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Multiple gestation associated with infertility therapy: a committee opinion

Practice Committee of the Society for Reproductive Endocrinology and Infertility, Quality Assurance Committee of the Society for Assisted Reproductive Technologies, and the Practice Committee of the American Society for Reproductive Medicine

This Committee Opinion provides practitioners with suggestions to reduce the likelihood of iatrogenic multiple gestation resulting from infertility treatment. This document replaces the document of the same name previously published in 2012 (Fertil Steril 2012;97:825–34 by the American Society for Reproductive Medicine). (Fertil Steril® 2021;■:■–■. ©2021 by American Society for Reproductive Medicine.)
Key words: Assisted reproductive technology, multiple pregnancy, ovulation induction, triplets, twins

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The goal of infertility treatment is for each patient to have one healthy child at a time. The challenges associated with achieving that goal differ by treatment and clinical context. In ovulation induction (OI), which is used in cases of oligo- or anovulation, ovulation of more than the targeted single oocyte occasionally results. In ovarian stimulation (OS), which is used in ovulatory women with other infertility diagnoses, implantation of more than one embryo may follow the fertilization of oocytes from supernumerary follicles. With assisted reproductive technologies (ART), multiple embryos may be transferred, or monozygotic twinning can occur. Regardless of which treatment is performed, the objective is the same: to maximize the probability of pregnancy while minimizing the risk of a multiple gestation. The objectives of this committee opinion include the following:

1) Review the incidence, recent trends, and modes of conception associated with multiple gestations in the US.
2) Consider the different factors associated with the increased risk for multiple pregnancies in OI, OS, and ART.
3) Discuss the complications and economic impact of multiple pregnancies.
4) Summarize current and emerging strategies aimed at limiting the risk of multiple gestations associated with treatments for infertility.

The overarching purpose of this document is to provide physicians with pertinent information that may help to prevent or avoid multiple gestations and to improve patient counseling regarding the risk of multiple gestation associated with treatment.

MULTIPLE BIRTHS IN THE US

The incidence of multiple births in the US has risen since 1980, which is considered as the reference year for estimating the relative contributions of different infertility treatments to the multiple birth rate. At that time, clinical practice in the US did not include in vitro fertilization (IVF), and the use of exogenous gonadotropins for OI and OS was limited [1]. From 1980 to 2014, the twin birth rate in the US increased from 1 in 53 births to 1 in 29 births, a 79% relative increase [2]. This was the result of a 2% annual increase in twin rates from 1980–2003 and a 1% annual increase from 2003–2014 (Fig. 1). After more than 3 decades of rising twin birth rates, there was a 1% reduction per year from 2014–2018, resulting in a 4% overall decrease in the twin rate [2].

Higher-order multiple gestation births (triplets or higher) in the US increased from <45 per 100,000 births in 1980 to its acme of 193 per 100,000 in 1998. This 400% increase in higher-order multiple gestation pregnancies over this time frame was likely driven almost entirely by infertility treatments. The rate remained relatively stable from 1998 through 2003 and then began to steadily drop (Fig. 2) [3]. In 2018, the high-order multiple gestation pregnancy rate was 93 per 100,000 births, a 52% drop over the prior 2 decades.

These trends both up and down in multiple gestation birth over time are clearly related to the increasing utilization of OS, number of embryos transferred in ART cycles, and increasing ART success rates. For example, IVF twin births reported by the Society of Assisted Reproductive Technology (SART) have dropped from over 30% in 1998 to only 9.7% in 2018, and IVF

FIGURE 1

[1]Significant increasing trend for 1980–2007 (p < 0.05); significant decreasing trend for 2007–2018 (p < 0.05).
[2]Significant increasing trend for 1980–2014 (p < 0.05); significant decreasing trend for 2014–2018 (p < 0.05).
NOTE: Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db351_tables-508.pdf#1.
SOURCE: NCHS, National Vital Statistics System, Natality.
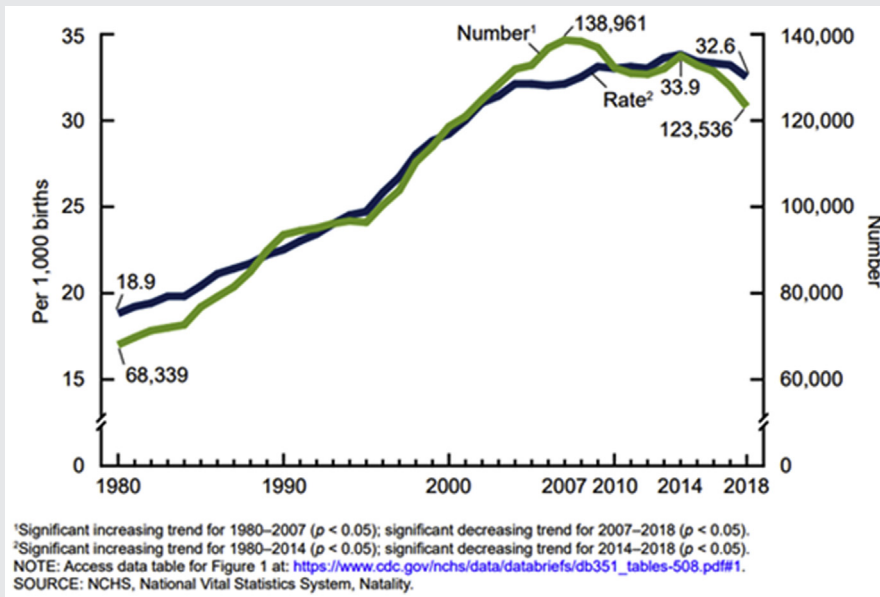
The trends in twin live births in the United States from 1980 to 2018. The *green line* is the absolute number, and the *blue line* is the twin multiple gestation rate (2).
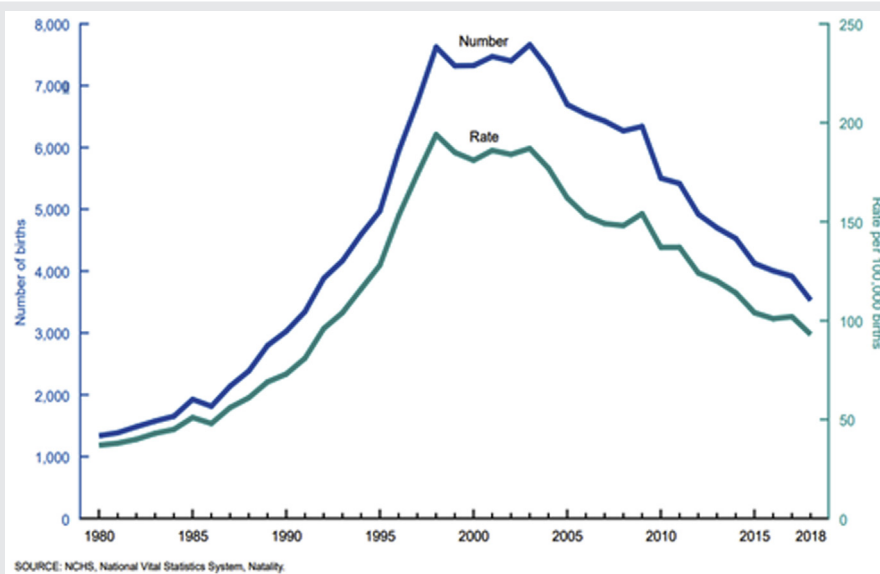
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high-order multiple gestations have dropped from 7%–0.2% over the same time frame (4).

Accurate estimates of the relative proportions of multiple births attributable to OI/OS are difficult to determine, as these cycles are not currently captured in a national registry. The estimated contribution of OI/OS cycles was derived from the total number of multiple births nationally minus the sum of the ART contribution and the estimated number from natural

FIGURE 2

SOURCE: NCHS, National Vital Statistics System, Natality.

The trends in high-order multiple live births (triplets or higher) in the United States from 1980 to 2018. The *blue line* is the absolute number, and the *green line* is the high-order multiple gestation rate (3).

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conception. Even with these caveats, there is consensus that most of the twin births result from natural conception (60%), with OI/OS and ART treatments accounting proportionally for the remainder (OI/OS: range 21–32%; ART: range 8–16%) (1, 5–7). Although there is agreement that 20% of high-order multiple gestations result from natural conception (1, 5–8), allocation of the remainder to OI/OS vs. ART varies widely (OI/OS: range 39–67%; ART: range 13–44%) (1, 5, 7).

Although naturally conceived twins account for most of all multiple births, the incidence of twins among births resulting specifically from infertility treatments is more than 20 times greater than that for births resulting from natural conception, and that of high-order multiple gestation is more than 100 times higher (6). Therefore, attention must remain focused on efforts to decrease the risk of multiple gestation associated with infertility treatment.

RISK FACTORS FOR THE OCCURRENCE OF MULTIPLE GESTATIONS

In naturally conceived multiple gestation, the prevalence of dizygotic twinning varies with ethnicity (1.3/1,000 in Japan, 8/1,000 in the US and Europe, and 50/1,000 in Nigeria) (9, 10). Dizygotic twinning is also associated with increased maternal age, greater parity, and a maternal family history of twinning (9, 11, 12). In contrast, the rate of monozygotic twinning is relatively constant (4/1,000 live births) (13), regardless of maternal age, race, or parity (14), although genetic predisposition may have some influence (15).

Multiple follicular development is the dominant risk factor for dizygotic twinning and high-order multiple gestation in OI and OS cycles (16). In ART treatment, the main risk factor for dizygotic and high-order multiple pregnancies is the transfer of more than one embryo (17, 18). The risk of monozygotic twinning may be increased by approximately twofold in ART cycles, and the contributions of specific ART techniques have been investigated (14, 19, 20). Data from the National ART Surveillance System demonstrated that assisted hatching was associated with an increased risk of monozygotic twins (21). This was consistent with the results of a meta-analysis of 16 studies and nearly 300,000 ART cycles (22), which found mixed results for monozygotic twinning with intracytoplasmic sperm injection compared to conventional insemination. A number of studies have concluded that the risk of monozygotic twinning is increased when culture is extended to the blastocyst stage (15, 21, 22). One report suggested that the risk may be related to the composition of culture media (23).

COMPLICATIONS OF MULTIPLE GESTATIONS

Multiple gestation increases maternal morbidity and fetal and neonatal morbidity and mortality. The most important maternal complications associated with multiple gestation are preeclampsia, gestational diabetes, and preterm labor and delivery (Table 1) (24–31). Other complications of multiple gestation include cholestasis, dermatoses, excess weight gain, anemia, hyperemesis gravidarum, and exacerbation of pregnancy-associated gastrointestinal symptoms (reflux, constipation) (31–34). Chronic back pain,

intermittent dyspnea, postpartum laxity of the abdominal wall, and umbilical hernias also occur frequently. Most of the excess perinatal morbidity and mortality associated with multiple gestations is directly related to the consequences of preterm birth (Table 1).

The risks for fetal demise during the third trimester, perinatal mortality, preterm birth, and both low (<2,500 g) and very low (<1,500 g) birthweight increase with the number of fetuses in a multiple gestation pregnancy (Table 2) (25, 29, 31, 35, 36). Fetal growth restriction and discordance also contribute to the increased perinatal morbidity and mortality in multiple pregnancies (35). Multifetal reduction decreases, but does not eliminate, the risk of fetal growth restriction (36) or loss of the entire pregnancy (37).

An arrest of development or absorption of one or more embryos or fetuses in a multiple gestation (i.e., a "vanishing twin") is common in the first trimester. The true incidence of vanishing twins is difficult to determine owing to variations in ultrasonographic technology, methodology, and diagnostic criteria, but estimates range from 12–38% (32, 38, 39) in multiple gestations resulting from ART. Early studies suggest that after the transfer of 2 embryos, demise of 1 twin in a dizygotic pair is unlikely to adversely affect the mother or surviving fetus (40, 41). More recent evidence indicates that the mean birthweight of surviving twins is approximately 120 g lower than that of singleton births after transfer of a single embryo (3,204 g vs. 3,325 g) (42) although this difference may not be clinically relevant. The risk that a surviving twin will be small for gestational age increases when the demise of its twin occurs after 8 weeks of gestation (8–22 weeks: odd ratio [OR] 2.78, 95% confidence interval [CI] 1.11–7.14) (43), and increases with gestational age at the time of the demise (>22 weeks: OR 9.09, 95% CI 1.72–50) (44). The incidences of preterm birth (<37 weeks), very preterm birth (<32 weeks), low birthweight, and very low birthweight are all significantly increased in surviving twins compared to those in singleton pregnancies (Table 3) (43). Limited data suggest that surviving twins also may be at increased risk for cerebral impairment (risk ratio 6.1, 95% CI 1.5–8.3), as assessed using a standardized mental and developmental rating system (45), and for cerebral palsy (OR 1.9, 95% CI 0.7–5.2) (43), but additional larger studies are required to confirm these observations.

The demise of one fetus in a twin pregnancy after the first trimester is more common in monochorionic twin pregnancies, ranging in incidence from 0.5%–6.8% (46). The death of one monochorionic twin in late gestation may threaten the surviving twin owing to twin-to-twin transfusion, in which blood volume is shunted into the dying twin's circulation through shared vascular connections within the placenta, leading to acute hypovolemia and hypotension. Twin-to-twin transfusion is also associated with polyhydramnios and certain gastrointestinal and neurologic anomalies in the recipient twin, and oligohydramnios, renal anomalies, and growth restriction in the donor twin.

Placenta previa, vasa previa, and abruptio placenta also occur more frequently in multiple gestations (47, 48), with abruptio placenta being the most common. Postpartum hemorrhage also complicates approximately 12% of multifetal

TABLE 1

Incidence (%) of major maternal complications in multiple pregnancies (24–29).

	Singleton	Twin	Triplet	Quadruplets
Pre-eclampsia	6	10–12	25–60	>60
Gestational diabetes	3	5–8	7	>10
Preterm labor	15	40	75	>95
Delivery at <37 weeks	10	50	92	>95
Delivery at <32 weeks	2	8	26	>95

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deliveries (33). The risks associated with multiple gestation include the consequences of preterm birth (cerebral palsy, retinopathy, and bronchopulmonary dysplasia) and those of fetal growth restriction (polycythemia, hypoglycemia, and necrotizing enterocolitis). To what extent multiple gestation itself may affect neurobehavioral development in the absence of these complications remains unclear.

ECONOMIC CONSIDERATIONS FOR MULTIPLE GESTATIONS

The economic costs relating to excess perinatal and maternal morbidity and mortality associated with multiple gestations resulting from OI, OS, and ART are substantial and include both the immediate costs of maternal hospitalization and neonatal intensive care and the lifetime costs of care for chronic illness, rehabilitation, and special education. The immediate costs associated with multiple gestation can be estimated from hospital charges, whereas the lifetime costs are more difficult to determine–although they have been estimated in several studies from Europe, Canada, and the US (49). The medical expenses associated with twin gestation are approximately 5 times greater than those associated with singleton pregnancies, and pregnancies with delivery of high-order multiples cost nearly 20 times more (50). Even after birth, the hospital costs until the age of 5 years are significantly higher for multiples compared to that for singletons born after IVF (51). Aside from the medical costs associated with obstetric and neonatal management of multiple gestation, raising twins is likely to be more expensive for a family compared to the cost of raising 2 singletons. The US Department of Agriculture estimates that the cost for a middle-income family to raise a set of twins ($499,680) is more than double the cost of raising a singleton ($233,610) (52).

FACTORS CONTRIBUTING TO THE INCREASED RISK OF MULTIPLE GESTATION ASSOCIATED WITH TREATMENTS FOR INFERTILITY

Several factors contribute to the increased incidence of multiple gestation resulting from treatments for infertility. An increased sense of urgency leads many couples with infertility to pursue more aggressive treatments involving the use of exogenous gonadotropins or to accept the risks associated with the transfer of greater numbers of embryos in IVF cycles. Although multiple birth rates are lower in states having comprehensive health care insurance mandates that include IVF, it is unclear whether the differences relate to more conservative embryo transfer practices or to the characteristics of patient populations having greater access to such treatment (53–55). Inadequacy or absence of health insurance coverage for IVF may encourage some to pursue OS as a less costly alternative. Another strategy when health insurance coverage is inadequate is to increase the number of embryos transferred in the one or few IVF cycles that limited resources will allow (56).

In 1998, SART and American Society for Reproductive Medicine published the first practice guidance documents for the maximum numbers of embryos to transfer in IVF cycles according to maternal age and other prognostic factors. Recommendations were adjusted downward in subsequent updates issued in 2004, 2006, 2008, 2009, 2013, and 2017,

TABLE 2

Major perinatal morbidity and mortality outcomes in multiple pregnancies (31, 35, 39).

	Singleton	Twin	Triplet
Prospective risk of fetal death (%)[a]	0.03	0.09	0.14
Gestational diabetes (%)	0.06	0.31	1.38
Neonates <2500 g (%)	6.2	53.2	93.2
Neonates <1500 g (%)	1.2	10.5	37.5
Average gestational age (weeks)	39.1	35.3	32.2
Average birth weight (g)	3,358	2,347	1,687

[a] Prospective risk of fetal death between 24 and 43 weeks of gestation in a singleton pregnancy, 41 weeks in a twin pregnancy, and 38 weeks in a triplet pregnancy; prospective risk is calculated as a proportion of all fetuses still present at a given gestational age, because gestational age varies by the number of fetuses.

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TABLE 3

Neonatal outcome in singleton and vanishing twin gestations (Pinborg 2005).

	Singleton	Surviving Twin
Delivery at <37 weeks (%)[a]	9.0	13.2
Delivery at <32 weeks (%)[a]	1.3	3.8
Neonates <2500 g (%)[a]	6.3	11.7
Neonates <1500 g (%)[a]	1.5	4.1

[a] $P<.001$ for comparison between singleton and surviving twin for each outcome.

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as IVF success rates and multiple gestation increased (53, 57–61). In these documents, multiple embryo transfer was still considered acceptable in all but the most favorable patients <35 years of age. The updated committee opinion for the maximum numbers of embryos to transfer published in 2017 was significantly different (61). Based on registry data showing that clinics performing high rates of single embryo transfer (SET) in woman <38 years of age have reduced multiple gestation rates without a negative impact on cumulative live birth rates, and single blastocyst transfer was recommended in all patients younger than 38 years of age with a favorable prognosis (61, 62). With the increasing use of blastocyst-stage biopsy for preimplantation genetic testing for aneuploidy (PGT-A), the 2017 document included, for the first time, guidance on the transfer of euploid embryos. Single embryo transfer was recommended for euploid embryos regardless of maternal age or prognosis. The decline in IVF-related and overall US high-order multiple gestation births has temporally followed the release of each new guidance document with a continued decline in triplet births, accounting for only 0.2% of ART deliveries in 2018 (63, 64).

Single embryo transfer rates remained below 10% for all ages through 2009. With the increasing use of extended embryo culture and blastocyst vitrification, there was a dramatic increase in SET. In 2018, 67.3% of all transfers were SETs (65). Due to the change in transfer practices, the twin rate has recently dramatically declined to <10% of all IVF births (66).

Gestational carriers (GCs) are being increasingly utilized in IVF cycles as they present an alternative to adoption and allow the intended parent(s) to potentially maintain a genetic link with their offspring. In the US, GC use in IVF cycles has increased from 1%–3.5% of all IVF cycles (67–69). There is also increasing utilization of GCs in the US by individuals from foreign nations where GC use is much more restricted (67). Due to the high cost of GC IVF cycles, many intended parents are tempted to transfer multiple embryos to increase their odds of live birth. This was confirmed by a survey of Centers for Disease Control and Prevention ART data, in which >30,000 GC IVF cycles were reviewed, of which 78.6% had >1 embryo transferred (68). Unsurprisingly, this same study also reported that of 13,380 deliveries, 34% were twins, and 2% were high-order multiples, which is significantly higher than the incidence of twins and high-order multiples in naturally conceived pregnancies

(69). Similarly, in a more recent analysis of oocyte-donor recipient GC IVF cycles from 2014–2016 SART data, of 4,776 IVF cycles analyzed, 48.7% involved transfer of >1 blastocyst with an overall mean of 1.5 ± 0.5 embryos transferred. Transfer of >1 blastocyst in these patients resulted in multiple pregnancy rates between 41.5% and 45.6% (70). Given the significant maternal and neonatal risks of multiple gestation that we have already summarized, it is crucial to prioritize the health and safety of these altruistic women and preserve the invaluable service they provide by promoting the use of SET.

STRATEGIES FOR LIMITING THE RISK OF MULTIPLE GESTATION IN ART

The most direct way to limit the risk of multiple gestation from ART is to transfer a single embryo. Transferring multiple embryos results in higher overall live birth rates per transfer but also incurs an increased risk of multiple gestation with increased obstetric and neonatal complications (71). Methods for embryo selection have evolved using technologies but still do not perfectly predict the single embryo having the greatest implantation and developmental potential. It is also difficult to predict the likelihood of pregnancy and of multiple gestation on the basis of patient characteristics. Therefore, efforts to reduce multiple gestation have focused on increasing utilization of SET.

Many factors influence the application of elective SET (eSET), a few of which are mentioned below:
- The desire to achieve a higher per transfer pregnancy rate.
- The education of both clinicians and patients on the health and wider societal benefits of eSET.
- The availability of health insurance coverage for IVF sufficient to permit repeated attempts at fresh and frozen embryo transfer.
- The economic pressure on patients restricting the number of ART cycles that they can attempt.
- Other socioeconomic, cultural, and religious factors.

Embryo transfer policies vary among countries and range from strict government regulations to more flexible professional guidelines. In the US, ART professionals have developed prognosis-dependent guidelines that allow for greater individualization of patient care while still limiting the risk for multiple gestation (64). Such practice guidelines ultimately leave the decision to physicians and their patients (Table 4) (53) but recognize that patients having the best prognosis should have fewer embryos transferred.

Current embryo transfer guidance considers the following characteristics to be good prognosis in addition to patient age:

1) Expectation of one or more high-quality embryos available for cryopreservation.
2) Previous live birth after an IVF cycle.
3) For frozen embryo transfers (FETs): vitrified blastocysts, euploid embryos, first FET cycle, previous live birth from IVF.

TABLE 4

Recommendations for limiting the number of embryos to transfer (53).

	Age (years)			
Prognosis	< 35	35–37	38–40	41–42
Cleavage-stage embryos				
Euploid	1	1	1	1
Other Favorable[b]	1	1	≤3	≤4
Embryos not Euploid[a] or Favorable[b]	≤2	≤3	≤4	≤5
Blastocysts				
Euploid[a]	1	1	1	1
Other Favorable[b]	1	1	≤2	≤3
Embryos not Euploid[a] or Favorable[b]	≤2	≤2	≤3	≤3

Please note that the justification for transferring additional embryos beyond recommended limits should be clearly documented in the patient's medical record.
[a] Demonstrated euploid embryos, best prognosis.
[b] Other Favorable = Any ONE of these criteria: *Fresh cycle*: expectation of 1 or more high-quality embryos available for cryopreservation or previous live birth after an IVF cycle; *FET cycle*: availability of vitrified day-5 or day-6 blastocysts, euploid embryos, first FET cycle, or previous live birth after an IVF cycle.

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Single embryo transfer is recommended for embryos deemed euploid after PGT-A and donor oocyte cycles where the donor is <38 years of age. The development and rapid application of the reliable vitrification method for cryopreservation of embryos has resulted in a shift in practice patterns with an increasing number of freeze-only cycles and subsequent frozen embryo transfers (72). Therefore, an important addition to the 2017 guidelines was the recommendation to avoid double-embryo transfer (DET) in good-prognosis patients until they had failed multiple embryo transfers and to further expand what defined good-prognosis scenarios in frozen embryo transfer cycles. Single embryo transfer should be strongly recommended in all GC cycles, given the health risks associated with multiple gestation for the GC. At a minimum, it is recommended to follow age-related limits on the number of embryos to transfer in GC cycles on the basis of age of the oocytes from the intended parent or oocyte donor.

The first randomized controlled trials (RCTs) and cohort studies to evaluate the efficacy of SET focused on young patients at the highest risk for twins (73, 74). A meta-analysis of 8 trials involving 1,367 patients who underwent cleavage-stage transfer and were randomized to eSET or DET showed that the overall live birth rate was significantly lower in the SET group (27% vs. 42%; adjusted OR [aOR] 0.5, 95% CI 0.39–0.63), as was the multiple birth rate (2% vs. 29%; aOR 0.04, 95% CI 0.01–0.12) (75). These observations illustrate the importance and impact of clinical judgment in selecting the best candidates for SET. A subanalysis of 2 of the trials in this meta-analysis (73) confirmed the independent findings of one of the trials (76) that the difference in success rates observed after SET and DET is mitigated by a subsequent SET of a cryopreserved embryo (cumulative live birth rates: 38% vs. 42% for eSET vs. DET; aOR 0.85, 95% CI 0.62–1.15). It is important to note the limitations of applying data on cleavage state embryo transfer to vitrified blastocysts.

Single Embryo Transfer

Increasing the likelihood of live birth from each transfer event could theoretically increase the willingness of patients and providers to use SET, both in the initial embryo transfer and in subsequent transfer cycles. Strategies to improve live birth have primarily focused on maximizing embryo selection and endometrial synchrony. These strategies include PGT-A, freezing only embryo transfer cycles, endometrial synchrony testing, and time lapse imaging and other noninvasive embryo testing strategies. There is currently a lack of robust and consistent evidence that these strategies improve the chances of achieving a live birth. Furthermore, while strategies to improve live birth are aimed at improving the live-birth success of each embryo transfer, they are not required to reduce multiple gestation. Performing SET without additional embryo or endometrial testing is sufficient to reduce the multiple gestation rate down to the background 1–2% risk of monozygotic twins in ART (74, 77, 78). Single embryo transfer, regardless of additional testing, should be considered the gold standard to reduce multiple gestation. Given the lack of robust evidence or conflicting evidence for many of these tests to improve clinical outcomes, they are currently not routinely recommended as a strategy to increase SET.

Extended Culture–Single Blastocyst Transfer

The effectiveness of SET may be maximized by transfer of a blastocyst rather than a cleavage-stage embryo. In one program in the US, implementation of a policy to transfer a single blastocyst, combined with an educational program relating specifically to the potential risks and consequences of multiple births, resulted in a substantial decrease in the average number of embryos transferred and in the incidence of multiple gestation (from 35%–19%), while overall pregnancy rates were maintained (79). This result was replicated in another US center where introduction of a single blastocyst transfer policy in good-prognosis patients maintained clinical pregnancy at 63% but reduced twin gestation from 44%–15% (80).

A randomized trial comparing single cleavage-stage embryo transfer vs. single blastocyst-stage embryo transfer found that the blastocyst-stage group had a significantly higher rate of live birth (32.0% vs. 21.6%, relative risk [RR] 1.48 [95%CI 1.04–2.11]) (81). This difference may be partially

attributable to a higher rate of pregnancy loss in the first trimester in the cleavage-stage group than in the blastocyst-stage group, although this difference was not significant (33.9% vs. 19.2%). There were 2 monozygotic twin pregnancies, both occurring in the cleavage-stage transfer group (81)

A small, randomized trial from a single center did not show a significant difference between the transfer of 1 vs. 2 blastocysts, with ongoing pregnancy rates of 60.9% and 76%, respectively, and twin rates of 0% and 47.4%, respectively (74). The study did not include a discussion of how the sample size was chosen. Since it included only 48 patients, SET could have been as much as 41% inferior to DET (95% risk difference). While intriguing, these 2 trials did not significantly change clinical practice, as transfer of 2 blastocysts remained the predominant practice throughout the early 2000s.

However, there are several theoretical concerns with blastocyst transfer, including an increased incidence of monozygotic twinning with one large registry study finding a 2% risk among cleavage-stage transfers and a 3.4% risk among blastocyst transfers (OR 1.7, 95%CI 1.05–2.76). Elective SET was also an independent risk factor for monozygotic twinning. There also are fewer embryos available for cryopreservation (81) after blastocyst transfer, possibly limiting cumulative pregnancy rates. Based on animal data (82), there is theoretical concern that extended culture to the blastocyst stage may be associated with epigenetic changes in the embryo (83). While these theoretical concerns exist, the vast majority of data suggest that blastocyst-stage transfer is safe and effective.

Preimplantation Genetic Testing for Aneuploidy

While originally developed to improve outcomes for poor prognosis IVF patients (prior failed cycles, advanced age, recurrent pregnancy loss), in recent years, PGT-A has been used as a strategy to enhance selection for eSET. In a retrospective study, Forman et al. (84) found that single euploid blastocysts resulted in a 55% ongoing pregnancy rate compared to 41.8% among untested blastocysts. A randomized, noninferiority trial by the same group showed that euploid eSET resulted in similar live birth rates as that of the transfer of 2 untested blastocysts, with a significantly lower risk of multiple gestation. Among 175 randomized patients up to age 42 years with normal ovarian reserve, there was a 60.7% ongoing pregnancy rate after euploid eSET vs. 65.1% after untested DET (85). Follow-up of randomized patients including a subsequent transfer for those who did not deliver on their first attempt, demonstrated improved obstetric outcomes in the eSET group (86). While these studies used a real-time polymerase chain reaction for PGT-A, next generation sequencing has become more widely used. The STAR Trial was an RCT comparing FET of a single euploid blastocyst testing with next generation sequencing to SET of a blastocyst selected by morphology. Embryos with a mosaic result on PGT-A were excluded from transfer. Overall, the study did not show improved ongoing pregnancy rates after PGT-A (87). The data on PGT-A are insufficient to recommend its routine use for the purpose of increasing SET.

STRATEGIES FOR LIMITING THE RISK OF MULTIPLE GESTATION IN OVULATION INDUCTION AND OVARIAN STIMULATION TREATMENTS

The historic and putative goals of OI and OS differ significantly depending on the clinical context. The ideal goal of OI in oligo-ovulatory or anovulatory women should be ovulation of a single mature oocyte. In contrast, the goal of OS in ovulatory women is to cautiously manage multi-follicular recruitment in an effort to increase cycle fecundity, while also minimizing the increased risk of multiple gestation.

Anovulatory Infertility

It is imperative to tailor a patient's stimulation regimen to their specific clinical circumstance and need. There are multiple OS agents that can be used, varying from oral agents to gonadotropin injections. For anovulatory women, such as those with polycystic ovary syndrome, the most recent Cochrane review showed that letrozole compared to clomiphene citrate (CC) increased live birth rates (OR 1.68;95% CI 1.42–1.99) without increasing the multiple pregnancy rate (1.7% with CC vs 1.3% with letrozole; OR 0.69%;95% CI 0.41–1.16) (88). A meta-analysis of 57 RCTs with 8,082 women also confirmed that letrozole resulted in significantly higher live birth rates compared to clomiphene and with a lower incidence of multiple gestation compared to gonadotropins, which had the greatest risk of multiple gestation (89). However, if ovulation is not achieved using oral agents, low-dose exogenous gonadotropins are acceptable to use for OI cycles with a strict cancellation policy. It is recommended to start at a low dose of 37.5–75 IU a day, with slow increases of dosing to achieve mono-follicular development. Further, cycle cancellation is strongly recommended for patients with >2 follicles ≥16 mm or if there are ≥3 intermediate sized follicles to reduce the risk of multiple gestation and ovarian hyperstimulation syndrome (90).

Unexplained Infertility

It is not recommended for most couples with unexplained infertility to undergo OS with gonadotropins. A recent systematic review and meta-analysis of 8 RCTs (2,989 women) showed no increase in live birth rates with gonadotrophins as compared to oral agents if gonadotropins were used in low doses or with a strict cancellation policy (91). However, if gonadotrophins were used in higher doses or without a strict cancellation policy, there was an increased pregnancy rate (RR 1.09) but with a concurrent increase in multiple gestations (RR 1.20 for higher doses and 1.15 for lax cancellation policy). Another meta-analysis had similar findings, indicating that gonadotropins had the highest live birth and ongoing pregnancy rates, but at the expense of a higher risk of multiple gestation (92). Considering all the associated maternal and neonatal complications with multiples, this increase in the rates of pregnancy and live birth does not ameliorate the negative outcomes of a similar increase in multiple gestation. Based on these findings, it is prudent to offer a course of OS

with oral medications and intrauterine insemination (IUI) followed by IVF for those not successful (93, 94).

Ovulatory Women Undergoing Donor Insemination

Donor insemination is utilized in ovulatory women who are infertile due to being same sex couples, single females, heterosexual couples with azoospermia, and other clinical scenarios. When ovulatory women are using donor sperm, both natural cycle and OS are management options. A recent retrospective cohort study (76,643 IUI cycles) compared natural cycle vs. OS in ovulatory women using donor sperm. There was a <1% increase in ongoing pregnancies with oral medications compared to the natural cycle, but ongoing multiple gestations increased from 2.4%–10.8%. Based on limited data, natural cycle IUI should be considered as the first-line treatment for ovulatory women who are using donor sperm insemination (95).

Mitigating the Risk of Multiples

In a multicenter RCT involving 1,220 OS cycles in which human chorionic gonadotropin was withheld when the E_2 level exceeded 3,000 pg/mL or when >4 follicles >18 mm in diameter were observed, the multiple pregnancy rate was very high at 31%, with 6% of pregnancies being triplets (96). In another trial involving 449 OS cycles in which human chorionic gonadotropin was withheld if >6 follicles >14–15 mm in size were observed, the overall multiple pregnancy rate was 23.5%, of which 92% were twins, and 8% were high-order multiples (97). These data clearly demonstrate that lax cancellation policies during OS result in a significant risk of both twin and high-order multiple gestation. Conversely, another study showed that when cycles were cancelled if >3 follicles ≥14 mm developed, multiple gestation could be limited to only 2% (98). Evidence derived from experience in ART cycles indicates that follicles as small as 10 mm in diameter may yield mature and fertilizable oocytes (99).

Specifically looking at age and number of follicles during OI or OS, a retrospective cohort study with 50,473 OI/OS and IUI cycles concluded there was a marked increased risk of multiple gestation if proceeding with IUI in women younger than age 40 years with >2 follicles ≥14 mm (100). In addition, there was no improved chance of a singleton clinical pregnancy and minimal increase in overall pregnancy with >2 follicles. When comparing 1 mature follicle vs. 5 at time of IUI in women <38 years of age, clinical pregnancy rates ranged from 14.6%–21.9% but with an increase in multiple gestation risk from 4%–31.8% with 1 vs 5 follicles. Similar findings were noted in the 38–40 years of age group. Conversely, in women > 40 years of age, up to 3 follicles increased the odds of pregnancy (aOR 5.76 [95%CI 0.69–48.25]) while keeping the rate of multiple gestation per pregnancy at <8%. Subanalysis demonstrated that with increasing follicle number, the increased risk of multiple gestation and minimal benefit in pregnancy persisted in patients with both anovulation and unexplained infertility (100). This challenges the historic approach of trying to develop more follicles in ovulatory patients with infertility

to increase the chance of pregnancy. Though this model outlined by the investigators serves as a helpful clinical counseling tool, it is not an established predictor given that the studied population represents a heterogeneous group with a wide range of prognosis for both fecundity and multiple gestations.

When gonadotropins are used for treatments outside of ART, low-dose gonadotropins (37.5–75 IU per day) should be utilized to minimize the risk of multiple gestation. However, the above evidence demonstrates that the benefit of low-dose gonadotropin use is primarily in the setting of anovulatory patients who do not respond to oral medications. In the setting of ovulatory patients, the data demonstrate that gonadotropin use increases pregnancy only when used at high enough doses that the risk of multiple gestation is also increased. When gonadotropins are used on ovulatory women at low doses with a strict cancellation policy, live birth is not increased, and cost is increased (101).

The clinical utility of preovulatory ultrasound-guided aspiration of excess follicles for reducing the risk of multiple gestation in OI and SO has been examined (102–104). In 2 studies, aspiration was performed when >3 follicles having a mean diameter of >14 mm were observed, leaving the 3 largest follicles undisturbed (93, 102). The multiple gestation rate was approximately 10%, and the overall pregnancy rates ranged between 20% and 25%. In the third study, in which aspiration was performed when >3 follicles measuring >15 mm in mean diameter were observed, and all follicles <15 mm in size were aspirated (105), the pregnancy rate was 26.9% per cycle, and no multiple pregnancies occurred. Taken together, these data suggest that additional studies are warranted to better define the optimal criteria and methods for aspiration and the overall cost-effectiveness of the strategy. Overall, regardless of which medication or stimulation regimen is used, it may not be possible to entirely eliminate the risk of multiple gestation associated with OI or OS. Follicle aspiration to reduce the risk of multiple gestation in this setting should only be considered as a risk mitigation strategy for unanticipated over response to medication, not as a standard approach for non-ART treatments.

MULTIFETAL PREGNANCY REDUCTION

High-order multifetal gestation must be regarded as an adverse outcome of treatment for infertility. The risk for adverse perinatal and maternal outcomes increases progressively with the number of fetuses (106, 107) Patients with high-order multiple gestations must choose one of 3 options: continuing the pregnancy, accepting all of the risks previously described; terminating the pregnancy; or multifetal pregnancy reduction (MFPR) to reduce the number of fetuses and the associated risks of maternal and perinatal morbidity and mortality (106, 108, 109). Multifetal pregnancy reduction decreases the risks associated with preterm delivery (109–111), whether in quadruplets or above (110), trichorionic triplets reduced either to twins (112) or to singletons (106, 113, 114), or after reduction of a monochorionic pair in a triplet pregnancy (115). However,

because MFPR can present patients with a profound ethical dilemma and cause significant psychologic trauma (107, 116), thorough counseling must be provided (105). A study of 91 patients indicated that despite feelings of loss and guilt for at least a year (117), most (93%) would make the same decision for MFPR if faced with a similar situation in the future (118). Patients who describe themselves as "pro-choice" are more likely to consider MFPR than those who do not, and their views do not change after having an embryo transfer (119). The primary risks of MFPR are pregnancy loss and preterm birth. However, as experience with the procedure has grown, the incidence of pregnancy loss and premature birth has further declined (109, 110, 113). It is recommended that MFPR should be performed only in specialized centers with fetal medicine practitioners experienced in the procedure (109, 110).

Literature on the benefits of MFPR is limited by a lack of randomized trials assessing efficacy (owing to obvious ethical considerations) and a paucity of meta-analyses. Consequently, a systematic review concluded that the data are insufficient to recommend a general policy of MFPR for women with a high-order multiple pregnancy (120). Nevertheless, several analyses have shown that MFPR does appear to benefit quadruplet and higher-order pregnancies wherein the procedure clearly prolongs the length of gestation for the remaining fetuses (109, 110, 120). Moreover, the results of one meta-analysis of 11 nonrandomized studies of triplet pregnancies of varying quality (109) showed that the pregnancy loss rate at <24 weeks was similar in triplet pregnancies reduced to twins and in unreduced triplets (7% vs. 7.4%; OR 0.95, 95% CI 0.66–1.4). However, the preterm delivery rate at <28 weeks was significantly lower in the reduced triplets (2.9% vs. 9.8%; OR 0.30, 95% CI 0.18–0.5), as was the rate of preterm delivery at <32 weeks (8.9% vs. 25.1%; OR 0.36, 95% CI, 0.27–0.46) (109).

Therefore, available evidence indicates that MFPR appears to be associated with a reduced risk of prematurity, although the true benefit of this intervention is difficult to enumerate owing to potential bias in interpreting the data.

SUMMARY

- The goal of infertility treatment is for each patient to have one healthy child at a time. The challenges associated with achieving that goal differ by treatment and clinical context.
- The incidence of multiple births in the US has risen since 1980, likely driven almost entirely by infertility treatments.
- Subsequently, the percentage of high-order multiple gestations in the US has decreased since 1998, and twin gestation has decreased since 2014.
- A desire to achieve pregnancy expeditiously with fertility treatment must be balanced against the substantial family, medical, social, and economic consequences of multiple gestations.
- It is recommended that intentional strategies to reduce multiple gestation be employed in all infertility treatments, as multiple gestations are associated with major maternal and fetal risks.

- It is recommended that cycle cancellation should be considered if >2 follicles ≥16 mm develop or >3 follicles ≥14 mm develop in non-ART treatments in women <40 years of age. It should be noted that OI and OS result in more twin gestation than do ART treatments. Most of the high-order multiple gestations result from OI and OS rather than from ART or natural conception.
- It is recommended that in women with anovulatory infertility who require gonadotropins, the lowest dose possible be used to induce ovulation of a single follicle. Starting doses of 37.5–75 IU are recommended with small incremental increases as needed on the basis of ovarian response.
- It is not recommended to use gonadotropins for ovulatory women utilizing timed intercourse or IUI.
- It is recommended to use SET in all good-prognosis ART cycles. Elective SET is the most effective strategy for reducing the risk of multiple pregnancy with ART.
- Single embryo transfer should be strongly recommended in all GC cycles, given the health risks associated with multiple gestation for the GC. At a minimum, it is recommended to follow age-related limits on the number of embryos to transfer in GC cycles, on the basis of age of the oocytes from the intended parent or oocyte donor.
- It is not recommended to use alternate embryo and endometrial testing strategies purely for the purpose of increasing SET, as alternate strategies have not been proven to improve live birth or reduce multiple gestation compared to SET in good-prognosis patients.
- It is recommended to use patient educational strategies regarding the risks of multiple gestation to increase acceptance of SET and safe OS.

CONCLUSIONS

- Current efforts should continue to focus on reducing the overall incidence of multiple pregnancies, with increasing priority for reducing the twin rate.
- Greater efforts are needed to reduce the multiple gestation risk in non-ART infertility treatments, which estimates suggest are the greatest contribution to iatrogenic multiple gestation.
- Further research is needed on alternate methods of testing embryo and endometrial capacity to optimize live birth before they become routinely recommended.
- Physicians should counsel their patients carefully on the risks and benefits of eSET.
- Single embryo transfer should be utilized for all good-prognosis patients.

reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, considering the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committees, the Quality Assurance Committee, and the Board of Directors of the American Society for Reproductive Medicine have approved this report. This document was reviewed by ASRM members, and their input was considered in the preparation of the final document. The following members of the ASRM Practice Committee participated in the development of this document: Alan Penzias, M.D.; Kristin Bendikson, M.D.; Marcelle Cedars, M.D.; Tommaso Falcone, M.D.; Karl Hansen, M.D., Ph.D.; Micah Hill, D.O.; Sangita Jindal, Ph.D.; Suleena Kalra, M.D., M.S.C.E.; Jennifer Mersereau, M.D.; Richard Reindollar, M.D.; Chevis N Shannon, D.P.H., M.P.H., M.B.A.; Anne Steiner, M.D., M.P.H.: Cigdem Tanrikut, M.D.; Belinda Yauger, M.D. The Practice Committee acknowledges the special contribution of Task Force members Micah J Hill, D.O. (Chair), Erica Lowden, M.D., Eric Forman, M.D., Daniel Grow, M.D., and Mae Healy, D.O. in the preparation of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

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