Iatrogenic Multiple Pregnancy Epidemiology, Risks, and Ethical Dilemmas

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By Louis Keith, MD [1], Susan Klock, PhD [2], and Sanjay Gandhi, MD [3]

This article discusses the nature of infertility treatment and its relation to infertile couples' desires for multiple pregnancy, the special risks of iatrogenic multiple pregnancy (IMP), the informed consent process in assisted reproductive technology, and the ethical dilemma of IMP and methods for its resolution.

In little more than two decades, the subject of multiple pregnancy has evolved from an obstetric curiosity to an issue of international medical and social concern. The overall number of multiple pregnancies has increased dramatically, not only for twins, but also for triplets and higher-order births. In addition, physicians and society are now concerned with a previously unknown type of multiple birth—the iatrogenic multiple pregnancy (IMP). Many new forms of assisted reproductive technology (ART) are now available to help infertile couples achieve a pregnancy. Clearly, IMP is not a desired outcome of ART and must, instead, be considered a complication of ART.

Concerns regarding IMP relate primarily to three issues. First, the possibility of truly higher-order multiples (three to nine fetuses) is clinically real. Second, multiples, particularly those of higher orders, mirror and magnify what are generally acknowledged as two of the major obstetric concerns worldwide: low birth weight and preterm delivery. And third, the risk of pregnancy loss following multifetal reduction (MFR) is real and substantial. The benefits of MFR are most obvious in with higher-order pregnancies (four or more fetuses); without reduction, prematurity is a certainty. Overall, only about 40% to 45% of pregnancies undergoing MFR are delivered at term. Issues such

as these form the basis of an emerging international debate on the ethics of creating multiple pregnancies and the subsequent need for facilities to care for large numbers of preterm infants.

The "new" epidemiology Traditional statements about expected numbers of multiple pregnancies have undergone considerable revision in the last two decades. It is now apparent that the total number of multiple pregnancies in any country represents the sum of the number of natural multiple pregnancies plus the number of IMPs. Neither component is fixed. Even if one recognizes that naturally occurring multiple pregnancies vary greatly by race (highest in women of African descent and lowest among Asian women), the number of IMPs is increasing in both developed and developing countries. Published data on twinning rates are often suspect because, in many instances, they are based on nonrepresentative, older, hospital-based studies. Even in the United States, where virtually 100% of births are reported, no central agency published reliable numbers of higher-order births above quadruplets until very recently. Furthermore, there are no means to differentiate a set of twins or triplets that represents the "remainder" of a reduced quintuplet or higher-order pregnancy from a set of naturally occurring or ART-created twins or triplets.

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>1971 (%)</th>
<th>1990 (%)</th>
<th>1996 (%)</th>
<th>1971-1997 % increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.7</td>
<td>2.2</td>
<td>2.6</td>
<td>53</td>
</tr>
<tr>
<td>African-American</td>
<td>2.2</td>
<td>2.7</td>
<td>2.9</td>
<td>32</td>
</tr>
<tr>
<td>Native American</td>
<td>1.6</td>
<td>1.8</td>
<td>2.1</td>
<td>31</td>
</tr>
<tr>
<td>Japanese</td>
<td>1.2</td>
<td>1.9</td>
<td>2.2</td>
<td>83</td>
</tr>
<tr>
<td>Mexican-American</td>
<td>1.7 (1980)</td>
<td>1.8</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Cuban-American</td>
<td>1.4 (1980)</td>
<td>2.3</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Twin Births in the United States, 1971-1997*
In the United States, the total number of live births in multiple deliveries rose to the all-time high of 101,709 by 1995.4 This number represents a 46% increase from 69,676 in 1980. Moreover, the rate of multiple births increased from 19.3 per 1000 live births in 1980 to 26.1 per 1000 live births in 1995, with the twin birth rate increasing from 18.9 to 24.8 per 1000 live births (+31%). The birth rate for triplets and other higher-order multiples increased even more steeply, from 37 per 100,000 live births in 1980 to 127.5 per 100,000 live births in 1995 (+245%). Among the births in the 1995 cohort, 4551 were triplets, 365 were quadruplets, and 57 were quintuplets or higher-order multiples.

As shown in Table 1, twin birth percentages increased in major American racial groups. Table 2 shows the changes in higher-order births over a three-decade period.

The clinical impact of what now can justifiably be termed an "epidemic" of multiple births is not reflected in the data presented above. All types of multiple pregnancies are associated with high rates of preterm delivery, low birth weight, and the increased costs of caring for preterm infants.

Luke et al's recent assessment of costs of multiples lays the blame where it should rest—that is, on preterm delivery rather than on plurality. Recent US data show the differences in the rates of preterm delivery and low birth weight among singletons, twins, and triplets (Table 3). This Table uses commonly accepted terminology for preterm (<37 weeks' gestation) and very preterm (<33 weeks' gestation) births, as well as for low birth weight (<2500 g) and very low birth weight (<1500 g). The trends illustrated in Table 3 appear to be global. Unfortunately, comparable data for quadruplet and higher-multiple births are not available. Regardless, intuition dictates that the problems of preterm delivery and low birth weight are exaggerated in quadruplets and higher-multiple pregnancies.

### Table 1. Twin Births in the United States

<table>
<thead>
<tr>
<th>Year</th>
<th>Twin Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>69,676</td>
</tr>
<tr>
<td>1995</td>
<td>101,709</td>
</tr>
</tbody>
</table>

### Table 2. Higher-Order Multiples in the US, 1971-1997*

<table>
<thead>
<tr>
<th>Year-Range</th>
<th>Number of Births</th>
<th>Rate per 1000 Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971-1977</td>
<td>296</td>
<td>37.0</td>
</tr>
<tr>
<td>1990</td>
<td>861</td>
<td>116.9</td>
</tr>
<tr>
<td>1996</td>
<td>1361</td>
<td>185.2</td>
</tr>
</tbody>
</table>


INFERTILITY TREATMENT

Because infertility is not a disease, nor is it even life threatening, all forms of treatment are ultimately used to "grant a wish." Because in most instances patients are abjectly unaware of treatment consequences, the principle of Primum non nocere ("Above all do no harm") should guide physicians as they propose various therapeutic options. This latter statement is particularly true for pregnancies that might follow ART, as they have considerable potential to violate this ancient principle.

Whereas it is axiomatic that most infertile couples desire a single child, information about desires of infertile couples for multiples is scant. In 1995, Gleicher et al published a survey of 3800 consecutive unselected couples with infertility.
Although their reported response rate of 15% is too low to impute validity to study results, two trends were apparent. First, whereas the desire for twins and triplets increased with the age of the couple (“Let's get it over with”), this desire was not apparent when participants were queried about quadruplets or quintuplets. And second, as the length of infertility increased, infertile couples became more receptive toward the concept of having a pregnancy with twins and triplets (in the absence of a concomitant increase in the desire to them). These data corroborate the impressions obtained from the medical director of the Center for Reproductive Medicine, the largest private infertility clinic in Germany, where service is provided to a multinational clientele. Older patients with longer histories of infertility treatment are more likely to ignore stated risks of IMP even after thorough counseling in their native language. In addition, patients from nonindustrialized countries (e.g., Turkey, Ukraine, Romania) and patients belonging to lower socioeconomic/educational classes are much more likely to openly express a desire for multiple pregnancy. In contrast, career-oriented women or couples from developed countries are more likely to be concerned with having a singleton pregnancy.

THE RISKS OF IMP
As is the case with natural multiple pregnancy, IMP following ART poses classic, well-known risks to the , the fetus, and the family unit. Classic maternal risks mentioned in most standard texts of obstetrics include the pentad of pre-eclampsia, postpartum hemorrhage, anemia, polyhydramnios, and preterm labor. In addition, cesarean delivery poses a distinct risk for bleeding, infection, thromboembolic phenomena, and, although rare, death. Finally, women who have had higher-order pregnancies may be at greater risk for cardiomyopathy than previously thought.

Classic short-term fetal risks include low birth weight and preterm delivery, as well as their consequences. Long-term problems include growth restriction, neurologic deficits, and cerebral palsy, all of which place enormous financial burdens on the family and on society.

To these concerns must be added potential psychosocial risks. The few data that are available come from outside the United States, but the themes appear to be universal. Reported problems include unrealistic expectations about parenting and attendant problems, marital strain, separation and divorce, financial hardship, and, notably, maternal depression. In one well-documented French follow-up study of , Robin et al described the need for psychiatric intervention for the mother, father, or both parents, as well as the frequent use of psychotropic medications, particularly among mothers of triplets.

INFORMED CONSENT
For nearly three decades, OB/GYNs have been refining their ability to obtain informed consent. As treatment modalities increase in complexity, physicians can no longer rely solely on a discussion of the risks, benefits, and alternatives in order to obtain informed consent. This is particularly true for ART, because the risks may be multigenerational, involving mothers and children. Moreover, the complexity of specific ART procedures mandates delivery of detailed information in understandable terms. This discussion may be simplified by the use of written handouts that explain treatment-specific risks and provide relevant numbers and percentages for a broad range of problems associated with the contemplated procedure. Any individual attempting to obtain informed consent for ART, with its attendant risks of IMP, should remember the following: First, patients hear but often do not listen. Second, without listening, they do not comprehend. Third, without comprehending, they do not understand. And finally, without understanding, by default, they are no longer granting "informed" consent. A recent American College of Obstetricians and Gynecologists' committee opinion aptly noted that counseling should be considered an ongoing process, beginning before treatment decisions are made and continuing throughout the patient's care. In the case of ART, the consent process must include information about the potential for multifetal pregnancy and the associated maternal and fetal risks.

THE ETHICAL DILEMMA
The ethical and economic issues surrounding ART and IMP are complex, and cannot be resolved with simple answers of "right" and "wrong." Four distinct points of view compete and thus constitute a "quadratic" ethical dilemma. The elements involve the competing positions of the patient, the physician, the business, and the payer:

- Most patients desire a singleton pregnancy and hope to achieve it in a timely and
cost-effective manner.

- Infertility specialists generally must temper their personal desire to be beneficent with a recognition of patient autonomy.
- Business managers of infertility programs desire to achieve high pregnancy rates in order to attract more patients.
- The third-party payer desires to avoid the high cost of repeat treatment cycles and/or the attendant high cost of IMP.

Resolution of the quadratic ethical dilemma of IMP cannot occur without specific actions by all parties. The tasks for the patient are not insubstantial. First, she (and her partner, if applicable) must understand the risks of IMP for each therapeutic intervention undertaken or contemplated. Next, she must honestly assess her own potential for becoming pregnant. Third, she must once and for all confront the concept of “Enough is enough.” Last, she must consider the alternative of adoption or accept the prospect of child-free living—that is, life without the possibility of parenthood. Physicians are faced with no less daunting a task. First, they must recognize that beneficence—seeking the greater balance of benefits over harm—is not identical to nonmalfeasance—that is, doing no harm. Second, they must avoid judging the reasons behind patients’ decisions while remaining alert to the multitude of outside pressures influencing such decisions.

With regard to the business aspect of ART, four factors strongly affect profitability, at least in this country. First, there is no national single-fee scale for ART and in vitro fertilization (IVF). Second, there are no real financial disincentives to discourage high IMP rates in private offices or reproductive clinics. Third, the potential presence of a single-fee scale might be construed as destructive of profitability incentives. And fourth, reasonable profit margins for freestanding reproductive units have never been determined. It is not known whether the present circumstances would prevail if better insurance coverage were available. A recent editorial by Gleicher outlines several strategies to effect such a change.

The two higher-order multiple births recently reported in the media focused enormous attention on those women who traditionally seek infertility treatment from OB/GYNs. Some observers might suggest that these patients do not represent women from all walks of life. This is true, as Caucasian women seeking infertility treatment are disproportionate in number relative to the general population. Others would insinuate that the public ultimately pays for treatments after delivery and for long-term care in the cases where disability should ensue. This is also true, and the Iowa and Texas cases represent prime examples of high and as yet undisclosed peripartum costs, which will necessarily be followed by long (and presently incalculable) survivorship costs. Other critics might point out that countries such as the United Kingdom, Germany, Scandinavia, and France strictly prohibit the type of treatments that occur regularly in the United States, and are willing to assume the consequences of a strictly controlled fertility industry.

RESOLVING THE DILEMMA
The authors agree with Chervenak and McCullough that it is possible to develop a preventive ethical approach to IMPs that result from ART and IVF.

- With regard to ART, it is possible to satisfy the requirements of informed consent specific to the procedure contemplated, to inform patients of known IMP rates specific to the procedure contemplated, to fully discuss selective termination versus nonintervention if IMP were to occur, and to know before starting therapy whether the patient is unable to accept abortion or MFR as an option.

With regard to IVF, the policy of transferring no more than two embryos in any given cycle could be advocated, especially in younger patients. This method has been shown to be equally effective in this age group in terms of maintaining pregnancy rates while significantly reducing the number of multiples (especially higher-order multiples).

If such a policy were to be implemented in the United States, however, it would not be acceptable to all practitioners. Some would express concern about lower pregnancy rates or the potential exclusion of specific couples because of financial considerations. Furthermore, such a policy could never achieve its potential in the absence of some form of external surveillance, a concept that would not be popular. Regardless of whether this policy or some variant would be adopted, it still would be possible to grade embryos to enhance the quality of transfers or to consider blastocyst transfer to enhance the pregnancy rate.

Given our present state of knowledge, the better the quality of the embryo, the lower the need to transfer multiple
embryos to attain a singleton pregnancy.

Methods to avoid higher-order IMPs are now well discussed in the literature. In terms of ART, one can carefully select patients, tailor doses of, monitor estradiol levels and the number of growing follicles, and cancel cycles when the risk of IMP becomes apparent. In terms of IVF, the principal action appears to be limitation of the number of embryos transferred. Secondary actions are the use of blastocysts and grading of embryos based on validated scoring systems in order to achieve high implantation rates with low numbers of embryos transferred. The use of MFR, in the opinion of the authors, should remain as a backup procedure in the manner addressed by Evans and colleagues.

Finally, the authors agree with Verhoeven’s recent opinion that IVF, as well as all ART treatments, should be performed only by experienced practitioners with a sense of responsibility and ethical values.

CONCLUSION

In the opinion of the authors, the tenets of ethical practice involved in ART and the resultant IMPs do not differ in concept from those related to other, everyday physician-patient interactions. The ethical principles of beneficence and autonomy are at the core of such interactions. Respecting this absolute depends on recognizing and dealing with potential IMP before and after any contemplated ART procedure. Should physicians themselves not deal with these issues, it is conceivable that governmental commissions will be empowered to deal with them under the rubric of interstate commerce regulation.

References:

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17. Chervenak FA, McCullough LB. Ethical aspects of iatrogenic multiples. In: Blickstein I, Keith LG,

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