EDITORIAL

Multifetal Reduction in High-Order Gestations: A Nonelective Procedure?

The increased incidence of multiple gestations in women undergoing assisted reproductive technologies (ART) poses new dilemmas for the medical team. By advanced technology, high-order multiple gestations arise. By advanced technology, premature infants also survive, albeit often with severe disabilities. Fortunately, technological advances also allow multiple gestations to be reduced to more manageable numbers, most efficiently through injection of potassium chloride. This is the topic of an important study reported in this issue of *JSGI*.[1] Ultimately, the infertile couple that finally conceives—but has a high-order multiple gestation—must weigh the relative risks of success in various options: fetal reduction with a risk of pregnancy loss versus continuing the multiple gestation with a risk of severely premature infants who will either die or may have marked disabilities.

What is the propriety and success of decreasing the number of ostensibly normal fetuses (multifetal reduction) in high-order gestation? The multicenter data reported by Evans et al[1] provide useful information. In experienced centers, loss rates after multifetal reduction approximate 10–11%. Loss rates with triplets, quadruplets, quintuplets, and sextuplets (before reduction) were 7.6, 13, 17.1, and 20.9%, respectively. The frequency of very premature infants (25–28 weeks) was 4.5% in continuing pregnancies. Prematurity rates and mean gestational ages at delivery were inversely proportional to the number of gestations remaining after reduction. No differences in loss rates were observed for transabdominal versus transcervical procedures, surprisingly, given that many in the United States have the impression that the transabdominal approach is preferable. No unanimity exists concerning whether the optimal number of fetuses remaining after reduction is two or three; reduction to only a single fetus generally is not recommended because of the fear that that fetus, too, could be lost.

These data validate the efficacy of multifetal reduction in experienced hands. The real issue is no longer technical prowess, but rather how to obviate the necessity for multifetal reduction, a procedure all agree would best be avoided. However, it is equally clear that undergoing or not undergoing multifetal reduction is not a real option. The choice is either performing multifetal reduction, at least for quintuplets and sextuplets, or incurring an unacceptably high likelihood of either losing the entire gestation or having premature infants with severe disabilities. Thus, multifetal reduction cannot be considered an elective procedure.

This conundrum cries for solutions, and indeed there is no shortage of simplistic recommendations. Some state that the transfer of more than two embryos in a given cycle should be proscribed. Transferring only one or two embryos would indeed mitigate against the problem, and some data show that ART success rates are approximately equal if two versus three embryos are transferred.[2] By contrast, other data and clinical experience show higher pregnancy rates when three or more embryos are transferred when compared with only two.[3] Moreover, monozygotic twins and high-order gestations may still arise spontaneously; thus, limiting the number of embryos transferred is not the complete solution some imagine.

But is a restrictive policy wise or fair even if it does reduce high-order gestations? No. First, the policy smacks of paternalism, especially because ART couples are among the most well informed we encounter. Second, a strict "one size fits all" philosophy is not scientifically defensible because ART pregnancy success is inversely related to maternal age and possibly to other confounding factors.

A third argument against restricting the number of embryos transferred is that such a policy would lead to more high technology. If only two or three embryos can be transferred, it would seem irresistible not to verify that these embryos are cytogenetically normal. Indeed, fluorescent in situ hybridization (FISH) with chromosome-specific probes can readily detect numerical abnormalities in biopsied blastomeres.[4] After embryo biopsy, one could transfer only chromosomally normal embryos. Unfortunately, cytogenetic analysis of the early embryo is not straightforward. An astonishing number of blastomeres are aneuploid, perhaps 30–40% for X, Y, 13, 16, 18, and 21 alone. Whether a blastomere with a chromosomal abnormality will always connote the inability to yield a normal pregnancy is thus quite uncertain, particularly if the biopsied embryos appear morphologically normal. That so many chromosomal abnormalities are encountered probably means instead either 1) single-cell (blastomere) FISH diagnosis is less reliable in blastomeres than in other tissues, fortunately an unlikely explanation[5]; 2) single abnormal blastomeres are indeed common but selected against during development and, hence, of no clinical consequence; or 3) single abnormal cells are shunted to extraembryonic villi, where they cannot adversely affect the embryo per se. Nevertheless, embryo biopsy followed by FISH analysis with chromosome-specific probes requires more technology and thus more expense with no assurance that pregnancy rates will prove comparable to those in unbiopsied embryos.

What can or should be done? First, we must preserve the freedom of an individual ART program to perform its work in the manner that provides the fully informed couple their highest chance of pregnancy. Centers must be able to take into account the age of the patient, diagnosis, and prior experience in determining how many embryos should be transferred. While preserving this choice, transferring fewer embryos may

From the Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas.

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become more attractive as cryopreservation techniques improve. Second, couples should be informed of not just ART pregnancy rates but also of the existence and desirability of multifetal reduction should they unexpectedly have five or six fetuses. The couple would then be better prepared if later told that something must be done. Moreover, women undergoing multifetal reduction have been shown to be quite capable of handling the understandable stress.[6] If the couple does not wish to accept the option of multifetal reduction, transferring fewer embryos than usual might be strongly considered. The couple should not be allowed to conclude that *they* will become the lucky ones who will have a completely normal outcome despite a high-order gestation. The normal defense mechanisms of denial will always direct one toward this comfortable conclusion! Thus, a place exists for directive counseling.

A final question is whether genetic testing should be performed before multifetal reduction, especially for women over age 35 years. Brambati et al[7] have shown this to be an attractive option. Sixty-nine women with multiple gestations underwent chorionic villus sampling (CVS) on 135 fetuses. Cytogenetic analysis was performed with direct cytotrophoblast cultures, allowing abnormal fetuses to be pinpointed preferentially for reduction 3–5 days later. Diagnostic accuracy was high (98.5%) but not 100% (two sexing errors). Five abnormalities were found in the 69 tested pregnancies (135 fetuses). Loss rates were not increased over that shown in multifetal reduction cases not undergoing CVS. (Loss rates were 7.0% overall). Thus, cytogenetic analysis followed by preferential retention of normal fetuses is an attractive option. However, this may not always be practical. In the United States, multifetal reduction is usually performed on the more accessible embryos, typically those anterior and fundal; fetuses nearer the cervix usually are not reduced because of fears of infection. Testing all fetuses is thus not likely to prove practical. One reasonable compromise would involve testing only fetuses slated to remain, but these may not be the easiest to sample. Moreover, the policy recommended by Brambati et al[7] will require not just surgical expertise for CVS, but also cytogenetic expertise for performing either FISH with chromosome-specific probes (13, 18, 21, X, Y) or "direct" cytotrophoblastic analysis. One of these approaches is necessary to minimize the length of time between CVS and potassium chloride injection. By contrast, culturing mesenchymal core villous cells is now routine in United States centers processing CVS specimens, given that direct cytotrophoblastic analysis has been shown to be less representative of the embryo and, hence, not appropriate as the sole method of cytogenetic analysis.[8]

Overall, the success of assisted reproductive technology represents one of our discipline's greatest triumphs. Our generation can be proud of not only Robert Edwards and Patrick Steptoe for accomplishing human in vitro fertilization, but for the many who have made ART widely available. Results continue to improve, but complications will still arise. Perhaps each center should develop reasonable guidelines for multifetal reduction that preserve autonomy while eschewing rigid rules that may harm the very individuals we seek to help—infertile couples.

Joe Leigh Simpson, MD,
and Sandra A. Carson, MD

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