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Retinopathy of prematurity in extremely premature infants: multiple births versus single births

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Background/aim: This study aimed to compare the incidence of any stage of retinopathy of prematurity (ROP) and type 1 ROP between extremely preterm multiple- and single-birth infants.

Materials and methods: In this retrospective study, we included extremely preterm infants who were ≤27 weeks of gestational age at birth. The screened infants were divided into two groups: single and multiple births. The incidence of any stage of ROP and type 1 ROP was compared between the groups.

Results: This study included 301 infants; 225 were in the single-birth group and 76 were in multiple-birth group. The incidences of any stage of ROP and type 1 ROP among all infants were 70.7% (213 of 301) and 16.6% (50 of 301), respectively. Regression analysis showed that lower birth weight (OR = 0.99, P = 0.004) and longer length of stay in hospital (OR = 1.02, P = 0.002) were significantly correlated with any stage of ROP. Compared to single-birth infants, the risk of any stage of ROP and type 1 ROP did not statistically increase for multiple-birth infants (P > 0.05).

Conclusion: This study showed that multiple birth had no significant correlation with ROP development in extremely preterm infants.

Key words: Retinopathy of prematurity, extremely preterm infants, multiple birth

1. Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina, which is an important cause of childhood blindness and visual impairment in developing countries (1). Continuous improvements in neonatal intensive care have led to increased rates of survival of extremely preterm infants in Turkey. As a result, there are more extremely premature infants, who are at risk of developing ROP (2). In Turkey, according to results of screening performed in schools for visually impaired children, ROP is currently the leading avoidable and treatable cause of childhood blindness (3).

Over the past three decades, the rates of multiple births have risen in many countries due to increases in ovulation induction, in vitro fertilization, and childbearing at older ages; this situation results in an increased number of premature births (4–7). In many countries in the European Union, approximately half of multiple-birth infants are born preterm, and they account for 18%–25% of preterm births in Europe (6). In Turkey, according to unpublished data from the multicenter TR-ROP trial (clinicaltrials.gov, Identifier: NCT02814929), 28% of preterm infants who were ≤32 weeks of gestational age (GA) at birth were from multiple births.

There are conflicting results in the literature on multiple birth as a risk factor for ROP development. Some studies found that multiple birth is a risk factor for ROP (8–10); however, this was not found in others (11–14).

The objective of the present study was to compare the incidences of any stage of ROP and type 1 ROP between multiple- and single-birth infants and to define whether multiple birth is a risk factor for ROP development in extremely preterm infants who are at the greatest risk for ROP development.

2. Materials and methods

Records of infants from the Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Department of Ophthalmology, which is a reference center for the diagnosis and treatment of ROP, were retrospectively scanned. Preterm infants who were screened for ROP between February 2010 and May 2016 with a GA of ≤27

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weeks at birth and inpatients at the neonatal intensive care unit (NICU) were included in the study. Infants who were referred from another center, who were lost to follow-up, or who had a major systemic and/or eye abnormality were excluded. GA, birth weight (BW), sex, single/multiple-birth status, ROP examination results, treatment type for ROP if required, and postmenstrual age (PMA) at first ROP development and type 1 ROP onset were recorded from the files. Multiple-birth infants were defined as infants born after pregnancies with two or more fetuses simultaneously. The screened infants were divided into two groups: single and multiple birth. The stage of ROP, percentages of any stage of ROP and type 1 ROP, type of treatment, and PMA at first ROP development and type 1 ROP onset were identified in both groups.

The first ROP screening examination was performed at the 30th or 31st week of PMA in the NICU. PMA was calculated by combining GA at birth and postnatal age. Tropicamide 0.5% (Tropamid, Bilim, Turkey) and phenylephrine 2.5% (Mydfrin, Alcon, USA) were administered twice at an interval of 5 min at 1 h prior to the examination for pupil dilatation. The examination was performed under topical anesthesia with proparacaine HCl drops (Alcaine 0.5%, Alcon, Belgium). The examinations were performed using a lid speculum and scleral depressor with an indirect binocular ophthalmoscope (Omega 2C, Heine, Germany) with a 20- or 28-diopter lens. Findings were classified according to the International Classification of Retinopathy of Prematurity (15). Aggressive posterior AP-ROP was defined as severe plus disease, flat neovascularization in zone 1 or posterior zone 2, intraretinal shunting, or hemorrhages (15). The follow-up examinations of the infants were scheduled based on the persistence and severity of ROP.

Indications for treatment were for those whose retinopathy met the criteria established by the Early Treatment for Retinopathy of Prematurity study (16). According to these criteria, included were infants with type 1 ROP (high-risk prethreshold ROP), defined as zone I, any stage of ROP with plus disease; zone I, stage 3 ROP without the plus disease; or zone II, stage 2 or 3 with the plus disease. Treatments were provided using either laser photocoagulation or intravitreal bevacizumab injection (Avastin; Genentech Inc., South San Francisco, CA, USA). Intravitreal bevacizumab injection was performed in the eyes in which AP-ROP was detected. All injection doses for bevacizumab were 0.625 mg (0.025 mL). If the infants did not respond to intravitreal bevacizumab injection or if ROP recurred, the patients were treated further, using laser treatment. Other infants who met the criteria for type 1 (high-risk prethreshold) ROP were treated with transpupillary panretinal photocoagulation using an 810-nm diode laser (IRIDEX; OcuLight SLX, Mountain View, CA, USA).

This descriptive and retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the hospital's ethics committee.

Statistical analysis was performed using SPSS 21.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± SD and categorical variables are presented as number and percentage. The chi-square test was used for categorical variables. After normal distribution was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests, the differences between the means were analyzed by the t-test for normally distributed data and the Mann–Whitney U test for nonnormally distributed data. $P < 0.05$ was accepted as being statistically significant.

Multivariate logistic regression analysis was performed to evaluate the potential role of different risk factors to predict any stage of ROP or type 1 ROP as a binary outcome. For this purpose, variables such as BW, GA, and length of stay in the hospital (which were statistically significant in previous univariate logistic regression analyses) were included in the model each time (less than 10% of the cases). The backward stepwise (likelihood ratio) model was used for logistic regression analysis. The Nagelkerke R square index was then used to compare the strength of each model.

3. Results

Of the 449 extremely preterm infants identified from the records, 148 who were referred to another NICU for screening or for treating ROP were excluded. The remaining 301 extremely premature infants (160 males, 53.2%; 141 females, 46.8%) were included in this study. In the whole group, the overall mean BW was 970.90 ± 178.36 g (range: 540–1610 g) and the mean GA was 26.0 ± 1.0 weeks (range: 23–27 weeks).

The number of single-birth infants was 225 (74.8%) and the number of multiple-birth infants was 76 (25.2%). The multiple-birth group comprised 65 sets of twins (85.5%), 6 sets (7.8%) of triplets, and 5 sets of (6.5%) quintuplets. A comparison of the study groups according to the mean GA, mean BW, mean length of hospital stay, and sex is shown in Table 1. No statistical significance was observed between the groups regarding sex, GA, BW, and length of stay in hospital (Pearson chi-square test and Mann–Whitney U test, $P > 0.05$).

The overall incidence of any stage of ROP and type 1 ROP was 70.7% (213 of 301 preterm infants) and 16.6% (50 of 301 preterm infants), respectively. The mean PMA at the onset of ROP and the development of type 1 ROP in all infants was 32.4 ± 1.4 (range: 30–37) and 35.0 ± 1.7 (range: 32–40) weeks, respectively.

Table 1. A comparison of the distribution of sex and mean gestational age, birth weight, and length of stay in hospital between the groups.

		Single-birth group (n = 225)	Multiple-birth group (n = 76)	P-value
Sex (n, %)	Male	123 (54.7%)	37 (48.7%)	0.36*
	Female	102 (45.3%)	39 (51.3%)	
Gestational age (weeks)	Mean ± SD	26.0 ± 1.0	26.0 ± 1.0	0.19†
	Range	(23.0–27.0)	(23.0–27.0)	
Birth weight (g)	Mean ± SD	970.10 ± 182.47	971.01 ± 166.90	0.95†
	Range	(540–1610)	660–1320	
Length of stay in hospital (days)	Mean ± SD	79 ± 27	80 ± 23	0.44†
	Range	(27–184)	(14–147)	

SD: Standard deviation,*: Pearson chi-square test, †: Mann–Whitney U test, n: number.

There was no difference between the groups in terms of any stage of ROP and type 1 ROP. Furthermore, there was no difference between the groups in terms of PMA at ROP development and treatment. A comparison of the distribution of any stage of ROP, type 1 ROP, treatment type, and PMA at first ROP development and type 1 ROP onset in the groups is shown in Table 2.

Logistic regression analysis of the 301 infants indicated that lower BW (odds ratio (OR) = 0.99, 95% confidence interval (CI): 0.99–0.99, P = 0.004) and longer length of stay in hospital (OR = 1.02, 95% CI: 1.01–1.04, P = 0.002) were significantly correlated with ROP while multiple birth, sex, and GA had no significant effects. Logistic regression analysis results for risk factors for type 1 ROP revealed that only longer length of stay in the hospital (OR = 1.03, 95% CI: 1.01–1.04, P = 0.001) was effective. Multiple birth had no effects on the development of any stage of ROP and type 1 ROP (any stage of ROP: OR = 1.69, 95% CI: 0.90–3.18, P = 0.10; type 1 ROP: OR = 0.70, 95% CI: 0.32–1.48, P = 0.35) (Table 3).

Table 2. A comparison of the distribution of any stage of ROP and type 1 ROP and the treatment type between the groups.

		Single-birth group (n = 225)	Multiple-birth group (n = 76)	P-value
ROP (n, %)	Yes	164 (72.9%)	49 (65.5%)	0.16*
	No	61 (27.1%)	27 (34.5%)	
PMA at ROP (weeks)	Mean ± SD	32 ± 1	33 ± 2	0.67 †
	Range	(30–37)	(30–37)	
Type 1 ROP (n, %)	Yes	36 (16.0%)	14 (18.4%)	0.62*
	No	189 (84.0%)	62 (81.6%)	
PMA at treatment (weeks)	Mean ± SD	35 ± 2	35 ± 2	0.18 †
	Range	(32–40)	(32–38)	
Treatment type (n, %)	Laser	25 (11.1%)	11 (14.4%)	NA
	Anti-VEGF	8 (3.5%)	2 (2.6%)	
	Laser + Anti-VEGF	3 (1.3%)	1 (1.3%)	

*: Pearson chi-square test, ROP: retinopathy of prematurity, †: Mann–Whitney U test, n: number, PMA: postmenstrual age.

Table 3. Logistic regression analysis results for risk factors for any stage of ROP and type 1 ROP.

	Any stage of ROP			Type 1 ROP		
	P-value	OR	95% CI	P-value	OR	95% CI
Sex	0.414	1.26	0.71–2.24	0.065	1.99	0.95–4.16
Gestational age (weeks)	0.550	0.76	0.56–1.35	0.261	0.80	0.54–1.17
Birth weight (g)	0.004	0.99	0.99–0.99	0.097	0.99	0.99–1.00
Length of stay in hospital (days)	0.002	1.02	1.01–1.04	0.001	1.03	1.01–1.04
Multiple birth	0.100	1.69	0.90–3.18	0.353	0.70	0.32–1.48

ROP: Retinopathy of prematurity, OR: odds ratio, CI: confidence interval.

4. Discussion

This study investigated the incidence of any stage of ROP and type 1 ROP in 301 extremely preterm infants who were ≤27 weeks of GA at birth and who were born of multiple and single births in the NICU at a single medical center; no statistically significant difference was found regarding the incidence and severity stage of ROP between the groups. Controversies exist regarding the influence of multiple birth on the development of ROP according to the data presented in the literature. In a study conducted by Motta et al. (10), the incidence of any stage of ROP was higher in the multiple-birth group; there was no significant difference between the single- and multiple-birth groups regarding threshold disease rates. Sood et al. (9) concluded that multiple birth might be an independent risk factor for ROP development; however, they stated that further studies, particularly with a higher number of multiple-birth infants, would yield more statistically reliable results. In a Canadian study that compared data from 24 neonatal clinics, the rate of severe ROP was lower in multiple-birth infants than in single-birth infants (17).

Friling et al. (18) found that the incidence of ROP with or without treatment requirement was statistically higher in single-birth infants than in multiple-birth infants. In their study groups, GA and BW were lower in single-birth infants than in multiple-birth infants. In our study, the groups were similar in terms of GA, BW, and length of stay in hospital. Therefore, there was no significant difference between the groups in terms of any stage of ROP and type 1 ROP.

Low BW and early GA are the main issues leading to preterm morbidity rates in multiple births. Garite et al. (14) showed that neonatal morbidities associated with adverse long-term outcomes (intraventricular hemorrhage, ROP, necrotizing enterocolitis) were not different between multiple-birth infants and single-birth infants. Some studies compared the incidence of ROP between multiple- and single-birth infants and obtained similar results to ours (11–13). Friling et al. (12) showed that BW remains the most important predictive factor for the development of ROP. Riazi-Esfahani et al. (13) concluded that early GA and low BW were the most important risk factors for ROP development in single- and multiple-birth groups. In our study, multivariate logistic regression analysis revealed that lower BW and longer length of stay in hospital were significantly correlated with ROP development; however, multiple birth did not show any significant correlation.

The expectation of a quick outcome during the application of assisted reproductive techniques increases the risk of multiple birth (19). In Turkey, after single embryo transfer was legally adopted with changes made to the health policy from 2010, a significant decrease was seen in the rate of multiple births and perinatal complications (20,21). ROP is a major perinatal complication seen in premature infants. Our study also included preterm infants who were in the NICU in 2010 and after.

The present study showed that the overall incidences of any stage of ROP and type 1 ROP were 70.7% and 16.6%, respectively, in infants who were ≤27 weeks of GA at birth. The incidence of type 1 ROP was higher in our study in Turkey than in studies conducted in developed countries such as Canada and the United States (22,23). In Turkey, Baş et al. (2) reported that the incidence of any stage of ROP was 52.8% and that of type 1 ROP was 15.1% in extremely premature infants who were ≤28 weeks of GA at birth in a multicenter ROP study. The incidence of ROP was higher in our study, which can be explained as our study was conducted among infants who were ≤27 weeks of GA at birth. In Japan, Aikawa et al. (24) found that the incidence of ROP was 70.6% and that of severe ROP requiring laser treatment was 15.7% in extremely preterm infants. These rates were similar to those in our study.

One of the main limitations of our study was the inability to evaluate other systemic risk factors for ROP development. However, we attempted to ensure homogenization for perinatal care by excluding infants

who were referred from external centers and including those who had been monitored in the NICU. The fact that the groups did not have equal numbers of infants may be another limitation, but it was not possible to correct this due to the low incidence of multiple births. However, similar BWs, GAs, and lengths of stay in hospital between the groups seem to a strength of our study.

In conclusion, to the best of our knowledge, this is the first study on the effect of multiple birth on ROP in extremely preterm infants. Compared to single-birth infants, the risk of any stage of ROP and type 1 ROP did not statistically increase in multiple-birth infants. However, prospective studies on a larger number of infants in whom perinatal risk factors are also evaluated could help clarify the issue.

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