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Fetal Reduction: 25 Years' Experience

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Key Words

Cerebral palsy · Chorionic villus sampling · Chromosomal abnormalities · Fetal reduction · Higher-order multiple gestation · In vitro fertilization · Multifetal pregnancy · Multiple pregnancy · Perinatal outcome · Prematurity

Abstract

Fetal reduction (FR) began in the 1980s to salvage the pregnancies of couples needing fertility therapy who were finally successful but with too many fetuses. Since then, it has gone from a rarity performed in only the highest risk situations to an integral fail-safe of infertility practice. Our understanding of the problems of multiple and premature births has increased – even twins carry 4–5 times more risk than singletons. Evaluation of fetuses before FR has permitted more intelligent choices and improved resultant outcomes. We now perform chorionic villus sampling in approximately 85% of cases, obtain fluorescent in situ hybridization (FISH) results overnight, and then perform FR the next day. Decisions about which to reduce prioritize anomalies, but now can include fetal gender in the decision process, as couples are now just as likely to want girls as boys. In Mendelian cases, sophisticated molecular analyses permit diagnoses before FR, and new uses such as paternity analysis can be performed. Ethical arguments have also evolved; as with many technologies in which the start was for only 'life or death cases', FR has also moved into 'quality of life' issues. FR of twins to a singleton now compromise about 30% of our cases.

The Problem

Pregnancy management via fetal reduction (FR) has witnessed considerable changes over the last 25 years since we first published on the subject [1]. These changes have taken place in medical technology outcomes, patient choices, and the larger demographic and cultural shifts that are driving the pace and direction of change.

At its core, FR started out as a way of managing pregnancies in which the risks to both mother and fetuses from carrying multiple embryos were extreme. Selective termination (as it was called then) of some of the embryos to increase the viability of the remaining ones and reduce the risk of morbidity and mortality for the mother was a desperation approach to salvage the situation. As has been the case in numerous other technological changes, what began as a dominant concern with matters of 'life and death' has eventually become accepted and then indications transformed from the crisis of 'life and death' into issues of quality of life [2, 3].

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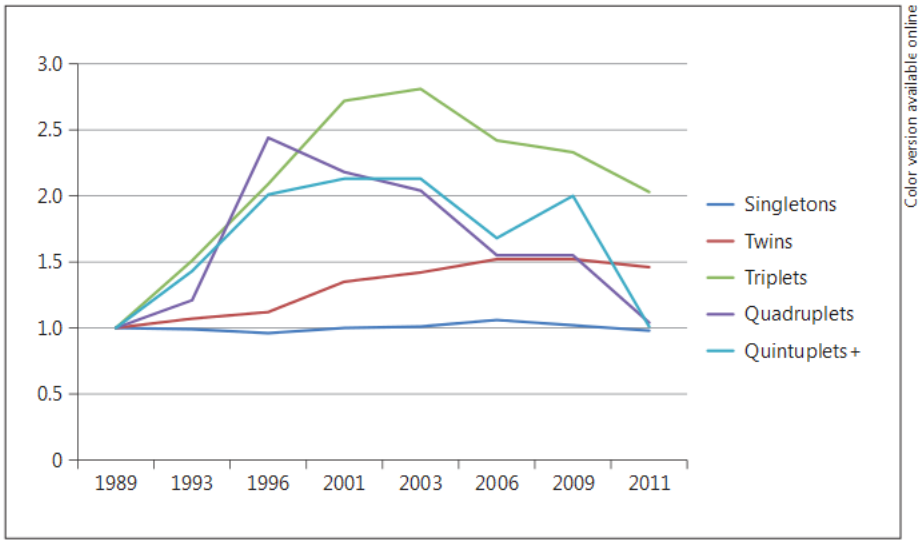


Fig. 1. Change in the ratio of births by plurality in given years compared to the 1989 baseline.

Table 1. Longitudinal trends in multiples in the USA [5]

Year	Twins	Triplets	Quads	Quints+
2011	131,269	5,137	239	41
2009	137,217	5,905	355	80
2006	137,085	6,118	355	67
2003	128,615	7,110	468	85
2001	121,246	6,885	501	85
1996	100,750	5,298	560	81
1989	90,118	2,529	229	40
Increase 1989–2011	45.7%	102.3%	4.36%	2.5%

Quads = Quadruplets; Quints = quintuplets.

Table 2. IVF management: maternal age and transfer values [8]

SART 2009	Maternal age, years		
	<35	35–39	40+
Mean transfer, n	2.1	2.5	3.0
Single embryo transfer, %	7	3	0.5

Louise Brown, the first person to be conceived through in vitro fertilization (IVF), was born in July 1978. In the 35+ years since and with more than 2,000,000 IVF babies born, a demonstrable common side effect of infertility treatments has been a skyrocketing incidence of multiple gestations. In the USA, twins have gone from the preinfertility treatment era background of 1/90 to now nearly 1/30 [4, 5]. A woman seen walking down the street with twins in a stroller has a nearly 70% chance of having achieved that pregnancy with medical assistance.

The incidence of higher-order multiples has somewhat plateaued, but many IVF programs create as many multiples as singletons [4, 5]. For 2009, the United States Society for Assisted Reproductive Technologies reported 32,305 singleton and 13,655 multiple pregnancies producing 60,190 infants. Thus, overall, nearly half the babies born from IVF in the USA are part of multiple pregnancies [5] (table 1).

Examining the trajectory of these multiple births over the last 25 years, however, a somewhat different picture emerges [5–7]. The number of twin births has escalated and stayed relatively constant, but the curves for triplets and above show a curvilinear pattern (fig. 1). The picture is most clear for quadruplets: an initial doubling and then a return to roughly the same number as in 1989 (which as a percentage of eligible women would be even lower). The occurrence of higher-order multiples may be thought of as an unintended consequence of the development of in vivo and in vitro fertilization techniques. Their occurrence then stimulated changes in medical technology and procedures that over time have afforded greater control of the clinical situation – a critical mediating concept in this discussion.

One of the key developments with respect to control of the clinical situation beyond that afforded from simply moving from the use of gonadotropins to IVF has been the development of norms and expectations regarding single-embryo transfer (SET) [5–7]. While SET can have

Table 3. CDC 2010 data

	Age, years	Fresh cycle				Frozen cycle			
		n	trans., n	LB/trans., %	mult., %	n	trans., n	LB/trans., %	mult., %
Nondonor	<35	41,744	2.0	47.6	34.0	12,631	2.0	38.4	?
	35–37	21,369	2.2	38.3	28.7	6,195	1.9	34.7	?
	38–40	21,741	2.6	28.1	23.3	4,682	2.1	28.4	?
	41–42	10,122	3.0	16.7	18.0	1,591	2.2	21.5	?
	43–44	4,501	3.2	7.4	10.2	710	2.2	16.8	?
	45+	1,347	2.7	1.8	(2/14)	432	2.0	13.0	?
Donor		9,866	2.0	55.8	?	6,665	2.0	34.9	?

trans. = Transfers; LB = live birth; mult. = multiples.

many medical advantages, the economics of IVF in the USA make it highly unlikely that SET will ever be predominant in the USA. As an illustration, Society for Assisted Reproductive Technology (SART) guidelines state that under the age of 35 years, only 2 embryos should be transferred. However, according to Centers for Disease Control and Prevention (CDC) and SART data, the average number is actually 2.4 [5–7]. With economic pressures resulting from high costs for every cycle (commonly USD 15,000 or more with variable insurance coverage), everyone – both patient and IVF provider – is under pressure to achieve a very high pregnancy rate with each cycle. This is not likely to change even with any health care 'reform' that may ultimately emerge in the USA. For example, SART data from 2009 show that only 7% of US cases in women under 35 years were SET, and the numbers were much lower in older women (table 2) [5–7].

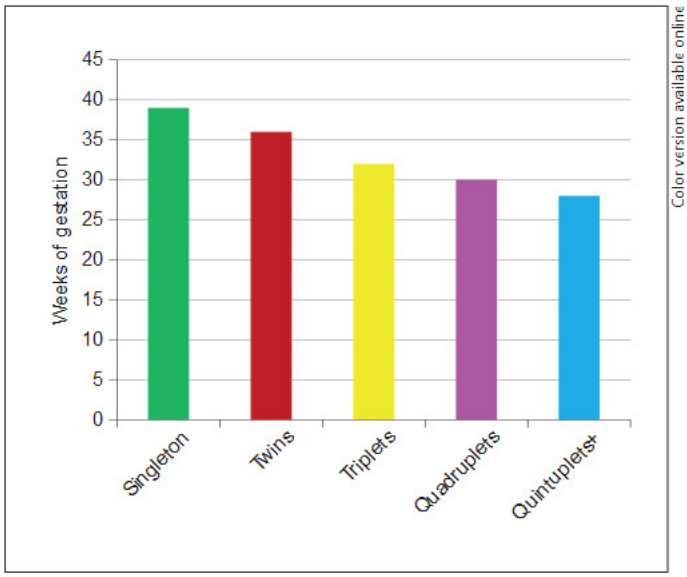
Furthermore, Lawlor and Nelson [8] in 2012 using UK data showed that the highest success rate for live-borns was higher by about 7% by transferring 2 embryos in 1 cycle rather than 1 each for 2 cycles. Regardless, the percentage of live births per transfer clearly diminishes with advancing maternal age – both for fresh and frozen cycles. Thus, being more aggressive in transfers is understandable, but also correlates with increased risks of multiples. Donors tend to be younger, so statistically they resemble the <35-year-old cohort (table 3).

The proportion of very-high-order multiples has diminished because of a shift in management from ovulation induction to IVF in which there is better control of the number of embryos transferred. We have seen that the average 'starting number' of patients presenting for FR procedures has slowly gone down from about 3.5 to now slightly under 3.0 (table 4) [5–8]. It is tempting to provide a simple explanation for the shape of these curves, but we suspect it is a result of tighter management control and the changing demographics of those seeking FR in their effort to improve outcomes.

Table 4. Number of embryos transferred for selected years (nondonor eggs)

Year	Maternal age, years					
	<35	35–37	38–40	41–42	43–44	45+
1998	3.4	3.6	3.7	3.9		
2001	2.8	3.1	3.4	3.7		
2004	2.5	2.7	3.0	3.3		
2007	2.2	2.5	2.8	3.1	3.2	
2010	2.0	2.2	2.6	3.0	3.2	2.7

As the risks have become better known and the general public has become more knowledgeable regarding the possibilities of intervention, there has been a shift toward skepticism. The Dionne quintuplets of the 1930s were treated as a miracle of sorts, met with awe and amazement which continued with other cases for over 60 years. Similarly, 'miracle' status was accorded to other highly publicized cases such as the Frustasci family in the 1980s and McCoys in the 1990s. A sentinel moment in the USA was the public response to the 2009 'Octomom' in California, which shifted public perception from the 'appreciative amazement' of the 1980s to elements of shock and disgust [9]. As a result, transfer of ≥3 embryos significantly diminished, and many intended ovulation induction cases were converted to IVF midcycle if ultrasound or hormone levels suggested a high risk of multiples [9].



Color version available online

Fig. 2. Multiples and prematurity.

Pregnancy loss is not the only deleterious outcome. Decades of data have shown the incidence of prematurity and related sequelae directly correlate with fetal number (fig. 2) [5–8]. However, it has not been well appreciated that about 20% of babies born at <750 g develop cerebral palsy [10]. In Western Australia, Petterson et al. [11] showed that the rate of cerebral palsy was 4.6 times higher for twins than singletons per live births, but 8.3 times higher when calculated per pregnancy. Pharoah and Cooke [12] calculated cerebral palsy rates per 1,000 1st-year survivor at 2.3 for singletons, 12.6 for twins, and 44.8 for triplets [13]. What we have witnessed is a greater sensitivity to these risks among older patients and a corresponding increase in the use of prenatal diagnosis and FR.

There are profound public health implications to prematurity, as US data from 2000 showed that of USD 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 of gestation [14]. In 2003, more than USD 10 billion was spent on the 12.3% born preterm [15]. Data from 2005 show that there is considerably higher neurologic and developmental disability in 6-year-olds who survived birth at 26 weeks of gestation or less [16, 17]. The rates of severe, moderate, and mild disability were 22, 24, and 34% respectively. Significant cerebral palsy was present in 12% [17]. Hack et al. [18] also showed that in babies born at <1,000 g, the rate of cerebral palsy was 14% as opposed to 0% for controls; asthma, poor vision, IQ <85, and poor motor skills were all also substantially higher. Improvements in neonatal care have had more impact on reducing mortality, particularly at early gestational ages with the resultant increase in compromised surviving infants [19]. As these costs escalate, we would expect corresponding changes in insurance coverage and the shaping of practice in IVF clinics, as well as a continued increase in sensitivity to these issues, especially among more at-risk patients.

Historical Approach of FR

FR was developed as a clinical procedure in the 1980s when a small number of clinicians in both the USA and Europe attempted to reduce the usual and high adverse sequelae of multifetal pregnancies by selectively terminating or reducing the number of fetuses to a more manageable number. The first European reports by Dumez and Oury [20], and the first American report by Evans et al. [1], followed by a further report by Berkowitz et al. [21] and later Wapner et al. [22], described a surgical approach to improve the outcome in such cases.

In the mid-1980s, needles were inserted transabdominally and maneuvered into the fetal thorax. Methods have included predominately injection of KCl, but also mechanical disruption of the fetus, air embolization, and electrocautery. Transcervical aspirations were also initially tried, but with little success. Some centers also used transvaginal mechanical disruption or KCl, but data suggested a significantly higher loss rate than with the transabdominal route [23]. Today virtually all experienced operators perform the procedure of inserting needles transabdominally under ultrasound guidance into the thorax, but transabdominal and intracranial injections have been used [24]. Some published and unpublished data have suggested that some centers still continue to use 6- to 8-week transvaginal reduction procedures despite considerably higher loss rates.

As with most surgical experiences, data over time have shown improvements with increasing understanding of the nature of the clinical situation, risks and benefits of any approach, and a feel for how those services should be best presented to patients and carried out by clinicians. A significant early milestone was the collaboration across major centers conducting FRs. Twenty years ago several centers with the world's largest experience began collaborating to leverage their data. In 1993 our first collaborative report showed a 16% pregnancy loss rate through 24 completed weeks of gestation [25]. At the time, such

Table 5. Risks of multiple pregnancies and improvements with FR

Starting, n	Spontaneous loss rates	Finishing, n	Reduction of risk of loss
6+	90–99%	2	90–10%
5	75%	2	50–7%
4	25%	2	25–4%
		1	25–7%
3	15%	2	15–3.5%
		1	15–4%
2	8%	1	8–2.5%

Data are extrapolations of multiple papers. When there are monozygotic twins as part of the multiple, the overall risk is increased as if there were 1 more as the starting number.

numbers represented a major improvement for higher-order multiple pregnancies. Further collaborative papers continued to show dramatic improvements in the overall outcomes of such pregnancies (table 5). In the 1980s the first question asked was, 'At how many fetuses is it reasonable to offer FR?' The answer generally varied between triplets and quadruplets, and there were wide differences in perceptions of risks by specialty and religious beliefs [26]. Multiple papers in the 1990s then demonstrated that with triplets or more, there was clear improvement in reducing to twins. Numerous papers argued whether triplets had better outcomes 'reduced' or not. Yaron et al. [27] compared triplets →twins data to unreduced triplets with two large cohorts of twins. The data show substantial improvement of reduced twins as compared to triplets. The data from the 2001 collaborative series and others suggested that pregnancy outcomes for cases starting at triplets or even quadruplets reduced to twins at about 12 weeks of gestation do fundamentally as well as starting as twins. Antsaklis et al. [28] showed a reduction of losses from 15.41 to 4.76% for twins and diminishment of low birth weight from 28 to 11%.

These data supported some cautious aggressiveness in infertility treatments to achieve pregnancy in difficult clinical situations. However, when higher numbers occurred, good outcomes clearly diminished. Luke et al. [29] suggested in twin pregnancies with assisted reproduction that FR increased the risks for birth at <30 weeks of gestation, very low birth weight, and slowed midgestational growth. This analysis, however, ignored the starting conditions (i.e. as compared to keeping the quadruplets, how did they do?). Kozinsky et al. [30] showed that the perinatal outcomes of singleton and twin pregnancies following assisted reproductive technologies were comparable to spontaneously conceived, matched pregnancies. McDonald et al. [31] showed in a meta-analysis that twins from IVF, even when matched to spontaneously conceived twins, had a somewhat higher risk for preterm birth, but no significant differences in perinatal deaths, congenital malformations, or low birth weight. Several other papers over the last decade have likewise shown higher risks for 'unreduced' triplets than for reduced cases [32–35]. It is clear that one must use extreme caution in choosing comparison groups. Blickstein [36] reported that triplets did worse than reduced twins in every perinatal category in his large database.

Data from a 2001 collaborative study using late first-trimester procedures likewise clearly demonstrated that the outcome of triplets reduced to twins, and quadruplets reduced to twins, performed essentially as if they started as twins [37]. Not only was the pregnancy loss rate substantially lowered, but so was the rate of very early prematurity. Both continued to be correlated with the starting number and finishing number. More recent data have shown continued improvements in management and overall outcomes in the hands of experienced centers (table 5).

Increasing experience and changes in infertility management have also led to new situations. With changes in IVF laboratory techniques and increasing use of blastocyst transfers, the number and proportion of monozygotic twins has increased significantly in the last decade [7, 9, 38]. Approximately 7% of our triplets+ cases include a monochorionic-diamniotic twin pair [38]. Our experience shows that, provided the 'singleton' seems healthy [by chorionic villus sampling (CVS) and ultrasound], the best outcomes are achieved by reduction of the monozygotic twins. Obviously, if the singleton does not appear healthy, then keeping the twins is the next choice although not every center has shown comparable improved outcomes [39].

In the 2001 collaborative report, the subset of patients who reduced from 2 →1 suggested a loss rate comparable to 3 →2, but in about a third of the 2 →1 cases, there was a further complicating medical indication for the procedure, e.g. maternal cardiac disease, prior twin pregnancy with severe prematurity, or uterine abnormality, thereby raising the overall risks [36]. In recent years, however, the demographics have changed, and the vast majority of such cases are medically less complicated, but often come from women in their 40s, or even their 50s, some who of whom are using donor eggs. Many of these women, for both medical and social reasons, only want a singleton

pregnancy [40–42]. Our data suggest that twins reduced to a singleton do better than remaining as twins [40, 41]. Consistent with the above, more women desire to reduce to a singleton. In a series of triplets from the late 1990s, we found the average age of outpatients reducing to twins to be 37 years and to a singleton 41 years [27]. While the reduction in pregnancy loss risk for 3 →1 was in the 1990s not as much as 3 →2 (15 to 7% and 15 to 5%, respectively), the gestational age at delivery for the resulting singleton was higher, and the incidence of births <1,500 g was 10 times higher for twins than singletons. More recent data show the age difference between those reducing to twins and those to a singleton have disappeared as reducing to a singleton has become more mainstream [38]. 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, or even as to the total number wanted, which sometimes is more than 2 for one member of the couple [42]. As a result of all of the above and the changing demographics of who is having infertility and desiring reductions, we believe that reduction of twins to a singleton is reasonable and will continue to increase.

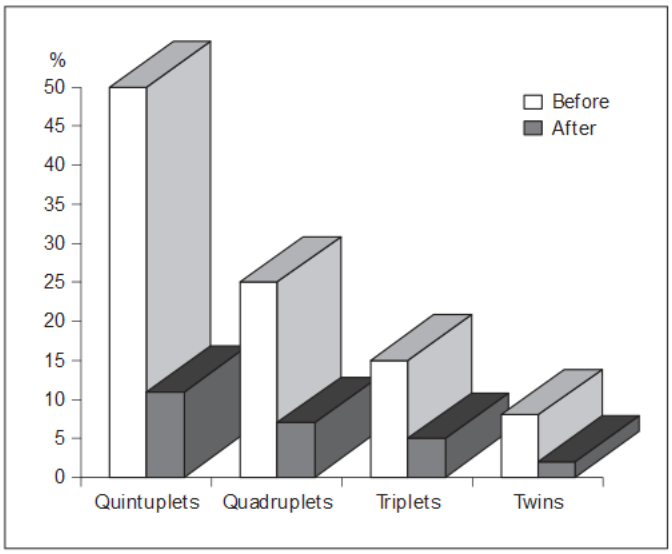


Fig. 3. Risk reduction: reduction of pregnancy loss with FR.

Changing Perspectives

Over the last 25 years we have witnessed changes in both outcomes and issues. Outcomes have steadily improved over the past two 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, and use of CVS reduces the risk of leaving behind sonographically or chromosomally abnormal fetuses, and (4) a cadre of extremely experienced physicians does a significant proportion of the cases (table 5) [40–44] (table 4, fig. 3).

There has also been a shift in the nature of the clinical dialog between patients and physicians over the last 25 years. The most obvious change has been the shift from questions of mortality to questions of morbidity. This appears traceable to an age increase among patients going through fertility treatment and a decrease in presenting numbers [45, 46]. These differences in turn appear to be changing due to advances in IVF technology and fundamental demographic changes in the age at which mothers are having their first child [4–6]. A further consequence of these trends has been the increased use of donor eggs and prenatal diagnosis [45, 46]. As we have indicated in a couple of more specific pieces, these changes are made visible through the clinical multifetal reduction situation as it itself has evolved from a clean-up operation for desperate situations to a pregnancy management strategy.

Overall, statistics on reductions have improved noticeably over these past 25 years [38, 45, 46]. In the early 1990s when half of the cases were quadruplets or more, loss rates (up to 24 weeks of gestation) were 13%. Early premature deliveries were an additional 10%. Now, with decreasing starting numbers, better ultrasound, better understanding of zygosity, and a limited number of practitioners with extensive experience accounting for a high percentage of reductions, they are overall down to about 4%. Counseling should be tailored to specific starting and finishing numbers (table 5; fig. 3). We still do most FR procedures in one session, but have learned that when reducing from higher orders (5+) to a singleton, it seems best to break it up into two sessions separated by about a week.

Over the past decade, the pattern of patients seeking FR has continued to evolve in response to predictable demographic and cultural shifts [4, 5]. There has been a strong trend of increasing age at which women give birth to their first child (fig. 4) – a trend that is common throughout the developed world. The increase is actually a function of two parallel but independent trends: fewer lower and middle class teenagers delivering (and having terminations), and more career women postponing child bearing for career reasons from their 20s to their 30s and

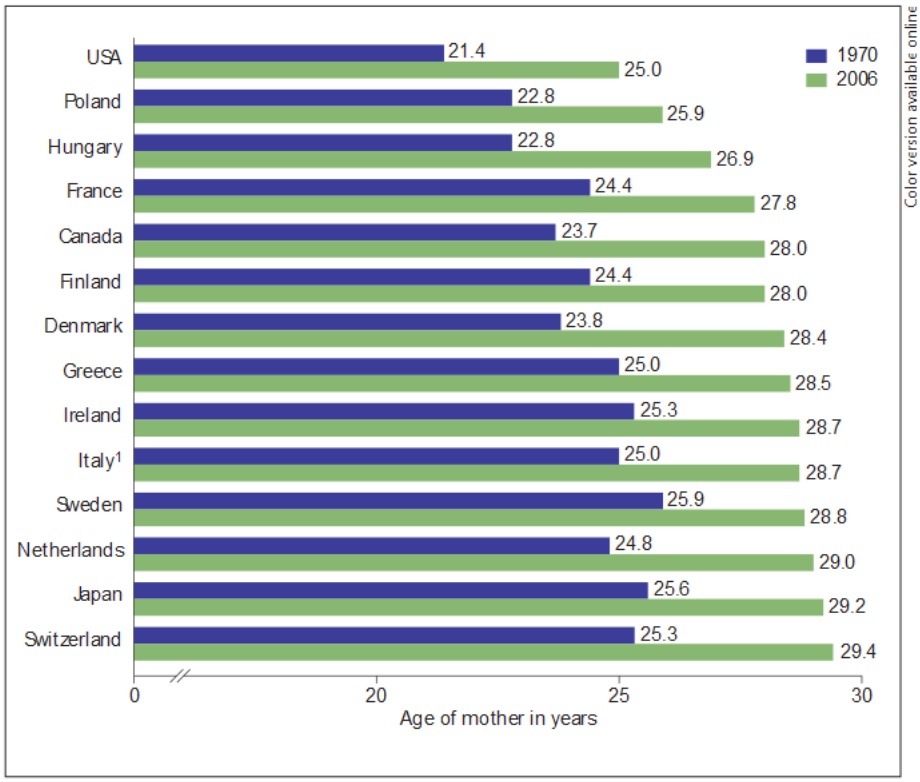


Fig. 4. Average age of the mother at first birth: selected countries, 1970 and 2006. [1] Latest data are for 2005. Sources: CDC/NCHS, National Vital Statistics System, Council of Europe, Vienna Institute of Demography, Statistics Canada, and Japanese Ministry of Health, Labour and Welfare.

40s. The latter is, of course, the group that mostly applies to our discussion here [5]. As the risks of delayed childbearing have become more widely known [16, 46], there has been a corresponding increase in the demand for donor eggs as a means of moderating the risks for older women [45].

With the rapid expansion of the availability of donor eggs, and the increasing sensitivity and specificity of diagnostic testing, the number of 'older women' seeking FR has increased dramatically. In our experience, over 10% of all patients we see seeking FR are now over 40 years of age, and nearly half of them are using donor eggs [38]. It would appear that as advances in care have developed of achieving pregnancies and ways of moderating the risk of older women who wish to have children, more of them are electing to do so.

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 2 →1 reductions is still very limited, but we believe based upon improvement of outcomes, that it can be justified in most circumstances. Twins currently constitute about 25% of the patients we see [38].

For patients who are 'older', particularly those using their own eggs, the issue of genetic diagnosis has become progressively more salient. In 2009, about 60% of patients in the USA having assisted reproductive technology cycles were over 35 years of age. Using the criteria of comparable risk to that of a 35-year-old, actually about 90% of IVF patients are at increased risk [1] (table 6).

For the past decades and currently, most FR practitioners made their decisions as to which fetuses to keep or reduce by ultrasound evaluation only. In the 1980s we performed most of our procedures between 9 and 10 weeks of gestation with decisions based principally on basic ultrasound and fetal position [1]. For those patients for whom genetic assessment was appropriate, we initially had them undergo amniocentesis several weeks later back at their home center [47]. We eventually changed to doing CVS a week after reduction to twins and then to doing CVS the day before with fluorescent in situ hybridization (FISH) analysis overnight. In the mid-1990s we began to have a small but increasing percentage of patients reducing to a singleton; it therefore seemed prudent to know what we were keeping before committing to it. However, waiting for a full karyotype was problematic for both the time interval to get results, and the fact that others reported a 1%

Fig. 5. Transcervical CVS on triplet. Catheter with stylet in place seen as a white line traversing lower placenta.

Table 6. Genetic risk factors in IVF patients

Factor	Risk	% of IVF
AMA	>0.5%	60
Twins+	age 30×2 = 35	34
ICSI	1%	66
PGD	1% error	4

AMA = Advanced maternal age; ICSI = intracytoplasmic sperm injection.

mistake rate as to which was which under these circumstances [48, 49]. As FISH technology became reliable, we began routinely to do procedures on 2 consecutive days [44, 45]. Over the last 20 years, the proportion of patients having CVS before FR has steadily risen from about 20% in 2000 to now about 85% of our patients [38].

While there have been many papers on the true risks of prenatal diagnosis with widely diverging statistics [50], we believe that in multiples, the net effect in the most experienced hands is zero sum since whatever risks there are of the diagnostic procedures are counterbalanced by the reduction of risk of loss by not inadvertently continuing a fetus with a serious problem that is more likely to have a spontaneous loss than a healthy one [38].

Another distinct cohort of patients are those who consider reduction procedures for a diagnosed abnormality in one fetus of a multiple pregnancy as opposed to the risks inherent with multiples [43, 44]. There has been a consensus in the literature to use FR for cases done – predominately in the first trimester – for fetal number, and to use selective termination (ST) for those cases done – often in the second trimester – for a diagnosed anomaly. Occasionally, diagnosed abnormalities are found initially even in the third trimester, which poses medical, ethical, and legal issues [51]. We and others have likewise published large series over the past decades that have delineated the similarities and differences when there is a confirmed abnormality [52, 53]. Much of this literature focuses on twins – many of which have twin-to-twin transfusion syndrome in which laser therapy has become the mainstay of therapy, but selective termination is still sometimes necessary [54]. A complete discussion of these issues is beyond the scope of this paper.

Modern Management

We believe that optimally there should be a rigorous evaluation of fetal status as part of the decision process prior to reduction, which includes more than just nuchal translucency ultrasound and position of the fetuses. Typically, we perform a 2-day procedure on most patients at about 12 weeks of gestation: CVS on the first day with FISH analyses overnight for chromosomes 13, 18, 21, X, and Y [38] (fig. 5). We get the results back the next afternoon, and can then do the reduction that day. By definition, FISH for 5 chromosomes cannot detect everything, but our experience and modeling suggest only about a 1/400 residual risk of a problem on karyotype [38] – 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 with potential confusion as to which embryo/fetus was which on the ultrasound [48, 49].

Over the past few years, about 85% of our patients have combined CVS and FR 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, and (3) the known 3–6% inaccuracy rate of preimplantation genetic diagnosis (PGD), we expect the utilization of CVS prior to reduction will likely increase even further [38, 44, 45]. We have also found that many couples in their 40s or even 50s who are using donor eggs – whose genetic risk is the age of the egg donor – nevertheless still want CVS prior to FR because their 'tolerance' for having a special needs child is more akin to their actual ages, not the egg donor's age.

Our recent data show that our protocol of CVS followed by overnight FISH analysis with FR the second afternoon significantly improves the outcomes in such cases. We recently published that in pregnancies with ultrasonographically normal fetuses, 3.1% of women with

normal-appearing fetuses prior to first-trimester FR had a fetus with an abnormal karyotype of which FISH detected 90% [38]. Of the remaining 10%, virtually all were confined placental mosaicisms for other chromosomes or culture artifacts. Of 350 patients with normal-appearing first-trimester fetuses, 6% had abnormal CVS on either karyotype or FISH. Those abnormal FISH and ultrasound results guided decisions at the time of the reduction procedure. Ultimately, 90% of those abnormal FISH results were confirmed on final karyotype. Of false negatives, most were for chromosomes for which FISH probes were not used, and most of them were actually confined placental mosaicisms. Ultimately, only 1 of the 350 cases (0.3%) had a clinically relevant false negative (sex chromosome mosaicism). On balance, we believe that the risk of a false negative is lower than the risks entailed in waiting between procedures, which increases loss rates because of the higher fetal number and the risk of making a mistake as to which fetus is which when returning for the FR procedure.

While it has worked best for us to use FISH for rapid diagnoses, other methods have been and will become feasible over the next few years. Inexpensive methods included direct preparation CVS which was used commonly in the 1980s, but largely abandoned because of high rates of mosaicism and aneuploidies that were not reflective of fetal status [55]. Quantitative fluorescent PCR can also be used for rapid preparation evaluation of chromosome number [56]. Microarrays can provide even more detail than whole chromosomes, but currently are far more expensive. As they come down in price and turn around speed increases, molecular subchromosomal techniques will clearly move into the mainstream of evaluation [57].

With increasing use of PGD as part of the IVF process, many patients question if traditional CVS still has application in reduction decisions [58]. Our experience has been that over the past 5 years, there has been about a 2–3% discordancy between PGD results and those we have seen on CVS – with chromosomal being higher than mendelian [38]. With new PGD microarray-like methods being incorporated, the discordancy rate is likely to decline. We speculate that ultimately the rate will be about 1%. Likewise, the same questions arise with the advent of noninvasive prenatal screening (NIPS) techniques [59]. Our perspective is that both PGD and NIPS are excellent screening tests, but they are not diagnostic, and we have observed a number of instances in which errors have occurred resulting in babies born with conditions for which screening was performed. Also in multiples, NIPS and PGD cannot distinguish which fetus is which such that if an anomaly is detected, diagnostic techniques will still be required.

An increasingly common scenario is the combination of monozygotic twins combined with one or more singletons [60]. Changes in IVF culture techniques, including increasing use of blastocyst transfers, have significantly increased the incidence of monozygotic twinning. Our data suggest that dichorionic and triamniotic triplets, for example, have far higher rates of pregnancy loss, twin-to-twin transfusion syndrome, and complications of prematurity [61].

In the vast majority of cases, the major risk factor in determining which fetuses to keep or reduce is a chromosomal risk. However, the same principles can be applied to mendelian risks. For example, we evaluated a couple with triplets who were both cystic fibrosis carriers. Using appropriate probes, we were able to determine that 2 of the fetuses were carriers, and 1 was affected, which was subsequently reduced.

As part of the FISH results, we also obtain gender. Historically, we perceived a significant bias among those patients who were interested and who mostly expressed a preference for males [42, 43]. These requests disproportionately came from patients of cultures that classically valued boys over girls. Because of such bias, we refused to let gender be a factor with the rare exception of genetic diseases with gender discordancy. Ironically, in X-linked disorders, it is the males at risk, making females the safer option. Over the past 15 years, however, we noticed a shift to requests coming from all ethnic groups and a perceived equalization of gender preferences. In the early 2000s, our ethics consultant, John Fletcher, PhD, pushed us to re-evaluate, and we began to be willing to consider under the following approach.

Overall, decisions about which fetuses to keep or reduce have evolved over the years from a relatively simplistic ultrasound assessment of abnormalities and position to a detailed evaluation of fetal status.

We prioritize FR decisions by:

(1) Do we find a 'problem'.

(2) Are we 'suspicious' about anything such as somewhat increased nuchal translucency (>2 mm), smaller fetal size (such as >0.5 week, smaller gestational sac size, or placental concern).

(3) If none of the above apply, then and only then, we will consider gender preference.

Patients are told that we will have a nongender disclosing 'poker-faced' discussion with them when we get the results. They will then choose which of 4 categories concerning gender they prefer. The groups are (1) patients who want to know 'everything', (2) those who want to know 'nothing', (3) those who have no preference but

Table 7. Fetal gender options and patient choices in FR

	Gender option	Chose all M	Chose all F	Chose MF twins	p
3 → 2	79 (51)	1 (1)	7 (9)	71 (90)	<0.001
3 → 1	20 (25)	10 (50)	10 (50)	NA	NS
2 → 1	44 (27)	20 (45)	24 (55)	NA	NS

Values represent n (%). NA = Not applicable; NS = not significant.

want to know what they have kept (but not the reduced), and (4) those who, all things considered, do have a preference (but do not want to know the reduced fetus' or fetuses' genders) [62].

Recently, we published data that show such requests now come from patients of all ethnic backgrounds and cultures [62]. When patients do have a gender preference, there is an equal preference for females as males. For patients reducing to twins, the overwhelming preference is for one of each; for those reducing to a singleton, it is essentially a 50/50 split (table 7) [62].

We have also recently been able to use our technology to extend services to a group of patients not previously well served. In the past few years, we have seen several gay male couples using surrogate carriers with egg donation when both partners fertilized the eggs. The couples desired FR for the usual clinical reasons, but they requested if possible to be left with twins – one fathered by each of them. We chose to consider this request in the same vein as gender preference, i.e. only if there are no higher clinical priorities. In several cases we have been able to assess the pregnancies with CVS and ultrasound, document normal genetic results, perform paternity testing, and discover that one man fathered two and the other one. In such cases we then reduced one of the twins fathered by the same man [63].

Ethical Issues

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. 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. [64]. Only moral compromise in policy and practice can 'split the differences' between such diverse interpretations [65].

When such conflicts arise in reproductive choices, our society does not generally interfere in parents' consultations with obstetricians, geneticists, or moral advisors which, however, has not stopped politicians from passing laws that seriously infringe upon the doctor-patient relationships particularly in regard to reproductive choice issues. Certainly, the right to privacy, as originally interpreted by Roe vs. Wade [66], is not absolute and has been scaled back several times in the 40 years since the US Supreme Court decision. The 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.

Compromise is often the right path because all moral judgments are fallible and their contours change as circumstances change. However, well-considered predictions of consequences are limited by the 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 and reductions more generally for individuals, families, and society, but we can see in retrospect how some of the issues have changed over time.

Improved outcomes, coupled with the ever-increasing use of assisted reproductive technology, have led to an evolution in the ethical questions being considered. Nearly 30 years ago, FR seemed warranted only in 'life and death' situations. As has been seen in numerous innovative technologies, once concepts are proven, the focus can shift from 'life and death' to 'quality of life'. Such has been the case here, but because of the context of the abortion debate, FR will always be controversial. Opinions on FR, in our experience, have never followed the classic 'pro-choice/pro-life' dichotomy [26, 44, 45].

It is almost impossible to separate ethical debates from the situation in which they occur – especially the presenting number of embryos with which patients enter an FR clinic. Those presenting with quadruplets and quintuplets have declined dramatically. The focus of care con-

tinues to be on fertilization strategies that offer more control over the chances of such high multiples.

Triplets are still plentiful. Even with the improved embryo-transfer control, the economics of IVF favor a modest risk of multiples, especially among women with fewer resources (for whom the cost of IVF cycles is a real consideration) and those who are over 35 years of age (where the chances of larger transfer numbers reflect greater difficulty in getting pregnant). The serious debate is no longer about whether it is appropriate to offer FR to triplets, but now centers on the question about whether or not it is appropriate to offer FR routinely for twins [41].

Our data show that reduction of twins to a singleton improves the outcome of the remaining fetus [43–45]. Despite the data, because of the sharp ethical divide over women's reproductive rights, no consensus on appropriateness of routine 2 → 1 reduction is ever likely to emerge. We expect that overall the number of women with twins reducing to a singleton will stay small. However, the proportion of patients reducing will steadily increase over the next several years, and we believe this option should be presented to all patients.

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 approximately 1/700, twins 1/100, and triplets 1/25–30 [11–13]. If one's definition of success is a healthy mother and healthy family, for both morbidity and mortality, the data show conclusively with multiples, fewer is always better.

Not surprisingly there are often differences between members of the couple as to the desirability of twins or singleton [43]. As a result of all of the above and the changing demographics of who is having infertility and desiring reductions, we believe that reduction of twins to a singleton is likely to continue increasing over the next several years. In our own personal experience the proportion is now 25% and may get to 50% [38]. 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 1 rather than 2 infants? This so-called 'negative right', i.e. to noninterference, differs from a 'positive right' to society's encouragement and aid in the action [67].

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.

We have previously developed the concept of 'frames' which are lenses through which patients incorporate and interpret information [68]. For this group, however, the escalation of mortality and morbidity risks is so pronounced that even those patients who rely on a 'conceptional frame' (a frame that defines the beginning of life as conception rather than viability) will follow a proportionality rule in which they try to balance the escalating risks and the problematics of reduction by reducing only to 3. Those having a 'medical frame' [one that focuses on maximizing the chances of having a successful birth(s)] or a lifestyle frame (one that emphasizes the balancing of career and family interests), the reduction to 2 or 1 is less challenging. With advances in technology, utilization is expanding to groups such as gay and lesbian couples who previously often could not take advantage of them.

Thus, we view framing as an ongoing process in society with highly different perceptions of reality being emphasized by different couples. All are trying to overcome the difficulties of having children and live some semblance of a normal family life. The concept of 'family' is not limited to heterosexual couples, but 'normal' is an attribution that might not be forthcoming in some conservative communities. We see evidence of these trends in how couples share what they have been going through after having chosen FR as a pregnancy management strategy and in the increasing frequency with which same-sex couples who have gone through (or had a surrogate go through) fertility therapy and end up choosing FR as a pregnancy management strategy.

We have studied sharing strategies among FR patients and delineated four sharing strategies that vary in how selectively they shared information [69]. Strategies for sharing range in terms of selectivity from a 'defended-relationship' approach in which only the partner and patient know about the problems the patient is facing and the decision to reduce, to 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 [68, 69].

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. In our experience, it appears that less selective, more open strategies are more prevalent in cosmopolitan environments, with more guarded strategies typical of more conservative environments. As our population shifts toward cities, one might expect an increasing proportion of open strategies across time.

Legal Issues

Legal concerns about IVF have been raised for over 30 years, including a paper we wrote in 1981 predicting the range of problems likely (almost all of which eventually occurred), e.g. such as the problems with surrogate mothers [70]. In contrast, while there has been extensive litigation – both civil and criminal – concerning abortion and restrictions imposed on its use, there has been a paucity of direct legal cases involving the legality of FR. Most US jurisdictions have been silent on the subject, although Michigan, for example, specifically required the same 24-hour waiting period between counseling and the procedure as it applied to abortions. There have been some malpractice litigation cases, but these have followed the expected scenarios such as reduction of the wrong fetus in situations with anomalies, alleged failures of informed consent as to procedure risks, and for various poor outcomes.

Even though there are distinct differences, most practitioners of fetal reductions have followed the guidelines applying to abortions, e.g. performing the procedures only at gestational ages that would be permissible for abortion, and following legally mandated informed consent procedures for abortion.

Summary

Over the past 25+ years, data from around the globe have shown that pregnancy outcomes are vastly improved by reducing the number of fetuses in multiples. All but the most conservative of commentators have long since accepted the efficacy or reduction of triplets or more. Medical data now show that reduction of twins to a singleton improves outcomes. The issue then shifts to an ethical one that will never be universally accepted, but we argue that from an autonomy and public health perspective, FR needs to be seen as a necessary but hopefully increasingly rare procedure.

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