

Multiple births from assisted reproductive technologies: a challenge that must be met

David Adamson, M.D.,^{a,b,c} and Valerie Baker, M.D.^a

Society for Assisted Reproductive Technology, Birmingham, Alabama

The success of assisted reproductive technologies (ART) has been accompanied by dramatic increases in multiple births and their associated costs. Physicians who perform ART must develop effective treatment paradigms to reduce multiple births or risk regulatory intervention. (*Fertil Steril*® 2004;81:517–22. ©2004 by American Society for Reproductive Medicine.)

Multiple births are now the biggest challenge facing assisted reproductive technology (ART) specialists in the United States. In 2000, 25,228 live-birth deliveries resulted from 99,629 ART procedures. Of the 35,025 infants born, 44% were twins and 9% were triplet or higher-order multiples, for a total multiple-infant birth rate of 53% (1).

Increases in utilization and pregnancy rates resulted in an estimated 0.9% of all babies in the United States being born as a result of ART, including 12% of all twins and 43% of all triplets (2). Use of other non-ART infertility treatments and delayed childbearing, with its increased risk of spontaneous multiple pregnancy, have contributed significantly to multiple births in the United States (3, 4). By 2000, only 67% of twin births and 18% of triplet or higher-order births occurred naturally (1). Viewed another way, the rate of twinning among patients undergoing ART is 22 times higher than that in the general U.S. population (2%), and the rate of triplets and higher-order multiples is 50 times the usual 0.18% (1).

There are many well-known reasons that multiple births are less desirable than a singleton birth, regardless of how the multiple birth was conceived. There is increased risk of maternal morbidity, including hypertension (odds ratio, about 2.0–3.0), postpartum bleeding (odds ratio, about 4.0) and maternal mortality (odds ratio, about 2.0–3.0), polyhydramnios, premature labor with prolonged bed rest, and Cesarean section. There also may be an in-

creased risk of gestational diabetes (odds ratio, about 1.6), maternal anemia (odds ratio, about 1.5), and antepartum bleeding from abnormal placentation (odds ratio, about 2.0) (3, 5). Multiple pregnancies are often associated with more nausea and vomiting, fatigue, weight gain, heartburn, and lack of sleep.

Risks to the babies, particularly the risk of prematurity, are significantly higher in multiple births. The relative risk that twins will be delivered before 37 weeks is 5.5 compared with singletons (5). Singletons weigh an average of 3,357 g at 39.0 weeks of gestation, twins weigh 2,389 g at 35.8 weeks, and triplets weigh 1,735 g at 32.5 weeks (6). Low birth weight (<2,500 g) occurs in 53.1% of twins compared with 5.9% of singletons, a ninefold increased risk.

Perinatal mortality rates are 5 to 10 times higher for twins than for singletons. Increased morbidity for twins includes mortality in childhood, congenital anomalies, cerebral palsy, intracranial hemorrhage, and blindness (7). Neonates who were conceived by using ART have been found in some, but not all, studies to have more respiratory distress, patent ductus arteriosus and sepsis than those not conceived by using ART (5).

Because a large proportion of ART babies are twins, more adverse perinatal outcomes occur in ART babies, and some studies suggest that ART babies may have poorer outcomes than those in the general population, even when matched for plurality (8). Other confounding

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Reprint requests: David Adamson, M.D., Fertility Physicians of Northern California, 540 University Avenue, Suite 200, Palo Alto, California 94301 (FAX: 650-688-7470; E-mail: info@fpnc.com).

^a Fertility Physicians of Northern California, Palo Alto, California.

^b Stanford University School of Medicine, Stanford, California.

^c University of California at San Francisco School of Medicine, San Francisco, California.

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variables, such as age, parity and diagnosis, complicate analysis of these studies. For triplets, approximately 90% of births are preterm and each baby is more than 20 times more likely to die in the first month of life. Although the risk of triplets is higher than twins, twins account for a much larger proportion of the preterm deliveries and low-birth-weight neonates than do triplets because twins are much more common (9).

These medical complications have an economic impact. More antenatal surveillance is needed, maternal hospitalizations are more frequent and longer, the rate of Cesarean section is higher, and neonatal costs are increased because of the higher preterm delivery rates and greater number of low-birth-weight infants. The average cost of a singleton delivery is estimated to be \$9,845, twin delivery \$37,947, and triplet delivery \$109,765 (10). Excess hospital costs for multiples resulting from ART were estimated to be \$640,000,000 in 2000 (11). These costs do not include infertility treatments, outpatient obstetric management, maternal admissions before delivery, and loss of work from these hospitalizations and home bed rest.

In addition, infants with very low birth weight cost 24-fold to 44-fold more during the first year of life than do normal-birth-weight infants. Low birth weight is associated with such additional costs as transportation and child care (5, 12). Twin survivors also have a higher relative risk for severe handicap of 1.7 and for overall handicap of 1.4 compared with singletons (13). Plurality is a more important factor than maternal age (13). Triplets have even poorer outcomes and higher costs. Low-birth-weight survivors are more likely to have health problems and rate their health-related quality of life lower than do normal-birth-weight controls (14, 15).

Also important is that families with multiple births face significant and increased parenting, marital, and social challenges, including impaired maternal bonding, maternal exhaustion, marital disharmony, sibling problems, lack of help at home, and major depressive illness and psychological problems. These difficulties can persist for years and can be overwhelming, especially if infant mortality or morbidity occurs (16).

Given these facts, why do many patients want multiple births, as has been demonstrated in several studies (17, 18)? First, the general public is unaware of the risks and consequences of preterm delivery: only 35% of the public appreciates that prematurity is a common and serious public health problem (19). For infertile patients, the wish for a child appears to be so strong that they underestimate the risks and seem to be willing to try almost anything. Patients often have a more positive view of multiple births than do their physicians and embryologists, even when they are aware of the risks, in recognition of the trade-off in ART between the risk of multiple pregnancy and prospects of pregnancy itself (20). Patients may develop this perspective for many reasons: the

emotional toll of infertility over the years, the legitimate concern that any single cycle has less than 50% chance of success among patients with the best prognosis, the risk of never getting pregnant or the prospect of having only one child because of advancing age, the lack of resources to continue treatment, the time commitment of infertility treatment, the availability of good obstetric care, and the option of induced fetal reduction.

The cost of infertility treatment, especially to those without insurance, can lead some couples to assume the greater risks of multiple gestation. One third to one half of patients in the United States drop out of care after they are visiting the reproductive specialist (21). For many of these patients, the major reason is the financial barrier to care. For some or all these reasons, up to 80% of patients in some studies find twins an acceptable outcome of treatment.

Patient preference or willingness to accept multiples creates a difficult moral situation for both the patient and physician with regard to counseling the patient and making a decision (22). Many U.S. patients face financial barriers to care, and decreasing the pregnancy rate per cycle would almost certainly mean that many more patients would not have a child. Thus, these facts are critical for clinicians to recognize and manage in their ART patients.

Others argue that patients are too emotionally involved with their infertility to make independent and realistic decisions about the number of embryos to replace, to balance the conflicting interests of society and personal desire for a child, and to understand the consequences of being parents to triplets (18). Some claim that the eventual pregnancy rate can be made equivalent even if fewer embryos are replaced each cycle, which can result in lower pregnancy rates, simply by performing more cycles. This idea is countered by the argument that if patients cannot afford more cycles, many will never have a family if each cycle has a lower pregnancy rate. A final major difficulty is that, at present, we have no methods of accurately predicting outcome in individual cases.

The response of U.S. professional societies to these issues has been significant. As early as 1994, the American Society for Reproductive Medicine (ASRM) Ethics Committee recommended that the number of embryos transferred be limited so that quadruplet pregnancy could be eliminated and triplets kept to 1% to 2% of all pregnancies (23). In 1998, the ASRM Practice Committee recommended upper limits for the number of embryos to be transferred based on age and prognosis (24). These guidelines were modified just 1 year later to recommend that two good-quality embryos be replaced in women younger than 35 years of age who have a good prognosis (e.g., sufficient embryos that extra ones are available for cryopreservation), three for other women younger than 35 years, up to four embryos for women 35 to 40 years, and up to five embryos for women older than 40 years. These numbers were evidence based, being derived

from the data that the Society for Assisted Reproductive Technology (SART) collects from all participating clinics annually (25). Clinicians responded to this recommendation: The average number of embryos replaced in women younger than 35 years of age decreased from 3.8 per transfer in 1996 to 2.9 in 2000, with a corresponding decrease in the triplet rate per delivery with a live birth from 6.5% to 4.3% (26, 27).

The Society for Assisted Reproductive Technology requires its members to document in the medical record cases in which the guidelines were not followed for whatever reason, and it evaluates a program's compliance with SART guidelines in random on-site inspections. Assisted reproductive technology programs can lose their SART membership for failure to comply. The Society for Assisted Reproductive Technology has also increased its emphasis on not using the annually published clinic-specific report to compare ART programs, because such comparisons encourage ART programs to increase the number of embryos replaced.

Furthermore, SART and ASRM have participated actively with government to create the Fertility Clinic Success Rate and Certification Act of 1992 (the Wyden law) and, with the Centers for Disease Control and Prevention, to develop the associated mechanisms for clinic-specific reporting of results and on-site validation of individual clinic reports (28). In addition, SART and ASRM have produced comprehensive clinical, laboratory, and ethical guidelines and created on-site laboratory accreditation with the College of American Pathologists.

The Society for Assisted Reproductive Technology and ASRM have also worked with the U.S. Food and Drug Administration (FDA) and others to develop mandatory laboratory regulations. The FDA has already begun to regulate embryology laboratory technologies and is expected in 2004 to implement mandatory embryology regulations that set standards and involve on-site FDA inspections (29).

The approach to multiple births in the United States has received substantial criticism from our European colleagues, who feel that the rates of twins and triplets in this country are far too high. In 2000, the rate of triplets in Europe was 2.0% overall, having been reduced from 3.7% in 1997. The twin rate was 24.0%, slightly less than that rate of 25.8% in 1997 (30). In contrast, the rate of triplets per delivery with a live birth in the United States for 2000 was 4.3%, and the twin rate was 30.7% (27). The major reason for the reduced rates of twins and triplets in Europe is that fewer embryos are transferred per cycle. Only 6.7% of patient transfers involved more than three embryos, whereas in the United States, approximately one third of patients had more than three embryos transferred (27, 30).

The European Society of Human Reproduction and Embryology held a consensus conference on multiple pregnancy that identified the many risks and costs. The conclusion was

that transfer of more than two embryos is not advisable and that if more than two embryos are replaced, the couple must be extensively informed about the risks of multiple gestation (31). Some countries such as Finland and England have laws limiting the number of embryos that can be transferred. Many countries in Europe have national health plans that cover ART procedures, and the pharmaceutical and other costs are less even in cases where insurance does not cover ART costs. Thus, patients have lower out-of-pocket costs and can undergo more ART cycles, reducing the financial pressure to replace larger numbers of embryos in any given cycle. Of note, the per capita utilization of ART in Europe is approximately three times that in the United States, and in Scandinavia it is five to eight times higher (30).

Importantly, the overall pregnancy rate is approximately 29% per fresh transfer in Europe and the average female patient age is 33 years, compared with 38% in the United States, with an average female patient age of 35 years. Some European countries also impose significant restrictions on reproduction, resulting in "reproductive tourism." In Scandinavia and some other countries, use of elective single embryo transfer is increasing, especially among younger patients, to reduce the number of twins as well as triplets. Across Europe, the strong trend is to replacing fewer embryos, although there is still wide variation from country to country. Europeans generally tend to accept, support, and promote a much stronger regulatory environment with mandatory clinical limitations than their U.S. counterparts.

It is clear that multiple births are more complicated and costly for the babies, mothers, families, and society and that the desired outcome of any ART cycle is a healthy singleton baby. The multiple birth rate in the United States is viewed as a serious problem, just as it is in other countries, and solutions to the problem have been and are being developed in a systematic, evidence-based manner. It is impossible to eliminate multiple births completely even with single embryo transfer; if ART is to be performed, some twins and possibly triplets will result. Of note, the monozygotic twinning rate is increased 6 to 12 times after ART (3). Certainly, it is not reasonable to argue that ART should be abandoned to prevent multiple births. Therefore, the harms of multiple births must be balanced against the benefits of any birth at all, as well as the multiple pregnancies that result in healthy babies.

The great majority of fertile and infertile women who have twin or triplet pregnancies will have healthy babies and a satisfactory outcome. Many perceive the multiple birth to have been an advantage (17). The economic assessment of the costs of multiple birth must take into account not only the increased costs of pregnancy, delivery, neonatal care, and other aspects but also the economic advantages: fewer ART cycles to pay for, two babies rather than one, and two people in society rather than one.

The value of a human being is difficult to quantify, but legal, public policy, and other sources place the value between several hundred thousand and several million dollars. Even if the lower estimates of the value of a human life are utilized, the benefit of an extra baby in a pregnancy greatly exceeds the costs that are commonly stated for each of those babies in a multiple birth. Such a calculation is not intended as an argument for a multiple birth, but simply part of the economic benefit that must be considered when developing guidelines for managing the issue of multiple pregnancy. Similarly, just as the emotional and other "soft" costs of multiple birth must be considered as negatives resulting from multiple birth, so must the "soft" benefits of having another child be considered a positive.

The reproductive rights of infertile patients must also be considered. Why should patients with infertility be discriminated against in their choice of family when other persons—for example, women with serious medical diseases, such as pulmonary hypertension, systemic lupus erythematosus, or diabetes mellitus—conceive at significant personal risk and risk to their children but do not require the consent of society? Should the state dictate whether or not these persons should be able to conceive because their cost to society often is greater than that of a multiple birth? At what point is it acceptable to place societal or professional limitations on personal reproductive choice?

Another contentious issue involves induced fetal reduction for patients who would ethically be willing to consider such a procedure. Many of those who argue against multiple births and regulation of the number of embryos to replace reject this procedure out of hand as unacceptable. This decision appears arbitrary and inappropriate in a pluralistic society. Because of the obvious emotional costs of this procedure, induced fetal reduction is not the optimal or desirable approach to dealing with multiple pregnancy. However, it is technically successful, and studies have shown that almost all patients who chose this option would make the same decision again if faced with the same situation (32, 33). In our pluralistic society, induced fetal reduction should remain an option for dealing with multiple pregnancy.

Given the difficult and emotional issue of multiple births, what should we do? First, we should all recognize the tension between social good and individual reproductive rights and freedoms. All reproductive specialists need to be knowledgeable about the very real increased risks and costs of multiple pregnancy for the woman, the babies, and her family and about the ethical, legal, and social issues. Physicians must educate patients about all of these risks, which is something we must do better in the future than we have in the past (34). The ASRM Patient Education Committee has recently prepared booklets and a fact sheet to help clinicians better inform patients about multiple pregnancies. In this area of great factual and psychological complexity, more

information and discussion are needed as soon as ART is considered a potential treatment possibility.

Treatment should be individualized for each patient, with the focus not on limiting reproductive choice but on avoiding adverse outcomes. Patients should be monitored closely in their ART cycles, and those at high risk for multiple pregnancy with controlled ovarian stimulation should undergo ART instead. All reproductive specialists should follow current ASRM guidelines and practice medicine responsibly. They should follow the guideline on not comparing IVF statistics from program to program so that competition does not result in poor-quality medical practice. They should stay up to date with new research in this area and support research studies whenever possible.

Obstetrician/gynecologists and all reproductive specialists should refer patients for whose cases they do not have the requisite expertise. Patients with multiple pregnancy should receive the best possible obstetrical care and management. However, preterm labor remains an enigma and difficult to prevent.

The Society for Assisted Reproductive Technology and ASRM should attempt to have the SART/Centers for Disease Control and Prevention report modified so that a singleton pregnancy is considered a successful outcome and triplets a complication of ART treatment. Twins are a more complex issue that requires further study, but they will probably also come to be considered a complication. More information about the use of induced reduction should be obtained. Efforts to collect data that would allow calculation of the total reproductive outcome of a cycle using both fresh and cryopreserved embryos would be helpful, as would publication of data on outcome in patients who have multiple cycles as opposed to the current reporting of individual cycles. Better data on outcomes must be collected through government-funded programs that do not contravene the Health Insurance Portability and Accountability Act but still protect the privacy of patients with infertility and their children. Long-term epidemiologic follow-up studies of ART babies, both singletons and multiples, are needed. Cost, logistics, and privacy issues remain significant barriers to such studies.

The professional societies should continue to promote prevention of infertility programs, such as the successful program just completed by the ASRM (35). Young men and women need to know about not smoking, maintaining appropriate weight, avoiding sexually transmitted diseases, and planning their families before their fertility is compromised by age.

The American Society for Reproductive Medicine and SART should continue and expand their focus on improving education and informed consent for patients through professional documents and education and through working with consumer organizations, such as RESOLVE and the American Infertility Association, and through the media. The

excellent work of the ASRM Practice Committee and SART Research Committee should continue to be supported and expanded so that these organizations can do research, evaluate new technologies and information, and modify practice guidelines.

Improved access to care through more financial support and insurance might reduce some of the pressure from patients to replace more embryos, although current data do not support that insurance coverage alone would significantly affect the rate of multiples (36, 37). Innovative, ethical and safe treatment packages, financing, and refund guarantees can also increase the number of patients who can afford treatment and give them their best chance of a singleton birth. The American Society for Reproductive Medicine and SART should also continue to educate other professions, government, the public, and others about ART so that regulations, policies, and laws that are created are not discriminatory, are ethical, do not criminalize medicine, do not unintentionally promote inappropriate medical practice, do not hinder scientific advancement or clinical care, and do not infringe on reproductive rights and freedoms (38, 39). The National Coalition for Oversight of ART, which was started by SART, is an excellent forum in which this can occur. International initiatives through participation in the International Committee Monitoring ART will help create international understanding and cooperation in finding solutions to the multiple birth problem. The hierarchy of interest holds that patients and their physicians have the greatest right to make decisions about an individual's health care, with input from professional guidelines and with the minimum number of legal constraints necessary to protect the legitimate interests of a pluralistic society (29, 40).

Basic and clinical scientists should continue their research so that we can improve our knowledge of which and how many embryos to replace. This includes basic research on embryo selection based on such factors as metabolic assessment, morphology, genetic evaluation (preimplantation genetic diagnosis), sperm chromatin, and uterine receptivity, as well as cryopreservation and thawing techniques. Elective double-embryo transfer is currently the recommended standard for the most favorable prognosis patients in the United States. Clinicians should research the advantages of elective single embryo transfer, which is being used more and more often in Europe (for example, in more than 50% of patients in at least one Finnish program) and is a successful strategy for an increasing number of patients with the most favorable prognosis.

Elective single-embryo transfer reduces the rate of twins to approximately 5% and the rate of triplets to much less than 1%, whereas the live birth rate per cycle is reduced to approximately 30% in highly selected patients with a good prognosis (41–43). A decrease in the number of embryos transferred from two to one is probably a reasonable option in one third of patients and will reduce the incidence of twins

to half its original without a decline in the overall ongoing pregnancy rate. SART supports the goal of elective single-embryo transfer when it is based on good evidence showing satisfactory pregnancy rates in well-defined samples. Such evidence is just now being developed. The proportion of patients for whom this option is appropriate will vary from program to program, depending on patient characteristics. An elective single-embryo transfer program should be implemented gradually in distinct clinical phases, with judicious patient selection based on patient characteristics, embryo characteristics, professional organization algorithms modified by IVF clinic experience, and informed consent.

Two reports have concluded that single-embryo transfer is more effective than double-embryo transfer in terms of cost per child born, if long-term morbidity is taken into account (44, 45). It should be noted, however, that the most recent reports (from 2000) suggest that for all of Europe, elective single-embryo transfer is being performed in fewer than 5% of patients (30).

A good cryopreservation program is a necessary adjunct. Further well-designed trials to determine the role, if any, of blastocyst transfer should also be performed (46, 47). Elective single-embryo transfer will almost certainly become a routine option in many United States programs, as effective protocols for patient and embryo selection are developed.

In summary, the occurrence of multiple births as a result of ART treatment is a serious problem facing all patients, professionals, and society. It is the responsibility of all ART practitioners to participate in solving this problem. The benefits and harms of what we do must be recalibrated to the desired outcome of a healthy singleton baby for every patient. Professional societies should set realistic goals for desired rates of live birth, twins, and triplets, and associated timelines for achieving these goals should be developed. Clinicians, embryologists, and scientists must do research to obtain the necessary information to reach these goals, professional societies must set new standards and guidelines based on this evidence, and practitioners must implement the guidelines using good clinical judgment. Such implementation will involve "counseling with courage" by practitioners, in that they must clearly formulate their own ethical professional standards, not fear a potential conflict between their standards and the couple's wishes, and take time to fully discuss all controversial points with respect to multiple pregnancy and dare to convince patients, realizing that "practitioners embody their patient's chances and patients embody their desires" (48). We must limit the economic burden to society and the medical risk to future offspring while offering patients a realistic hope for a child.

There are numerous strategies to achieve these goals, and we should all work together to achieve them. Although they are not directly related to this article, similar approaches must be developed to deal with the problem of multiple pregnancy resulting from controlled ovarian stimulation.

Some of our colleagues believe that such a voluntary approach cannot work for many reasons. Our patients' intense desire to get pregnant causes them to downplay the risks of multiple birth; the medical profession is unwilling to emphasize the dangers to patients; competition causes physicians to do whatever they can to maximize published pregnancy rates; the number of embryos per transfer has not been reduced sufficiently, given the scientific advances that have increased pregnancy rates; and lack of universal insurance coverage causes the number of ART attempts to be minimized (49). Our choice as reproductive specialists performing ART is to meet this challenge or to face regulations that control the practice of medicine and diminish our ability to individualize and optimize infertility treatment for our patients.

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