Received: 25.8.2008 **Accepted: 28.10.2008**

Original Article

The neonatal outcome in twin versus triplet and quadruplet pregnancies

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Abstract

BACKGROUND: To assess the risk of neonatal mortality and morbidity in twin, triplet and quadruplet pregnancies.

METHODS: In a retrospective study, the neonatal outcome of all twin, triplet and quadruplet gestations delivered from October 2001 to September 2006 was reviewed. The neonatal outcome of triples and quadruplets was compared with a matched group of twins for gestational age.

RESULTS: During a 5-year period, 511 sets of twin pregnancies, 42 sets of triplet and 5 sets of quadruplet pregnancies were studied. The mean of gestational age for twins, triplets and quadruplets were 33.92 ± 3.5 weeks, 30.92 ± 3.8 weeks and 31.60 ± 2.0 weeks, respectively, (P = 0.0001). Triplets and quadruplets weighed less than twins, (P = 0.0001). Neonatal mortality was 13.5% for twins, 26.8% for triplets and 30% for quadruplets. In vitro fertilization, use of ovulation induction agents, and cesarean delivery in the women with triplet and quadruplet were significantly higher than in those with twin pregnancies, (P = 0.0001). The mean age of mothers with triplets and quadruplets was significantly higher than with twins (P = 0.026). There was not a significant difference in respiratory and non-respiratory short outcomes between triplets, quadruplets and twins when matched for gestational age. Apgar score at 1 and 5 minutes was significantly lower in triplets and quadruplets than twins. There was no influence of birth order on neonatal mortality of triplet pregnancy. Neonatal mortality of triplet births was significantly decreased over the 5 years of the study period.

CONCLUSIONS: Triplets and quadruplets have a similar neonatal outcome as twins when matched for gestational age. There is no influence of birth on the neonatal mortality of triplet pregnancy. It appears that outcome is mainly dependent on gestational age.

KEYWORDS: Neonatal outcome, twins, triplets, quadruplets.

JRMS 2009; 14(1): 7-12

The incidence of multiple pregnancies has increased enormously over the last three decades due to increases in ovulation induction, in vitro fertilization (IVF) as well as childbearing at older ages.[1-3] Multiple gestations are high-risk pregnancies that may be complicated by maternal and neonatal morbidity and high neonatal and infant mortality.[4] The offspring of multiple gestations may carry additional risk for long-term consequences of perinatal complications, including cerebral palsy and learning disabilities.[5]

Luke et al demonstrated that the rates of infant mortality in the USA were 11, 66 and 190 for singletons, twins and high-order multiples respectively.[6] Ballabh and co-workers showed that triples have a similar neonatal outcome as twins and singletons when matched for gestational age.[7] Consistent with the most recent published literature, Barr et al revealed excellent survival rates with very low associated morbidity in triplet pregnancies.[3] It seems that marked improvement of neonatal care as well as thorough obstetric follow-up could positively influence the outcome of multiple pregnancies. To our knowledge, there is not any large study comparing morbidity and mortality of twins, and high multiples in Iran.

The aim of this study was to assess whether there is an increase in mortality and the risk of

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adverse neonatal short-outcome in triplets and quadruplets compared with twins matched for gestational age.

Methods

We retrospectively assessed the neonatal outcome of twins, triplets and quadruplets born at Beheshti Hospital (a territory care perinatal referral center) in Isfahan, Iran, from 2001-10-01 to 2006-09-30. Maternal and neonatal records from all twin, triplet and quadruplet gestations delivered at this hospital were reviewed and the following characteristics and risk factors were extracted: maternal age, methods of induction of ovulation, prenatal steroid (defined as receipt of maternal steroid within 7 days of the delivery), mode of delivery and gestational age at delivery, neonatal birth weight, Apgar score at 1 and 5 min, neonatal intensive care admission and neonatal length of stay in hospital.

Neonatal outcomes recorded were as follows: (1) Neonatal mortality was calculated as the number of deaths of live born infants less than 28 days of age per thousand live births. (2) Respiratory distress syndrome (RDS) was defied as requiring continuous positive airway pressure (CPAP) > 1 day, mechanical ventilation (IMV) > 1 day or supplemental oxygen more than 3 days with changes in chest X-ray suggestive of RDS. (3) Patent ductus arteriosus (PDA) was diagnosed by the presence of a murmur and confirmed by echocardiogram. (4) Intraventricular hemorrhage (IVH) was confirmed by head ultrasound and graded according to the classification of Papile et al.[8] (5) Necrotizing enterocolitis (NEC) as defined by the Bell classification.[9] (6) Jaundice was defied as bilirubin level high enough to require phototherapy. (7) Sepsis was defined as positive blood or spinal fluid culture for bacterial or fungal growth.

For comparison, a group of live born twins was matched for gestational age closest to the set of triplets and quadruplets under review.

Statistical analysis

SPSS version 13 was used for analyses, the χ^2 analysis for categorical variables and t-test for continuous variable were done to univariate comparison between twin and high-order gestation. Statistical significance was attributed to $P < 0.05$.

Results

The total number of deliveries at Beheshti Hospital was 30157 over the period of study. The prevalence of multiple pregnancies was 18.5 per thousand. There were 511 sets of twins, 42 sets of triplets and 5 sets of quadruplets.

Mothers of triplets and quadruplets were significantly older compared to those of twins (27.0 ± 4.16 years versus 25.38 ± 4.5 years, P = 0.026), but mothers of triples infants were of similar age as quadruplets. All quadruplet pregnancies were delivered by c-section whereas 90.5% of triplet and 82.4% of twin pregnancies were delivered by c-section. A total of 16.7% (7) of triplet and 40% (2) of quadruplets were the result of IVF whereas only 3.9% (20) of twins were the result of IVF (P = 0.0001).

The percentage of male infant was 50.5%, 57.9% and 40% for twins, triplets and quadruplets, respectively. The mean birth weight of triplets (1366.81 ± 527.25 g) and quadruplets (1427.00 ± 309.65 g) was similar but significantly less than twins (1963.25 ± 548.72 g, P = 0.0001).

The mean gestational age of twins, triplets and quadruplets were 33.92 ± 3.5 (24-41), 30.92 ± 3.4 (24-36) and 31.60 ± 2.1 (28-34) weeks, respectively. It was significantly higher in twins than triplets and quadruplets (P = 0.0001). All of triplet and quadruplet and 73% of twin pregnancies were delivered before 37 weeks of gestation.

Out of 1168 fetuses delivered, twenty were stillborn (16 twins, 3 triplets and 1 quadruplet) and there were 178 neonatal deaths. Neonatal mortality was 138 (13.7%) for twins, 33 (26.8%) for triplets and 6 (30%) for quadruplets. The overall neonatal mortality rate was 155 per 1000 live births of multiple gestations.

Table 1. Maternal and infant characteristics between matched groups for gestational age

	Triplets & Quadruplets (47 set)	Twins (47 set)	P value	95% CI
1) Maternal				
Age (Mean & SD)	27.08 ± 4.16	24.74 ± 2.93	0.002	- 3.81, - 0.86
Delivery				
C-Section	43 (91.4%)	33 (70.2%)	0.009	
Vaginal	4 (8.5%)	14 (29.8%)		
Prenatal steroid	27 (57.4%)	28 (59.5%)	0.832	
Use of induction ovulation drugs	29 (61.7%)	16 (34%)	0.007	
IVF/non- IVF				
IVF	11 (23.4%)	3 (6.4%)	0.02	
Spontaneous	36 (76.6%)	44 (93.6%)		
2) Infant				
Sex				
Male	64 (45%)	55 (59%)	0.028	
Female	78 (55%)	37 (40.2%)		
Weight (Mean & SD)	1401.05 ± 481.30	1619.66 ± 592.13	0.011	50.73 , 386.48
Apgar score (Mean & SD)				
1 min	7.27 ± 1.55	7.83 ± 1.76	0.001	0.23, 0.78
5 min	8.61 ±1.43	9.12 ± 1.48	0.0001	0.24, 0.87
NICU days (Mean & SD)	8.34 ± 9.5	7.32 ± 6.5	0.453	-3.25, 1.58

Maternal and neonatal characteristics after matching for gestational age are represented in table 1.

The respiratory and non-respiratory outcome of triplet and quadruplet infants compared with a matched group of twins for gestational age is shown in table 2.

Table 3 represents the comparisons of neonatal morbidity and mortality among first triplets (A), second triplets (B) and third born triplet (C). The need for mechanical ventilation and neonatal mortality were increased in triplet B and C versus triplet A, and incidence of jaundice was higher in triplet A versus triplet B and C, but was not significantly different.

The neonatal mortality and the mean birth weight and gestational age of triplet infants are illustrated in table 4. The number of triplet births increased nearly 50% from 2001 to 2006. The mean birth weight and gestational age of triplets did not change significantly over the time (P = 0.097 and P = 0.618, respectively). Although the number of triplet births was increased significantly over these years but the mortality rate of them was decreased significantly P = 0.001.

Table 2. The respiratory and non-respiratory short-outcome between matched groups.

	Triplets & Quadruplets (n = 142 neonates)	Twins (n = 92 neonates)	P value
RDS	27 (19.3%)	23 (25%)	0.268
Surfactant	10 (7%)	8 (8.6%)	0.637
Mechanical ventilation	36 (25.3%)	18 (19.5%)	0.305
PDA	3 (2.1%)	3 (3.2%)	0.861
Sepsis	21(14.7%)	10 (10.8%)	0.414
IVH	7 (4.9%)	3 (3.2%)	0.541
Jaundice	49 (34.5%)	27 (29.3%)	0.507
NEC	6 (4.2%)	6 (6.5 %)	0.432
NICU admission	99 (69.7%)	56 (61.5%)	0.197
Neonatal Mortality	40 (28.1%)	22 (24%)	0.471

Table 3. Outcome of triplet A vs B, triplet B vs C and triplet A vs C.

	Triplet A N= 41	Triplet B N= 41	Triplet C N= 41
Weight (g)	1348.62 ± 484.12	1420.32 ± 573.36	1329.42 ± 531.12
NICU admission	26 (63.4%)	29 (70.7%)	26 (63.4%)
Mean NICU days	9.40 ± 11.2	8.88 ± 11.56	7.28 ± 6.86
RDS	6 (14.6%)	7 (17%)	7 (17%)
Surfactant	3 (7.3%)	2 (4.8%)	3 (7.3%)
Mechanical Ventilation	4 (9.7%)	7 (17%)	8 (19.5%)
NEC	2 (4.8%)	2 (4.8%)	1 (2.4%)
IVH	3 (7.3%)	3 (7.3%)	1 (2.4%)
Jaundice	17 (41.4%)	10 (24.4%)	12 (29.2%)
Sepsis	7 (17%)	9 (22%)	3 (7.31%)
Anomalies	3 (7.3%)	3 (7.3%)	2 (4.8%)
Neonatal Mortality	8 (19.5%)	12 (29.2%)	13 (31.7%)
Apgar score (Mean & SD)			
1 min	7.10 ± 1.67	7.23 ± 1.80	7.25 ± 1.62
5 min	8.56 ± 1.50	8.52 ± 1.62	8.66 ± 1.43

P > 0.05 for all the above variables.

Discussion

Dramatic rise in the incidence of multiple gestations seems to be due to the use of ovulation induction drugs, in vitro fertilization and increase in maternal age of childbearing.[1,2,3] Morbidity and mortality of the multiple gestations is predominantly due to preterm birth. In the present study, we showed that triplets and quadruplets have a similar neonatal outcome as twins when matched for gestational age. Furthermore, in spite of a 50% rise in triplet births, neonatal mortality was significantly decreased over the study period.

Multiple gestations increase risk of preterm delivery and very low birth weight.[4] The most common complication observed in this study, was preterm delivery. This compares with a worldwide reported incidence of preterm delivery in multiple pregnancies.[10] Luke et al showed that there is a 4- fold and 8- fold increased risk for birth at < 29 weeks in triplet and quadruplet than in twin births.[11] In a very large study of birth in the USA, Alexander et al revealed that the mean gestational age at birth was 35.8 weeks in twins and 32.5 weeks in triplets.[12]

In the present study, we chose to match the triplets and quadruplets to twins for gestational age because their morbidity and mortality is predominantly due to preterm birth. After this adjustment, respiratory and non-respiratory outcome between triplets and twins were not significantly different in our series. These finding are in agreement with the findings of Luke and Ballabh's studies.[6,7]

Table 4. Neonatal mortality, birth weight and gestational age of live born triplets from 2001- 2006.

Year	Triplets	Weight (g)	Gestational age (weeks)	Neonatal Mortality
2001- 2002	n = 18	1565.83 ± 610.96	30.83 ± 5.56	62% (n = 11)
2002- 2003	n = 18	1507.00 ± 564.01	31.00 ± 2.23	33.3% (n = 6)
2003-2004	n = 25	1212.77 ± 345.04	30.20 ± 2.29	32% (n = 8)
2004-2005	n = 30	1648.75 ± 412.74	32.06 ± 3.16	16.6% (n = 5)
2005-2006	n = 32	1254.44 ± 557.94	30.25 ± 3.77	9.3 % (n = 3)

In our study incidence of cesarean section delivery was significantly higher in triplets and quadruplets than twins. It is now known that cesarean section triplets have a lower perinatal mortality and morbidity versus vaginally delivered triplets.[13] For this reason our gynecologists prefer to do cesarean section for triples and high-order pregnancies. The rate of cesarean section in our series was comparable with other studies.[7,14] Similar to Ballabh[7] and Luke's[11] studies, we found that maternal age was higher in triplet and high-order gestations.

In this study, triplets were smaller in weight compared to twins after adjustment for gestational age, suggesting growth restriction among triplets. In the study by Ballabh[7] et al, the birth weight of triplets was less than singleton although it was similar with twins. In contrast to our results, Shinwell et al,[15] found a small but statistically significant inverse relationship between plurality and gestational age and birth weight. In their study singletons were more often small for gestational age but the rate of growth restriction was similar in twins and triplets. This finding may reveal that triplets have a tendency to be born early primarily because of preterm labor due to lack of space in the uterus, whereas singletons more often suffer from problems affecting intrauterine growth.[15]

The neonatal mortality rate in multiple gestations is still high because the major determinant is prematurity and its complications. Prevention of prematurity is difficult when it is due to high-order multiple pregnancies in spite of recent advanced knowledge and research in this field. In the study by Ericson[16] in Swedish and Luke[6] in USA after correction for gestational age, triplets had higher mortality rates than twins and singletons. However, in other recent studies by Kaufman, Nielsen and Ballabh there was no difference in gestational age corrected mortality between premature singletons, twins and high multiples.[7,17,18] In this present study, gestational age-corrected mortality for high-order multiples was higher than twins but this difference was not statistically significant. Furthermore, the neonatal mortality for triplet births decreased significantly over the period of study, this should be explained by improvement in neonatal care and well equipped neonatal intensive care unit.

Similar to Ballabh et al study,[7] we did not observe any significant influence of birth order on neonatal mortality and morbidity of triplet pregnancies. In contrast, a higher incidence of neonatal death in 2nd and 3rd born triplets compared to 1st born triplet were reported during a period when triplets were delivered vaginally.[19,20] Coupling of surgical delivery with better perinatal care have improved the outcome of triplets. In our series more than 90% of triple pregnancies were delivered by c-section and attended by a neonatal fellow.

Conclusion

Triplets have a similar neonatal mortality and morbidity as twins when matched for gestational age. There is no influence of birth order on the short-term neonatal outcome of triplet pregnancies. It appears that outcome is mainly dependent on gestational age. Therefore, high multiple very low birth weight infants are still at increase risk for mortality and certain morbidities.

Conflict of interest

Authors have no conflicts of interest.

Authors' Contributions

FN carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript.

AA provide assistance in the design of the study and participated in manuscript preparation. All authors have read and approved the content of the manuscript.

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