Efficacy of Transabdominal Multifetal Pregnancy Reduction: Collaborative Experience Among the World's Largest Centers

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Objective: **To evaluate the safety and efficacy of transabdominal multifetal pregnancy reduction (MFPR) in the management of iatrogenic and spontaneous multifetal pregnancies.**

Methods: **Data were combined from 463 completed pregnancies that underwent MFPR at major worldwide centers.**

Results: **Multifetal pregnancy reduction was performed with a 100% technical success rate (there were no failed procedures); 83.8% had delivery of potentially viable fetuses (defined as 24 weeks' gestation or later), and 83.5% of these viable pregnancies delivered at 33 weeks or later. The risk of fetal loss was 3.9% at 2 weeks or less post-procedure, 4.6% at 4 weeks or less, and 16.2% at less than 24 weeks of gestation. Gestational age at delivery varied principally with the number of fetuses remaining, with 7.1% delivering prematurely at less than 28 weeks, and 9.4% at 29–32 weeks. The incidence of obstetric and medical complications appeared to be unaffected, and there was no increase in congenital malformations.**

Conclusions: **Multifetal pregnancy reduction is an efficient and safe way of improving outcome in multifetal pregnancies, unambiguously for quadruplets or more, and arguably for triplets. However, particularly at higher starting numbers, there are still suboptimal outcomes. We cannot answer the question of whether MFPR should be offered to women with triplets or twins. The only major risk appears to be fetal loss per se, and because the procedure itself does not damage the survivors, parental autonomy should be given a higher priority in the decision process than previously. However, to obviate the need for this procedure, infertility specialists must continue to be vigilant in the use of fertility drugs.** *(Obstet Gynecol 1993;82:61–6)*

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During the last decade, the widespread introduction of assisted reproduction techniques has been accompanied by a dramatic increase in multifetal pregnancies.[1] Although occasional case reports have focused on the successful outcome of some multifetal pregnancies, such as the Dionne quintuplets in the 1930s, the perinatal outcome of multifetal pregnancies is generally poor.[2–4] To improve the outcome of such pregnancies, several techniques have evolved to reduce the number of fetuses.[5–13] The most widely accepted technique is first-trimester intrathoracic injection of KCl under ultrasound guidance.[6–13] Initial publications on multifetal pregnancy reduction (MFPR) have stressed the inadequate data base concerning risks and benefits of the procedure.[5–8] The purpose of this report was to examine the safety and efficacy of MFPR by combining data from several of the world's centers that have among them considerable experience with the procedure.

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Materials and Methods

A total of 463 consecutive, completed pregnancies having MFPR between 1986–1991 were analyzed from several centers (collaborative French group, 139; Wayne State University, 78; Mt. Sinai Medical School, 85; Jefferson Medical College, 57; University of California, San Francisco, 70; and Kings College Hospital, London, 34). In nearly 100% of all cases of triplets or more, the pregnancies were the result of infertility treatment. In all cases, MFPR was performed by transabdominal needle injection of KCl into the fetal thorax under ultrasound guidance, with a 100% technical success rate (ie, there were no failed procedures). Data recorded included starting and finishing numbers of fetuses, gestational age at procedure, gestational age at delivery or pregnancy loss, obstetric complications, and congenital malformations. Procedural data were collected by each center. Outcome data were obtained by each center from either the patient or referring physician, generally by telephone. There was no systematic examination of neonates or detailed dysmorphology assessment, which may be in part responsible for the low rate of congenital abnormalities reported. There were no major differences in the approaches of the various centers, except that most of the cases reduced to singletons came from two of the centers. For most centers, reduction to a singleton required a belief that a twin pregnancy had a high-risk status.

For the purpose of clarity, "pregnancy loss" was defined as the end of the entire gestation, ie, all fetuses. "Fetal loss" was defined as the death of a particular fetus, with continuation of other fetuses at the same time. Pregnancy losses were categorized as 2 weeks or less post-procedure and 4 weeks or less post-procedure, as more possibly representing procedure-related losses. Late complete pregnancy losses, at more than 4 weeks after the procedure but before 24 weeks, were considered more likely to be background and not procedure-related. A pregnancy was considered potentially viable after 24 weeks.

Data were analyzed by stepwise multiple regression, discriminant function analysis, and χ^2 as appropriate.

Table 1. Distribution of Multifetal Pregnancy Reduction Cases

Finishing no.	Starting no. 9	8	7	6	5	4	3	2	Total
3	0	1	2	3	7	13	0	0	26
2	1	2	5	10	43	170	149	0	380
1	0	0	0	1	2	10	26	18	57
Total	1	3	7	14	52	193	175	18	463

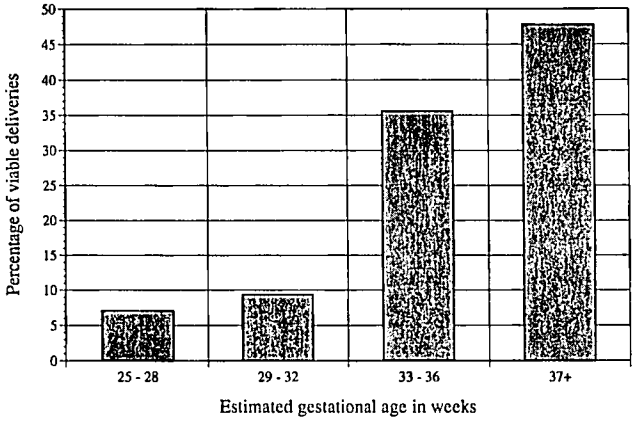

Figure 1. Gestational age at delivery of viable pregnancies (N = 388). Of the total, 7.1% were between 25–28 weeks and 9.4% were between 29–32 weeks.

Results

Table 1 presents the numbers of fetuses before and after MFPR. The mean (± standard deviation [SD]) gestational age at the procedure was 10.8 ± 2.0 weeks. Multifetal pregnancy reduction to the intended number was accomplished in all cases. In the vast majority of cases, there was one needle insertion per embryo, with injection of about 1 mL of KCl per embryo.

Forty-nine of the 463 completed pregnancies (10.5%) were lost at or before 20 weeks' gestation. An additional 26 patients delivered between 21–24 completed weeks, for a pre-viable percentage of 16.2%. Three hundred eighty-eight of the 463 gestations (83.8%) delivered after 24 weeks, and were therefore potentially viable. One of the principle justifications of MFPR remains prevention of early prematurity; the statistics on such demonstrated that 28 of 393 fetuses delivered between 25–28 weeks, and 37 of 393 delivered between 29–32 weeks (7.1 and 9.4%, respectively). Thus, 83.5% of the patients with viable pregnancies delivered at 33 weeks' gestation or later (Figure 1).

Of the 57 pregnancies reduced to singletons, 43 infants were live-born at 25 weeks or later and 14 had a spontaneous abortion at less than 24 completed weeks. Of the 380 pregnancies reduced to twins, 328 were live-born and 52 were lost, and of the 26 reduced to triplets, 19 were live-born and seven were lost. Figure 2 illustrates the gestational age distribution of the losses. There was no correlation between the starting number and the rate of losses at 4 weeks or less or at greater than 4 weeks (χ^2 = not significant). The overall loss rates are related to both the starting number and the finishing number. Using the total loss rate at 24 weeks or less, our data suggest that total loss rates of pregnancy were lower when triplets were

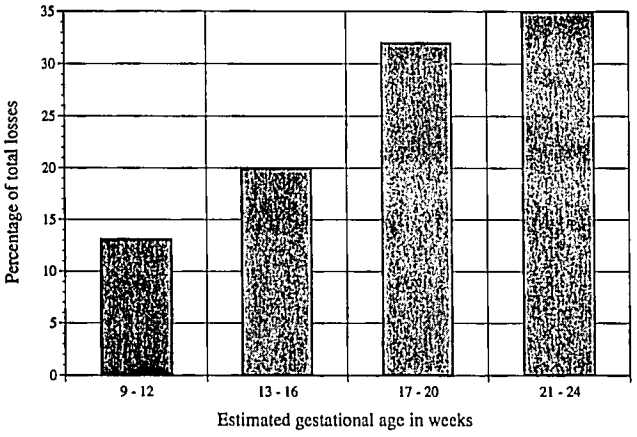

Figure 2. Histogram detailing gestational ages at pregnancy loss ($N = 75$).

reduced to twins than when triplets were reduced to singletons ($\chi^2 = 7.1$, $P < .01$) (Table 2). However, this may reflect the fact that several centers in this study performed MFPR to singletons only for medical indications, eg, septate uterus, unicornuate uterus, prior history of preterm delivery, medical contraindication, etc.

Analysis of pregnancies that were lost at 24 weeks or earlier demonstrated that 12 of the 75 losses occurred within 1 week of the procedure. Using all losses, plus viable pregnancies as the denominator, the loss rates at 1, 2, and 4 weeks were 3.0% ($n = 12$), 3.9% ($n = 16$), and 4.6% ($n = 19$), respectively. Pregnancy losses at 4 or more weeks from the procedure but at 24 weeks' gestation or earlier equaled 56 of 463 or 12.1%, which is believed to be comparable to background expectations for spontaneous loss in twin pregnancies ascertained in the first trimester.

The most accurate data on pre-viable pregnancy losses come from the In Vitro Fertilization-Embryo Transfer Registry of the American Fertility Society.[1] We believe that this Registry provides the best comparison data because almost 100% of our patients had pregnancies secondary to infertility treatment, for which group early-pregnancy detection is universal. As such, the parallels of assisted reproduction and early detection allow the most straightforward comparisons. The American Fertility Society study showed a 22% spontaneous abortion rate following clinical pregnancies.[1] The overall 16.2% loss rate before 24 weeks compares favorably to the Registry data. Evaluation of 2- and 4-week losses as a function of starting number showed a marked increase in risk beginning at quintuplets and increasing with higher numbers. Late losses were excluded from the denominator to be most conservative (Table 3). Analysis of 2- and 4-week losses by gestational age at the time of the procedure revealed no dramatic variation. Increases seen at 6–7 and 13–14 weeks had too few cases to be reliable (Table 4).

There were no major variations in the approaches of the centers, and there was no variation in the gestational age at which the procedure was performed. Specific comparison of gestational age at delivery by finishing number demonstrated a relationship between finishing number and gestational age ($\chi^2 = 15.7$, $P < .02$) (Table 5). Analogously, there was an association between the starting number of fetuses and gestational age at delivery; however, these data were confounded by a parallel increase in the finishing number in such cases. Forty-three pregnancies with a mean starting number of 2.9 were reduced to singletons with a mean gestational age at delivery of 37.1 weeks. Three hundred twenty-eight pregnancies were reduced to twins with a mean starting number of 3.8 and a mean gestational age at delivery of 35.6 weeks. Nineteen pregnancies were reduced to triplets with a mean starting number of 4.8 and a mean gestational age at delivery of 33.3 weeks. Evaluation of fetuses reduced to twins by the week of the procedure showed no significant variation between weeks 8 and 12 in terms of gestational age at delivery. However, there was a markedly decreased gestational age at delivery for those relatively few procedures performed at weeks 13 or 14 (Table 6).

Congenital anomalies were recorded in four of the 463 fetuses, including one with Potter syndrome, one with anencephaly, one with hydrocephaly, and one with a digital anomaly. Fetal growth retardation was seen concordantly in two sets of twins and discordantly in ten sets, of whom one died in utero. There was one abruption at 34 weeks; three mothers developed preeclampsia, and one manifested thrombocytopenia. There were 35 losses of one of the remaining fetuses, with successful delivery of the other. In all

Table 2. Loss of Pregnancy at 24 Weeks or Earlier by Finishing Number

	Starting no.				
Finishing no.	2	3	4	5+	Total
Singletons					
Losses	3	6	3	2	14
Total	18	26	10	3	57
Percentage	16.7%	23.0%	30.0%	66.7%	24.6%
Twins					
Losses		10	26	18	54
Total		149	170	61	380
Percentage		6.7%	15.3%	29.5%	13.7%
Triplets					
Losses			2	5	7
Total			13	13	26
Percentage			15.4%	38.5%	26.9%

Table 3. 2- and 4-Week Post-Procedure Losses as a Function of Starting Number

	Starting no.						
	2	3	4	5	6	7+	Significance
Losses (≤2 wk)	1	4	4	3	3	1	$\chi^2 = 18.8$, $P < .01$
Loss rate (%)	6.3	2.5	2.4	7.5	25.0	10	
Losses (≤4 wk)	1	8	5	7	3	1	$\chi^2 = 18.9$, $P < .01$
Loss rate (%)	6.3	4.8	3.0	15.9	25.0	10	
Late losses	2	11	28	9	5	4	$\chi^2 = 16.3$, $P < .01$
Loss rate (%)	11.8	6.5	15.4	19.6	35.7	30.8	
Viable (≥25 wk)	15	159	164	37	9	9	
Viable rate (%)	83.3	89.3	83.2	69.8	52.9	64.3	$\chi^2 = 19.3$, $P < .01$

pregnancies in which the finishing number equaled the number at delivery, the gestational age at delivery was 33.1 weeks. However, among those cases involving subsequent loss of one or more fetuses, the gestational age at delivery was only 29.7 weeks.

Discussion

The data from this multicenter study demonstrate that in these centers with experience in MFPR, the procedure can be performed with essentially a 100% success rate. The overall fetal loss rate before 24 weeks' gestation was 16.2%, and the rate of premature deliveries at 32 weeks or earlier was 16.5%.

Overall assessment of perinatal morbidity and mortality suggests a fetal loss rate, up to 24 weeks, of approximately 16%. Comparison with data on the outcome of well-documented early gestations suggests a roughly comparable fetal loss rate.[1] Loss rates increased with greater starting and finishing numbers. There were no outcome correlates within the 8–12 weeks' procedure time frame, but there was an increase in fetal losses and earlier gestational age at delivery for those cases performed at 13 weeks or later.

The higher loss rate with singletons may suggest that the number of needle insertions and quantity of nonviable tissue may be more important than the number of fetuses remaining, and that although a singleton may be an easier pregnancy, it is not "safer." However, these data are particularly confounded by selection bias, as many such cases were performed because of concern about the ability of the mother to carry twins. Thus, this high-risk status makes conclusions about the relative safety of singletons versus twins impossible to ascertain. Despite the size of our data set, there were still too few losses in this category to answer these specific questions.

Only 7.1% of women with viable pregnancies delivered at or before 28 weeks, and another 9.4% delivered between 29–32 weeks. Reasons for preterm delivery were almost exclusively fetal, eg, preterm labor or premature rupture of the membranes. The larger the starting and finishing numbers, the earlier the ultimate delivery. The 83.5% rate of delivery at 33 weeks or later represents a marked improvement upon expected outcomes for the neonates, who otherwise would have been part of larger multifetal pregnancies. Several authors have suggested an average delivery of 33 weeks for triplets and about 28–31 weeks for quadruplets.

The incidence of obstetric complications such as premature rupture of membranes, preeclampsia, fetal growth retardation, and other maternal and obstetric complications did not appear to be significantly different from that reported for spontaneously conceived twins (some data not shown).[3,12,14] In fact, the incidence of preeclampsia was far lower than that expected for multifetal pregnancies, suggesting another

Table 4. 2- and 4-Week Losses as a Function of Gestational Age at Procedure

	Gestational age (wk)								
	6	7	8	9	10	11	12	13	14
Losses (≤2 wk)	0	0	0	0	4	3	6	1	2
Loss rate (%)	0	0	0	0	4.6	2.4	5.2	3.6	16.7
Losses (≤4 wk)	1	1	0	0	7	5	6	3	2
Loss rate (%)	16.7	16.7	0	0	7.8	3.9	5.2	10.0	16.7
Late losses	0	0	4	1	15	20	13	4	0
Loss rate (%)	0	0	7.3	4.5	14.3	13.6	10.2	11.8	0
Viable (≥25 wk)	5	5	11	21	83	122	109	27	10
Viable rate (%)	83.3	83.3	73.3	95.5	79.0	83.0	85.2	79.4	83.3

Table 5. Gestational Age of Viable Deliveries by Finishing Number

Finishing no.	Gestational age (wk)				
	25–28	29–32	33–36	37+	Mean
3	3	4	9	3	33.3
2	20	30	121	157	35.6
1	3	3	10	28	37.1
All	26	37	140	188	35.6

$\chi^2 = 15.7$, $P < .02$.

less obvious benefit of MFPR. The incidence of congenital anomalies was 1.02%, which is actually lower than that expected, especially with twins.[12] Both the rate of complications and of anomalies can be explained either by incomplete ascertainment, as these patients were delivered in many centers worldwide, or by the fact that there is some choice of which fetuses get reduced. All participants in this survey would choose to reduce a fetus that was noticeably smaller, appeared abnormal, or had oligohydramnios. Therefore, it is possible that to some degree, fetuses who would ultimately have abnormalities might be those more likely to be reduced.

There has been considerable debate in the medical literature and lay press as to whether it is appropriate to offer MFPR to women with twins, triplets, quadruplets, or more, and whether one should finish with a singleton, twins, or triplets. Assessment of our data suggests that MFPR can be successful and that it reduces perinatal mortality from the level of higher multifetal pregnancies to that of twins. However, the perinatal morbidity and mortality rates with twins, both in this series and from natural history data, are higher than with singletons. As experience and the technical success of the procedure have become established, new questions have arisen: whether it is appropriate to reduce three or more fetuses to a singleton pregnancy, and whether women who present with twins should be offered a reduction to a singleton pregnancy.

In the absence of reliable data, there have been varied opinions among the authors of this paper as to the appropriateness of reducing twins or more to a singleton. Those in favor of this position argue that, given a belief that abortion can be justified, there should be no a priori difference between going from one fetus to zero or going from two to one. Originally, several members of our group would not reduce the number of fetuses below two, arguing that potential risks to the survivor were of concern. However, we now know that the only major risk seems to be that of pregnancy loss per se, and not a damaged survivor, thereby bringing the question of maternal autonomy into more prominence. Furthermore, others have suggested that the generally appreciated better outcome of singletons versus twins makes reduction to a singleton an appropriate option. If anything, our data suggest a higher procedure-related loss rate with singletons. However, because of some selection bias in the choice of which pregnancies were reduced to a singleton, the issue cannot be decided here. Most of the authors still routinely suggest that the optimum stopping number is twins, except in circumstances such as poor prior outcome in a twin pregnancy or reason to believe that twins would be markedly compromised in a particular case.

These data support the safety and efficacy of MFPR as the centers have moved up the "learning curve." Preliminary analysis of the centers' first 300 cases showed a slightly higher 4-week loss rate, with greater loss-rate variation by starting number (unpublished). Each center individually has noted decreased loss rates with increased experience.

Overall, the combined data from the centers represented in this report suggest that the mortality (and morbidity) of multifetal pregnancies—certainly at four or more, and probably at three—can be reduced by MFPR. Several years of experience have increased both the confidence of the physicians performing the procedures and the patients' perceptions of its relative safety. However, particularly as fetal numbers increased, the outcomes were less optimal. Even though acceptable outcomes usually can be achieved even starting with high fetal numbers, there is still a "price to be paid" in increased fetal loss rates and an increased risk of prematurity. The point remains that overzealous infertility treatment does have deleterious effects even if MFPR can be performed by trained

Table 6. Reduction to Twins by Week of Procedure

	Week of procedure								
	6	7	8	9	10	11	12	13	14
Starting no.	3.6	3.2	3.4	4.0	4.0	3.9	3.5	3.4	3.4
GA at delivery (wk)	34.8	34.8	35.5	36.5	35.6	35.5	36.2	34.0	33.3
n	5	5	11	21	83	122	109	27	10

GA = gestational age.

physicians. Although most infertility specialists appear to be extremely cautious in the use of reproductive medicines and technologies, we are distressed that a few physicians have become aggressive with assisted reproduction technologies and view MFPR as merely an adjunct to such therapies with no major medical or ethical consequences (Ayers JWT, Peterson EP, Knight L, Peterson S. Incorporation of transvaginal embryo reduction (TVER) with an aggressive IVF/GIFT/ZIFT program to optimize pregnancy outcome [abstract]. Fertil Steril 1991;56:S173). It must be stressed that all of the authors of this publication view MFPR as a *temporary need* until such time as better assisted reproduction techniques obviate the necessity for its use.

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