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Maternal and Fetal Risk Associated With Assisted Reproductive Technology

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Infertility is a disease that affects up to 15.5% of reproductive-aged couples. Until the birth of the first neonate born from in vitro fertilization (IVF) in 1978, many infertile couples did not have an opportunity to conceive a biological child. Over the past 40 years, access to and effectiveness of IVF have increased; currently 1.7% of births in the United States result from IVF. As with any medical intervention, potential risk exists. In the case of IVF, both maternal risks (ovarian stimulation, oocyte retrieval, and subsequent pregnancy) and fetal risks that vary based on maternal age and fetal number must be considered. Importantly, risk quantification varies by comparison group, which is typically either spontaneous conception in a fertile couple or assisted non-IVF conception in an infertile couple. It must also be considered compared with the alternative of not undergoing IVF, which may mean not having a biological child. Although increased compared with spontaneous conception, absolute maternal–fetal-assisted reproductive technology risks are low and can be minimized by optimizing ovarian stimulation and transferring a single embryo. In this article, we aim to summarize maternal and fetal risk associated with use of assisted reproductive technology. The review focuses on ovarian stimulation and procedural risks as well as adverse perinatal outcomes among resultant singleton and twin pregnancies in young women and women of advanced maternal age.

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According to the World Health Organization, infertility "is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" that affects up to 15.5% of reproductive-aged couples.[1,2] As with all disease processes, treatment options for infertility have evolved over time and, over the past 40 years, have expanded to include the use of assisted reproductive technology (ART), more than 99% of which comprises in vitro fertilization (IVF) in the United States. Since the first IVF neonate was born in England in 1978, the number of births resulting from IVF has steadily increased worldwide and, as of 2015, comprises 1.7% of births in the United States.[3] Of the 56,028 IVF live birth deliveries in 2014, 43,544 (77.7%) were singletons and 12,484 (22.3%) were multiples resulting in 68,782 liveborn neonates.[4] In vitro fertilization is unique; the technology affords an otherwise relatively healthy patient population the opportunity to have biologically related offspring that may otherwise not be feasible. As with all medical interventions, particularly elective treatments, physicians aim to minimize the risks associated with the procedure and outcome. Risk minimization begins with quantification, which, for IVF, is particularly difficult. It is possible that infertility itself, rather than fertility treatment, affects maternal and perinatal outcomes. As a result, when

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comparing outcomes between populations, one must consider the comparison group, either spontaneous conception in a fertile couple or assisted non-IVF conception in an infertile couple. Additionally, particularly if the absolute risk to the mother and neonate remain low, the likely undesirable alternative of not having a biological child remains an important consideration.

The majority of significant adverse outcomes associated with fertility treatment are the result of multiple gestation. Even in light of this fact, however, the absolute risk of multiple gestation with IVF itself is actually lower than with other treatments. Often, ovulation induction or superovulation with intrauterine insemination serves as a prerequisite or alternative to IVF. Perhaps surprisingly, IVF, although more costly, is likely the less risky intervention when considering risk of multiple gestation with superovulation and resultant maternal and perinatal adverse outcomes. Nationally, the majority of twins are from a spontaneous conception. Among those who undergo fertility treatment, IVF is the least likely treatment to result in twins. More specifically, based on national data from 1997 through 2011, the largest proportion of twin births in the United States resulted from natural conception (64–77%) followed by non-IVF fertility treatment conception (14–19%) and IVF conception (9–17%).[5] For triplets and higher order multiples, the contribution from IVF has decreased from 1997 to 2011 from 44% to 32% with the contribution from natural conception ranging from 18% to 23% and non-IVF fertility treatment 39–45%.[5] Since 2011, the contribution of IVF to twins has decreased to 14.5% in 2015. In 2014, of all IVF-conceived neonates, 38% were twin neonates and 2% were triplet and higher order neonates.[4]

In this article, we aim to summarize maternal and fetal risk associated with use of ART. The review focuses on ovarian stimulation and procedural risks as well as adverse perinatal outcomes among resultant singleton and twin pregnancies in young women and women of advanced maternal age.

MATERNAL RISKS OF ASSISTED REPRODUCTIVE TECHNOLOGY ASSOCIATED WITH OVARIAN STIMULATION AND OOCYTE RETRIEVAL

The primary maternal risks associated with undergoing IVF include those associated with superovulation and with oocyte retrieval itself. Nonpregnancy-related potential risks include infection, medication adverse event, anesthetic complication, hemorrhage requiring transfusion, hospitalization, and death within 12 weeks of stimulation. In a national surveillance study of all ART procedures performed in the United States between 2000 and 2011 that included more than 1 million nondonor cycles, the most commonly reported patient complications were ovarian hyperstimulation syndrome, which peaked at 153.5 per 10,000 autologous cycles (95% CI 146.0–161.3), a rate of approximately 1.5%, and hospitalizations, which peaked at 34.8 per 10,000 autologous cycles (95% CI 30.9–39.3), a rate of 0.34%.[6] The reported rates of infection, medication adverse event, anesthetic complication, hemorrhage requiring transfusion, infection, and hospitalization were all less than 0.1%.[6] Zero deaths within 12 weeks of stimulation start were reported.[6]

Ovarian hyperstimulation, the most commonly reported complication, initially increased from 1.0% to 1.4% from 2000 to 2006, then decreased from 2006 to 2009 to 1.0% and has since remained stable from 2010 through 2014 between 0.8% and 0.9% (Schirmer DA, Kulkarni A, Kawwass JF, Boulet S, Kissin DM. Ovarian hyperstimulation syndrome after assisted reproductive technology: trends, predictors, and pregnancy outcomes [abstract]. Fertil Steril 2017;108: e23.). Ovarian hyperstimulation is a self-limited syndrome characterized by increased vascular permeability that results in hemoconcentration and ascites, which is likely mediated by vascular endothelial growth factor and exacerbated by the presence of β-human chorionic gonadotropin. It typically results from controlled ovarian stimulation, particularly in the setting of markedly elevated estradiol levels, and is more likely among cycles resulting in pregnancy.[7] Over the past decade, tactics have evolved to help minimize risk of ovarian hyperstimulation syndrome. These include identifying potential high responders before stimulation starts and tailoring the stimulation protocol to avoid excessively elevated estradiol levels. In addition, use of a gonadotropin-releasing hormone antagonist (rather than agonist) for hypothalamic suppression and use of a leuprolide rather than human chorionic gonadotropin for ovarian maturation trigger have been shown to decrease risk. There are adjunct medications, including metformin and baby aspirin during stimulation and cabergoline after retrieval that decrease risk. Finally, freezing all the embryos with delay of embryo transfer avoids the pregnancy human chorionic gonadotropin and late-onset ovarian hyperstimulation syndrome.[7]

Overall, maternal nonpregnancy-related risk associated with IVF remains very low. As of 2014, the most frequent complication, ovarian hyperstimulation syndrome, occurs in less than 1% of cycles (Schirmer, et al, Fertil Steril 2017;108:e23.). With

continued research regarding predictors and mitigators of ovarian hyperstimulation syndrome and persistent clinician effort to minimize its occurrence, the occurrence of ovarian hyperstimulation syndrome can likely be further minimized over time.

MATERNAL RISK ASSOCIATED WITH PRE-EXISTING MEDICAL CONDITIONS

The potential for adverse perinatal outcomes exists with all pregnancies including those resulting from ART. Pre-existing medical conditions should be fully evaluated and treated before beginning ART because optimal maternal health entering pregnancy provides benefit to both the mother and her neonate. A complete medical, surgical, and family history should be part of all ART evaluations and, when appropriate, referral to a maternal–fetal medicine specialist can ensure adequate counseling and maternal health optimization before conception.

Physiologic changes of pregnancy can exacerbate underlying medical conditions resulting in substantial maternal risks. Some medical conditions such as congestive heart failure with a low ejection fraction, end-stage renal disease, and pulmonary hypertension are considered contraindications to pregnancy and warrant a discussion about using a gestational carrier. Other more common medical conditions such as obesity, diabetes, and hypertension are less prohibitive but warrant counseling and optimization before conception. Obesity remains a known risk factor for many adverse perinatal outcomes including but not limited to miscarriage, congenital malformations, preeclampsia, gestational diabetes, stillbirth, indicated preterm birth, and cesarean delivery.[8] Maternal obesity also adversely affects the ART cycle and perinatal outcomes with lower live birth rates and should be incorporated into preconception counseling regarding weight optimization toward a healthy body mass index whenever possible before conception.[9–12] Poorly controlled diabetes is also associated with increased risk of miscarriage, congenital malformation, stillbirth, preeclampsia, preterm birth, cesarean delivery, and perinatal mortality.[13] Preconception normalization of blood glucose and strict control throughout pregnancy can improve perinatal outcomes in diabetic women.[14] Before pregnancy, women with chronic hypertension should be counseled about risks, which include, but are not limited to, development of preeclampsia, fetal growth restriction, worsening hypertension, and need for preterm delivery. Additionally, medications with known adverse fetal effects such as angiotension converting enzyme inhibitors and angiotension receptor blockers should be stopped before conception.[15]

FETAL RISKS OF ASSISTED REPRODUCTIVE TECHNOLOGY ASSOCIATED WITH TWINS AND HIGHER ORDER MULTIPLES

Trends in Multiples and Number of Embryos Transferred

In an effort to optimize perinatal outcomes by reducing risks of multiple gestation, it has become widely accepted that reproductive endocrinologists should aim to minimize the number of embryos transferred whenever feasible.[16] Practice guidelines were recently revised to more overtly encourage single-embryo transfer and to further restrict criteria for multiple-embryo transfer.[17] Improvement in embryo culture, the availability of preimplantation genetic screening, and growing knowledge about the risks associated with multiple gestation have made the focus on single-embryo transfer feasible. In concordance with a desire to optimize perinatal outcomes and to consider the cumulative chance of pregnancy rather than simply maximizing the chance of pregnancy at first transfer, rates of elective single-embryo transfer in the United States have steadily increased, particularly among young women, from less than 3% in 2006 to 35% in 2015 among women younger than 35 years and from 2% to almost 21% for women aged 35–37 years.[18,19] Although the contribution of IVF to twins born in the United States from 1997 to 2013 increased from 9% to 18.5%, the contribution of IVF to triplets decreased from 44% to 25%.[4,5] Since 2011, the contribution of IVF to twins has decreased to 14.5% in 2015. In 2014, of all IVF-conceived neonates, 38% were twin neonates and 2% were triplet and higher order neonates.[4] Among all IVF deliveries between 2009 and 2015, the percentage of singleton deliveries increased from 70.2% to 80.4% and the percentage of twin deliveries decreased from 29.8% to 19.6% (Fig. 1).[3] Although trends of higher order multiples are moving in the correct direction, further improvement in the rates of twins, triplets, and higher order multiples remains warranted. With the increasing availability of preimplantation genetic screening, even older women who may not otherwise have been candidates for elective single-embryo transfer may be able to transfer one euploid embryo at a time, rather than several unscreened embryos. That being said, preimplantation genetic screening is not without controversy or risk. The use of preimplantation genetic screening incurs additional theoretical although unproven risk in its need for biopsy of a blastocyst embryo and additional costs including embryo

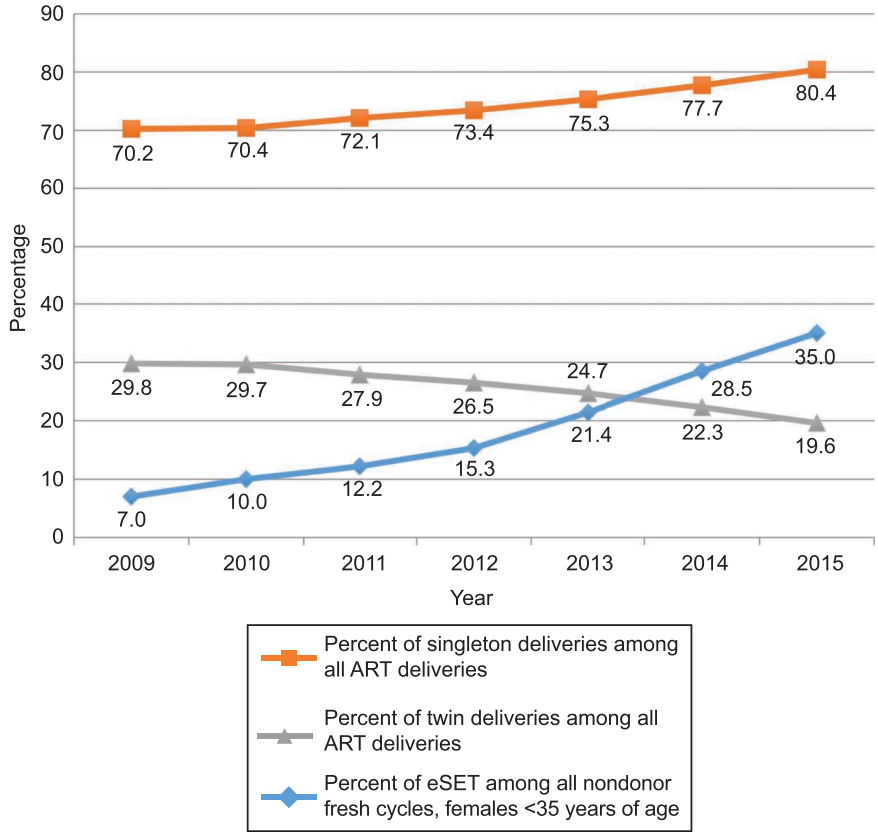

Fig. 1. Trends in percentage of elective single-embryo transfer (eSET) among all nondonor fresh cycles in women younger than 35 years of age and in percentage of singleton and twin deliveries among all assisted reproductive technology (ART) deliveries, 2009–2014. Data from Annual MMWR Surveillance Summaries. Assisted Reproductive Technology Surveillance, United States, 2009–2015.[3,4]

Kawwass. Maternal and Fetal Risks and IVF. Obstet Gynecol 2018.

biopsy, genetic testing, embryo cryopreservation, and subsequent frozen embryo transfer. Additionally, although consensus exists regarding viability of euploid and aneuploid embryos, mosaic embryo potential remains unclear.

Higher Order Multiples

Higher order multiples, defined as pregnancies with three or more fetuses, are most notably complicated by risk of spontaneous preterm delivery and the resultant perinatal morbidity and mortality. The mean gestational age of triplet delivery is 31.9 weeks, with a mean birth weight of 1,660 g. The risk of cerebral palsy is 28 per 1,000 live births, and the infant mortality risk is 52.5 per 1,000 live births.[20] For quadruplet pregnancies, the mean gestational age at delivery is 29.5 weeks, with a mean birth weight of 1,291 g and an infant mortality risk of 96.3 per 1,000 live births.[20] This reflects a sixfold increase in chance of preterm birth among multifetal pregnancies compared with singleton gestations, a fivefold increased risk of stillbirth, and a sevenfold increased risk of perinatal death.[20–22] Preterm delivery, particularly among multiple gestations, increases risk of intraventricular hemorrhage, periventricular leukomalacia, and cerebral palsy.[20]

In addition to the fetal risks associated with multiple pregnancy, maternal risk is also compounded. Compared with singleton pregnancies, multiple pregnancies are at increased risk of maternal gestational diabetes, hypertension, cesarean delivery, hyperemesis, anemia, and postpartum depression.[20]

Twins

Whether conceived spontaneously or with ART or non-ART fertility interventions, on average twin pregnancies deliver at 35.3 weeks of gestation with a mean birth weight of 2,336 g.[23] Twin pregnancies are at increased risk of preterm delivery (58.8% deliver before 37 weeks of gestation), cerebral palsy (7/1,000 live births), and infant mortality (23.6/1,000 live births).[23] Several studies have compared outcomes between twins conceived spontaneously, after superovulation with intrauterine insemination, and after IVF. Results have been conflicting. Several studies suggested increased perinatal risk associated with ART-conceived multiple gestations compared with spontaneously conceived counterparts.[20,24,25] It remains unclear whether this heightened risk reflects an association with the infertility itself or with the ART procedures. Additionally, increased relative risk

noted in a large population may reflect a very small absolute risk. Many large studies have shown no significant difference in perinatal and obstetric outcomes, particularly when correcting for chorionicity.[26,27] Most recently, a large Danish nationwide registry-based study including 6,694 women (470 after ovulation induction, 511 after intrauterine insemination after controlled ovarian hyperstimulation, 2,437 after IVF with intracytoplasmic sperm injection, and 3,276 after natural conception) that compared obstetric and perinatal outcomes of dizygotic opposite sex twins found comparable maternal and perinatal risk for twin pregnancies conceived after IVF and other medically assisted reproduction compared with unassisted natural conceptions (Table 1).[28]

Selective Reduction

In an effort to lessen some of the risk associated with high-order multiple gestation, selective reduction to a twin pregnancy has been shown to reduce the risk of preterm delivery, low birth weight delivery, cesarean delivery, neonatal death, and prenatal complications comparable with that of a spontaneously conceived twin pregnancy.[29] The risk associated with reduction itself is not insignificant and correlates with the initial number of fetuses in the pregnancy, ranging from 11.1% risk of unintended loss of a healthy fetus when reducing from three or more fetuses to a 2.4% unintended loss rate when reducing from twins to a singleton.[30]

Table 1. Risks Associated With In Vitro Fertilization–Conceived Pregnancies Compared With Naturally Conceived Counterparts—Singleton, Twin, and Nonstratified Gestations

Risk	Absolute Risk
Among singleton pregnancies	
Preterm delivery[50]	Half day earlier IVF–ICSI vs SC 9.7% IVF–ICSI vs 7.9% SC
Low birth weight delivery[50]	33 g less IVF–ICSI vs SC 6.8% IVF–ICSI vs 4.9% SC
Severe maternal morbidity (blood transfusion most common)[63]	273/10,000 IVF–ICSI vs 126/10,000 SC
Among twin pregnancies	
Monozygotic twins[31,32]	1.2–2.5% IVF–ICSI vs 0.4% SC
Preterm delivery[26–28]	Comparable
Low birth weight delivery[26–28]	Comparable
Not stratified	
DNA methylation[71,72]	Comparable
Imprinting disorder[71,72]	0.15% IVF–ICSI vs 0.02% SC
Any cardiac defect including ASD, VSD[70]	1.30% IVF–ICSI vs 0.68% SC

IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SC, spontaneous conception; ASD, atrial septal defect; VSD, ventricular septal defect.

Monochorionic Twins

Chorionicity further accentuates the risks associated with multiple gestation. After correcting for chorionicity, the balance of evidence suggests similar clinical perinatal outcomes between IVF and non-IVF twins.[26–28] However, multiples conceived from ART may be at increased risk of monozygosity, resulting from embryo division between days 4 and 12 after fertilization.[31,32] The population estimate for naturally conceived monozygotic twins is approximately 4 per 1,000 births, or 0.4%. Among IVF twins, the rate of monozygous pairs ranges from 1.3% to 2.5% and may be increased by blastocyst transfer and assisted hatching (Table 1).[31,32] There is clear evidence that monochorionic twins carry a unique risk profile, specifically an 8–10% risk of twin-twin transfusion syndrome as well as an increased risk of selective intrauterine growth restriction, severe perinatal morbidity and mortality after the death of one of the cotwins, and risk of twin anemia polycythemia sequence.[33] Although the spontaneous occurrence of monozygotic–monozygotic twins is thought to be 1 in 10,000, evidence suggests that it may be higher in ART-conceived pregnancies, particularly after zona manipulation.[31,32]

FETAL RISKS OF ASSISTED REPRODUCTIVE TECHNOLOGY ASSOCIATED WITH SINGLETON GESTATION

Although perinatal risks are known to be higher with multiple gestation pregnancies, ART singleton pregnancies may be at higher risk of adverse perinatal outcomes including preterm birth and low birth weight compared with spontaneously conceived singletons, even after controlling for known risk factors such as maternal age, weight, and tobacco use.[34–37] Four meta-analyses have suggested an association between adverse perinatal outcomes and prior ART use.[35,38–40] Most recently, a 2016 meta-analysis of 50 cohort studies including 161,370 ART and 2,280,241 spontaneously conceived singleton pregnancies found increased risks of pregnancy-induced hypertension, placenta previa, abruption, antepartum hemorrhage, oligohydramnios, cesarean delivery, preterm birth, very low birth weight, low birth weight, perinatal mortality, and congenital malformation in ART compared with spontaneously conceived neonates.[41] Although the associated relative risk is higher in the ART group,

for each of these outcomes, the absolute risk differences are not clearly delineated and are likely small. Additionally, meta-analyses are limited by heterogeneity among included studies, residual confounding, and publication bias. The underlying mechanism by which ART may be associated with increased risk remains uncertain and may include ovarian stimulation and the resultant effect on the uterine hormonal milieu, gamete manipulation, embryo exposure to culture media, or the couple's underlying infertility itself. Recent evidence suggests that frozen transfer may be associated with lesser obstetric and perinatal risk.[42]

EFFECTS OF UNDERLYING INFERTILITY ON ADVERSE PERINATAL OUTCOMES

Multiple studies have focused on the role of reduced fertility as the etiology of increased adverse perinatal outcomes in IVF and non-IVF births.[43–47] Adverse perinatal outcomes found to be associated with ART may be confounded by inherent features that affect both fertility and pregnancy outcome. A discordant sibling design has been used in an attempt to evaluate the inherent risk with ART compared with the risk related to underlying maternal or paternal factors that result in infertility and may themselves cause adverse perinatal outcomes. A few early relatively small studies using this model found conflicting results on the association between ART and adverse perinatal outcomes.[48,49] Although still imperfect, comparing pregnancies in the same woman keeps many maternal factors constant minimizing confounding. In 2016, Dhalwani et al[50] used this study design to evaluate a larger cohort of discordant sibling pairs restricted to singleton live births in which one sibling was conceived through ART and the other was conceived without ART, regardless of conception order. Assisted reproductive technology use remained associated with increased likelihood of low birth weight and preterm birth. In these 6,458 sibling pairs, the absolute risk of preterm birth and low birth weight was 9.7% and 6.8%, respectively, in the ART group and 7.9% and 4.9% in the non-ART group. In absolute terms they found the ART-conceived singletons were 33 g lighter (95% CI 18–49 g) and born 1 half day (95% CI 0.14–1.02 of a day) sooner than singletons conceived naturally (Table 1). Of note, the risk of adverse perinatal outcomes differed depending on the underlying infertility cause; female infertility was found to have a 35% increased risk of preterm birth associated with ART, whereas no significant increased risk was associated with underlying male infertility. Importantly, the discordant sibling study results may not be applicable to all women undergoing ART because many of these women cannot achieve a non-ART pregnancy and thus are inherently a slightly different population.

A more recent study by Woo et al[51] compared the perinatal outcomes between singleton ART pregnancies carried by a gestational carrier and spontaneous, naturally conceived singletons carried by the same women. Neonates from ART pregnancies carried by gestational surrogates had an increased risk of preterm birth, low birth weight, hypertension, placental previa, and gestational diabetes compared with neonates conceived spontaneously carried by the same women, suggesting an effect of ART itself or the source oocyte or sperm on perinatal outcomes.[51] Overall the data support a persistent increased risk for preterm birth and low birth weight in ART pregnancies even after controlling for maternal factors using surrogate and sibling studies.

SINGLETON PREGNANCIES: EFFECTS OF NUMBER OF EMBRYOS TRANSFERRED

Even among singleton pregnancies, the number of embryos transferred has been shown to affect perinatal outcomes.[52] Additionally, the number of supernumerary embryos at the time of transfer may reflect embryo quality and underlying prognosis. Elective single-embryo transfer, defined as "an embryo transfer in which more than one high-quality embryo exists, but it was decided to transfer only one embryo," differs subtly from nonelective single-embryo transfer, the transfer of only one embryo because only one is available. Although nonelective single-embryo transfer usually represents women with poor ovarian stimulation response or poor-quality embryo progression that may represent an underlying pathophysiology indicative of increased perinatal risks, elective single-embryo transfer typically suggests excellent ART prognosis.[16] A study evaluating the effect of elective single-embryo transfer, nonelective single-embryo transfer, and double-embryo transfer on perinatal outcomes among IVF singleton pregnancies compared with spontaneously conceived singleton pregnancies found singletons born after either elective single-embryo transfer or nonelective single-embryo transfer to have similar risk as spontaneously conceived singletons.[52] However, double-embryo transfer resulting in a singleton pregnancy was at increased risk of adverse perinatal outcomes compared with spontaneously conceived singletons.[52] Elective single-embryo transfer clearly results in improved perinatal outcomes because it not only minimizes twin risk, but may also confer a perinatal advantage even compared with singletons resulting from double-embryo

transfers. Notably, elective single-embryo transfer candidates represent women with highest likelihood of ART success and, possibly, lower baseline risk of adverse perinatal outcomes. Nonetheless, for its effect on likelihood of multiple gestation alone, single-embryo transfer, whether elective or not, remains the primary mechanism to optimize maternal and perinatal IVF outcomes.[17]

RISKS ASSOCIATED WITH ADVANCED MATERNAL AGE

Advancing age remains the single most important factor associated with infertility. Given societal evolution toward later marriage, improved contraception, and female career development, women increasingly purposefully delay childbearing and, as a result, face biological fertility decline and increased maternal morbidity and adverse perinatal outcomes when pregnant.[53] Advanced maternal age is associated with increased risks including preterm birth, low birth weight, hypertensive disorders, stillbirth, and cesarean delivery.[54–58] The increased risk associated with advancing age may be compounded by use of ART, although age appears to be the primary predictor independent of ART use.[59] The use of donor oocytes further extends the reproductive window, is becoming more common, and is increasingly associated with good perinatal outcomes likely reflective of a trend toward single-embryo transfer.[60] Although many women do not purposely delay childbearing, those who have the opportunity or desire to conceive at a younger age should do so. From a public health perspective, there is benefit in honest physician counseling regarding the risks associated with pregnancies at advanced maternal ages.

SEVERE MATERNAL MORBIDITY RISK ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGY

Severe maternal morbidity represents the unexpected outcome of labor and delivery that results in significant short- or long-term consequences to a woman's health.[61] Severe maternal morbidity often heralds the most catastrophic obstetric outcome, maternal mortality. Assisted reproductive technology has been linked to adverse perinatal outcomes that place women at increased risk of morbidity including hypertensive disorders, placental abruption, placental previa, antepartum hemorrhage, and cesarean delivery.[35,36,62]

Overall severe maternal morbidity has decreased significantly from 2008 to 2012 and was found to be significantly greater in ART compared with non-ART pregnancies only in singleton, not multiple, gestations.[63] The inherent increased maternal risk of multiples likely overshadows any potential added risk specific to ART. Severe maternal morbidity, including blood transfusion, disseminated intravascular coagulation, acute renal failure, shock, and hysterectomy, occurred in 273 per 10,000 ART compared with 126 per 10,000 non-ART singleton deliveries.[63] Blood transfusion was the most common complication. As with all perinatal outcomes, it is unclear whether the ART procedures, the infertility itself, or both contribute to increased risk. A retrospective cohort study using Massachusetts Outcome Study of Assisted Reproductive Technology in 2016 found women with ART pregnancies had an elevated risk of severe maternal morbidity at delivery compared with both fertile and subfertile pregnancies.[64] The crude prevalence of severe maternal morbidity among fertile, subfertile, and ART deliveries was 1.09%, 1.44%, and 3.14%, respectively. Again, the most common severe maternal morbidity was blood transfusion.[64] Severe maternal morbidity warrants continued surveillance and further investigation of both ART and non-ART pregnancies to help decrease its occurrence.

RISK OF BIRTH DEFECTS ASSOCIATED WITH ASSISTED REPRODUCTIVE TECHNOLOGY

Since the birth of the first IVF neonate, physicians and researchers have wondered whether ART in general, intracytoplasmic sperm injection (ICSI) specifically, or infertility confer increased birth defect risk. Several heterogeneous cohort studies and meta-analyses have noted an increased risk of pooled birth defects in ART neonates compared with spontaneously conceived neonates.[35,65–67] A 2012 meta-analysis including 46 studies found significantly increased risk of birth defects (pooled risk estimation of 1.37 [95% CI 1.26–1.48]) in conventional and ICSI-conceived neonates compared with spontaneously conceived neonates; no difference was noted between conventional and ICSI fertilization.[66] As with other adverse perinatal outcomes, the contribution of parental infertility is unclear. In an effort to account for underlying infertility, a study comparing birth defect risk among ART pregnancies, spontaneous pregnancies in women with prior ART, pregnancies in women with infertility but no ART, and pregnancies in fertile women found no significant risk in ART pregnancies after adjusting for paternal factors.[68] Moreover, the incidence of ART-related birth defects is decreasing and the published rates are comparable with the nationally reported rates of 3% per year.[65,69]

Several studies specifically focus on congenital heart defect risk in ART neonates, which has resulted

in an American Institute of Ultrasound in Medicine and American Heart Association recommendation for fetal echocardiogram in ART-conceived pregnancies.[70] Notably, a recent meta-analysis reported absolute rates of any cardiac defect (including minor defects such as atrial and ventricular septal defects) of 0.68% in the spontaneously conceived group and 1.30% in the IVF–ICSI group (Table 1).[70] Another specific area of focus, DNA methylation and imprinting disorders, has shown an increased association with imprinting disorders but not with overall DNA methylation patterns in children conceived through IVF–ICSI.[71,72] The absolute risk remains low at 0.15% in IVF–ICSI conceptions and 0.02% in spontaneous conception.[71,72] Because the balance of evidence suggests an association with pooled birth defects, it is reasonable to inform patients of potential increased risk keeping in mind the low absolute risk and limited alternatives to conception.

DISCUSSION

Over the past 40 years, the field of ART has made tremendous strides forward. As IVF has grown increasingly effective, the improvement in implantation rates and the availability of preimplantation genetic screening when indicated have allowed continued improvement not only in pregnancy rates, but also in minimizing risk of multiple gestation pregnancy and optimizing maternal and perinatal outcomes. Preimplantation genetic screening allows for transfer of a single euploid embryo in an older woman who may otherwise transfer two or more unscreened blastocyst embryos. Elective single-embryo transfer rates in the United States are increasing in women of all ages, but there is room for further improvement. A combination of continued research pointing to the risks associated with multiple gestation, scientific progress in embryo selection, tailoring of IVF practice norms, and improved financial support from insurance companies may help to further improve elective single-embryo transfer rates.

Although IVF-conceived pregnancies have been shown to be associated with increased perinatal risk of preterm delivery and low birth weight delivery compared with spontaneously conceived pregnancies, the absolute risk to an individual fetus remains low. Given the alternative of not conceiving or having a child with an inheritable genetic disease, moving forward with ART remains a logical next step for many couples with infertility or another medical diagnosis that warrants IVF. Moreover, the risk of multiple gestation remains lower with IVF than with other fertility treatments such as superovulation intrauterine insemination. In the future, physicians can work to minimize risks associated with stimulation, retrieval, and subsequent pregnancies by following the most current guidelines published by the American Society of Reproductive Medicine. Additionally, involvement of a maternal–fetal medicine specialist before conception can help ensure adequate informed decision-making in women who desire to pursue conception despite underlying medical conditions or advanced maternal age.

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