Neonatal Course and Outcome of Twins from Reduced Multifetal Pregnancy versus Non-Reduced Twins

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Abstract

Background: Multifetal pregnancy reduction has been implemented for improving the outcome of multifetal pregnancies. Recent studies reported no difference in pregnancy outcome between reduced twins and non-reduced twins, but the neonatal course and subsequent outcome in reduced twin pregnancies were not well documented.

Objective: To compare the neonatal course and outcome, as well as the gestational and labor characteristics in twins from reduced multifetal pregnancies and in non-reduced twins.

Methods: This is a retrospective case-control study of the neonatal course of twins from reduced multifetal pregnancies. We found 64 mothers with multifetal pregnancy reduction who delivered twins during 1989–1997; 64 gestational age-matched non-reduced twin pregnancies served as controls. The following neonatal variables were examined: major malformations; small birth weight for gestational age; and neonatal morbidities including respiratory distress syndrome, apnea, pneumothorax, bronchopulmonary dysplasia, hyperbilirubinemia, sepsis, necrotizing enterocolitis, retinopathy of prematurity, seizures, intraventricular hemorrhage, periventricular leukomalacia, ventriculomegaly, and hydrocephalus. In addition, we evaluated several neonatal interventions (surfactant replacement, mechanical ventilation, phototherapy, total parenteral nutrition), and some laboratory abnormalities (thrombocytopenia, leukopenia, anemia, and hypoglycemia), duration of hospitalization, and neonatal mortality.

Results: Gestational and labor variables were not significantly different between multifetal pregnancies reduced to twins and non-reduced twin pregnancies. The neonatal morbidity and mortality were not significantly different between twin neonates from multifetal pregnancy reduction and non-reduced control twins.

Conclusions: Multifetal pregnancy reduction to twins appears to bear no adverse effect on the intrauterine course of the remaining fetuses or their neonatal course and outcome when born after 28 weeks of gestation.

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The prevalence of multifetal pregnancy has increased as a result of assisted reproduction procedures such as in vitro fertilization and controlled ovarian stimulation. Maternal and perinatal morbidity are usually higher in multifetal pregnancy because they are associated with increased rates of prematurity, pregnancy-induced hypertension, malpresentation, gestational diabetes, and intrauterine growth restriction [1–3]. Neonatal morbidity and mortality are predominantly a result of prematurity.

Intrauterine manipulation such as fetal reduction could potentially impose adverse effects on the remaining fetuses. Following fetal reduction there might be a decrease in decidual function [4], and the absorption process of a reduced fetus could induce a release of various agents that might be deleterious to the remaining fetuses. Such an argument has been raised for explaining the observed correlation between a spontaneously vanishing twin and cerebral palsy in the remaining twin neonate [5–7].

Multifetal pregnancy reduction was implemented in the last decade for improving the outcome of multifetal pregnancies [8–10]. Recent studies reported no difference in pregnancy outcome between reduced twins and non-reduced twins [9]. However, the neonatal course and subsequent outcome in reduced twin pregnancies were partially studied in four previous investigations [11–14] but were not adequately evaluated. The most worrisome finding was reported by Geva et al. [12] regarding a possible increased risk of periventricular leukomalacia in the remaining neonates following reduction.

In the present study we compared the gestational and neonatal variables, complications and outcome between two groups of twin neonates: twins of reduced multifetal pregnancies and matched non-reduced twins.

Materials and Methods

Study design and population

This retrospective case-control study was performed in the Rambam Medical Center, a tertiary care center for fetomaternal medicine and neonatology in northern Israel. During a 9 year period (1989–1997), 112 multifetal pregnancies were reduced to twins in this center.

Of the 112 reduced-to-twins pregnancies, 67 were originally triplets, 35 were quadruplets and 10 were quintuplets. Of these 112, 104 delivered after 24 weeks of gestation, and complete data were available on a total of 64 MPR (128 neonates), which constituted the study group. The other 40 mothers with MPR delivered in other institutions and data regarding their neonates were not available for analysis. The control group consisted of 64 matched non-reduced (67% naturally conceived) twin deliveries in our institution (128 neonates). Controls were selected by matching each MPR delivery to the subsequent non-reduced twin delivery of similar gestational age (about 3 days) that occurred within the subsequent 3 months.

Technique of fetal reduction

Fetal reduction was performed using a transvaginal technique [15] during weeks 7–11 of gestation. Two methods of reduction were used: a) fetal aspiration at weeks 7–8, or b) intracardiac injection of potassium chloride at weeks 9–11 of gestation.

MPR = multiple pregnancy reduction

Data collection

We evaluated retrospectively various gestational, labor and neonatal variables of twin neonates from both the study and control groups.

- *Gestational and labor variables:* gestational age at delivery, first-trimester bleeding, preeclamptic toxemia, gestational diabetes mellitus, prolonged rupture of membranes, mode of delivery, fetal distress (defined as repeated late decelerations or persistent fetal bradycardia), heavily stained meconial fluid, treatment with tocolytics (ritodrine or indomethacin), antenatal steroid therapy (betamethasone), Apgar score, gender, birth weight, and resuscitation in delivery room (mechanical ventilation, cardiopulmonary resuscitation).
- *Neonatal variables:* major malformations, small for gestational age (birth weight <3 percentile) [16], respiratory distress syndrome (moderate to severe), administration of surfactant, mechanical ventilation, duration of mechanical ventilation, phototherapy for neonatal hyperbilirubinemia, clinical neonatal sepsis (negative bloodstream cultures), proven neonatal sepsis (positive blood cultures for bacteria or fungi), thrombocytopenia (platelets < 100,000/mm^3), leukopenia (white blood cells < 5,000/mm^3) and anemia (hemoglobin <14 g/dl) in the first 72 hours of life, hypoglycemia (<40 mg/dl) in the first day of life, apnea (>20 seconds), pneumothorax, pneumonia, seizures (focal or generalized), duration of hospitalization, total parenteral nutrition of more than 7 days, bronchopulmonary dysplasia (diagnosed at 28 days of life), necrotizing enterocolitis, retinopathy of prematurity, and neonatal mortality (<28 days of life). Preterm infants were also evaluated for possible brain insult by serial cranial ultrasonography for detection of possible intraventricular hemorrhage, periventricular leukomalacia, ventriculomegaly and hydrocephalus [17].

Statistical analysis

Inasmuch as one twin cannot be regarded to be totally independent of the other, we opted to perform a paired comparison between matched pregnancies, thus considering every set of twin neonates as one unit. Occurrence of a variable in at least one of the twin neonates was considered a positive result, while its absence denoted a negative result. In the case of a positive result, further evaluation was undertaken in order to verify whether such variable had affected both twin neonates or only one. For all gestational and labor characteristics, paired comparison of variables was performed per pregnancy (64 versus 64). We used the paired Wilcoxon test for comparison of ordinal variables (such as Apgar scores) when values showed a non-normal distribution. The McNemar test was used to compare proportions in paired samples. Student's *t*-test was used to compare mean values. Chi-square test and Fisher's exact test were used for comparison of proportions between groups. A *P* value of less than 0.05 was considered statistically significant.

Results

MPR characteristics

Of the 64 MPRs, 50 were reduced to twins by transvaginal aspiration at 7.6 ± 0.6 weeks gestation, and 14 by injection of KCl at 9.4 ± 1.1 weeks gestation [Table 1]. The initial number of embryos was 3 in 43 cases, 4 in 17 and 5 in 4 cases.

Gestational and labor variables

The mean gestational age at delivery in both groups was similar, as controls were matched to their study mates according to gestational age. As shown in Tables 2 and 3, the MPR group was not significantly different from the control group in any of the gestational and labor characteristics, or complications and outcome, including when the observations were stratified for gestational age subgroups at delivery.

Neonatal variables

The MPR infants group was not significantly different from controls in all examined neonatal variables [Table 4]. As delineated in the Methods section, results were considered positive when at least one of the twins was affected. We did not find significant differences between first twins and second twins. Furthermore, the results did not change when we divided the twins with positive variables into

Table 1. Selected clinical characteristics of multifetal pregnancy reduction group (n = 64)

	Multifetal pregnancy reduction to twins
Initial no. of embryos	
3	43
4	17
5	4
Reduction technique	
Aspiration	50
KCl injection	14
Gestational age at reduction (weeks)	
Aspiration	7.6 ± 0.6
KCl injection	9.4 ± 1.1

Table 2. Gestational variables in the study (n = 64) and control (n = 64) groups

Variable	Multifetal pregnancy reduction*	Controls*
Spontaneous pregnancy	1	43
Induced pregnancy		
Ovarian stimulation	25	7
In vitro fertilization	38	14
First trimester vaginal bleeding (%)	6.3	3.1
Preeclampsia (%)	14.1	14.1
Gestational diabetes mellitus (%)	7.8	1.5
Prolonged rupture of membranes (%)		
6–24 hours	6.3	14.1
More than 24 hours	6.3	4.7
Prenatal medication (%)		
Betamethasone	12.5	6.3
Ritodrine	15.6	12.5
Indomethacin	7.8	10.9

* Variables were not statistically different between MPR and control groups, except for mode of conception (spontaneous and induced).

Table 3. Demographic and labor variables in the study (n = 64) and control (n = 64) groups

Variable	Multifetal pregnancy reduction*	Controls*
Gestational age at birth (weeks)	35.7 ± 3.1	35.6 ± 3.1
> 37	24	23
32–37	32	33
28–32	7	6
24–28	1	2
Birth weight of twin I and twin II (g)	I : 2281 ± 529	II : 2248 ± 547
	I : 2307 ± 586	II : 2296 ± 577
Small for gestational age (%)	39.1	34.1
Male sex (%)	I : 48.4 (n=64)	I : 46 (n=63)
	II : 55.6 (n=63)	II : 42.4 (n=59)
Fetal distress (%)**◆	10.9	18.8
Heavily stained meconial fluids (%)◆	4.8	3.2
Abnormal mode of delivery (%)◆ (cesarean/vacuum extraction/forceps)	64.1	62.5
Resuscitation (%)◆ (delivery room)	21.9	29.7
5 min Apgar score ⩽ 8 (%) (n=61)	18.0	18.0
Hospitalization (days)	14.8 ± 15.3	14.2 ± 14.1
Neonatal mortality: 0–28 days	I : 1/64	I : 1/64
	II : 1/64	II : 3/64

* Variables were not statistically different between MPR and control groups.

** Fetal late deceleration or persistent fetal bradycardia.

◆ Data indicate the occurrence of variables in at least one of the twin neonates.

those with one affected twin neonate and those where both twin neonates were affected.

Discussion

Multifetal pregnancies are usually a result of assisted reproduction treatment. MPR is an accepted method of decreasing neonatal morbidity and consists mostly of triplets being reduced to twins. Hence, verifying whether MPR has deleterious effects on the remaining fetuses would be of prime importance. Such potential complications of MPR might become apparent during gestation or during the neonatal period.

The experience and pregnancy outcome with MPR in the last decade was recently reported by Evans et al. [18] in a large multicenter study that included 3,513 cases of MPR from 11 American and European centers. These authors concluded that MPR pregnancy outcomes for both losses and early prematurity have improved with the increasing experience in fetal reduction. In addition, reduction from triplets or quadruplets to twins achieves pregnancy outcomes as good as those of non-reduced twin pregnancies. It was also found that higher starting numbers of embryos or fetuses carry a worse outcome in terms of fetal loss, growth and prematurity.

In the present study we compared neonatal morbidity and outcome of two matched groups of twin neonates, namely multifetal pregnancies reduced to twins and non-reduced twins, and found no significant statistical differences between the groups regarding the evaluated variables. Knowing that fetal reduction from triplet to twins is still controversial, it was important to differentiate the group of quadruplets or higher-order pregnancies reduced to twins from the group of triplets reduced to twins. Unfortunately, in our study the size of quadruplets or higher-order pregnancies reduced to twins was small (n=21) and did not allow statistical comparison of their neonatal course and outcome with those of triplets reduced to twins.

Several studies referred to neonatal morbidity and outcome following MPR [11–14], but to our best knowledge, the present study is the first to comprehensively address all possible neonatal complications. Lipitz et al. [11] reported a greater frequency of neonatal complications in a group of triplets as compared to reduced twins. However, the reduced twins in their study had a significantly higher gestational age, and no comparison was made between reduced and non-reduced twins. Boulot and co-workers

Table 4. Neonatal variables in the study (n = 64) and control (n = 64) groups

Variable*	Multifetal pregnancy reduction (MPR)**	Control**
Major malformations (%)◆	4.7	7.8
Respiratory distress syndrome (%) (gestational age < 36 weeks) (n=28)	14.3	32.1
Surfactant treatment (%)	6.3	10.9
Apnea (%)	14.1	7.8
Pneumothorax (%)	3.1	3.1
Pneumonia (%)	0	0
Mechanical ventilation (%)	19 (n=17)	27 (n=23)
Duration (days)	2.79 ± 2.1	4.49 ± 8.0
Phototherapy (%)	43.8	46.9
Neonatal sepsis (n=54)		
Clinical	16.7	5.6
Proven	3.7	14.8
Thrombocytopenia (%)	2.8 (n=35)	4.8 (n=41)
Anemia (%)	7.9 (n=38)	9.3 (n=43)
Leukopenia (%)	2.9 (n=34)	0 (n=40)
Hypoglycemia (%)	20.3	15.6
Total parenteral nutrition >7 days (%) (n=60)	18.3	18.3
Bronchopulmonary dysplasia (%)	0	4.7
Necrotizing enterocolitis (%)		
Grade IB–IIA	1.6	0
Grade IIB – III	3.1	1.6
Retinopathy of prematurity (%)	1.6	0
Seizures (%)	0	3.1
Intraventricular hemorrhage (%) (n=28) (gestational age < 36 weeks)		
Grade 1–2	10.7	10.7
Grade 3–4	0	10.7
Periventricular leukomalacia (%) (n=28) (gestational age < 36 weeks)	0	0
Ventriculomegaly (%) (n=28) (gestational age < 36 weeks)	7.1	7.1
Hydrocephalus (%) (n=28) (gestational age < 36 weeks)	0	0

* Data are presented as percentage (%) and indicate the occurrence of variable in at least one of the twin neonates.

** Variables were not statistically different between MPR and control groups.

◆ Including: pulmonary stenosis, patent ductus arteriosus, complex congenital heart disease, small left colon.

[13] compared 65 sets of twins after MPR with 83 sets of triplets that were not reduced and found that MPR from triplets to twins decreased the incidence of prematurity and of intrauterine growth restriction, with no effect on perinatal mortality. Therefore, the results of these two studies [11,13] could not be compared to our results due to different study designs.

We could compare our findings with those of Selam et al. [14], who addressed a few neonatal variables (gestational age at birth, birth weight, Apgar scores, admission to the neonatal intensive care unit, respiratory distress syndrome, hematocrit, and blood glucose and bilirubin). Our findings conform with those of Selam et al. [14] on the lack of significant differences between MPR to twins and non-reduced twin pregnancies, with regard to pregnancy complications and neonatal variables. However, in our study we did not find a higher incidence of polycythemia in the MPR group, as reported by Selam et al. [14].

Previous studies reported an increased risk for periventricular leukomalacia in twin neonates after MPR, attributed to a possible inflammatory response (release of cytokines, such as interleukins 1 and 6, and tumor necrosis factor) that might be induced by the demise of fetuses after MPR [5–7,12]. However, these observations afforded no explanation to why such adverse phenomena could be detected only postnatally in premature infants and could not be demonstrated on fetal brain ultrasonography. Our results do not support the previous reports on an increased risk for periventricular leukomalacia as a consequence of MPR in reduced twin neonates (no cases in both groups). Furthermore, there was no evidence for physical or psychomotor impairments in seven infants (1 to 3 years old) who were born after fetal reduction, as would have been expected if periventricular leukomalacia in the surviving fetuses had been caused by MPR [19].

The present work has some pitfalls that might affect the results of this study. The first is the lack of reference to chorionicity that might affect the pregnancy outcome in twin pregnancies. Unfortunately, these data were not regularly recorded in our delivery records. Nevertheless, the rates of low birth weight were not different between groups and only one case of twin-to-twin transfusion was found in our study. Secondly, absence of data in 40 of 104 MPR pregnancies might have affected our results and conclusions. Third, the low frequency of some neonatal endpoints could limit the statistical power in detection of differences between groups. A larger, prospective and controlled study is warranted in order to achieve adequate statistical power and avoid this pitfall.

In our study, the neonatal outcome of reduced twins was similar to that of non-reduced twins, which should lead us to conclude that fetal reduction does not adversely affect the remaining surviving fetuses. The optimal way to minimize neonatal morbidity is by attempting in the first place to produce single fetus pregnancies on assisted reproduction. Such an approach would decrease the need for MPR with its associated potential complications.

According to our results, the pregnant mother with a multifetal pregnancy and its inherent risks can be offered fetal reduction with a fair degree of confidence that the procedure, whether embryo aspiration or KCl injection, will not involve a threat of undue deleterious effects on the remaining fetuses.

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References

1. Lynch L, Berkowitz RL, Chitkara U, Alvarez M. First-trimester transabdominal multifetal pregnancy reduction: a report of 85 cases. *Obstet Gynecol* 1990;75:735–8.
2. Petrikovsky BM, Vintzileos AM. Management and outcome of multiple pregnancy of high fetal order: literature review. *Obstet Gynecol Surv* 1989; 44:578–84.
3. Sassoon DA, Castro LC, Davis JL, Hobel CJ. Perinatal outcome in triplet versus twin gestation. *Obstet Gynecol* 1990;75:817–20.
4. Abbas A, Johnson M, Chard T, Nicolaides KH. Maternal plasma concentrations of insulin-like growth factor binding protein-1 and placental protein 14 in multifetal pregnancies before and after fetal reduction. *Hum Reprod* 1995;10:207–10.
5. Pharoah PO, Cooke RW. A hypothesis for the aetiology of spastic cerebral palsy – the vanishing twin. *Dev Med Child Neurol* 1997;39:292–6.
6. Pharoah PO, Cooke T. Cerebral palsy and multiple births. *Arch Dis Child Fetal Neonatal Ed* 1996;75:174–7.
7. Verma U, Tejani N, Klein S, et al. Obstetric antecedents of intraventricular hemorrhage and periventricular leukomalacia in the low-birthweight neonate. *Am J Obstet Gynecol* 1997;176:275–81.
8. Donner C, deMaertelaer V, Rodesch F. Multifetal pregnancy reduction: comparison of obstetrical results with spontaneous twin gestations. *Eur J Obstet Gynecol Reprod Biol* 1992;44:181–4.
9. Lipitz S, Uval J, Achiron R, Schiff E, Lusky A, Reichman B. Outcome of twin pregnancies reduced from triplets compared with nonreduced twin gestations. *Obstet Gynecol* 1996;87:511–14.
10. Smith-Levitin M, Kowalik A, Birnholz J, et al. Selective reduction of multifetal pregnancies to twins improves outcome over nonreduced triplet gestations. *Am J Obstet Gynecol* 1996;175:878–82.
11. Lipitz S, Reichman B, Uval J, et al. A prospective comparison of the outcome of triplet pregnancies managed expectantly or by multifetal reduction to twins. *Am J Obstet Gynecol* 1994;170:874–9.
12. Geva E, Lerner-Geva L, Stavorovsky Z, et al. Multifetal pregnancy reduction: a possible risk factor for periventricular leukomalacia in premature newborns. *Fertil Steril* 1998;69:845–50.
13. Boulot P, Vignal J, Vergnes C, Dechaud H, Faure JM, Hedon B. Multifetal reduction of triplets to twins: a prospective comparison of pregnancy outcome. *Hum Reprod* 2000;15:1619–23.
14. Selam B, Lembet A, Stone J, Lapinski R, Berkowitz RL. Pregnancy complications and neonatal outcomes in multifetal pregnancies reduced to twins compared with nonreduced twin pregnancies. *Am J Perinatol* 1999;16:65–71.
15. Itskovitz J, Boldes R, Thaler I, Levron J, Rottem S, Brandes JM. First trimester selective reduction in multiple pregnancy guided by transvaginal sonography. *J Clin Ultrasound* 1990;18:323–7.
16. Usher R, McLean F. Intrauterine growth of live born Caucasian infants at sea level. *J Pediatr* 1969;74:901–10.
17. Levene MI, Williams JL. Sequelae of PVH. In: Levene MI, Williams JL, eds. Ultrasound of the Infant Brain. 1st edn. Philadelphia: JB Lippincott, 1985:68–9.
18. Evans MI, Berkowitz RL, Wapner RJ, Carpenter RJ, et al. Improvement in outcomes of multifetal pregnancy reduction with increased experience. *Am J Obstet Gynecol* 2001;184:97–103.
19. Brandes JM, Itskovitz J, Scher A, Gershoni-Baruch R. The physical and mental development of co-sibs surviving selective reduction of multifetal pregnancies. *Hum Reprod* 1990;5:1014–17.

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