

Multiple pregnancy associated with infertility therapy

The Practice Committee of the American Society for Reproductive Medicine

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Educational Bulletin

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. While this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it neither defines the standard of practice nor does it dictate the only appropriate course of medical care. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. Accepted by the Practice Committee of the American Society for Reproductive Medicine, August 2000, and approved by the Board of Directors of the American Society for Reproductive Medicine, August 2000. No reprints will be available.

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The incidence of twin and high-order (triplet or greater) multiple gestations has increased over the past 15 years primarily due to the increased use of drugs for ovulation induction (OI), superovulation (SO) and assisted reproductive technologies (ART) including in vitro fertilization

(IVF), gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) (1). From 1980 through 1997, the number of annual live born babies from twin gestation rose 52% (from 68,399 to 104,137) while the number of high-order multiple gestations increased 404% (from 1,377 to 6,727) (2). Ovulation induction is responsible for a greater percentage of high-order multiple gestations than ART. In a recent review, ovulation induction accounted for 10-69% of triplet gestations compared to 24% to 30% associated with ART and 7% to 18% arising spontaneously (3). Quadruplet and greater multiple gestations were associated with ovulation induction in 5% to 72%, with ART in 42%, and in 6% to 7% with cases of spontaneous conceptions (3). In an analysis of recent Society for Assisted Reproductive Technology (SART) databases and the Center for Disease Control's (CDC) National Center for Health Statistics data, the CDC has estimated that for triplets and higher-order multiple births approximately 20% were attributable to spontaneous events (related to the age of the female partner), 40% were attributable to ovulation inducing drugs without ART, and 40% were attributable to ART (4). Further analysis of the same data indicates that 10% of all multiple births, the overwhelming preponderance of which are spontaneous twins, are associated with IVF and related procedures. The purposes of this educational bulletin are to review the risks associated with multiple gestations and to

discuss approaches to reducing the risk of multiple gestation with infertility therapy in order to provide physicians with appropriate information to counsel couples contemplating treatment for their infertility.

RISK FACTORS FOR THE OCCURRENCE OF MULTIPLE GESTATIONS

Monozygous twinning is usually a random event. However, the rate of monozygosity is 2- to 3-fold higher in pregnancies associated with ovulation induction including IVF when compared to spontaneous conceptions (5). Dizygosity is more common in African-Americans, women over 35 years of age, women of greater parity, and those with a maternal family history of twins (3, 6, 7).

COMPLICATIONS OF HIGH-ORDER MULTIPLE GESTATIONS

The most important maternal complications associated with multiple gestation are pre-eclampsia, preterm labor and delivery, and gestational diabetes (Table 1). Others include cholestasis, dermatoses, excess weight gain, anemia, hyperemesis gravidarum, and exacerbation of pregnancy-associated gastrointestinal symptoms including reflux and constipation (8-11). Chronic back pain, intermittent dyspnea, postpartum laxity of the abdominal wall, and umbilical hernias occur frequently.

Prematurity accounts for most of the excess perinatal morbidity and mortality with multiple gestations (Table 1). Moreover, ovulation induction and ART are associated with an increased risk of prematurity independent of maternal age and fetal numbers (12, 13). Fetal

TABLE 1

Rates of major maternal complications^(16–19)

Number of fetuses	Preterm labor	Preterm delivery*	Gestational diabetes mellitus	Pre-eclampsia
1	15%	10%	3%	6%
2	40%	50%	5%–8%	10%–12%
3	75%	92%	7%	25%–60%
4	>95%	>95%	>10%	>60%

* Delivery at <37 weeks' gestation.

growth restriction and discordant growth in the fetal cohort lead to perinatal morbidity and mortality (14). Multifetal reduction reduces but does not eliminate the risk of fetal growth restriction (15).

Fetal death rates are 4.3 per 1000, 15.5 per 1000, and 21 per 1000 for singleton, twins, and triplets respectively (8). The death of one or more fetuses in a multiple gestation is more common in the first trimester and may be observed in up to 25% of pregnancies arising from ART (9, 20). Loss of a fetus in the first trimester is unlikely to adversely affect the surviving fetus or mother (21). No excess perinatal or maternal morbidity has been described resulting from a vanishing embryo (22).

Demise of a single fetus in a twin pregnancy after the first trimester is more common with monochorionic placentation, ranging in incidence from 0.5% to 6.8% (23). Death of one fetus among monochorionic twins later in gestation may harm the remaining twin if acute hypovolemia and hypotension occur secondary to partial exsanguination into the dying twin's circulation through anastomoses within the placenta. Renal cortical necrosis and multicystic encephalomalacia may lead to death of one twin with preterm birth of the surviving twin (24, 25).

Polyhydramnios may result from twin-to-twin transfusion syndrome (recipient) and fetal gastrointestinal or neurological anomalies. Conversely, oligohydramnios may result from twin-to-twin transfusion syndrome (donor), fetal renal anomalies, and isolated fetal growth restriction. Placenta previa and vasa previa are more common complications with multiple gestations (26, 27). Abruptio placenta is more common and postpartum hemorrhage may complicate 12% of multifetal deliveries (10).

Consequences of multiple gestations include the major sequelae of prematurity (cerebral palsy, retinopathy of prematurity, and bronchopulmonary dysplasia) as well as those of fetal growth restriction (polycythemia, hypoglycemia, necrotizing enterocolitis). It is unclear to what extent multiple gestations themselves affect neuro-behavioral development in the absence of these complications. Rearing of twins and high-order multiples generates physical, emotional, and financial stress with a reported increased incidence of mater-

nal depression and anxiety in women raising multiples (28). At mid-childhood, prematurely born offspring from multiple gestations have lower IQ scores, and multiple birth children have an increase in behavioral problems compared with singletons (28).

ECONOMIC CONSIDERATIONS FOR MULTIPLE GESTATIONS

In addition to the excess perinatal and maternal morbidity and mortality linked to the increased numbers of multiple births due to ovulation induction and ART, there are issues of significant associated costs due to the expense of providing care for premature infants. Thus, when considering the economic impact of a multiple pregnancy, the immediate costs of maternal hospitalization and neonatal intensive care, as well as the lifetime costs for chronic medical care, rehabilitation and special education related to extreme prematurity should be considered. While the former costs can be estimated from hospital charges, the latter costs have not been analyzed. The total charges (maternal hospitalization and neonatal intensive care) for a singleton delivery at a major Boston teaching hospital in 1991 was estimated to be \$9,845, whereas the cost for a twin delivery was \$37,947, and that for a triplet delivery was \$109,765 (\$36,588/infant). In this report ART accounted for 2% of the singletons, 35% of the twins, and 77% of the high-order multiples (29). The projected cost of care for ART multiple births in the United States in the year 2000 is \$640 million, compared with \$470 million for all IVF and ICSI cycles. The estimated costs for twins, triplets and quadruplets are \$377 million, \$220 million and \$43 million, respectively (30).

FACTORS THAT INCREASE MULTIPLE PREGNANCY RATES DURING INFERTILITY THERAPY

Several issues arise in infertility care that promote the creation of high order multiple pregnancies. A sense of urgency on the part of the infertile couple may lead to a preference for more aggressive treatment with gonadotropins or more embryos transferred at IVF. Clinicians may feel competitive pressures to achieve higher pregnancy rates and

may be inclined to turn to SO or IVF earlier or transfer a greater number of embryos. Inadequate or absent health coverage may force couples to chance a less expensive option (SO) or limit the number of IVF cycles and request that more embryos be transferred.

ATTEMPTS TO LIMIT MULTIPLE PREGNANCY IN ART

The objective of infertility treatment is a healthy child. Multiple pregnancy jeopardizes that goal. The desire of both the patient and the physician to achieve conception expeditiously must be balanced against the substantial risks and costs of multiple gestation. The ability to limit the number of embryos transferred is an effective remedy for multiple gestation associated with ART. The Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) have jointly published guidelines recommending an optimal number of embryos for transfer based on patient age, embryo quality, and other criteria (31). Although the clinical impact of adopting these guidelines to reduce multiple gestations has not yet been assessed, additional advances may permit further reduction in the number of embryos transferred. Recent modifications to embryo culture allow programs to transfer two blastocysts while maintaining acceptable pregnancy rates and reducing the incidence of high-order gestation (32–34).

ATTEMPTS TO LIMIT MULTIPLE PREGNANCY WITH OVULATION INDUCTION AND SUPEROVULATION

The overall goal for follicular response to ovarian stimulation varies with the clinical context. Ovarian stimulation to induce ovulation in oligo- or anovulatory women including polycystic ovary syndrome or hypothalamic amenorrhea is ideally directed towards producing one or two mature follicles. In contrast, the goal of SO for ovulatory women is the maturation of multiple (often greater than two) mature follicles in an effort to improve fecundity in subfertile couples. Stimulation protocols should be tailored to each patient's specific clinical circumstance. Lower doses of exogenous gonadotropins, are generally administered for ovulation induction in anovulatory women than for SO. Patients with polycystic ovary syndrome are often exquisitely sensitive to gonadotropins and using an even lower dose over an extended period of time may reduce the number of follicles recruited. Multiple gestation and ovarian hyperstimulation syndrome are complications.

Efforts to reduce multiple gestation in patients undergoing ovulation induction or superovulation by utilizing arbitrary ultrasonographic criteria and serum estradiol limits have been ineffective. In a multicenter randomized clinical trial involving 1,255 ovulation induction cycles the multiple pregnancy rate was 30% (35). HCG was withheld if the estradiol concentration was greater than 3,000 pg/mL or

more than 6 follicles greater than 18 millimeters in diameter were present. Another trial involving 449 SO cycles examining the efficacy of intrauterine insemination (IUI) performed twice reported a 25.5% multiple pregnancy rate (36). HCG was withheld if more than 6 follicles were present. In a retrospective study examining possible risk factors for high-order gestations in 3,347 consecutive ovulation induction cycles, estradiol levels, number of follicles greater than 15 millimeters in mean diameter, and total number of follicles on the day of hCG could not define a group of patients at high risk for high-order multiples (37).

These studies document that using specific ultrasound and estradiol parameters do not prevent high-order gestations. Patients undergoing ovulation induction and SO are a heterogeneous population, and their fecundity with therapy varies according to age, presence of other infertility factors, and clinical setting. While ultrasound and serum estradiol monitoring (37) has not reduced the incidence of multiple gestation and ovarian hyperstimulation syndrome, risk of multiple pregnancy is correlated with the magnitude of follicular response as indicated by follicle number and serum estradiol levels. However, there is no consensus among centers regarding specific ultrasound criteria or estradiol levels above which hCG should not be administered. Additional studies evaluating lower or more rigorous thresholds for hCG administration are needed and may offer more explicit parameters to reduce the incidence of multiple gestation. Until such definitive guidelines for ovulation induction and SO therapy are established, other strategies to reduce the risk of multiple gestations should be considered.

Recently, two studies from the same group based on performing preovulatory vaginal ultrasound-guided aspiration of supernumerary follicles demonstrated a significant reduction in multiple gestation rates without a change in pregnancy rates (38, 39). Aspirations of additional follicles were performed if more than 3 follicles with mean diameter of at least 14 millimeters were noted on ultrasound but the three largest follicles were not disturbed. The reported multiple pregnancy rate was approximately 10% with overall pregnancy rates ranging between 2% to 25%. Although this approach may be promising, its role, cost and effectiveness remain to be defined.

RECOMMENDATIONS

1. Consideration may be given to performing preovulatory vaginal ultrasound-guided aspiration of supernumerary follicles after the administration of hCG if the follicular response is excessive.
2. IVF with transfer of limited numbers of embryos (1-3) offers the most reliable option to reduce the risk of high-order pregnancy and should be considered in individuals at particularly high risk with ovulation induction and superovulation (i.e., young age, PCO).

TABLE 2

Loss rates and gestational age (GA) at delivery for data collected during different years⁽⁴⁴⁾

Years data collected	Losses (weeks GA)		Delivery GA (weeks)			
	<24	>24	25–28	29–32	33–35	37+
1986–90	13.2%	4.5%	10.0%	21.1%	15.7%	35.4%
1991–94	10.8%	1.2%	2.2%	5.7%	17.2%	62.8%
1995–97	7.5%	1.7%	3.7%	9.3%	25.7%	52.2%

MULTIFETAL PREGNANCY REDUCTION (MFPR)

High-order multifetal pregnancy is an adverse outcome in the care of the patient. The greater the number of fetuses within the uterus, the greater the risk for adverse perinatal and maternal outcome. Patients with high-order multiple gestations are faced with the options of continuing the pregnancy with all risks previously described, terminating the entire pregnancy, or reducing the number of fetuses in an effort to decrease the risk of maternal and perinatal morbidity and mortality through MFPR. The latter decreases risks associated with preterm delivery (40–43). However, it creates a profound ethical dilemma. Pregnancy loss and prematurity are the main risks of MFPR, but recent data suggest that these complications have decreased substantially as experience with the procedure has grown (Table 2).

In general, the greater the number of fetuses at the beginning of the procedure, the greater the risk of loss. While there is little difference in loss rates when the finishing number of fetuses is two versus one, a higher loss rate occurs when a pregnancy is reduced to triplets.

Pregnancies that are reduced to twins appear to do as well as twin gestations originally conceived as such. The benefit is best documented in quadruplet and high-order gestations because reduction prolongs the length of gestation of the surviving fetuses (45).

CONCLUSIONS

The incidence of high-order multiple gestations has increased dramatically over the past 15 years as a consequence of increased use of gonadotropins for ovulation induction, superovulation therapy, and assisted reproductive technologies, especially IVF. Ovulation induction and superovulation therapy account for the majority of high-order gestations and, unlike IVF, are not amenable to simple strategies to reduce risk. High-order gestations are associated with major maternal and fetal risks with enormous economic consequences.

Strategies to reduce the risk of multiple pregnancy during ovulation induction by utilizing arbitrary serum estradiol levels and sonographic criteria have not been successful, but

more stringent criteria have not been adequately tested in prospective trials. Novel techniques such as aspiration of supernumerary follicles after hCG administration show preliminary promise. IVF offers a successful strategy to reduce the risk of high-order gestations if the number of embryos transferred is limited. If these strategies fail and high-order pregnancy occurs, MFPR offers a salvage option to reduce risk for the remaining fetuses.

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