

Provision of fertility services for women at increased risk of complications during fertility treatment or pregnancy: an Ethics Committee opinion

Ethics Committee of the American Society for Reproductive Medicine

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This opinion addresses the ethics of providing fertility treatment to women at elevated risk from fertility treatment or pregnancy. Providers ethically may treat women at elevated risk provided that they are carefully assessed; that specialists in their medical condition are consulted as appropriate; and that patients are fully informed about risks, benefits, and alternatives, including oocyte and embryo donation, use of a gestational surrogate, not undergoing fertility care, and adoption. Providers also may conclude that the risks are too high for them to treat particular patients ethically; such determinations must be made in a medically objective and unbiased manner and patients must be fully informed of the decision. Counseling of women who wish to initiate fertility treatment with underlying medical conditions that confer increased risk during treatment or pregnancy should incorporate the most current knowledge available, being cognizant of the woman's personal determinants in relation to her reproductive desires. In such a way, both physician and patient will optimize decision making in an ethically sound, patient-supportive context. (Fertil Steril® 2016; ■:■-■. ©2016 by American Society for Reproductive Medicine.)

Key Words: Fertility treatment, assisted reproductive technology, ethics, complications, high risk pregnancy

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KEY POINTS

- All patients presenting for fertility services should be assessed for their risk of complications during treatment and pregnancy.
- Clinicians should thoroughly counsel women at increased risk of complications during fertility treatment or pregnancy regarding these risks. Such counseling will often involve subspecialists in maternal-fetal medicine and physicians with expertise in the woman's medical condition in order to optimally convey the risks to her, her pregnancy, and the resulting child. Such counseling should occur in advance of a decision

to initiate or decline to initiate treatment.

- Reproductive liberty is a core value in the provision of fertility care and includes the right of individuals to make informed choices about whether and how to reproduce. Reproductive liberty also means the right to receive fertility care in a non-discriminatory manner. Clinicians may ethically treat a woman at elevated risk if the patient is fully informed of her risks, benefits, and alternatives. Clinicians also may decline to provide care based on evidence-based, reasoned judgments that the risks of mortality or morbidity from fertility treatment

or pregnancy are too high for treatment to be provided ethically and with professional integrity. In situations where a physician either provides or declines to provide reproductive assistance to a high-risk woman, it is appropriate to recommend that the patient obtain a second opinion from experts both within and outside the field of reproductive medicine.

- Whenever possible, physicians should encourage patients to reduce their modifiable risk factors. In cases where the patient is unable or unwilling to modify her risk, physicians may differ regarding whether or not to treat the patient. Treatment decisions must be based on medical considerations and applied without bias. It is acceptable for physicians to decline to provide fertility treatment.
- Clinicians may differ ethically about what constitutes a reasonable level

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of risk to the pregnant woman. Clinicians must make these judgments in a non-discriminatory fashion and without bias. It is ethically acceptable for clinicians, based on their unbiased assessments of risk, to decline fertility treatment to women at high risk of complications to themselves or their resulting children. Counseling a woman at high risk of complications to her, her pregnancy, or the resulting child should include a discussion of alternatives to her carrying a pregnancy, such as the pregnancy being carried by a gestational carrier, adoption, or foregoing fertility treatment. The impact of cost and how it may limit available options should be included as part of this discussion.

- Clinicians should encourage high-risk women to involve their parenting partner, if present, in deciding whether to undergo fertility treatment. In doing so, care should be taken to support the autonomy of the woman, as she is the one who ultimately bears the greatest burden from treatment and pregnancy. To protect patient autonomy, reasonable efforts should be made to ensure that women at increased risk of complications have chosen to initiate fertility treatment independently and without undue influence from others.
- When clinicians determine that a fertility treatment or the resulting pregnancy may pose increased risk, consideration should be given to providing care in a setting that can best meet the patient's needs. Often, the involvement of a center with expertise in treating her particular medical condition during part or all of her care will be helpful in achieving this goal.

INTRODUCTION

Generally, when women become pregnant they anticipate that at the end of their pregnancy both they and their newborns will be healthy. In most cases, this is the outcome. Indeed, maternal mortality in the U.S. is approximately 17.8 per 100,000 women (1). There is some controversy as to whether maternal mortality is overall increased or decreased in women using in vitro fertilization (IVF) (2, 3). Regardless of the baseline risk to women conceiving with IVF, it is clear that some women are at higher risk of having complications during either fertility treatment or the ensuing pregnancy due to underlying and pre-existing conditions. Women who do not need help conceiving usually decide whether to try to become pregnant or continue their pregnancy in the privacy of their own homes and within their individual social structures. For those women who will require medical assistance to conceive, a discussion of the risks and benefits of pregnancy can occur prior to conception between the woman, her partner (if she has one), and the reproductive medicine professional(s). When prospective patients are at increased treatment- or pregnancy-related risks, the provider's approach to counseling should take these risks into account. Women at higher risk of complications resulting from fertility treatment or pregnancy include those with disorders such as Turner syndrome, end-stage renal disease or a history of cardiomyopathy. In addition to routine counseling in advance of initiating fertility treatment, which includes a discussion regarding risks such as ovarian hyperstimulation

syndrome (OHSS) and multiple gestation, reproductive endocrinologists should take particular care to counsel women with specific treatment- or pregnancy-related risks so that they are able to make informed decisions regarding their reproductive care. Recently, a preconception risk stratification tool has been developed to help physicians assess and counsel women who are at increased risk for complications during treatment or pregnancy (4).

RISKS INHERENT TO FERTILITY TREATMENT

Women who undergo fertility treatment may face increased risks both during the process of conceiving and during pregnancy. These risks can be divided into those resulting from the treatment and those relating to the pregnancy itself. Stimulation-related risks include OHSS and an increased incidence of thromboembolic events such as deep venous thrombosis and pulmonary embolism. Pregnancy-related risks include an increased incidence of ectopic gestation and its associated morbidity and mortality. Another risk is that of multiple gestation, which includes a higher incidence of prematurity, gestational diabetes, and preeclampsia. This risk can be minimized by avoiding controlled ovarian hyperstimulation cycles with intrauterine insemination (IUI) in favor of IVF, and by adhering to protocols that strictly limit the number of embryos transferred during IVF (5). While these risks apply to some extent to all women undergoing fertility treatment, certain populations of women are at higher risk of complications during this process. These include women with medical conditions such as underlying thrombophilias who are at increased risk of clotting disorders, obese women, and women with polycystic ovary syndrome. These also include women with psychiatric disorders that may be exacerbated by the hormonal changes of ovarian stimulation, by the increased stress that fertility treatments can induce, and by the decision to discontinue their psychotropic medication (6).

RELATIVE VERSUS ABSOLUTE CONTRAINDICATIONS TO PREGNANCY

For most women, even those with significant comorbidities, pregnancy remains a reasonable option. Women with underlying medical conditions may require increased monitoring by subspecialists in maternal-fetal medicine during pregnancy, as well as consultation with specialists outside the field of obstetrics. They may also benefit from receiving some or all of their care at a medical center with expertise in treating their particular medical condition during part or all of their care. Reproductive endocrinologists play a vital role in identifying which women are at increased risk of treatment- and pregnancy-related complications, and of delineating the magnitude of this increase as part of the fertility evaluation. This may include obtaining background studies and seeking out consultation from experts to assist in counseling the patient such that she is fully informed of her risks when entering a pregnancy, and ensuring that she start fertility treatment and become pregnant in as healthy a state as possible. This also includes having a plan of care which includes the provision of a safe and seamless transfer of care to a provider or center that can best meet her needs once the patient becomes pregnant.

Some risks are modifiable, and patients should be strongly encouraged to optimize their health prior to attempting pregnancy. These include changes such as weight loss, smoking cessation, and optimal blood sugar control in diabetics.

For most preexisting conditions and comorbidities, pregnancy will be possible with appropriate planning. While it is true that a woman may choose to become pregnant without assistance regardless of the risk that this poses to her, it is less clear whether physicians ethically may or must offer fertility treatment to women regardless of the health risks posed by such treatment or resulting pregnancy. There may be situations in which the reproductive endocrinologist reasonably determines it is not sufficiently safe to provide fertility services to a woman at increased risk of treatment- or pregnancy-related complications and therefore justifiably declines to provide fertility assistance. Prior to making this determination, the reproductive endocrinologist should seek out consultation from specialists expert in the patient's particular condition to further delineate her risk. When care is declined, it should be done after careful consideration of the medical facts and without bias. It is ethically acceptable for clinicians, based on their evidence-based and unbiased assessments of risk, to decline fertility treatment to women at high risk of complications to themselves or their children. Similarly, the Ethics Committee has previously determined that it is ethically acceptable to decline to provide fertility care in light of unbiased assessments about risks to future offspring (6).

Patients should be provided with meaningful counseling regarding the differences between absolute and relative risk. An increase in relative risk, when absolute risk is low, may be of different ethical significance than an increase in relative risk when absolute risk is high. For example, for a 1/1,000 absolute risk, a 100% increase in relative risk brings the risk to 2/1,000. However, for a 1/10 absolute risk, it brings the risk to 2/10, etc. Some discussions in the literature point out the importance of explaining this distinction to patients in determining what risks are reasonable (7).

RISKS ASSOCIATED WITH UNDERLYING MEDICAL CONDITIONS OR DISEASE PREDISPOSITION

Examples of comorbidities that may provide exceedingly high absolute risks in pregnancy include Turner syndrome, which carries a 3.3% risk of potentially life threatening complications (8) and 2% risk of mortality (9). Some patients with Turner syndrome, particularly those with an aortic size index $>2.0 \text{ cm/m}^2$, are particularly at risk for pregnancy-associated morbidity and mortality. According to the ASRM Practice Committee, this finding represents an absolute contraindication for attempting pregnancy (9). Another example is a subsequent pregnancy in women with peripartum cardiomyopathy. When persistent left ventricular dysfunction is present, a 9% mortality rate was reported in one study (10). A final example is a report describing women with primary pulmonary hypertension as having as high as a 33% maternal mortality rate (11).

In cases of significantly heightened absolute risk, counseling is crucial. The level of risk that a woman judges to be

acceptable will likely depend on a constellation of factors. These include the risk to her and her pregnancy, the risk to her fetus, her level of risk aversion, and the development of a plan of action in case complications arise. Additionally, the availability and extent of her support system and social structure may play a role in the level of risk she is willing to take. This includes the presence and willingness of someone to provide care for her during the pregnancy as well as someone to care for the resulting offspring should she become too sick to do so or in the event of her death. This also includes whether she already has individuals who depend on her to care for them, including children and older dependent adults. Women may differ in the decisions they make, based on their unique situations, coupled with the potential risks that fertility treatment and pregnancy may pose for them. Fertility preservation and pregnancy in patients with cancer may also raise ethical issues due to risk during treatment and pregnancy, and is discussed in detail elsewhere (12).

MODIFIABLE RISK FACTORS

In some cases, the risks associated with fertility treatment or pregnancy can be modified. Reflecting a commitment to patient safety, clinicians and patients should work toward decreasing risk whenever possible. Sometimes the modifications involve clinical treatment decisions, and other times they involve improving patient health determinants. Some examples of modifiable risk factors include decisions about the number of embryos to transfer (5). With single-embryo transfer, the risk of twins and high-order multiples can be significantly reduced. Similarly, limiting the amount of gonadotropins used to stimulate the ovaries or using an alternate ovulation trigger and cryopreserving all embryos for later use can decrease OHSS risk and therefore reduce risk of untoward health outcomes for the woman undergoing IVF or controlled ovarian hyperstimulation.

There are times when it is not the fertility treatment but the resulting pregnancy that confers increased risk. For example, when a patient is obese, she should be encouraged to delay treatment to allow time for weight loss. Women with uncontrolled medical conditions such as diabetes may benefit from a delay of treatment until the disease is adequately managed. Delaying treatment must be balanced with the risk of declining fertility with increasing age. One option to consider is performing IVF in a timely fashion and cryopreserving embryos or oocytes, but delaying pregnancy until the modifiable risk factors are decreased. For example, a woman diagnosed with breast cancer may benefit from timely IVF but a delay in transferring her embryos until she has completed the prescribed course of adjuvant therapy.

SITUATIONS IN WHICH RISK TO THE PATIENT ALSO CONFERS RISK TO THE RESULTING CHILD

In some situations, a woman entering a risky pregnancy is also endangering the health and well-being of her intended child. One example is the case of Ehlers-Danlos syndrome. This is an autosomal dominant genetic disorder which can have severe vascular complications (aortic dissection, arterial

rupture) and which has one of the highest maternal mortality rates of any condition. There are various reports of maternal mortality in the literature, with one study reporting a 6.5% overall risk of maternal death (13, 14). Women with Ehlers-Danlos who undertake pregnancy not only endanger their lives but also convey a 50% chance of transferring the very disease that places them at high risk of death to their offspring. These situations raise especially difficult ethical questions. Such women could undergo preimplantation genetic testing (PGT) for the purpose of selecting an unaffected child, but the pregnancy would still place her at increased risk of complications. Choosing to transfer the unaffected embryos into a gestational carrier would remove both the pregnancy-related risks to the patient and the disease-related risks to the resulting child. In such cases, attention should be paid not only to the desires of the woman, but also to the cost of genetic analysis and third-party reproduction. Cost may present a barrier to care for some women, and this may lead them to choose riskier options. Such options may be acceptable, when the woman is fully informed of the risks that she is taking and those that she is potentially conferring on any resulting children. In other situations, such as women at high risk of severe preeclampsia (due for example to a history of previous preeclampsia, a history of renal transplantation, or systemic lupus erythematosus), the risks to the mother also confer risks to the child, primarily relating to prematurity. Decisions to pursue or decline fertility treatment are best made carefully and after insightful deliberation and expert consultation among the patient, her physician, and outside experts when warranted.

ETHICAL CONSIDERATIONS

Reproductive liberty is a core value in the provision of fertility care and includes the right of individuals to make informed choices about whether and how to reproduce.

Women for whom pregnancy presents elevated risks may decide to try to conceive without assistance, and once pregnant should receive the best available medical care. Some women at elevated risk may need assistance in becoming pregnant, and the importance of reproductive choice supports access to treatment for them. Nonetheless, different interests in reproduction may be at issue, and women and their physicians may weigh these interests differently. For some women, fertility treatment may enable them to bear a child with their own gametes and the gametes of their chosen partner. Others may be able to provide their own oocytes and transfer the resultant embryos into a gestational carrier, achieving a genetically related child without the experience of pregnancy. For still others, such as patients with premature ovarian failure or those whose ovarian reserve has been adversely affected by chemotherapy, pregnancy may be achieved but with donated gametes; these women may want the experience of pregnancy and birth but will not be able to have a genetically related child.

The value of reproductive choice is a primary consideration in favor of treating women at elevated risk. In such contexts, it is especially important to ensure that choices are made without pressure and are well informed. Patients may lack needed information, may receive misleading information from other

sources, or may be pressured by family members or cultural contexts to try to achieve pregnancy or the birth of a genetically related child. In light of these concerns, providers must work with patients to explore their reasons for choosing treatment and their understanding of risks and alternatives. Providers should make a reasonable effort to ensure that patients fully appreciate the risks to themselves and their potential offspring. Providers must counsel patients about alternatives that might be available to them, such as oocyte donation or use of a gestational surrogate to carry their pregnancy.

Conversely, providers may be concerned that women at elevated risk may be under especially strong personal or social pressures to achieve reproduction. These pressures may make informed consent difficult, in which case the argument from reproductive choice is undermined. Some ethicists have argued that professional duties require providers to act in the best health-related interests of their patients. If so, providers who believe that ovarian stimulation or pregnancy is not in the best health-related interests of their patients will choose not to offer fertility treatment to these women (15). In such cases, it is reasonable to obtain a second opinion to ensure that the physician's clinical assessment is reasonable and made without bias.

Providers may also be concerned that pregnancy in some high-risk women poses risks to the fetus. In the context of human immunodeficiency virus (HIV), for example, ASRM has taken the position that it is ethical to provide fertility care if all reasonable precautions to guard against maternal transmission of HIV to the fetus are undertaken (16). Other high-risk situations include women with uncontrolled diabetes, increasing the risk of congenital anomalies to the resulting children.

Another concern is that some women at higher risk may not survive pregnancy or may be unable to care for their children until they reach adulthood (17). Such an argument may also apply to those conceiving at advanced ages (18). These issues should be explored with the woman. She should be encouraged to involve her partner, if she has one, in these discussions.

Providers thus may reasonably differ on the level of elevated risk they are willing to accept in treating patients. In making such judgments, providers may benefit from seeking the assistance of specialists in the patient's condition, both to minimize risks of fertility care and pregnancy, and to assure that judgments are fully informed. Providers must also be careful to guard against bias arising from nonmedical factors or unrelated to patient well-being when providing or declining fertility care.

PROFESSIONAL JUDGMENT—CHOOSING TO PROVIDE OR DECLINE TREATMENT

In providing fertility treatment, physicians have the professional responsibility to assess the baseline health of the woman and her treatment and pregnancy-associated risks. When patients face increased risks that are modifiable in ways that reduce risks, efforts should be made to decrease these risks (19). Some examples include weight loss, smoking cessation, and blood sugar regulation in diabetics. In cases where the patient is unable or unwilling to modify their risk, physicians may differ regarding whether or not to treat

the patient. So long as treatment decisions are based on reasonable medical considerations and applied without bias, physician autonomy should be respected.

In some cases, due to an evidence-based concern, the physician may determine that it is unsafe to provide care due to a concern that the morbidity and mortality to the woman and potentially her offspring may be too high. In such cases, the reproductive endocrinologist should seek expert advice, including relevant practice guidelines (9) regarding the actual risks to the woman and her offspring. Asking the woman to obtain a second opinion should be considered as part of a reasonable effort to ensure that there is some consensus regarding the level of risk to her, her pregnancy, and the resulting child. When declining to provide treatment, physicians must ensure that these decisions are made after careful consideration of the medical facts and without bias toward the woman or her partner. Such bias could include the physician's feelings towards the patient's age, ethnicity, socioeconomic status, parenting unit, medical condition or disability. In cases where the underlying disease is caused by behavioral factors such as smoking or alcohol intake, the physician may have bias as well. It is important for physicians to fully assess their reasons for denying care, and ensure that it is not discriminatory.

CONCLUSIONS

When women are at elevated risk from fertility treatment or pregnancy, decisions about whether to undergo treatment are difficult. In such cases, clinicians must carefully assess the patient, and this may include consulting other specialists knowledgeable about the patient's condition and treatment risks. Clinicians must thoroughly counsel patients about risks of treatment, methods for modifying risks, and available alternatives including oocyte and embryo donation, gestational surrogacy, and adoption. Clinicians must make reasonable efforts to ensure that patients' decisions are voluntary and not pressured by external circumstances. Based on unbiased, evidence-based judgments, clinicians may also conclude that risks are too high for them to ethically provide care and decline treatment as a result. These decisions must be made in a sound, patient-supportive context.

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Women at increased risk of complications during fertility treatment or pregnancy should be counseled appropriately about their risks. Physicians should be able to treat or decline to treat such women based on a medically supported and unbiased assessment of patient risks.