Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion

Practice Committee of the American Society for Reproductive Medicine

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The purpose of this committee opinion, which replaces the 2006 ASRM Practice Committee document titled *Multiple Pregnancy Associated with Infertility Therapy*, is to provide physicians with pertinent information that may help to avoid multiple gestations and to aid in patient counseling regarding the associated risks. (Fertil Steril® 2012;97:825–34. ©2012 by American Society for Reproductive Medicine.)

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 with the treatment and the clinical context. In ovulation induction (OI), which is used in cases of oligo- or anovulation, more than the targeted ovulation of a single oocyte may result. In superovulation (SO), which is used in ovulatory women with unexplained or age-related subfertility, implantation of more than one embryo may follow fertilization of oocytes from supernumerary follicles. With assisted reproductive technologies (ART), multiple embryos may be transfered after in vitro fertilization (IVF), with or without intracytoplasmic sperm injection (ICSI). 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, whether two or more than two fetuses (i.e., a high-order multiple).

The objectives of this committee opinion are: 1) to review the incidence, recent trends, and modes of conception associated with multiple gestations in the U.S.; 2) to consider the different factors relating to the increased risks for multiple pregnancies in OI, SO, and ART; 3) to discuss the complications and economic impact of multiple pregnancies; and 4) to summarize current and emerging strategies aimed at limiting the risk of multiple gestations associated with treatments for infertility. The overarching purpose of this bulletin 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 U.S.

In 2008, multiple births accounted for 3.26% of all births in the U.S. (1). The incidence of multiple births has risen steadily since 1980, which may be considered as the reference year for estimating the relative contributions of different infertility treatments to the multiple birth rate, because at that time clinical practice in the U.S. did not include IVF and the use of exogenous gonadotropin-induced OI or SO was quite limited (2). From 1998 through 2008, high-order multiple births (as a percentage of all births) decreased (from 0.193% to 0.148%), but the twin birth rate continued to rise (from 2.80% to 3.41%).

Accurate estimates of the relative proportions of multiple births attributable to OI/SO and ART are difficult to determine, because OI/SO cycles are not currently captured in a national registry. The contribution of OI/SO cycles has been derived from the total number of multiple births nationally, minus the sum of the ART contribution and the estimated number from natural conception. In addition, the ART estimates may not be accurate, because not all U.S. ART programs report to the Centers for Disease Control (CDC) and the Society for Assisted Reproductive Technology (SART); only 91.8% reported in 2008.

Even with these caveats, there is consensus that the majority of twin births result from natural conception (~60%), with OI/SO and ART treatments accounting proportionally for the remainder (OI/SO: range 21% to 32%; ART: range 8% to 16%) (2–5). Although

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there is agreement that ~20% of high-order multiple gestations result from natural conception (2–6), allocation of the remainder to OI/SO versus ART varies widely (OI/SO: range 39% to 67%; ART: range 13% to 44%) (2, 3, 5).

Although naturally-conceived twins account for the majority of all multiple births, the incidence of twins among births resulting specifically from SO and ART is more than 20 times greater than for births resulting from natural conception, and that of high-order multiple gestation is more than 100 times higher (4). Therefore, attention must remain focused on efforts to decrease the risk of multiple gestation associated with treatment for infertility.

RISK FACTORS FOR THE OCCURRENCE OF MULTIPLE GESTATIONS

In naturally-conceived multiple gestation, the prevalence of dizygotic twinning varies with ethnicity (1.3 per 1,000 in Japan, 8 per 1,000 in the U.S. and Europe, and 50 per 1,000 in Nigeria) (7, 8). Dizygotic twinning is also associated with increasing maternal age, greater parity, and a maternal family history of twinning (7, 9, 10). In contrast, the rate of monozygotic twinning is relatively constant (4 per 1,000 live births) (11), regardless of maternal age, race, or parity (12), although genetic predisposition may have some influence (13).

Multiple follicular development is the dominant risk factor for dizygotic twinning and high-order multiple gestations in OI and SO cycles, and it can be difficult to prevent (14). It also increases the risk of monozygotic twinning by two- to threefold and contributes to the overall increased risk of multiple gestation in OI cycles compared with that in natural conception cycles (15).

In ART treatment, the main risk factor for dizygotic and high-order multiple pregnancies is the transfer of more than one embryo (16, 17). The risk of monozygotic twinning may be increased by approximately twofold in conventional IVF cycles (13) and increases further in ART cycles involving ICSI (12, 18, 19). In one case series, assisted hatching also was associated with an increased risk of monozygotic twinning (20). However, a 2009 Cochrane review of four studies with a total of 524 patients concluded that available data were insufficient to determine whether assisted hatching increased the risk of monozygotic twinning (odds ratio [OR] 3.26, 95% confidence interval [CI] 0.14–77.84) (21). A number of studies have concluded that the risk of monozygotic twinning is increased when culture is extended to the blastocyst stage (13). One report suggested that the risk may be related to the composition of culture media (22). Another found no association between the type of culture medium and risk of monochorionic twinning (the subclassification of monozygotic twinning in which twins share a chorion), but did observe a 24-fold increased risk in cycles involving both ICSI and extended culture (23).

COMPLICATIONS OF MULTIPLE GESTATIONS

Multiple gestation increases maternal morbidity and both 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 relates directly to the consequences of preterm birth (Table 1).

Even singleton births after ART are associated with increased risks, such as prematurity, independently from maternal age and fetal numbers (35–38), but the risks are far greater with multiple gestations. 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) birth weight increase with the number of fetuses in a multiple gestation (Table 2). Fetal growth restriction and discordance contribute to the increased perinatal morbidity and mortality in multiple pregnancies (41). Multifetal reduction decreases, but does not eliminate, the risk of fetal growth restriction (42) or loss of the entire pregnancy (43).

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 and methodology and diagnostic criteria; estimates have ranged from 12% (44) to 30%–38% (32, 45) in multiple gestations resulting from ART. Early studies suggested that after the transfer of two embryos, demise of one twin in a dizygotic pair was unlikely to adversely affect the mother or surviving fetus (46, 47). However, more recent evidence indicates that the mean birth weight 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) (48). 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: OR 2.78, 95% CI 1.11–7.14) (49), and increases with gestational age at the time of the demise (>22 weeks: OR 9.09, 95% CI 1.72–50) (50). The incidences of preterm birth (<37 weeks), very preterm birth (<32 weeks), low birth weight, and very low birth weight are all significantly increased in surviving twins compared with singleton pregnancies (Table 3) (49). Limited data suggest

TABLE 1

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

	Singleton	Twin	Triplet	Quadruplet
Preeclampsia	6	10–12	25–60	>60
Gestational diabetes	3	5–8	7	>10
Preterm labor	15	40	75	>95
Delivery at <37 wk	10	50	92	>95
Delivery at <32 wk	2	8	26	>95

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TABLE 2

Major perinatal morbidity and mortality outcomes in multiple pregnancies (25, 29, 31, 39, 40).

	Singleton	Twin	Triplet
Prospective risk of fetal death (%)[a]	0.03	0.09	0.14
Gestational diabetes (%)	0.06	0.31	1.38
Neonates <2,500 g (%)	6.2	53.2	93.2
Neonates <1,500 g (%)	1.2	10.5	37.5
Average gestational age (wk)	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' gestation in a singleton pregnancy, at 41 weeks in a twin pregnancy, and at 38 weeks in a triplet pregnancy; prospective risk 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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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 (51), and for cerebral palsy (OR 1.9, 95% CI 0.7–5.2) (49), 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% to 6.8% (52). 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, resulting in acute hypovolemia and hypotension. Twin-to-twin transfusion also is associated with polyhydramnios and certain gastrointestinal and neurologic anomalies in the recipient twin and with oligohydramnios, renal anomalies, and growth restriction in the donor twin.

Renal cortical necrosis and multicystic encephalomalacia may cause the death of one twin and result in preterm birth of the surviving twin (53, 54). Placenta previa, vasa previa, and abruptio placenta also occur more frequently in multiple gestations (55, 56), with placental abruption being the most common. Postpartum hemorrhage also complicates approximately 12% of multifetal 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 is not clear. Physical, emotional, and financial stresses increase the incidence of depression and anxiety disorders among mothers rearing twins and higher-order multiples (57). The incidence of behavioral problems is increased in children from multiple births compared with children from singleton births, and those born prematurely have lower IQ scores at mid-childhood (57).

TABLE 3

Neonatal outcome (%) in singleton and vanishing twin gestations (49).

	Singleton	Surviving twin
Delivery at <37 wk	9.0	13.2
Delivery at <32 wk	1.3	3.8
Neonates <2,500 g	6.3	11.7
Neonates <1,500 g	1.5	4.1

Note: $P < .001$ for comparison between singleton and surviving twin for each outcome.

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ECONOMIC CONSIDERATIONS FOR MULTIPLE GESTATIONS

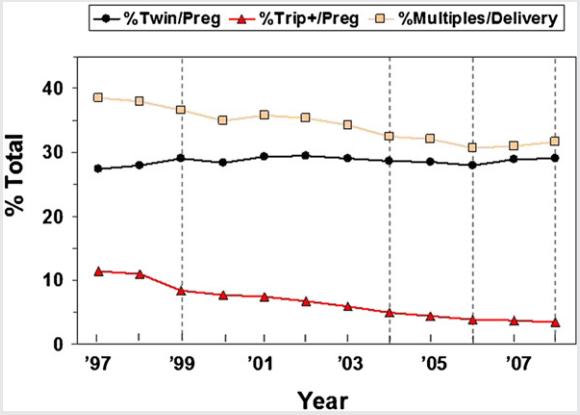
The economic costs relating to the excess perinatal and maternal morbidity and mortality associated with multiple gestations resulting from OI, SO, and ART are substantial and include both the immediate costs of maternal hospitalization and neonatal intensive care and the lifetime costs of care for chronic illness, rehabilitation, and special education. Whereas the immediate costs associated with multiple gestation can be estimated from hospital charges, the lifetime costs are more difficult to determine, although they have been estimated in several studies from Europe, Canada, and the U.S. (58). Compared with singletons, the known costs associated with twin gestation and their sequelae are increased fourfold, and with triplets tenfold. In 2004, approximately 4% of all preterm births in the U.S. resulted from ART, with associated costs reaching $1 billion (59).

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 infertile couples 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. Inadequacy or absence of health insurance coverage for IVF may encourage some to pursue SO as a less costly alternative. Another strategy when health insurance coverage is inadequate is to increase the number of embryos transfered in the one or few IVF cycles that limited resources will allow (60). Finally, competitive pressures may drive clinicians to apply SO or IVF earlier in treatment to produce and maintain high pregnancy rates for clinic advertising purposes. 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 (61).

In 1998, SART and ASRM published the first practice guidelines for the maximum numbers of embryos to transfer in IVF cycles according to maternal age and other prognostic factors. Recommendations were adjusted downward in revised guidelines issued in 1999, 2004, 2006, and 2008 as IVF success rates increased (62). Since the introduction and promulgation of the guidelines, the overall multiple birth rate/delivery in ART cycles in the U.S. underwent a steady decrease through 2006 (63), but then a slight increase in the

FIGURE 1



Assisted reproductive technology outcomes in U.S. related to SART/ASRM guidelines for number of embryos to transfer. Data derived from http://www.cdc.gov/ART/ARTReports.htm. *Dashed lines* indicate years SART/ASRM guidelines were introduced (1998) and subsequently revised (1999, 2004, 2006, and 2008). Multiple births are expressed per delivery; twin and triplet+ pregnancies are expressed per clinical pregnancy.

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subsequent 2 years. The high-order multiple rate/pregnancy continued to decline through 2008, whereas the twin rate/pregnancy underwent a slight increase (27.4% in 1997 to 29.0% in 2008; Fig. 1) (63, 64). The impact of the 2008 revised embryo transfer guidelines (62) is not yet known.

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. Unfortunately, current methods for embryo selection still do not allow identification of the single embryo having the greatest implantation and developmental potential. It is also difficult to predict the likelihood of pregnancy and of multiple gestation based on patient characteristics. Consequently, criteria for identifying the best candidates for elective single-embryo transfer (eSET) are still evolving, and the prevalence of eSET in the U.S. remains quite low. In 2008, 3.3% of ART cycles in the U.S. used eSET (65).

Many factors influence the application of eSET, a few of which are:

- 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.
- The availability of effective cryopreservation protocols.
- Potential commercial competition among IVF programs to achieve the highest fresh embryo transfer delivery rates.
- Other socioeconomic, cultural, and religious factors.

Embryo transfer policies vary among countries, ranging from strict government regulations to more flexible professional guidelines. In Sweden, SET is mandatory except when the risk of twinning is considered to be low, in which cases the transfer of two embryos is permitted (66). In Belgium, more liberal funding and wider access to ART is provided in exchange for the concerted efforts of ART professionals to use SET except when patient age and previous ART experience clearly justify the transfer of more embryos (25). In the U.S., ART professionals have developed prognosis-dependent guidelines that allow for greater individualization of patient care while still limiting the risk for multiple gestation (63). Such practice guidelines ultimately leave the decision to physicians and their patients, but recognize that patients having the best prognosis should have fewer embryos transfered. Current embryo transfer guidelines consider patient age, embryo quality, and other criteria and recommend serious consideration of eSET for patients under age 35 years having the most favorable prognostic features, defined as first IVF attempt, with good-quality embryos, and excess embryos of sufficient quality to warrant cryopreservation (62).

The varying regulations and guidelines that govern the number of embryos to transfer in different countries have resulted in significant differences in live birth rates and multiple gestation rates that emphasize the need to strike the best possible balance in formulating an embryo transfer strategy (67). In the U.S., live birth rates with ART have increased steadily since the early 1990s and in 2003 were 10% higher than in Sweden (35% vs. 25%). Whereas live birth rates have remained stable in Sweden since 1993, the multiple birth rate per delivery has steadily decreased and was 5.8% in 2006, compared with 30.6% in the U.S. (Table 4). However, it must be noted that comparisons are difficult because of socioeconomic, treatment, and other differences.

Varying guidelines and regulations have been examined in several randomized controlled trials (RCTs) and cohort studies aimed at evaluating the efficacy of eSET among young patients at risk for twins (69). A recent meta-analysis of eight trials involving 1,367 patients who underwent cleavage-stage transfer and were randomized to eSET (n = 683) or double-embryo transfer (DET) (n = 684) showed that the overall live birth rate was significantly lower in the eSET 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) (70). These observations illustrate the importance and impact of clinical judgment in selecting the best candidates for eSET. A subanalysis of two of the trials in this

TABLE 4

Assisted reproductive technology outcomes (%) in Sweden and U.S., 2006 (65, 68).

	Per embryo transfer		Per live birth	
Country	Live birth	Singleton birth	Multiple birth	Singleton birth
Sweden	27.2	25.6	5.8	94.2
U.S.	35.4	24.6	30.6	69.4

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meta-analysis (70) confirmed the independent findings of one of the trials (71) that the difference in success rates observed after eSET and transfer of two embryos 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). This meta-analysis included the data from the two earlier independent studies addressing the efficacy of eSET versus DET (71, 72).

The effectiveness of eSET might be maximized by transfer of a blastocyst rather than a cleavage-stage embryo. In one program in the U.S., 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 transfered and in the incidence of multiple gestation (from 35% to 19%), while overall pregnancy rates were maintained (73). However, there are several risks and limitations to blastocyst transfer, including an increased incidence of monozygotic twinning (ranging from 2.7% (74) to 13.2% (75, 76) and monochorionic twinning (23), in addition to fewer embryos available for cryopreservation (77). Based on animal data (78), there is concern that extended culture to the blastocyst stage may be associated with epigenetic changes in the embryo (79, 80).

Whereas the maternal and fetal benefits to be gained by SET are clear, additional research in the following areas could do much to help identify the best candidates for eSET:

1) *Evaluation of cumulative pregnancy rates resulting from a single IVF cycle:* Two studies have demonstrated the promise of a strategy involving two consecutive SET cycles. In one, the cumulative pregnancy rate achieved with transfer of two good-quality embryos, one at a time, was not statistically different (absolute number 4% lower) than that achieved with a single transfer of two good embryos (71). In the other, eSET in two consecutive fresh cycles achieved a pregnancy rate 5% greater than that achieved with one DET (81). Because the differences in outcomes were not significant in either study, further research and additional trials are clearly required to better define the overall success of such treatment strategies and in which populations of patients.
2) *Evaluation of the optimum day for eSET:* Modifications to embryo culture allow some programs to transfer two or even one blastocyst while maintaining acceptable pregnancy rates and reducing the incidence of high-order multiple gestation (71, 73, 82–84). In one RCT involving 352 women, the delivery rate after day 5 SET was 32%, compared with 22% after day 3 (OR 1.48, CI 1.04–2.11) (77). However, because significantly more embryos were frozen in the group receiving day 3 transfer, more research is needed to determine how the day of transfer affects cumulative pregnancy rates achieved with SET.
3) *Evaluation of patient and clinician attitudes for eSET:* Further studies examining the factors that shape patients' and physicians' attitudes about the number of embryos transfered are warranted, particularly as they relate to acceptance that more than one IVF cycle may be required to achieve a successful outcome. The issues involved are complex. However, physicians should be encouraged to counsel good-prognosis patients to accept eSET. Further studies are needed to learn how best to garner clinician and patient (85) support for wider application of eSET.
4) *Evaluation of patient dropout rates:* Several studies have shown that patients drop out of IVF treatment for a variety of reasons (86–88). The effect of dropout rates on eventual cumulative live birth rates needs further evaluation.
5) *Effects of patient education:* It is becoming increasingly clear that providing patients with information about the risk of twin pregnancy markedly improves acceptance of eSET (85, 89). Providing the information via a DVD, rather than an educational booklet, may have a greater effect in leading patients to choose eSET (89). However, not surprisingly, such risk information appears to have value only if patients do not perceive that their likelihood of pregnancy will be lower if they undergo an eSET (90).

STRATEGIES FOR LIMITING THE RISK OF MULTIPLE GESTATION IN OVULATION INDUCTION AND SUPEROVULATION

The goals of ovarian stimulation differ significantly with the clinical context. The goal of OI in oligo- or anovulatory women, including those with polycystic ovary syndrome or hypothalamic amenorrhea, ideally should be ovulation of a single oocyte. In contrast, the specific goal of SO in ovulatory women with unexplained or age-related subfertility is to stimulate the development and ovulation of more than one mature follicle in an effort to increase cycle fecundity. Stimulation regimens therefore must be tailored to each patient's specific clinical circumstance and need. In general, lower doses of exogenous gonadotropins are administered to achieve OI in anovulatory women than are used for SO in ovulatory infertile women. Because anovulatory women, especially those with polycystic ovary syndrome, may be hyperresponsive to gonadotropins, lower doses over a longer interval of stimulation may help to limit the number of follicles recruited and reaching maturity. Multiple gestation and ovarian hyperstimulation syndrome are the obvious potential complications of treatment with gonadotropins.

Although the risk of multiple gestation associated with OI and SO does correlate with the magnitude of the response to stimulation, as reflected by the size and number of follicles and serum E_2 concentrations, efforts to establish threshold parameters that can effectively prevent multiple gestations have failed. In a multicenter RCT involving 1,255 SO cycles in which hCG was withheld when the E_2 level exceeded 3,000 pg/mL or when more than six follicles $>$18 mm in diameter were observed, the multiple pregnancy rate was 19% (25/134 live births), 72% of which were twins and 28% high-order multiples (91). In another trial involving 449 SO cycles (293 also including intrauterine insemination [IUI]) in which hCG was withheld if more than six follicles $>$14–15 mm in size were observed, the overall multiple pregnancy rate was 25.5%, 92% of which were twins and 8% high-order multiples (92). A retrospective analysis of 3,347 consecutive OI cycles was unable to define specific

parameters for serum E_2 concentrations, number of follicles >15 mm in mean diameter, or total number of follicles observed on the day of hCG administration that could identify a group of patients at high risk for high-order multiple pregnancy (93). The most likely reason is that follicular size cannot accurately predict the maturity of the oocyte within. Evidence derived from experience in ART cycles indicates that follicles as small as 10 mm in diameter may yield mature and fertilizable oocytes (94). The heterogeneity of the population receiving OI and SO, varying in age and in the cause and duration of infertility, is another important confounding factor. In the absence of any established predictors for multiple pregnancies in OI and SO cycles, it is not possible to propose valid guidelines for reducing the rate of multiple gestations.

Low-dose gonadotropin stimulation is one strategy that merits serious consideration. In nine studies that have examined the outcomes achieved with such treatment, the average clinical pregnancy rate was 11.1% per cycle start and the high-order multiple pregnancy rate 1.0% (95% CI 0.4–2.1%) (95). Among the studies that also applied specific cancellation criteria, the high-order multiple rate was reduced to 0.3% (95% CI 0.1–1.2%) although the overall clinical pregnancy rate was still 10.2% per cycle. In the largest single case series (3,219 SO-IUI cycles) (96), the pregnancy rate, twin rate, and high-order multiple gestation rate were 10.4%, 10.2%, and 0.4%, respectively. Although these data are in many ways encouraging, large prospective trials are needed to confirm the efficacy and cost-effectiveness of low-dose stimulation strategies, to investigate the potential benefit of adding a GnRH antagonist to the treatment regimen (95), and to define optimal cancellation criteria.

One retrospective study compared the results of treatment with clomiphene citrate (CC) and IUI to those achieved with SO and IUI (97). When only one follicle >14 mm in diameter was observed in CC-stimulated cycles, the pregnancy rate achieved with SO was higher, but when CC stimulated the development of two or more mature follicles, the outcomes were not different. Given the higher risk of multiple pregnancy associated with SO and the difficulty of preventing this complication, some have argued that the best strategy may be to begin treatment with CC-IUI, to proceed directly to IVF in those who fail, and to avoid SO-IUI altogether (98).

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 in three studies (99–101). In two, aspiration was performed when more than three follicles having a mean diameter of ≥14 mm were observed, leaving the three largest follicles undisturbed (98, 99). 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 more than three follicles measuring ≥15 mm in mean diameter were observed and all follicles <15 mm in size were aspirated (97), 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 eliminate entirely the risk of multiple gestation associated with OI or SO.

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 (102, 103) Patients with high-order multiple gestations must choose one of three options: 1) continuing the pregnancy, accepting all of the risks previously described; 2) terminating the pregnancy; and 3) multifetal pregnancy reduction (MFPR) to reduce the number of fetuses and the associated risks of maternal and perinatal morbidity and mortality (102, 104, 105). MFPR decreases the risks associated with preterm delivery (105–107), whether in quadruplets or above (106), trichorionic triplets reduced either to twins (108) or to singletons (102, 109), or after reduction of a monochorionic pair in a triplet pregnancy (110). However, because MFPR can present patients with a profound ethical dilemma and cause significant psychologic trauma (103, 111), thorough counseling must be provided (103). Despite the feelings of loss and guilt for at least a year (112), a study of 91 patients indicated that most (93%) would make the same decision for MFPR if faced with a similar situation in the future (113). Patients who describe themselves as "pro-choice" are more likely to consider MFPR than those who do not, and their views did not change after having an embryo transfer (114).

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 (105, 106). It is recommended that MFPR should be performed only in specialized centers with fetal medicine practitioners experienced in the procedure (105, 106).

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 (115). 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 (106). Moreover, the results of one meta-analysis of 11 nonrandomized studies of triplet pregnancies of varying quality (105) 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, 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).

Overall, available evidence therefore 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 percentage of high-order multiple gestations in the U.S. has decreased since 1998, and the percentage of twin births has increased.
- A desire to achieve pregnancy expeditiously with fertility treatment must be balanced against the substantial family, medical, social, and economic consequences of multiple gestations.
- Multiple gestations are associated with major maternal and fetal risks.
- The majority of high-order gestations result from OI and SO rather than from ART or natural conception.
- Strategies for OI in anovulatory women should use the lowest doses possible with the goal of ovulating a single oocyte.
- Owing to the high risk of multiple gestation with SO in ovulatory women, moving directly from CC-IUI to IVF should be considered.
- Elective SET is an effective strategy for reducing the risk of multiple pregnancy with ART. In select populations, cumulative pregnancy rates with fresh and cryopreservation SET are similar to those with DET.
- Education regarding the risks of multiple pregnancy leads to increased acceptance of eSET.
- When other strategies fail and treatment results in a high-order multiple pregnancy, MFPR offers an option for reducing the risk for the remaining fetuses.

CONCLUSIONS

- Current efforts should continue to focus on reducing the overall incidence of multiple pregnancies, with increasing priority for reducing the twin rate.
- Physicians should counsel their patients carefully on the risks and benefits of eSET.
- Elective SET should be seriously considered for good-prognosis patients, assuming the availability of effective cryopreservation protocols that help to maximize cumulative pregnancy rates.

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