is, the physician's beneficence-based clinical judgment. This reasonable person has emerged as the ethical standard, and we therefore urge perinatologists to adopt it. On this standard, the physician should disclose to the patient her or the fetus's diagnosis (including differential diagnosis when that is all that is known), the beneficence-based (and therefore medically reasonable) alternatives to diagnose and manage the patient's condition, and the short-term and long-term benefits and risks of each alternative.

THE INTERACTION OF BENEFICENCE AND RESPECT FOR AUTONOMY IN CLINICAL JUDGMENT AND PRACTICE IN MATERNAL—FETAL MEDICINE

The ethical principles of beneficence and respect for autonomy play a complex role in obstetric clinical judgment and practice. There are obviously beneficence-based and autonomy-based obligations to the pregnant patient: the physician's perspective on the pregnant woman's health-related interests provides the basis for the physician's beneficence-based obligations to her, whereas her own perspective on those interests provides the basis for the physician's autonomy-based obligations to her. Because of an insufficiently developed central nervous system, the fetus cannot meaningfully be said to possess values and beliefs. Thus, there is no basis for saying that a fetus has a perspective on its interests. There can therefore be no autonomy-based obligations to any fetus. Hence, the language of fetal rights has no meaning and therefore no application to the fetus in obstetric clinical judgment and practice despite its popularity in public and political discourse in the United States and other countries. Obviously, the physician has a perspective on the fetus's health-related interests, and the physician can have beneficence-based obligations to the fetus, *but only when the fetus is a patient*. Because of its importance for obstetric clinical judgment and practice, the ethical concept of the fetus as a patient requires detailed consideration (4).

The *ethical concept of the fetus as a patient* is essential to obstetric clinical judgment and practice. Developments in fetal diagnosis and management strategies to optimize fetal outcome have become widely accepted, encouraging the development of this concept. This concept has considerable clinical significance because when the fetus is a patient, directive counseling, that is, recommending a form of management, for fetal benefit is appropriate, and when the fetus is not a patient, nondirective counseling, that is, offering but not recommending a form of management for fetal benefit, is appropriate. However, there can be uncertainty about when the fetus is a patient. One approach to resolving this uncertainty would be to argue that the fetus is or is not a patient in virtue of personhood or some other form of independent moral status. We now show that this approach fails to resolve the uncertainty, and we therefore defend an alternative approach that does resolve the uncertainty.

One prominent approach for establishing whether or not the fetus is a patient has involved attempts to show whether or not the fetus has *independent moral status*. Independent moral status for the fetus means that one or more characteristics that the fetus possesses in and of itself and, therefore, independently of the pregnant woman and physician, generate and therefore ground obligations to the fetus on the part of the pregnant woman and her physician. Many fetal characteristics have been nominated for this role, including moment of conception, implantation, central nervous system development, quickening, and the moment of birth. It should come as no surprise that there is considerable variation among ethical arguments about when the fetus acquires independent moral status. Some take the view that the fetus has independent moral status from the moment of conception or implantation. Others believe that independent moral status is acquired in degrees, thus resulting in "graded" moral status. Still

others hold, at least by implication, that the fetus never has independent moral status so long as it is in utero (13,14).

Despite an ever-expanding theologic and philosophical literature on this subject, there has been no closure on a single authoritative account of the independent moral status of the fetus. This is an unsurprising outcome because, given the absence of a single method that would be authoritative for all of the markedly diverse theologic and philosophical schools of thought involved in this endless debate, closure is impossible. For closure ever to be possible, debates about such a final authority within and between theologic and philosophical traditions would have to be resolved in a way satisfactory to all, an inconceivable intellectual and cultural event. The concept of the independent moral status of the fetus has no stable or clinically applicable meaning. We therefore abandon these futile attempts to understand the ethical concept of the fetus as a patient in terms of independent moral status of the fetus and turn to an alternative approach that makes it possible to identify ethically distinct senses of the fetus as a patient and their clinical implications for directive and nondirective counseling.

Our analysis of the ethical concept of the fetus as a patient begins with the recognition that being a patient does not require that one possesses independent moral status. Rather, being a patient means that one can benefit clinically from the applications of the clinical skills of the physician. Put more precisely, a human being without independent moral status is properly regarded as a patient when two conditions are met: that a human being (i) is presented to the physician and (ii) there exist clinical interventions that are reliably expected to be efficacious, in that they are reliably expected to result in a greater balance of clinical benefits over harms for the human being in question (15). This is the sense in which the ethical concept of the fetus as a patient should be understood, what we call the dependent moral status of the fetus.

The authors have argued elsewhere that beneficence-based obligations to the fetus exist when the fetus is reliably expected *later* to achieve independent moral status as a child and a person (4). That is, the fetus is a patient when the fetus is presented for medical interventions, whether diagnostic or therapeutic, that reasonably can be expected to result in a greater balance of goods over harms for the child and the person the fetus can later become during early childhood. The ethical significance of the concept of the fetus as a patient, therefore, depends on links that can be established between the fetus and its later achieving independent moral status.

The Viable Fetal Patient

One such link is viability. Viability, however, must be understood in terms of *both* biologic and technologic factors. It is only by virtue of *both* factors that a viable fetus can exist ex utero and thus achieve independent moral status. When a fetus is viable, that is, when it is of sufficient maturity so that it can survive into the neonatal period and achieve independent moral status given the availability of the requisite technologic support, and when it is presented to the physician, the fetus is a patient.

Viability exists as a function of biomedical and technologic capacities, which are different in different parts of the world. As a consequence, there is, at the present time, no worldwide

uniform gestational age to define viability. In the United States, we believe, viability presently occurs at approximately 24 weeks of gestational age (16,17).

When the fetus is a patient, directive counseling for fetal benefit is ethically justified. In clinical practice, directive counseling for fetal benefit involves one or more of the following: recommending against termination of pregnancy, recommending against nonaggressive management, or recommending aggressive management. Aggressive obstetric management includes interventions such as fetal surveillance, tocolysis, cesarean delivery, or delivery in a tertiary care center when indicated. Nonaggressive obstetric management excludes such interventions. Directive counseling for fetal benefit, however, must take account of the presence and severity of fetal anomalies, extreme prematurity, and obligations to the pregnant woman.

It is very important to appreciate in obstetric clinical judgment and practice that the strength of directive counseling for fetal benefit varies according to the presence and severity of fetal anomalies. As a rule, the more severe the fetal anomaly, the less directive counseling should be for fetal benefit. In particular, when lethal anomalies such as anencephaly can be diagnosed with certainty, there are no beneficence-based obligations to provide aggressive management. Such fetuses are dying patients, and the counseling, therefore, should be nondirective in recommending between nonaggressive management and termination of pregnancy, but directive in recommending against aggressive management for the sake of maternal benefit (18). By contrast, third-trimester abortion for Down syndrome, or achondroplasia, is not ethically justifiable, because the future child with high probability will have the capacity to grow and develop (19,20).

Directive counseling for fetal benefit in cases of extreme prematurity of viable fetuses is appropriate. In particular, this is the case for what we term just-viable fetuses, those with a gestational age of 24 to 26 weeks, for which there are significant rates of survival but high rates of mortality and morbidity. These rates of morbidity and mortality can be increased by nonaggressive obstetric management, whereas aggressive obstetric management may favorably influence outcome. Thus, it appears that there are substantial beneficence-based obligations to just-viable fetuses to provide aggressive obstetric management. This is all the more the case in pregnancies beyond 26 weeks of gestational age. Therefore, directive counseling for fetal benefit is justified in all cases of extreme prematurity of viable fetuses, considered by itself. Of course, such directive counseling is appropriate only when it is based on documented efficacy of aggressive obstetric management for each fetal indication. For example, such efficacy has not been demonstrated for routine cesarean delivery to manage extreme prematurity.

Any directive counseling for fetal benefit must occur in the context of balancing beneficence-based obligations to the fetus against beneficence-based and autonomy-based obligations to the pregnant woman. Any such balancing must recognize that a pregnant woman is obligated only to take reasonable risks of medical interventions that are reliably expected to benefit the viable fetus or child later. A unique feature of obstetric ethics is that the pregnant woman's autonomy influences whether, in a particular case, the viable fetus ought to be regarded as presented to the physician.

Obviously, any strategy for directive counseling for fetal benefit that takes account of obligations to the pregnant woman must be open to the possibility of conflict between the physician's recommendation and a pregnant woman's autonomous decision to the contrary. Such conflict is best managed preventively through the informed consent process as an ongoing dialogue throughout a woman's pregnancy, augmented as necessary by negotiation and respectful persuasion (21).

The Previaable Fetal Patient

The only possible link between the previable fetus and the child it can become is the pregnant woman's autonomy. This is because technologic factors cannot result in the previable fetus becoming a child. The link, therefore, between a fetus and the child it can become when the fetus is previable can be established only by the pregnant woman's decision to confer the status of being a patient on her previable fetus. The previable fetus, therefore, has no claim to the status of being a patient independently of the pregnant woman's autonomy. The pregnant woman is free to withhold, confer, or, having once conferred, withdraw the status of being a patient on or from her previable fetus according to her own values and beliefs. The previable fetus is presented to the physician as a function of the pregnant woman's autonomy (4).

Counseling the pregnant woman regarding the management of her pregnancy when the fetus is previable should be nondirective in terms of continuing the pregnancy or having an abortion if she refuses to confer the status of being a patient on her fetus. If she does confer such status in a settled way, at that point beneficence-based obligations to her fetus come into existence, and directive counseling for fetal benefit becomes appropriate for these previable fetuses. Just as for viable fetuses, such counseling must take account of the presence and severity of fetal anomalies, extreme prematurity, and obligations owed to the pregnant woman.

For pregnancies in which the woman is uncertain about whether to confer such status, the authors propose that the fetus be provisionally regarded as a patient. This justifies directive counseling against behavior that can harm a fetus in significant and irreversible ways, for example, substance abuse, especially alcohol, until the woman settles on whether to confer the status of being a patient on the fetus.

In particular, nondirective counseling is appropriate in cases of what we term near-viable fetuses, that is, those that are 22 to 23 weeks of gestational age, for which there are anecdotal reports of survival (16,17,22). In our view, aggressive obstetric and neonatal management should be regarded as clinical investigation (a topic addressed in the next section of this chapter), not a standard of care. There is no obligation on the part of a pregnant woman to confer the status of being a patient on a near-viable fetus, because the efficacy of aggressive obstetric and neonatal management has yet to be proven (17).

ETHICS OF RESEARCH IN MATERNAL FETAL MEDICINE

Definition of Research

The definition of research in the federal regulations in the United States is the following: "an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge" (23).

Three Components of Research Ethics

The history of human experimentation appears to be coincident with the history of medicine. Concern about the scientific and ethical quality of research with human subjects begins to emerge in eighteenth-century medical ethics. One of major figures of that period, Dr. John Gregory (1724–1773) of Scotland, wrote the first modern medical ethics in the English language (24). He developed a research ethics to address the potential abuse of patients in the Royal Infirmary of Edinburgh by younger physicians anxious to establish their reputations. These physicians would pronounce Infirmary patients incurable, not to abandon them (which was the common practice), but to justify introducing experimental medicines into patient care.

Gregory condemned this practice. His first concern was that such experimentation was premature: standard remedies had not yet been attempted and shown to be ineffective in a patient's care. His second concern was that experimentation was often poorly designed. For example, compound drugs would be used without attention to the question of which elements of the compound might cause observed clinical effects. His third concern was that such physicians used the sick poor to advance their own reputational interests, subjecting them to unnecessary risk of clinical harm (a violation of the ethical principle of beneficence) out of personal self-interest. Gregory called this "sporting" with the sick poor; we now call it exploitation.

Gregory's research ethics introduced one of the key components of any adequate research ethics: the protection of research subjects. Such protection was gained by ensuring that there is a clinical justification for research and that the research is scientifically well designed. A second key component of any adequate research ethics, the consent of research subjects, was introduced in the nineteenth century.

Making a reasonable effort to prevent what is known as the *therapeutic misconception* is one of the major responsibilities of clinical investigators in the informed consent process. The therapeutic misconception occurs when potential subjects fail to appreciate that some aspects of what they will experience in a study are not justified by a clinical judgment of what is in the patient's health-related interest but by scientific considerations. Subjects, instead, confuse these scientific study design issues with regular medical care (25). For example, pregnant women being asked to enroll in a randomized fetal research trial should understand that intervention will be randomly selected rather than individually tailored by their physician's clinical judgment.

The need for both scientific and ethical integrity as components of research ethics was reinforced by the scientific and ethical catastrophe of the Nazi medical war crimes. A major result of the trials of the Nazi physicians was the promulgation of the Nuremberg Code. This is regarded as the founding document of contemporary research ethics and insists on sound scientific method and consent, which have become two of the three main components of research ethics globally (26).

The third and final key component of research ethics was introduced by the Declaration of Helsinki. It requires independent overview of clinical investigation, for both its scientific and its ethical integrity (26).

As a result of this centuries-long history of medical ethics, there has emerged an international consensus that there are three key components of research ethics: (27)

1. Clinical research with human subjects must be clinically justified and scientifically sound. The clinical need for research should be well established on the basis of a critical, evidence-based evaluation of current clinical practice. Clinical research should be well designed scientifically, with clearly stated research questions and testable hypotheses and a method adequate to test the hypotheses and this answers the research questions.
2. Informed consent is required. The Nuremberg Code did not allow any exceptions to this requirement, a position that is no longer part of the international consensus. It has been recognized in recent decades that there are populations of patients for whom we need to improve the quality of medical care but who cannot consent to becoming research subjects. This may be a result of the clinical circumstances of research (e.g., in emergencies where there is no time for the consent process) or the inability of the potential subject to engage in the informed consent process (e.g., fetuses).
3. Oversight of research is required. Investigators are obligated to prepare research protocols that establish clinical need, meet standards of scientific integrity, and describe the informed consent process (or justify its waiver) and submit protocols for prospective review by independent committees established for this purpose (known in the United States as Institutional Review Board and in most of the rest of the world as Research Ethics Committees).

Ethical Criteria for Innovation in Maternal–Fetal Medicine

Innovation in maternal–fetal medicine should begin with the design of an intervention and its implementation in animal models, followed by a single case and then case series. This rigorous approach is required to determine the feasibility, safety, and efficacy of innovations in fetal research. It is a basic tenet of research ethics that potential subjects should be protected from potentially harmful innovation. Three criteria must be satisfied in order to conduct such preliminary investigations in fetal research in an ethically responsible fashion, by taking into account beneficence-based obligations to the fetal patient and beneficence-based obligations to the pregnant woman. The previable fetus is a patient in these cases because, as explained above, the woman has made a decision to continue her pregnancy, in order to have the opportunity to gain the potential benefits of the innovation. She remains free to withdraw that status before viability:

1. the proposed fetal intervention is reliably expected on the basis of previous animal studies either to be life-saving or to prevent serious and irreversible disease, injury, or handicap for the fetus;
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 (which is required by beneficence and will satisfy

the U.S. research requirement of minimal risk to the fetus); (23) and

3. on the basis of animal studies and analysis of theoretical risks both for the current and for the future pregnancies, the mortality risk of the fetal intervention to the pregnant woman is reliably expected to be low and the risk of disease, injury, or handicap to the pregnant woman is reliably expected to be low or manageable (28).

The first two criteria are based on beneficence-based obligations to the fetal patient. Research on animal models should suggest that there would be therapeutic benefit without disproportionate iatrogenic fetal morbidity or mortality. If animal studies result in high rates of mortality or morbidity for the animal fetal subject, then innovation should not be introduced to human subjects until these rates improve in subsequent animal studies.

The third criterion reflects the fact that fetal intervention in the form of fetal surgery is necessarily also as maternal surgery and that ethically and clinically the fetal patient is not a separate patient. This criterion reminds investigators that the willingness of a subject, in this case, the pregnant woman, to consent to risk does not by itself establish whether the risk/benefit ratio is favorable. Judgments about an acceptable risk/benefit ratio should not be autonomy based, but beneficence based. This is because investigators have an independent beneficence-based obligation to protect human subjects from unreasonably risky research and should use beneficence-based, not autonomy-based, risk–benefit analyses. Phrases such as “maternal–fetal surgery” are useful if they remind investigators of the need for such comprehensive analysis. If they are used systematically to subordinate fetal interests to maternal interest and rights, and therefore to undermine the concept of the fetus as a patient in favor of the concept that the fetus is merely a part of the pregnant woman, such phrases lack ethical utility.

Ethical Criteria in Randomized Trials in Maternal–Fetal Medicine

Preliminary innovation should end and randomized clinical trials begin when there is clinical equipoise. Until recently, equipoise has meant that there is “a remaining disagreement in the expert clinical community, despite the available evidence, about the merits of the intervention to be tested” (26). Brody notes that one challenge here is identifying how much disagreement can remain for there still to be equipoise (26). Lilford has suggested that when two-thirds of the expert community, measured reliably, no longer disagree, equipoise is not satisfied (29).

This older concept of equipoise is based on the distribution of opinion in the clinical community, which may or may not be evidence based. To make judgments of equipoise more rigorous, it has been argued that it should be evidence based. This is known as normative equipoise or evidence based, which is the preferred concept (27). When evidence-based evaluation of clinical experience and the current literature supports the judgment that the experimental intervention is more harmful than nonintervention, equipoise cannot be achieved.

The satisfaction of the previous three criteria for innovation, with slight modifications, should count as equipoise in the expert community:

1. the initial case series indicates that the proposed fetal intervention is reliably expected either to be life-saving or to prevent serious and irreversible disease, injury, or handicap;
2. among possible alternative designs, the intervention continues to involve the least risk of morbidity and mortality to the fetus; and
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 handicap to the pregnant woman, including for future pregnancies, is reliably expected to be low or manageable (28).

One good test for the satisfaction of the first and third criteria is significant trends in the data from the case series. When evidence-based equipoise has been achieved on the basis of these three criteria, randomized clinical trials should commence. They must have relevant and clearly defined primary and secondary endpoints and a design and sample size adequate to measure these endpoints.

The above three criteria can be used in a straightforward manner to define stopping rules for randomized clinical trials in fetal research. When the data support a rigorous clinical judgment that the first or third criterion is not satisfied, the trial should be stopped.

Criteria for Making the Transition from Research to Clinical Practice

When a clinical trial in fetal research is completed, its outcome can be assessed to determine whether the investigational fetal intervention should be introduced into clinical practice. Trial results should meet the following three criteria in order to make this important transition:

1. the fetal intervention has a significant probability of being lifesaving or preventing serious or irreversible disease, injury, or handicap for the fetus;
2. the fetal intervention involves low mortality and low or manageable risk of serious and irreversible disease, injury, or handicap to the fetus; and
3. the mortality risk to the pregnant woman is low and the risk of disease, injury, or handicap is low or manageable, including for future pregnancies (28).

Brody has underscored the value of data safety and monitoring boards to prevent investigator bias and to protect subjects (26). Such boards should be used in fetal research, especially to ensure adherence of the above-mentioned ethical criteria as a basis for monitoring such research.

CONCLUSION

Ethics is an essential dimension of clinical practice and research in maternal–fetal medicine. An understanding and clinical application of the ethical principles of beneficence and respect for autonomy and of the ethical concept of the fetus as a patient should guide clinicians and investigators, to better serve pregnant and fetal patients.

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