

Fetal Reduction in Triplet Gestations: Twins Still Fare Better

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ABSTRACT: **Background:** Reduction of fetal number has been offered in high order multiple gestations but is still controversial in triplets. Since recent advances in neonatal and obstetric care have greatly improved outcome, the benefits of multifetal pregnancy reduction (MFPR) may no longer exist in triplet gestations.

Objectives: To evaluate if fetal reduction of triplets to twins improves outcome.

Methods: We analyzed the outcome of 80 triplet gestations cared for at Rambam Health Care Campus in the last decade; 34 families decided to continue the pregnancy as triplets and 46 opted for MFPR to twins.

Results: The mean gestational age at delivery was 32.3 weeks for triplets and 35.6 weeks for twins after MFPR. Severe prematurity (delivery before 32 gestational weeks) occurred in 37.5% and 7% of twins. Consequently, the rate of severe neonatal morbidity (respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage) and of neonatal death was significantly higher in unreduced triplets, as was the length of hospitalization in the neonatal intensive care unit (31.4 vs. 15.7, respectively). Overall, the likelihood of a family with triplets to take home all three neonates was 80%; the likelihood to take home three healthy babies was 71.5%.

Conclusions: MFPR reduces the risk of severe prematurity and the neonatal morbidity of triplets. A secondary benefit is the reduction of cost of care per survivor. Our results indicate that MFPR should be offered in triplet gestations.

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KEY WORDS: multifetal pregnancy reduction (MFPR), triplets, prematurity, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage

in quadruplets and in higher order multiple gestations and is generally considered not acceptable in twins, performing multifetal pregnancy reduction in triplets is controversial today, as it was more than 20 years ago [1]. Moreover, recent advances in neonatal intensive care and in obstetric care have greatly improved the outcome for younger and lighter neonates. Thus, the perceived benefits of performing MFPR in order to improve neonatal outcome in triplets may no longer exist [2,3].

PATIENTS AND METHODS

We compared the obstetric and neonatal outcomes of trichorionic triamniotic triplet gestations that either continued as triplets or underwent reduction to twins at Rambam Health Care Campus in the last decade (2002–2011). Chorionicity was determined according to Sepuvela et al. [4]. Only patients who were treated and delivered in our institution were included in this study. Thus, complete follow-up was available. Obstetric characteristics and outcome were obtained from maternal electronic medical records. Neonatal outcomes were obtained from the medical records of the neonatal intensive care unit. Outcome measures were compared by chi-square with Yeats correction, by Fisher's exact test or by *t*-test and ANOVA for non-parametric values, as appropriate. A two-tailed probability value below 0.05 was considered significant.

Multifetal pregnancy reduction was performed at 12–14 weeks of gestation, after evaluation of nuchal translucency in the triplets. Unless dictated otherwise by nuchal translucency or crown-rump-length measurements, the upper and easiest to approach fetus was elected for reduction. All procedures were performed by two authors (A.D., A.W.). Using a trans-abdominal approach and sonographic guidance, a #22 gauge needle was advanced into the fetal chest and aliquots of 2 ml KCl were injected until cardiac standstill was obtained. Patients were released after a few hours of bed rest.

Pregnancy follow-up was conducted in high risk pregnancy clinics, with hospitalization as required for obstetric indications.

MFPR = multifetal pregnancy reduction

Reduction of the number of fetuses in utero has been proposed as a morally acceptable and medically justified procedure to reduce the risks of prematurity associated with high order multiple gestations. While this procedure with its inherent risk of pregnancy loss is widely accepted

RESULTS

In the last decade 82 triplet gestations were cared for at Rambam Health Care Campus; 36 families decided to continue the pregnancy as triplets and 46 opted for MFPR to twins. After MFPR, the rate of pregnancy loss before 24 weeks gestation was 6.5%; three pregnancy losses were experienced in this group at 16 weeks, 18 weeks and 21 weeks of gestation. Two of the non-interrupted triplet pregnancies were also lost, at 18 weeks and at 21 weeks of gestation, for a calculated loss rate of 5.6%. Our study group comprised 34 triplet and 43 twin gestations. The pregnancy characteristics and obstetric outcomes are presented in Table 1. The mean hospital stay before delivery was longer in untreated triplets (range 0–62 days). Moreover, only 4 of 34 mothers of triplets (11.7%) were not hospitalized at all before delivery, as compared to 20 of 43 parturients of twins (46.5%, $P = 0.002$, Fisher's exact test).

Neonatal outcomes are given in Table 2. In the triplets group 7 neonates died in the NICU and 20 had severe complications associated with prematurity, some with more than one complication. We calculated the chance for a specific

NICU = neonatal intensive care unit

Table 1. Pregnancy characteristics and obstetric outcomes in the study groups

	Triplets (n=34)	Twins (n=43)	P
Mean maternal age (yr)	30.72 ± 5.27	30.35 ± 5.38	NS
Mean parity	1.39 ± 0.55	1.425 ± 0.59	NS
Following in vitro fertilization*	14 (38.9%)	16 (34.8%)	NS
Post-induction of ovulation*	22 (61.1%)	30 (65.2%)	NS
Mean hospital stay (wk)**	16.6 ± 15.7	4.55 ± 7.8	< 0.001
Mean gestational age at delivery	32.3 ± 2.1	35.6 ± 2.1	< 0.00001
Delivered ≥ 35 wk (%)	6 (18.8%)	27 (62.8%)	< 0.001
Delivered ≤ 32 wk (%)	13 (37.5%)	3 (7%)	< 0.0001
Cesarean delivery (%)	34/34 (100%)	37/43 (86%)	0.026

*Maternal hospitalization before delivery

**Percent calculated from initial number of patients, before pregnancy loss

Table 2. Neonatal outcomes in the study groups

	Triplets (n=34)	Twins (n=43)	P
Mean weight (g)	1654.4 ± 451.1	2192.9 ± 584.3	< 0.0001
Neonatal death	7	0	0.02
Severe respiratory distress syndrome	18	2	0.0016
Bronchopulmonary dysplasia	14	2	0.015
Intraventricular hemorrhage grade 3-4	8	0	0.02
Mean stay in NICU (days)	31.4 ± 23.1	15.7 ± 14.2	< 0.0001

family with triplets to take home all three neonates as 80% and to take home healthy babies as 71.5%.

DISCUSSION

Our results show that triplets are at high risk of poor perinatal outcome, despite prolonged maternal hospitalization in some cases and improved modern neonatal care. Twins still do a lot better. Thus, fetal reduction of triplets to twins definitely improves neonatal outcome and the chance to take home healthy infants, while the rate of pregnancy loss before viability in reduced triplets compares favorably with that of untreated triplets. Papageorghiou et al. [3] calculated that fetal reduction in triplets adds an additional 4% to the risk of pregnancy loss noted in multiple gestations. In our study, the risk of pregnancy loss after fetal reduction to twins was 6.5%, comparable to that recently reported by Kuhn-Beck et al. [5], and not significantly different to the rate of spontaneous pregnancy loss before 24 weeks in untreated triplets. Most losses were observed several weeks after the procedure. As noted by Papageorghiou and colleagues [3], most of the excess loss with fetal reduction is likely to be the consequence of the resorbing dead fetoplacental tissue rather than faulty MFPR technique. We unequivocally recommend avoiding reduction of the lower lying fetus, intending not to leave necrotic tissue as a nidus to infection in close proximity to the cervical canal.

The tradeoff of a somewhat higher risk of pregnancy loss conferred by fetal reduction is a significant reduction in early preterm births. In our series, the rate of early premature delivery (before 32 weeks of gestation) decreased from 37.5% in untreated triplets to 7% in those reduced to twins. Our results are somewhat better than those reported by Papageorghiou et al. [3], from 28% to 10%, who calculated that seven reductions (95% confidence interval 5–9) needed to be performed to prevent one early preterm delivery, while the number of reductions that will cause one miscarriage was 26 (95%CI 14–193). Our data show that five fetal reductions need to be performed in order to prevent one early preterm delivery.

The mean stay in the NICU in our study (31 days) is comparable to that reported by Barr and co-authors [2] and shorter than that reported by Suri and team [6], at 31 weeks, probably because the mean gestational age at delivery in our series was one week later than in Suri's study. It should be noted, however, that despite a similar mean gestational age at delivery, Barr's series [2] demonstrated very low rates of morbidity associated with triplet birth, without reports of intraventricular hemorrhage or retinopathy of prematurity, and rates of only 3% for chronic lung disease (bronchopulmonary dysplasia) and necrotizing enterocolitis. In our experience with untreated triplet gestations, the rate of intraventricular hemorrhage and

CI = confidence interval

bronchopulmonary dysplasia were 8% and 14%, respectively, and the rate of necrotizing enterocolitis was 3%; two of the cases were managed conservatively and the third necessitated a total colectomy. These results are also comparable with those of a previous report on triplets from our group [7], suggesting that nothing has really changed in the last two decades and that the major determinant of neonatal morbidity and mortality remains gestational age at delivery.

An important aspect substantiated in our study is the prolonged hospitalization before delivery associated with multifetal gestation. To the best of our knowledge, this aspect has not been addressed in previous studies. Prolonged hospital stay implies a significant emotional and financial burden on both the family and the health care system. In our experience, the need for hospitalization in the high risk pregnancy unit and the length of hospitalization declined after fetal reduction to twins. More importantly, the length of hospital stay in the NICU was halved by fetal reduction and the number of cases affected by prolonged disability also decreased.

In summary, our study shows that despite advances in modern neonatal care, triplet pregnancies are still at high risk for significant prematurity and its associated complications. Fetal reduction of triplet gestations to twins does not noticeably increase pregnancy loss rates but significantly improves

perinatal outcomes. Moreover, MFPR in triplets may be beneficial to the health care system as well, by reducing the cost per treated patient, enabling better allocation of limited resources.

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Capsule

Staphylococcus δ -toxin induces allergic skin disease by activating mast cells

Atopic dermatitis is a chronic inflammatory skin disease that affects 15–30% of children and approximately 5% of adults in industrialized countries. Although the pathogenesis of atopic dermatitis is not fully understood, the disease is mediated by an abnormal immunoglobulin E immune response in the setting of skin barrier dysfunction. Mast cells contribute to immunoglobulin E-mediated allergic disorders including atopic dermatitis. Upon activation, mast cells release their membrane-bound cytosolic granules leading to the release of several molecules that are important in the pathogenesis of atopic dermatitis and host defense. More than 90% of patients with atopic dermatitis are colonized with *Staphylococcus aureus* in the lesional skin whereas most healthy individuals do not harbor the pathogen. Several staphylococcal exotoxins can act as superantigens and/or antigens in models of atopic dermatitis. However, the role of these staphylococcal exotoxins in disease pathogenesis remains unclear. Nakamura and team report that culture supernatants of *S. aureus* contain potent mast cell degranulation activity. Biochemical analysis identified δ -toxin

as the mast cell degranulation-inducing factor produced by *S. aureus*. Mast cell degranulation induced by δ -toxin depended on phosphoinositide 3-kinase and calcium (Ca²⁺) influx; however, unlike that mediated by immunoglobulin E cross-linking, it did not require the spleen tyrosine kinase. In addition, immunoglobulin E enhanced δ -toxin-induced mast cell degranulation in the absence of antigen. Furthermore, *S. aureus* isolates recovered from patients with atopic dermatitis produced large amounts of δ -toxin. Skin colonization with *S. aureus*, but not a mutant deficient in δ -toxin, promoted immunoglobulin E and interleukin-4 production, as well as inflammatory skin disease. Furthermore, enhancement of immunoglobulin E production and dermatitis by δ -toxin was abrogated in *Kit^{W-sh/W-sh}* mast cell-deficient mice and restored by mast cell reconstitution. These studies identify δ -toxin as a potent inducer of mast cell degranulation and suggest a mechanistic link between *S. aureus* colonization and allergic skin disease.

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Eitan Israeli

“It is a glorious thing to be indifferent to suffering, but only to one’s own suffering”

Robert Lynd (1879-1949), Irish journalist and Sinn Fein activist