

# Multifetal Pregnancy Reduction: Evolution of the Ethical Arguments

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## ABSTRACT

Multifetal pregnancy reduction (MFPR) was developed over 20 years ago to rescue higher-order multifetal pregnancies and has become a major component of improving the outcomes in infertility therapies. By definition, MFPR will always be controversial, but opinions do not follow the traditional “pro-life/pro-choice” dichotomy that has sabotaged the more generalized abortion debate. If one defines *success* as a healthy mother and healthy offspring, clearly, with multiples, fewer are always safer. The ethical issues surrounding MFPR are for most people not a clear black-or-white but varying shades of gray. The ethical principle of proportionality takes precedence (i.e., trying to obtain the most good for the least harm while looking for areas of moral compromise to achieve the best outcomes).

**KEYWORDS:** Multiple pregnancy, multifetal pregnancy reduction, cerebral palsy, fetal loss

## HISTORICAL CONTEXT

Louise Brown, the first baby to come from in vitro fertilization (IVF), was born in 1978. In the more than 30 years since that event, millions of babies have been born through infertility therapies, including more than 2,000,000 IVF babies. These incredible success stories, however, have had a corresponding “price to pay.” The twin pregnancy rate, commonly quoted for decades to be 1 in 90, now has more than doubled to ~1 in 40.<sup>1</sup> Almost 70% of all twins in the United States now come from infertility treatments. Some IVF programs create as many multiples as singletons. Overall, half the babies born from IVF in the United States are part of multiple pregnancies.<sup>2</sup>

Rates of multiple pregnancies have continued to rise, and the incidence of prematurity and related sequelae clearly correlate with fetal number (Fig. 1).<sup>1</sup> With increasing public and professional attention, some of the

very high-order multiples have diminished, mostly secondary to a shift of cases from ovulation induction to IVF, which has better control of the number of embryos. The average “starting number” of patients presenting for reduction procedures has slowly gone down from ~3.5 to ~3.0. The public response to situations like the 2009 “Octomom” in California have shifted from one of “appreciative amazement” of the 1980s to elements of shock and disgust in 2009.<sup>3</sup>

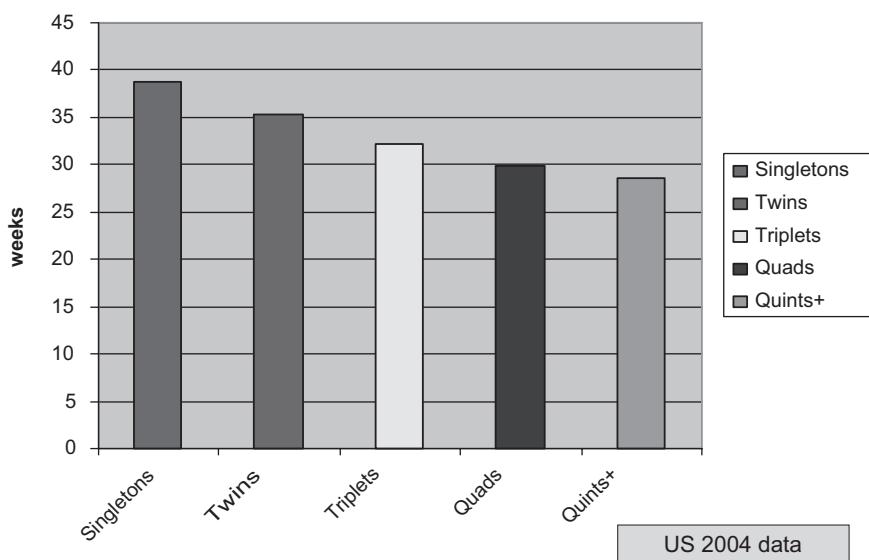
Another article in this issue will address the issue of how many embryos to transfer, so all we will say on that point is that although single-embryo transfer (SET) has many medical advantages, the economics of IVF in the United States make it highly unlikely that SET will be very common in the United States. As an illustration, despite Society for Assisted Reproductive Technology guidelines that state that under age 35, only two embryos should be transferred, the average number is 2.4. With

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Ethical Controversies in Reproductive Medicine; Guest Editor, Mark V. Sauer, M.D.

Semin Reprod Med 2010;28:295–302. Copyright © 2010 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.  
DOI: <http://dx.doi.org/10.1055/s-0030-1255177>.  
ISSN 1526-8004.



**Figure 1** Multiple pregnancies and prematurity.

the economic pressures resulting from high costs for every cycle, everyone is under pressure to achieve a very high pregnancy rate with each cycle. Such is not likely to change even with the recent health care “reform” passed into law in the United States.

Over the past decade, the pattern of patients seeking multifetal pregnancy reduction (MFPR) has evolved considerably.<sup>4,5</sup> With the rapid expansion of availability of donor eggs, the number of older women seeking MFPR has increased dramatically. In our experience, over 10% of all patients we see seeking MFPR are now over 40 years of age, and nearly half of them are using donor eggs.<sup>5</sup> As a consequence of the shift to older patients, many of whom already had previous relationships and children, there is an increased desire by these patients to have only one further child. The number of experienced centers willing to do two-to-one reductions is still very limited, but we believe it can be justified in the appropriate circumstances, and it currently constitutes ~10% of the cases we see.<sup>6</sup>

For patients who are older, particularly those using their own eggs, the issue of genetic diagnosis comes to the forefront of considerations. By 2005, more than 50% of patients in the United States having

assisted reproductive technology (ART) cycles were over 35 (Table 1), and thus more at risk for fetal anomalies<sup>1,7,8</sup> Hence, we believe that there should be a rigorous evaluation of fetal status as part of the decision process prior to reduction.

Typically, we perform a 2-day procedure on most patients at ~12 weeks: chorionic villus sampling (CVS) on the first day with fluorescence in situ hybridization (FISH) analyses overnight for chromosomes 13, 18, 21, X, and Y. We get the results the second afternoon, and we can then do the reduction that day. By definition, FISH for five chromosomes cannot detect everything, but our experience and modeling suggest only about a 1/400 residual risk of a problem, which we believe to be a lower risk than sending the patient home to return nearly 2 weeks later and risk loss from the higher-order multiple and confusion as to which embryo/fetus was which on the ultrasound.

Over the past few years, ~80% of our patients have combined CVS and MFPR procedures. With an increasing proportion of (1) older patients, (2) data now suggesting increased risks of chromosomal and other anomalies in patients conceiving by IVF and especially with intracytoplasmic sperm injection (ICSI), and (3)

**Table 1** Multiple Pregnancies from Assisted Reproductive Technologies: The 2005 Society for Assisted Reproductive Technology Report

	Age (y)				
	< 35	35–37	38–40	41–42	43–44
Number of cycles	37,223	20,570	17,805	8337	4680
Average number transferred	2.4	2.6	3.0	3.3	3.3
% twins	33.0	27.2	21.7	13.1	7.6
% triplets +	4.3	5.0	4.4	2.5	1.8

the known 3 to 6% inaccuracy rate of perimplantation genetics (PGD), we expect the utilization of CVS prior to reduction will likely increase even further.<sup>4,8–12</sup> We have also found that many couples in their 40s or even 50s who are using donor eggs—the genetic risk of which is the age of the egg donor—nevertheless still want CVS prior to MFPR because their “tolerance” for having a special needs child is more akin to their actual ages, not the donor’s age.

For over 20 years, the world’s leading centers have published collaboratively and individually showing improvement in outcomes. In the 1980s, about half of our patients were quadruplets or more. Now quadruplets (or more) constitute only ~15% of cases.

Outcomes have steadily improved over the past decades as:

1. A better understanding of the clinical situation has emerged.
2. There is a smaller percentage of very high-order multiples that have worse outcomes even with reduction.
3. Better ultrasound allows for better visualization; use of CVS reduces the risk of leaving behind abnormal fetuses.
4. A cadre of extremely experienced physicians does a significant proportion of the cases.
5. Triplets and quadruplets reduced to twins clearly do as well as pregnancies starting as twins. With higher-order multiples, there still is increased pregnancy loss, and prematurity increases (Table 2).<sup>5</sup>

These improved outcomes, coupled with the growing use of ART, have led to an evolution in the ethical questions being considered. Early on, MFPR seemed warranted only in life and death situations—where the mother was of small stature and carrying four or more embryos, for example. As has been seen in numerous innovative technologies, once the concepts are proven and the foundation for their use developed, the focus can shift from “life and death” to “quality of

**Table 2 Risks of Multiple Pregnancies**

Starting Number	Spontaneous Loss Rates (%)	Finishing Number	Reduction of Risk of Loss (%)
6+	90–99	2	90–12
5	75	2	50–8
4	25	2	25–5
		1	25–7
3	15	2	15–4
		1	15–6
2	8	1	8–3

Data are extrapolations of multiple papers. When monozygotic twins are part of the multiple, the overall risk is increased as if there were one more than the starting number.

life.” Such has been the case here, but because of the emotionally charged context of the abortion debate, MFPR will always be controversial. Opinions on MFPR, in our experience, have never followed the classic “pro-choice/pro-life” dichotomy.<sup>4–6</sup> We believe that the real debate over the next 5 to 10 years will not be whether or not MFPR should be performed with triplets or more. A serious debate will emerge over whether or not it will be appropriate to offer MFPR routinely for twins, even natural ones for whom the outcome has commonly been considered “good enough.”<sup>6</sup> Our data suggest that reduction of twins to a singleton actually improves the outcome of the remaining fetus.<sup>6</sup> No consensus on appropriateness of routine two-to-one reductions, therefore, is ever likely to emerge, and the decisions regarding whether to reduce will still be fraught with anxiety. We do, however, expect the proportion of patients reducing to a singleton to steadily increase over the next several years.

With a gradual decrease in starting numbers, the emphasis has somewhat shifted to prevention of serious morbidity (i.e., cerebral palsy from prematurity). Several studies have suggested that the rate of cerebral palsy for singletons is ~1/700; twins, 1/100; and triplets, 1/25 to 30.<sup>13,14</sup> If one’s definition of success is a healthy mother and healthy family, for both morbidity and mortality, the data show conclusively with multiples, less is always better.

## MFPR IN SOCIETY

We have argued that when controversial, high-anxiety decisions are concerned, patients treat these decisions as an ongoing part of the social reality that they are creating to live in and raise a family.<sup>15</sup> This reality-construction process is variably proactive, with couples aware of the potential consequences of sharing with others what they are going through. In a recent study among MFPR patients, we discovered four sharing strategies that varied in how selectively information on their situation and choices was shared.<sup>16,17</sup> Strategies for sharing ranged in terms of selectivity from a *defended-relationship* approach in which only the partner and patient knew about the problems the patient was facing and the decision to reduce, through a *qualified family and friends* strategy in which information is shared only with those who appear to be trustworthy in terms of their reactions. Two less selective strategies also emerged from our analysis. In the first, *both sets of parents* are privy to what the couple is going through, and finally, there is an extended, *open network* strategy of family, friends, and colleagues being in the loop.

No sharing strategy is completely free of the risk of encountering hostility. Even so, the odds of encountering hostility are significantly greater with the more open, less selective strategies. MFPR and ART clinics

will vary in terms of the cultural style they have for handling patient anxiety and stress, and it may be that all successful clinics have found a combination of procedures and people that help patients through these anxieties.<sup>18,19</sup> These results suggest that some way should be found to sensitize couples to the fact that selectively sharing what they are going through is an effective technique for at least neutralizing some of the hostility that they are at risk of confronting from family, friends, and others. Because anxiety and stress have implications for clinic success rates, such results regarding sharing strategies and the development of appropriate interventions become doubly important.

The realities people construct—composed of supportive people and institutions together with complexes of supportive values, norms, and attitudes—are the source of *frames* that the patients use to view the data.<sup>20,21</sup> The decisions they make, and how they justify those decisions, may help resolve incompatible elements in the realities in which they find themselves enmeshed. It may often happen, for example, that parents who have gone through reduction to two or one live in families and/or work in communities where having engaged in reduction would be considered as something shameful. The less control they have over the selection of family, friends, and workplaces, given the prospect of such stigma, the more likely they are to simply present their pregnancies to these publics as if their pregnancies had always involved twins or singleton. Where they have more control over the situation—as typically happens with friends versus family—they may be more likely to selectively share their real experiences.

## FRAMING

The social realities in which people live, however, involve more than people: they also involve values, norms, and attitudes.<sup>16,17</sup> There are three resolutions that have presented themselves from our analyses. The term *framing* is a sociological concept that examines how people take in information. The first of these, a rational Medical frame, in which scientific data are paramount to decision making, looks superficially like what one would expect from the rational analysis model. But the commitment to factual analysis comes typically from patients having selected themselves into the hard sciences, medicine, dentistry, engineering, or the law—disciplines in which an appreciation of and trust in “facts” form a fundamental part of their disciplinary identity. Such women will want to see the numbers regarding the relative risk associated with different reduction choices and will want to engage in a rigorous discussion of the data and their implications even if it is relatively painful to do so. And they will be likely to choose a final number for reduction that maximizes the chances of a “take-home” baby.

For those who have immersed themselves in a social reality that has a strong emphasis on norms against abortion and/or reduction, such that they themselves have such normative beliefs and are heavily involved in religious institutions that reinforce similar beliefs, a detached examination of the “facts” is simply not possible. These “facts” hold no special moral authority and need not be trusted in and of themselves. Their beliefs and those of the individuals and social institutions in which they have selected themselves have a moral authority as well. The balance that such women will likely seek is one that reduces their relative risk to only acceptable limits. So, unless the consequences are dire, they will not reduce at all or choose to reduce only to three. We labeled such a resolution a “Conceptional frame” because believing that life begins at conception seems to be a central tenet.

Finally, there are those for whom the demands of career and/or existing children constitute powerful elements in their constructed realities. For such women—and, importantly, this includes many of the older patients we encountered—the essential balance that they seek is a more secular one, a Lifestyle frame, one that emphasizes creating a family situation in which having a family can be balanced with working, though the commitment to working is less than the intense career commitment seen among Medical frame patients. Such women will more than likely choose reduction to two or even one embryo, depending on the number of other children they have and the level of resources that the family has.

To reprise the argument to this point, there has been an evolution of the nature of ethical decisions with respect to MFPR from an early preoccupation with life and death situations, through a longer period during which arguments centered around the sacrificing of some embryos to increase the viability of others (a line of argument inescapably intertwined with the statistics regarding outcomes) and the conditions under which women accepted this argument on its face, to a discussion now of the proper role of lifestyle factors in such decisions. Improvements in technology and skill have reduced the number of women presenting with four or more embryos, changing the context within which women must make these decisions along with it. Longer-term changes in the timing of having children and the representation of women in careers have intersected with these technological and skill changes to create contexts within which women make such decisions. It appears, however, that as women and their partners construct and adapt to social and normative realities to live in that are differentially conducive to different reduction-decision justifications, lifestyle factors are playing more of a role than they used to, especially for older women who already have careers and families. How patients come to grips with their situation is

seldom an absolute primacy of one of the above three frames but varying contributions of the three. Our friend John Fletcher summarized these arguments as the ethical principle of “proportionality” (i.e., trying to get the most benefit for the least harm).<sup>6</sup>

Clinicians and their counseling staff need to be aware that for women who have selected themselves into and/or been trained to accept the legitimacy of rigorously determined statistics regarding relative risk (a Medical frame), reduction choices *can* be straightforward—or at least they can appear to be relatively straightforward. This is usually not the case, however, for women who must forge a resolution among potentially incompatible elements, as for women who are struggling to reconcile the potentially oppositional elements of religious beliefs and involvement with risks associated with higher-level pregnancies (Conceptional frame), or those who are struggling to reconcile the potentially conflicting identities of home and work (Lifestyle frame).

There are both short- and longer-term implications of women varying in the combinations of frames, biography, and social situation. The overwhelming majority of women who choose MFPR as a pregnancy management strategy have been through fertility therapy. The multiple sources of stress and strain engendered by that experience have been well documented,<sup>22–24</sup> and the variability of reactions to these stresses and strains has been analyzed.<sup>25</sup> Some of the longer-term consequences will be mediated in part by low birth weight and whatever decisions are made with respect to reduction; there will be challenges that families must work through.<sup>16,23,24</sup> The culture of clinics has (albeit unevenly) caught up with the complexity of situations and emotions during and after fertility therapy and during MFPR. Still lacking is a systematic approach to longer-term support. Whatever the outcomes of having gone through these processes, dialogue and support are needed.

Although there are still some arguments, particularly from conservative commentators, our experiences suggest that triplets reduced to twins do much better in terms of loss and prematurity than do unreduced triplets. We believe that if a patient’s primary goal is to maximize the chances of surviving children, that reduction of triplets to twins or a singleton achieves the best live-born results. The trade-off is between morbidity and mortality. More recent analyses suggest that although mortality is lowest with twins, morbidity is lowest with remaining singletons.<sup>5,6</sup> A small but increasing number of women want to reduce from twins to a singleton. The vast majority of such cases are from women in their 40s or even 50s, some who of whom are using donor eggs and who, more for social than medical reasons, only want a singleton pregnancy.<sup>5,6</sup> Our data suggest that twins reduced to a singleton do better than remaining as twins.<sup>5,6</sup> In a recent series of triplets, we found the

average age of outpatients reducing to twins to be 37 years and to a singleton, 41 years.<sup>6</sup> Although the reduction in pregnancy loss risk for three-to-one reduction is not as much as three-to-two deduction (15 to 6% and 15 to 4%, respectfully), the gestational age at delivery for the resulting singleton is higher, and the incidence of births < 1500 g is 10 times higher for twins than singletons.<sup>1</sup>

These data have made counseling of such patients far more complex than previously. Not surprisingly, there are often differences between members of the couple as to the desirability of twins or singleton.<sup>18</sup> There are also profound public health implications to these decisions, as 2000 U.S. data showed that of \$10.2 billion spent per year on initial newborn care, 57% of the money was spent on the 9% of babies born at < 37 weeks.<sup>26</sup> In 2003, more than \$10 billion was spent on the 12.3% born preterm.<sup>26</sup> The Institute of Medicine in 2006 reported that preterm births cost the United States approximately \$26 billion per year.<sup>26</sup> Data are now also emerging that there is considerably higher neurological and developmental disability in 6-year-olds who survived birth at 26 weeks or less. The rates of severe, moderate, and mild disability were 22, 24, and 34%, respectively. Significant cerebral palsy was present in 12%.<sup>27</sup> Hack et al also have now shown that in babies born at less than 1000 g, the rate of cerebral palsy was 14% as opposed to 0% for controls.<sup>28,30</sup> Asthma, poor vision, IQ < 85, and poor motor skills were all also substantially higher.

As a result of all of the above and the changing demographics of who is having infertility treatment and desiring reductions, we believe that reduction of twins to a singleton is likely to become more common over the next several years. In our own personal experience, the proportion is between 10 and 15%.

## THE CASE FOR MORAL COMPROMISE

*Prima facie* respect for the intrinsic value of human life is a common moral norm. *Prima facie* means that a norm is binding absent conflicting obligations; *intrinsic* means to value something in and for itself, independent of its results for or our relations to us or other people. Convictions about intrinsically valuing human life are universal.<sup>29</sup> However, these convictions often conflict with obligations of other moral norms (e.g., to do justice, to benefit others, to respect and protect autonomous choices, to prevent or minimize harm or suffering, to use proportionality when risk is inevitable, etc.). Dworkin<sup>30</sup> shows how, in the abortion issue, liberals and conservatives affirm the same principle of respect for the intrinsic value of human life but interpret and apply it differently in the abortion issue. Only moral compromise in policy and practice can “split the differences” between such diverse interpretations.<sup>31</sup>

Conflicts between norms regarding respect for the value of human life, reduction of harm, prevention of suffering, or benefit of health are legion. When these conflicts emerge in research, society benefits by a public, deliberative process that can yield workable compromises for public policy. In addition to respect for human life, society has other interests to balance in policy about reproduction (i.e., protection of reproductive liberty, fairness in distributing resources to promote reproductive health, prevention of harms of assisted reproduction, e.g., multifetal pregnancies) and protection of legitimate scientific inquiry.<sup>29</sup>

When such conflicts arise in reproductive choices, our society does not interfere in parents' consultations with obstetricians, geneticists, or moral advisors. Society does not dictate one option over others, nor does it require parents to justify their reasoning before a committee or in public. This policy stems from respect for autonomous choice and privacy. However, the right to privacy, as interpreted by *Roe v Wade*,<sup>32</sup> is not absolute. The Supreme Court's opinion expects physicians to counsel patients about their reasons and be responsible in providing abortions. The value of respect for human life lies behind this concern. Society also protects conscientious refusal of clinicians to participate in abortions or reductions, constrained by the duty to refer patients to competent sources of help.<sup>33</sup>

Returning to the main topic, the central moral question is: how can it be right or good to take the life of a twin for reasons other than a genetic diagnosis or the woman's health? If a woman has a history of multiple fibroids, extensive surgery, or exposure to drugs like diethylstilbestrol, the higher risks of premature labor ought to be minimized. Are reasons based on quality of life in a family or marriage morally acceptable?

As numbers in infertility treatment have grown, concerns about family size and resources mix with desires for a healthy child. Couples with older children from a prior marriage may desire only one child. Some couples believe that they cannot live up to a standard of good parenthood to two children, given limited personal and family resources. Adoption of twins is a time-honored tradition. However, we find that those referred to us have often already considered adoption seriously but favor reduction. Furthermore, recent work shows differing appreciation of the risks of twins between partners.<sup>34</sup> We have previously reported such incongruity between partners concerning genetic risks.<sup>35</sup>

Many couples or single mothers would not act on social or economic reasons to reduce twins to a singleton. However, if it is right for a pluralistic society to curb a state's interference with the choice of abortion or other reproductive options, how could it be wrong for society to respect and protect the freedom of couples to choose to have one rather than two infants? This so-called "negative right" (i.e., to noninterference) differs from a

"positive right" to society's encouragement and aid in the action.<sup>36</sup>

Other parental choices also deserve respect and protection from interference. Some couples with few assets want twins, knowing that one has or both have a genetic condition requiring lifelong care. Society does not and should not interfere with this choice or withhold resources to care for children with disabilities.

## RECOMMENDATIONS

To reduce twins to a singleton for significant reasons of maternal health or genetic diagnosis is generally seen as an accepted practice in obstetrics. Obstetricians now see more twin pregnancies in which social, economic, and quality-of-life reasons mingle with needs to lower risks of premature delivery and its consequences. In this context, we propose change in traditional obstetric practice in the form of a moral compromise.

On one side, twin reduction for social reasons is defensible as a reproductive right. Respect for parental decisions is the governing norm in these cases. Women have a right to choose to continue a planned or unplanned pregnancy, and this is considered a "right." Education of women carrying twins needs to include current data on the relative risks of prematurity in twins and singletons and an opportunity to consider all options. Probably only a small proportion of patients with twin pregnancies would be interested in reduction. They should be referred to centers with experience in MFPR and personnel trained to educate and counsel patients carrying twins. A serious examination of the psychological and moral issues in reduction requires time.

On the other side, although respect for autonomy has force in reproductive ethics, no ethical principle is absolute or immutable. Competing or conflicting claims must be weighed. In some cases, claims of autonomy are not as compelling as pursuit of social goods or prevention of harms to other persons. For example, using arguments based on equity and social harmony, well-considered statements of geneticists and infertility specialists have recommended denial of parental requests for prenatal or preimplantation embryo sex selection.<sup>37</sup>

Compromise is often the right path, because all moral judgments are fallible. However well-considered, predictions of consequences are limited by inability to know the future. Moral assessment cannot be purged of political and social interests. Advocates for both sides need to remember that integrity does not disappear in an authentic compromise. We acknowledge moral uncertainty about unknown effects of twin reduction for individuals, families, and society. Fetal reduction of any number is emotionally and morally troubling for couples, even when couples make educated decisions after an extensive consent

process.<sup>38</sup> How does a decision about twins affect parents' relationship with each other or with the child? There are reports about bereaved persons who describe great relief of lifelong guilt on learning of a twin who died.<sup>39</sup> Relief could be explained by the unveiling of a deep family secret, but how can we know? The long-term effects of reduction, on a twin, are unknown. Follow-up studies are ethically problematic because of privacy concerns. There will also be effects on the population of twins and on their parents.

These considerations lead us to recommend that the obstetrics community not adopt elective twin reduction as a general practice but refer patients who make this request to centers with experience in MFPR that also offer counseling about this choice. More cases and case-controlled studies are needed to prove safety and efficacy. We urge other centers to publish their experience in twin reduction. In our experience, this choice can be right in some cases, but troubling questions remain about a general practice of twin reduction in obstetrics.

## SUMMARY

We expect the vast majority of patients with twins to continue with twins. However, there is a continually increasing proportion of the infertility population, particularly those over 40 years of age, who for a variety of medical and social reasons only want to have a singleton pregnancy. Our data suggest that for such patients, MFPR is safer than continuing with twins. As with all other technologies, as its safety and efficacy have been proven, indications will liberalize. In the 1980s and 1990s, as MFPR was being developed and improved, there was little debate, except among the most strident opponents, that MFPR from quadruplets or more was the best way to improve outcomes in such cases. In the last decade, the major debate was over the outcome of triplets. Several studies have addressed that issue, and those with the most data suggest improved outcomes with reduction of triplets to twins. Interestingly, reduction of triplets to a singleton has a higher loss rate (7 versus 4.5%) but lower morbidity, yet both resultant twins or singletons are much less risky than attempting to carry the triplets (15%).<sup>6</sup> However, for those patients starting with twins, reducing from twins to a singleton seems to significantly lower risks and improve outcomes.

## ACKNOWLEDGMENT

The authors wish to acknowledge the contributions to our thinking on this subject of John C. Fletcher, Ph.D., who before his death several years ago laid the foundation for the ethical analysis of this subject.

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