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Committee on Obstetric Practice
Committee on Genetics

The American Society for Reproductive Medicine and the Society for Maternal–Fetal Medicine endorse this document. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the Committee on Genetics in collaboration with committee members James Sumners, MD and Jeffrey L. Ecker, MD, and the U.S. Food and Drug Administration's representative member Rhonda Hearns–Stokes, MD. The views do not necessarily represent those of the Food and Drug Administration or the U.S. government.

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Perinatal Risks Associated With Assisted Reproductive Technology

ABSTRACT: Over the past decades, the use of assisted reproductive technology (ART) has increased dramatically worldwide and has made pregnancy possible for many infertile couples. Although the perinatal risks that may be associated with ART and ovulation induction are much higher in multifetal gestations, even singletons achieved with ART and ovulation induction may be at higher risk than singletons from naturally occurring pregnancies. However, it remains unclear to what extent these associations might be related to the underlying cause(s) of infertility. Before initiating ART or ovulation induction procedures, obstetrician–gynecologists and other health care providers should complete a thorough medical evaluation to ensure that patients are in good health and should counsel these women about the risks associated with treatment. Any maternal health problems or inherited conditions should be addressed. Couples at risk of passing genetic conditions on to their offspring, including those due to infertility-associated conditions, should be counseled appropriately. When a higher-order (triplet or more) multifetal pregnancy is encountered, the option of multifetal reduction should be discussed. In the case of a continuing higher-order multifetal pregnancy, ongoing obstetric care should be with an obstetrician–gynecologist or other obstetric care provider and at a facility capable of managing anticipated risks and outcomes.

Recommendations

Based on the available data and expert opinion, the American College of Obstetricians and Gynecologists (ACOG) makes the following recommendations:

- Perinatal risks that may be associated with assisted reproductive technology (ART) and ovulation induction include multifetal gestations, prematurity, low birth weight, small for gestational age, perinatal mortality, cesarean delivery, placenta previa, abruptio placentae, preeclampsia, and birth defects. Although these risks are much higher in multifetal gestations, even singletons achieved with ART and ovulation induction may be at higher risk than singletons from naturally occurring pregnancies. However, it remains unclear to what extent these associations might be related to the underlying cause(s) of infertility. Patients who plan to use assisted reproductive technologies should be counseled about using this information.
- With ART and ovulation induction, higher-order multifetal pregnancy may occur. Multifetal pregnancy and its associated outcomes is the greatest risk of ART and ovulation induction and, consequently, every effort should be made to achieve a singleton gestation. These efforts include following professional society guidelines for number of embryos to be transferred, such as those from the American Society for Reproductive Medicine (ASRM), and continuing to encourage and expand use of single-embryo transfer. Patients and couples should be counseled

about the risks of multifetal gestation with these techniques.

- Before initiating ART or ovulation induction procedures, obstetrician–gynecologists and other health care providers should complete a thorough medical evaluation to ensure that patients are in good health and should counsel these women about the risks associated with treatment. Any maternal health problems or inherited conditions should be addressed.
- Couples at risk of passing genetic conditions on to their offspring, including those due to infertility-associated conditions, should be counseled appropriately.
- When a higher-order (triplet or more) multifetal pregnancy is encountered, the option of multifetal reduction should be discussed. In the case of a continuing higher-order multifetal pregnancy, ongoing obstetric care should be with an obstetrician–gynecologist or other obstetric care provider and at a facility capable of managing anticipated risks and outcomes.

Introduction

Over the past decades, the use of assisted reproductive technology (ART) has increased dramatically worldwide and has made pregnancy possible for many infertile couples. According to the Centers for Disease Control and Prevention (CDC), in 2014 a total of 208,786 ART procedures were reported. These procedures resulted in 57,332 live-birth deliveries and 70,352 infants (1). Today, more than 1.5% of all infants born in the United States every year are from women who achieved their pregnancies by using ART (2). In 2009, almost one half of ART infants (41.1%) were from multifetal pregnancies, compared with only 3.5% of infants among the general birth population (2). However, in 2014, 78% of infants born to women who underwent ART procedures were singletons (3). In a large, U.S. population-based, cohort study from 1998 to 2011, the proportion of twin births attributable to ART was 36% in 2011, with 17% attributable to in vitro fertilization (IVF) and 19% attributable to other treatments (ie, ovulation induction and ovarian stimulation). The proportion of triplet and higher-order births attributable to ART was 77% in 2011, with 32% attributable to IVF and 45% attributable to other treatments (4).

The focus of this document will be on IVF with or without intracytoplasmic sperm injection (ICSI), but the risks of multifetal pregnancies associated with superovulation should not be forgotten, and the summary recommendations for physicians prescribing ART also should be applicable for physicians prescribing ovulation induction.

Overview of Risks

To start, although other risks should not be ignored, the risks of multifetal pregnancies are of substantial importance and are addressed first in this document along with methods to limit such multiples. Whenever ART is considered, risks from preexisting conditions on maternal health or pregnancy outcome should be addressed before initiating ART, whether or not these conditions are the source of compromised fertility. The latter part of this opinion will then address the potential for adverse outcomes, which is present in all pregnancies that result from ART regardless of fetal number. Ideally these risks should be discussed with the patient before pregnancy, but also can be reviewed during pregnancy and while establishing perinatal care. Careful counseling with regard to all of the types of risks listed previously and, when possible, treatment or intervention to reduce risk should be undertaken and should take precedence before proceeding with ART procedures.

Risks of Multifetal Gestations

As mentioned before, use of ART carries a substantial increase in the risk of multiple gestation (5). The increased risk of maternal and fetal morbidity and mortality associated with multifetal gestation as a result of preterm birth, preeclampsia, and other pregnancy complications is well described (6). Limited data argue that these risks may be further increased in multifetal gestations that result from ART. In a 2010 meta-analysis that included 12 studies with a total of 4,385 twins born to women who became pregnant through IVF or IVF/ICSI and 11,793 naturally occurring pregnancy twins, the authors concluded that IVF twins are at increased risk of preterm birth and low birth weight (7). Importantly, use of ART techniques has been associated with an increased risk of monozygotic twinning, which brings additional risk of growth abnormalities and twin-to-twin transfusion (8).

Managing the Risks of Multifetal Gestations

As noted by the Committee on Ethics, "The first approach to the problem of multifetal pregnancies should be prevention, and strategies to limit multifetal pregnancies, especially high-order multifetal pregnancies, should be practiced by all physicians who treat women for infertility" (9). Methods to limit high-order multifetal gestations include use of low-dose stimulation protocols and close monitoring of hormone levels and follicle number during superovulation cycles (10). Among those undergoing IVF, limiting transfer to fewer embryos per cycle has been an efficacious method to reduce multifetal gestations (11, 12). It is critical that couples are informed of the risk and associated morbidity of higher-order multifetal pregnancy as a balance to financial and other pressures to transfer multiple embryos. As the ASRM notes in its 2012 statement, patients perceive financial

disincentives to reducing the number of embryos transferred per cycle (13). These perceived financial risks may be reduced by increasing insurance coverage for ART and by patients' entering shared risk arrangements with infertility providers (13–20).

Further important reductions in ART-associated multifetal pregnancy rates will be found with increasing adoption of conservative numbers for embryo transfer, including elective single embryo transfer (commonly known as eSET) as outlined by ASRM (13, 21), and these efforts should be encouraged (22). There are now several studies that demonstrate the effectiveness of elective single embryo transfer in good prognosis patients. Single embryo transfer results in high pregnancy rates and a drastic reduction in multifetal gestations (23–26).

The Committee on Ethics recommends that when a multiple pregnancy is diagnosed, risks associated with such and possible management should be discussed. The committee specifically indicates that when there is a higher-order multiple gestation, the option of multifetal pregnancy reduction should be introduced. In some cases, it may be appropriate to discuss this option with patients in advance of undertaking ART treatment (9, 27). Termination of one or more fetuses to a lower fetal number (singleton or twins) decreases the risk of preterm delivery (28, 29), although the decrease should be balanced against a procedure-associated risk of miscarriage (4.7% in one series of consecutive procedures) (29). Benefits of multifetal pregnancy reduction exist for triplets and higher-order multifetal gestations (30). Although controversial, reduction of twins to a singleton may be indicated to decrease risk of preterm delivery, particularly in patients whose history or other factors places them at marked risk for such. But such potential reduction must again be balanced against the procedure-associated risk of miscarriage. Finally, with regard to counseling and access to the procedure, the Committee on Ethics recommends that "no physicians need to perform multifetal pregnancy reductions if they believe that such procedures are morally unacceptable, [but] all obstetricians and gynecologists should be aware of the medical risks of multifetal pregnancy, the potential medical benefits of multifetal pregnancy reduction, and the complex ethical issues inherent in decisions regarding the use of multifetal pregnancy reduction. When a patient request for multifetal pregnancy reduction is discordant with the physician's value system, the patient should be referred to a physician with expertise in performing multifetal pregnancy reductions" (9).

Maternal Conditions and Previous Obstetric History Complications

Before initiating ART or ovulation induction procedures, obstetrician–gynecologists and other health care providers should complete a thorough medical evaluation to ensure that patients are in appropriate health and that their health status has been optimized. Some maternal conditions may limit the physiologic support a woman can provide to a pregnancy and, as a result, a pregnancy may represent a significant risk to the woman's life and health. The presence of preexisting medical conditions requires careful assessment of the patient's condition and function before initiating ART plans. In particular, a history of a preexisting cardiopulmonary disorder or a condition (such as Marfan or Turner syndromes) that may lead to significant cardiopulmonary compromise resulting from the increased cardiopulmonary demands of pregnancy should lead to specific evaluation and to risk counseling. Even for more common medical disorders (such as diabetes, hypertension, epilepsy, or obesity), optimization of weight, maternal medical status, treatment regimen, and other aspects of care may have salutary effects on becoming pregnant and pregnancy outcomes. Therefore, prepregnancy assessment of pregnancy-related risks and counseling regarding risk reduction strategies should be a key element of care before the initiation of ART or any infertility treatment.

Risks Regardless of Fetal Number

Studies that compare obstetric outcome of singleton ART and naturally occurring pregnancies suggest that the former are at increased risk of preterm birth, low birth weight, and perinatal mortality rate, even after adjusting for age, parity, and multifetal gestations—although the magnitude of relative risk is small (31–34). A meta-analysis of 15 studies comprising 12,283 singleton infants of women who underwent IVF and 1.9 million singleton infants of women who had naturally occurring pregnancies showed higher odds of perinatal mortality (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.6–3.0), preterm delivery (OR, 2.0; 95% CI, 1.7–2.2), low birth weight (OR, 1.8; 95% CI, 1.4–2.2), very low birth weight (OR, 2.7; 95% CI, 2.3–3.1), and small-for-gestational-age status (OR, 1.6; 95% CI, 1.3–2.0) in IVF pregnancies, after adjusting for maternal age and parity (35). A more recent secondary analysis of the first and second trimester evaluation of risk (FASTER) trial did not find an association of ART and prematurity but did find that ART was associated with an increased risk of cesarean delivery (OR, 2.3), placenta previa (OR, 6.0), abruptio placentae (OR, 2.4), and preeclampsia (OR, 2.7) (36). Additionally, vasa previa has been noted to be more common in pregnancies achieved with IVF (1/250 with IVF and 1/2,500 without IVF) (37). Similarly, stillbirth is more frequent in pregnancies achieved through IVF/ICSI at a rate of 16.2/1,000 compared with a rate of 2.3/1,000 in naturally occurring pregnancies (38). A 2016 analysis of Massachusetts State data found an elevated risk of severe maternal morbidity––blood transfusion was the most common indicator of severe maternal morbidity––among women who became pregnant through ART even when those outcomes were compared with a subfertile population (39).

In considering the aforementioned findings, however, it is important to note that data pertaining to the risks associated with ART are limited by data collection and study design. Currently, the Society for Assisted Reproductive Technology collects data on number of live births, twins, and triplets or more (3), but systematic collection of data on outcomes such as preterm birth, birth weight, pregnancy complications and perinatal mortality would improve risk assessment and counseling. Given the nature of the condition, there are no randomized controlled trials, and cohort and case–control trials are limited by confounding from coexisting conditions (including conditions associated with or causes of infertility) and differences in health risks and behaviors between groups. In addition, studies of these questions may be limited by treatment (variations in obstetric practice such as induction of labor or elective cesarean birth), recall, ascertainment, and reporting bias (early pregnancies may be more easily diagnosed and reported after ART). Therefore, it is unclear to what extent infertility, ovulation induction, or ART may contribute to the negative ART-associated obstetric outcomes described in some, but not all, studies. This information with regard to potential risks and its limitations should be included in patient counseling, counseling that is ideally considered in advance of infertility treatment. Continued tracking of outcomes of ART pregnancies, to include data beyond birth, is appropriate.

Birth Defects

Although data regarding the association of ART and congenital anomalies are at risk of the same limitations and biases noted previously for obstetric outcomes, several studies have documented small increases in birth defects among infants of women who became pregnant through ART (40–44). A systematic review of 45 cohort studies that evaluated the rate of birth defects among infants born after ART demonstrated a higher risk of birth defects among ART infants (n=92,671) compared with non-ART infants (n=3,870,760) (relative risk [RR] 1.32; 95% CI, 1.24–1.42) (45).

Any elevated risk of birth defects associated with ART could be due to manipulation of the oocyte and embryo that are necessary with ART procedures or to factors related to the stimulation. However, risks also may be related to the underlying cause of infertility or other specific health risks and behaviors in those undergoing ART. Indeed, several studies have found higher rates of birth defects among couples with infertility who achieved pregnancy without treatment (43, 46). Recent studies have sought to address these questions by examining whether the increase in birth defects is related to identifiable factors in the patients or procedures related to ART. A population-wide cohort study evaluated 308,974 births from 1986 to 2002 in South Australia and compared risks of birth defects in naturally occurring pregnancies, pregnancies achieved with ART in a prior or current birth, and in women with a history of infertility without treatment (43). Pregnancies achieved with any type of ART had a significantly increased risk of birth defects after multivariate adjustment (adjusted OR, 1.28; 95% CI 1.16–1.41). Specifically, however, the use of ICSI was associated with a higher risk of birth defects (adjusted OR, 1.57; 95% CI, 1.30–190), although the use of IVF without ICSI did not demonstrate an increased risk (adjusted OR, 1.07; 95% CI, 0.90–1.26). It is interesting to note that another 2012 Australian study reported that the magnitude of the increased risk of birth defects associated with ART had decreased with time (1994–1998; RR, 1.84 versus 1998–2002, RR, 1.3 for ART assisted versus naturally occurring pregnancies), which suggests that changes in population or ART techniques have reduced potential concerns (47). There does not appear to be any specific pattern of anomalies or disorders associated with ART for which targeted screening or evaluation can be endorsed. However, alterations in methylation, epigenetics, and imprinting have been reported in ART pregnancies and associated with disorders such as Beckwith–Wiedemann and Angelman syndromes (48–55). Unless additional studies clarify or refute these risks, it seems judicious to make patients aware of the low level risk of birth defects and to offer ultrasonographic surveillance for structural abnormalities in these pregnancies. Some professional organizations recommend fetal echocardiography (56, 57) in all ART pregnancies, but the incremental yield of such studies after a targeted ultrasonography that is reassuring is unclear and needs to be balanced against available resources. Of course, patient-specific risks identified during evaluation of a patient's medical history may indicate need for specific studies or other fetal evaluation during pregnancy.

Long-term Pediatric Outcomes

In considering long-term pediatric outcomes associated with ART, it is vital to distinguish those outcomes related to multifetal gestations (58, 59) and associated prematurity from those potentially related to the techniques themselves. Outside the risks from multifetal pregnancies, studies have provided conflicting results about any increase in adverse neurodevelopmental outcomes (60–67). Therefore, recommendations about specific advice to patients with regard to long-term pediatric outcomes will require further study and data.

Male Factor Infertility

In vitro fertilization and ICSI can be used to achieve pregnancy for a couple in which there is a diagnosis of male factor infertility. Oligospermia and azoospermia, common findings in cases of male infertility, are themselves associated with single gene or chromosomal anomalies such as sex chromosome aneuploidy and microdeletions in the long arm of the Y chromosome in the offspring that can be inherited (68–73). The American Society for Reproductive Medicine recommends karyotyping

and cystic fibrosis and Y microdeletion testing in men presenting with oligospermia and azoospermia before beginning IVF, ICSI, or other fertility treatments (74). Cystic fibrosis testing is especially indicated in couples undergoing ART because of congenital absence of the vas deferens in the male partner given the high frequency of cystic fibrosis transmembrane conductance regulator mutations in such individuals (75). Genetic counseling with regard to these risks is appropriate for these individuals.

Conclusion

The use of ART has increased dramatically worldwide and has made pregnancy possible for many infertile couples. However, perinatal risks associated with any ART and ovulation induction pregnancy remain, particularly in multifetal gestations. To promote optimal outcomes, obstetrician–gynecologists and other health care providers should complete a thorough medical evaluation and address maternal health problems or health conditions before initiating ART and, when proceeding with ART, make every appropriate effort to achieve a singleton gestation. Patients should receive appropriate counseling about the risks associated with ART, especially risk associated with multifetal pregnancy and the option in such cases for multifetal reduction.

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