Retinopathy of Prematurity: Single versus Multiple-Birth Pregnancies

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Purpose: To compare the frequency and severity of retinopathy of prematurity (ROP) among singleton and multiple-birth neonates referred to Farabi Eye Hospital, Tehran-Iran.

Methods: In this retrospective study, records of 99 consecutive neonates from multiple-gestation pregnancies including 68 twins, 26 triplets and 5 quadruplets who were screened for ROP from 2002 to 2004 were reviewed. The frequency, severity and risk factors for ROP were determined and compared to a group of singletons who were matched in terms of gender, birth weight (BW), gestational age (GA), oxygen therapy, respiratory distress syndrome, blood transfusion, sepsis and phototherapy.

Results: ROP was present in 12.1% of multiple-birth neonates as compared to 15.1% of singletons (P=0.53). Threshold ROP was present in 6.1% of multiple-birth neonates versus 7.1% of singletons (P=0.62). ROP was detected in 60% of quadruplets versus 9.6% of twins and triplets; threshold disease was observed in 40% of quadruplets as compared to 4.2% of twins and triplets (P<0.03). However, considering the effect of BW and GA, logistic regression analysis revealed no statistically significant difference in the frequency and severity of ROP among subgroups of multiple-gestation pregnancies.

Conclusion: There was no significant difference between multiple-birth neonates and matched singletons in terms of frequency and severity of ROP. Any apparent higher rate may be due to independent risk factors such as low birth weight and gestational age rather than multiple pregnancies per se. Screening for ROP in multiple gestation births may be conducted according to standard protocols applied for singletons.

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INTRODUCTION

Recent advances in neonatology and the increasing survival rate of premature and low birth weight neonates has increased the incidence of retinopathy of prematurity (ROP).[1,2] Low birth weight and low gestational age are two major risk factors for ROP,[3,4] however numerous other factors such as oxygen therapy, respiratory distress syndrome, sepsis, blood transfusion and multiple-birth have also been implicated.[5-8] Studies have been inconclusive regarding the association between multiple births and the incidence and severity of ROP.[9-16] This study was undertaken at a tertiary referral eye center to evaluate the effect of multiple-birth pregnancy as an isolated risk factor for ROP.

METHODS

This retrospective study was performed on hospital records of 99 consecutive multiple-birth neonates with gestational age (GA) of 30 weeks or less and birth weight (BW) of 2500 gram or less who were referred for ROP screening from neonatal wards at medical centers affiliated to Tehran Medical University from 2002-2004. Records of 99 singleton newborns with the same GA and BW were selected during the same period of time using random block sampling, these subjects were matched with the multiple-gestation group in terms of gender, gestational age, birth weight, oxygen therapy, blood transfusion, phototherapy, sepsis and respiratory distress. The study groups were then compared in terms of the prevalence, laterality and stage of ROP.

All infants underwent dilated fundus examination at 4-9 weeks by two experienced ophthalmologists using indirect ophthalmoscopy with +30 and +20 diopter aspheric lenses. Pupil dilation was achieved by twice instilling one drop of phenylephrine 1% and one drop of tropicamide 0.5% within a 5-minate interval. ROP was staged according to the international classification system.[17] Examinations were repeated 1-4 weeks thereafter based on the results of the initial examination. Threshold ROP was treated with diode laser treatment via an indirect ophthalmoscope delivery system.[18] All infants were followed until complete circumferential development of normal retinal vasculature up to the ora serrata or after the subject reached a total age of 45 weeks including gestational age. Subjects with incomplete follow-up and deceased infants were excluded from the study. Data analysis was performed using *t*-test, Chi-square test and logistic regression analysis with significance set at 0.05.

RESULTS

The multiple-birth group consisted of 68 twins (68.7%), 26 triplets (26.3%) and 5 quadruplets (5%). The frequency of ROP and threshold ROP was not statistically different among singleton and multiple-birth neonates (Table 1). Risk factors for ROP were comparable among singleton and multiple-birth infants with no statistically significant difference (Table 2). ROP was unilateral in two singletons and three cases of multiple-births. Interocular difference in ROP stage was less than two stages in bilateral cases. Mean GA was 31.96±2.89 weeks in the singleton group vs 32.12±2.52 weeks in the multiple-birth group (P=0.24). All cases of ROP occurred in neonates with BW ≤ 2000 gram or GA ≤ 30 weeks in both groups. GA was ≤30 weeks in 83.1% of multiple-births and 76.3% of singletons with ROP (P=0.38).

Table 1 Incidence of retinopathy of prematurity

	No (%)	
	Overall	Threshold stage
Singletons	15 (15.2)	7 (7.1)
Multiple-births	12 (12.1)	6 (6.1)
P value*	0.53	0.62

*Chi-square test

Mean BW was 1697.38±391.46 grams in twins and 1682.71±402.35 grams in triplets (P=0.34). Mean GA was 32.45±2.59 weeks in twins and 32.04±2.41 weeks in triplets (P=0.68). In the quadruplet subgroup, both mean BW (1116.00±368.25 grams, P=0.02) and mean GA (29.2±2.98 weeks, P=0.03) were significantly less than twins and triplets. ROP was detected in 60% of quadruplets vs 9.6% of twins and triplets (P<0.03), with threshold ROP in 40% of quadruplets vs 4.2% of twins and triplets (P<0.03). Considering the effect of GA and BW, regression analysis revealed no significant difference (P=0.79) between quadruplets and twins and triplets.

Multivariate logistic regression analysis revealed that only GA<33 weeks (OR=4.31; 95% confidence interval [95%CI], 1.63-19.96) and BW<1500 gram (OR=1.92; 95%CI, 1.04%-7.97%) had significant correlation with ROP; other potential risk factors such as multiple-birth, sex, oxygen therapy and sepsis had no significant effect.

Table 2 Risk factors of retinopathy of prematurity in the study groups

Risk factors		No (%)		P value*
		Singleton	Multiple-birth	
Sex				
	Male	52 (52.5)	51 (51.5)	0.89
	Female	47 (47.5)	48 (48.5)	
Gestational age				
	≤ 33 wk	69 (69.7)	70 (70.7)	0.87
	34-33wk	30 (30.3)	29 (29.3)	
Birth weight (gram)				
	650-1000	7 (7.1)	9 (9.1)	
	1001-1250	14 (14.1)	13 (13.1)	
	1251-1500	21 (21.2)	22 (22.2)	0.94
	1501-2000	43 (43.4)	40 (40.4)	
	2001-2500	14 (14.2)	15 (15.2)	
Oxygen therapy		68 (68.7)	63 (63.7)	0.27
RDS		35 (35.4)	30 (30.3)	0.44
Blood transfusion		14 (14.1)	12 (12.1)	0.57
Septicemia		22 (22.2)	26 (26.3)	0.50
Phototherapy		63 (63.7)	66 (66.7)	0.66

RDS, respiratory distress syndrome
*Chi-square test

The quadruplet subgroup included 5 neonates from three pregnancies. In one pregnancy following use of clomiphene, two neonates were alive who had GA of 26 weeks and BW of 940 and 800 grams; both had bilateral stage 3 threshold ROP and underwent laser therapy. In another pregnancy, only one neonate with GA of 30 weeks and BW of 990 grams was alive who had stage 2 ROP but did not require laser therapy during the follow-up period. Another pregnancy which occurred following using clomiphene resulted in two live neonates with GA of 32 weeks and BW of 1500 and 1350 grams neither of whom had any sign of ROP.

DISCUSSION

Recent years have witnessed an increasing number of multiple pregnancies which is due to higher age at first pregnancy, extensive use of hormones and development of new methods for treatment of infertility.[19] In the USA, the rate of very low BW is 10 times higher in multiple versus singleton pregnancies.[20] The higher rate of mortality and morbidity in multiple-birth neonates is mainly due to low BW and low GA; multiple pregnancy per se does not seem to be an independent risk factor.[21-23]

The relationship between multiple pregnancies and ROP has been investigated since 50 years ago. Despite advances in diagnostic and therapeutic modalities, controversy still surrounds the correlation between multiple gestation and ROP. For the first time in 1956, the relative risk for cicatricial ROP was reported to be 3 times higher in multiple pregnancies as compared to singletons; however, the study groups were not matched for BW and GA.[9] This finding was not confirmed in another study in 1977.[11] By performing regression analysis, Bossi et al[24] reported that twins are at higher risk of ROP as compared to singletons and in 1993, Schaffer et al[12] reported an increased risk of threshold ROP in twins as compared to singleton neonates. However, in 1997, Friling et al[10] found no significant difference in the incidence and severity of ROP after matching singletons and multiple-births for other risk factors. In yet another study, Friling et al[16] reported an increased risk for developing

advanced stages of ROP in singletons versus multiple-births.

We evaluated singleton and multiple-birth neonates matched for established risk factors for ROP including BW, GA and oxygen therapy and found no difference between them in terms of the incidence and severity of ROP. In a similar study, Friling et al[10] compared singletons and multiple-births (twins and tripletes) who were matched for GA, BW, respiratory distress and oxygen therapy and reported no significant difference between them in terms of the incidence of ROP.

Our results demonstrated that the incidence of ROP in quadruplets (60%) was significantly ($P<0.03$) higher than twins and tripletes (9.6%); however, after adjusting for GA and BW regression analysis revealed no significant difference ($P=0.79$). Although the quadruplet subgroup included only five neonates from three pregnancies, the relationship between GA and BW and ROP was demonstrated very well. We also found no significant difference between twins and tripletes in the incidence of ROP indicating that the number of gestations per se is not a risk factor for ROP. Multivariate logistic regression analysis revealed that only low BW and low GA are important risk factors; even oxygen therapy had no significant effect on the occurrence of ROP which is consistent with findings from our previous study.[25] Limitations of the current study include the relatively small sample size which was retrieved from a limited number of neonatal care centers and the fact that the proportion of monozygotic multiple-births was undetermined.

In summary, the higher incidence of ROP in multiple-birth neonates seems to be mainly secondary to lower BW and GA which are the most important risk factors for ROP in both singleton and multiple-birth groups. The ROP screening protocol for singletons may be applied to multiple pregnancy births. Larger studies are needed to confirm our findings. We suggest evaluation of monozygotic condition in future studies to evaluate the possible role of heredity.

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