Ethical Dimensions of the Number of Embryos to be Transferred in In Vitro Fertilization

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Purpose: We propose an ethically justified policy for the number of embryos to transfer in an in vitro fertilization (IVF), by considering four factors: medical outcomes, patient's preferences, costs, and market forces of providers.

Methods: We develop an ethical framework that incorporates three ethical principles: beneficence, respect for autonomy, and justice; and three professional virtues: integrity, compassion, and self-sacrifice.

Results: This ethical framework calls for an informed consent process for IVF that provides: information about medical outcomes; information about the risks of multiple gestation; the opportunity to weigh the goal of pregnancy and live birth against the medical and moral risks of multiple gestation; evidence-based recommendations; protection of the woman from potentially coercive influences; and discussion of living with infertility and going to better centers.

Conclusion: The number of embryos to be transferred in IVF should mainly be a function of the pregnant women's informed decision. Limiting the number of transferred embryos to two in all cases is not ethically justified at this time.

KEY WORDS: ethics; in vitro fertilization; embryo transfer; informed consent.

INTRODUCTION

How many embryos to transfer in in vitro fertilization (IVF) cycles is a current controversy in assisted reproductive technologies (1–14). In our judgment, four main factors shape this controversy. First, the issue is addressed by the medical outcomes of pregnancy rate, live-birth rate, and the rate of multiple pregnancies stratified by high-risk groups and techniques. This first factor dominates the literature. However, three other factors have been discussed: the role of the patient's preferences; costs; and market forces of providers. There is an obvious need for an ethical framework that integrates all four factors into a coherent, clinically applicable account of the doctor's responsibility regarding the number of embryos to be transferred in IVF. Ethics provides the conceptual and clinical tools for creating such an account (12). The purpose of this paper is to present and defend an ethical framework for addressing how many embryos to transfer in IVF.

An Ethical Framework

Ethics is the disciplined study of morality and proceeds by asking in the medical context, What are the doctor's moral responsibilities to the patient, to health care organizations, and to society (12)? Throughout its history, medical ethics has successfully addressed many clinical controversies. It has done so utilizing the secular philosophical tools of ethical principles and professional virtues (15).

The ethical principle of beneficence has been developed since the time of Hippocrates in Western medical ethics to identify the physician's responsibilities to protect and promote the health-related

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interests of the patient, as these are understood from a rigorous clinical perspective. The principle of beneficence includes the principle of nonmaleficence (*Primum non nocere*). The principle of respect for autonomy has been developed in the 19th and 20th centuries to identify the physician's responsibility to protect and promote the patient's interest, as these are understood from the patient's perspective. The principle of justice, developed since the 18th century, identifies the physician's responsibilities to protect and promote the interests of health care organizations and society, particularly their economic interests in the allocation of scarce resources (12,16).

The professional virtues were developed in the 18th century in the English language literature of medical ethics by two physician-philosophers, Drs John Gregory and Thomas Percival (17–19). Their goal in writing and teaching medical ethics was to reform the marketplace, entrepreneurial, self-interested practice of medicine followed by most physicians of their time. Gregory and Percival called for a professional life of service to patients grounded in the professional virtues of the physician as moral fiduciary of the patient. These virtues create moral responsibilities for physicians by blunting self-interest and making the patients' interests the primary consideration in the physician's moral life. Two such virtues are especially relevant here (12). Self-sacrifice creates the responsibility to make reasonable sacrifices of self-interest, e.g., income and prestige, as required to protect the health-related interests of the patients. Integrity creates the responsibility to practice medicine consistently according to standards of intellectual and moral excellence. Practicing medicine according to the best evidence, as opposed to idiosyncratic bias, is required by the professional virtue of integrity.

The purpose of an ethical framework for clinical decision-making and practice is to integrate these principles and virtues into a coherent approach to guide and evaluate clinical judgment and practice. One does so by treating each principle and virtue as *prima facie*, i.e., as binding unless it is shown by argument to be overridden by another principle or virtue (16). This approach avoids the intellectual gridlock and clinical disutility of absolute principles and virtues, i.e., treating them as never allowing exceptions. A framework of *prima facie* principles and virtues makes possible more nuanced, and therefore more clinically applicable judgments about the physi-

cian's moral responsibility in matters of clinical controversy (12).

Beneficence-Based Considerations

In using IVF, the physician has beneficence-based obligations to the woman who wants to become pregnant and to fetal patients and future possible children who will result from the process. Beneficence-based obligations to the woman balance pregnancy success rates against the health-related risks of pregnancy with multiple gestations. The replacement of more embryos (provided that the replacement of more embryos results in higher pregnancy and live-birth rates) favors success rates, while the replacement of fewer embryos (provided that the replacement of fewer embryos results in fewer multiple gestations) reduces risks of multiple pregnancy. Considered by itself, the principle of beneficence, applied to the pregnant woman's health-related interests, does not automatically favor either more or fewer embryos being replaced.

In using IVF, the physician also has beneficence-based obligations to the fetal patient. The authors have argued elsewhere for this basic concept of obstetric and reproductive medical ethics (12). Four points of this argument are especially relevant in order to apply the principle of beneficence to the fetal patient. First, the concept of the fetus as patient does not rely on the concept of fetal rights or fetal personhood, in particular, the right to life. Second, for the previable fetus, the woman's autonomous decision to confer the status of being a patient is a necessary condition. Therefore not all previable fetuses are patients. Patienthood status is not dependent on geography (in vitro vs. in vivo), but rather dependent on the woman establishing a linkage between the fetus and the child the fetus can later become. Third, a woman is free to withdraw the status of being a patient from the previable embryo even when she has previously conferred such status. Therefore, within beneficence-based clinical judgement, abortion or fetal reductions are ethically justifiable options prior to fetal viability, because these do not involve killing a patient, which is (usually) prohibited in medical ethics.

Concerning the application of the principle of beneficence and the concept of the fetal patient, two subgroups should be considered. If fetal reduction is not an option (i.e., the woman would not withdraw the status of being a patient from any fetus), and the IVF procedure results in possibly more than two

gestations and definitely more than three gestations, the health-related interests of the fetal patients are adversely affected by increased morbidity and mortality from prematurity risks (20). In this situation when fetal reduction is not an option for the woman, based on her moral commitments and judgments, there is a strong beneficence-based obligation to replace fewer embryos.

In the situation where fetal reduction is an option of the pregnant woman, this strong beneficence-based obligation to replace fewer embryos is mitigated, but not entirely. This is because fetal reduction has an intrinsic risk of loss of the entire pregnancy.

Autonomy-Based Considerations

The principle of respect for autonomy is put into clinical practice through the informed consent process. This process has three basic elements: 1) the physician's obligation to disclose an adequate amount of information about the clinical benefits and risks of IVF in terms of the number of embryos to be replaced, and high-risk groups and techniques; 2) the patient's understanding of this information; and 3) the patient's process of deciding, including making a voluntary decision (12,16,21).

Beneficence-based clinical judgments and recommendations depend on the competence of physicians to evaluate patients' health-related interests. While pregnancy and childbirth have health-related aspects, the decisions to become pregnant, how aggressively to pursue treatment of infertility, and how many children should result from infertility treatment within beneficence-based constraints about excessive risks, appeal predominantly to nonhealth-related values such as personal preference, family traditions and expectations, economics and social resources, and religious beliefs. Medical education per se does not bestow authoritative judgment, nor should it be relied upon solely. These matters appropriately therefore fall under respect for autonomy. Thus, the woman's preference concerning how many children she would like to result from IVF treatment must be taken into clinical account in determining the number of embryos transferred (12).

Decisions about IVF for the woman are cognitively demanding, as are many other clinical decisions made by patients. When patients struggle with such cognitively demanding decisions, the principle of respect for autonomy creates a responsibility for physicians to structure the consent process in ways that em-

power the patient's decision-making capacities. Fisk and Trew have recently suggested that "even with counseling, the risks of triplets are generally underestimated by parents (1)." They conclude that the number of embryos to replace should not be left to the woman's choice. We disagree. Instead, woman should be assisted as necessary to estimate such risks reliably and balance them against the benefits of IVF. Fisk and Trew provide no evidence that woman are incapable of benefiting from such assistance or performing this cognitively demanding task. They do suggest that assisted reproduction technology (ART) specialists are distanced from clinical practice. However in our view, most ART practitioners are especially cognizant of such risks. Some patients may find it useful to consult with maternal-fetal and neonatal specialists who have experience with multiple gestations and can explain risks and benefits and assist her in her decision-making process.

Some may be skeptical about the pressures on voluntary decision making by women seeking IVF, thereby weakening autonomy-based obligations. We disagree, because autonomy-based obligations remain intact and take the form of efforts to shield women from undue pressure from family members, and take the necessary time to elicit from her her values and preferences, and assure her that the physician will support her in whatever decision she ultimately makes.

Another crucial responsibility regarding respect for autonomy is for the physician to take steps to ensure that the pregnant woman's decision about conferring or withdrawing patient status on the previable fetus(es) is ultimately hers. She is free to take account of the preferences of her partner, husband, or other family members and should be assured that they do not control this decision. In particular, while the husband and father's interests are surely at stake, there is obvious moral asymmetry in that the burdens of pregnancy, fetal reduction, and childbirth fall on the woman and not the husband (12).

In fulfilling the disclosure of obligation of the consent process, the physician is obligated to present and explain only medically reasonable alternatives, i.e., those that are expected on balance to protect the patient's health-related interests. Ineffective or harmful alternatives, should not be offered. The patient exercises autonomy to select the medically reasonable alternatives, not to define what those are. When adding embryos does not increase pregnancy or live-birth rates, then that number adds no

benefit, but introduces incremental risk of multiple gestation and therefore is medically unreasonable. When added embryos decrease pregnancy or live-birth rates they are intrinsically harmful and also add to the risk of multiple gestation, making them even more medically unreasonable. It has long been known that good ethics should be based upon good facts. Currently the facts appear to support that pregnancy and live-birth rates increase when more than two embryos are placed, especially for certain high-risk groups. Thus, Fisk and Trew's assertion "... but practice now is transfer of two embryos at IVF..." (1) appears to be scientifically, and therefore ethically, flawed as the basis of clinical practice and informed consent.

Justice-Based Considerations

There are major justice-based issues about IVF and about assisted reproduction technologies generally. Chief among these is whether these services should be covered by insurance and national health plans, and to what degree. This is a very large issue because it concerns rights or entitlements to health care and health care policy, and whether infertility is or is not a disease, topics far beyond the scope of this paper. The authors believe that infertility is a serious condition worthy of medical attention.

One major justice-based consideration is the legitimacy of policy constraints on the maximum number of embryos to be transferred. In Europe, such constraints between the government's responsibility to manage scarce health care resources and the patient's right of access to medically reasonable alternatives to manage infertility (when assisted reproductive technologies are available). Policies that limit the number of embryos as transferred to less than numbers that, on the basis of available evidence, increase live-birth rates, violate autonomy-based considerations, and to this extent, lack legitimacy.

Faber has recently called attention to another justice-based consideration that is relevant in the United States, where most insurance plans do not cover ART procedures, but do cover pregnancy. Thus patients take economic risks in starting a pregnancy, but not in continuing it. Thus, from the perspective of payers, a perverse economic incentive is introduced that gives patients little reason to take into account the overall subsequent costs of managing pregnancies initiated by IVF and ART (11). This is obviously an incoherent policy that, like all incoherent health care policy, strains against the demands of justice.

Virtue-Based Considerations

As in many other medical specialties, when patient services in IVF produce a significant revenue stream, and when patient services bring prestige to individual, physicians and their sponsoring institutions, self-interest can become a predominant consideration for the physician. This threatens the physician's professional virtues.

Professional integrity requires vigorous adherence to the responsibilities of the informed consent process. In particular, the woman seeking IVF services should be provided with institution-specific information about that institution's outcomes of pregnancy rates, live-birth rates, and rates of multiple gestation per number of embryos transferred, stratified by high-risk group, embryo quality, and techniques used, as well as national information on the same parameters, so that the patient can make an informed comparative choice. However, there are limitations and perhaps even bias related to patient selection and practice in registries that can affect outcomes. Individual physicians and centers must be willing to accept the consequences of the virtue of self-sacrifice when patients, on the basis of this information, elect to go to centers with better outcomes. After all, IVF services in the United States function in a marketplace model and the ethics of the market strictly require informed consumer choice. Thus, failure to provide such information violates the virtues of integrity and self-sacrifice and the ethics of the market.

Professional integrity also requires that the informed consent process be as free as possible from the bias introduced by self-interest, e.g., a physician who starts the informed consent process by emphasizing the increased pregnancy rates from added embryos while underemphasizing the risks of multiple gestation, in order to gain market advantage from high-pregnancy rates. This is obviously inappropriate and self-sacrifice as well as integrity prohibit this morally corrupt practice.

CONCLUSION

The question of the number of embryos to be transferred is part of a larger question, namely what the informed consent process should be for IVF services. First, the patient should be provided with comparative information about the relationship between the number of embryos transferred and increased pregnancy and live-birth rates stratified by high-risk factors and techniques. Limits on appropriate numbers

to be transferred, based upon these outcomes, should be explained, such as those recently approved by the American Society for Reproductive Medicine (ASRM) (6). Second, the patient should be provided with information about multiple gestation and assisted to understand and appreciate these risks (22), i.e., that they could happen to her and the children she would like to have. Third, the woman should be assisted to weigh the goal of pregnancy and live-birth versus multiple gestation. In particular, she needs to consider on the basis of her values and commitments, the moral risk of IVF, namely, confronting the unwelcome or even abhorrent alternative of abortion in the form of fetal reduction. Fourth, evidence-based recommendations with the goals of maximizing pregnancy and live-birth rates and minimizing the risks of multiple gestations should be made at this point. Fifth, the physician should be alert to potentially coercive influences on the woman's decision making and seek to protect her from them. Sixth, the physician should discuss the alternative treatments and their relative success rates and risks as well as the alternative of living with infertility and going to better centers, to protect the patient from undue forms of self-interest and to implement the ethics of the market. The number of embryos to be replaced in IVF should therefore be a function of the woman's autonomy, exercised in an informed consent process shaped by these ethical considerations.

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