Original Article

Effect of birth weight on retinopathy of prematurity in discordant twin pairs

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Purpose: Since twin pairs with discordance have equal gestational age (GA), discordant twins may constitute an appropriate group to investigate the specific effect that birth weight (BW) has on the development of retinopathy of prematurity (ROP). The present study aims to investigate the effect of BW on any and severe stages of ROP development in twin pairs. **Methods:** Fifty-two discordant twin pairs (104 preterms) born ≤32 gestational weeks, who were diagnosed with a minimum of 18% discordance between their BWs, were retrospectively analyzed. Twin pairs were separated into two groups based on the BW of each pair. The rate of any stage of ROP, Type 1 ROP, and perinatal risk factors were compared statistically among twin pairs. **Results:** The rate of any stage of ROP and Type 1 ROP was 24.0% and 4.8% in the whole group, respectively. A statistically significant difference was shown between lower and higher BW groups at any stage of ROP development (34.6% vs. 13.4%, $P = 0.02$). However, no difference was observed in Type 1 ROP development (7.7% vs. 1.9%, $P = 0.17$). No significant differences were found between twin pairs regarding neonatal morbidities. The number of small GA (SGA) infants in the smaller twin group was statistically higher than larger group and regression analysis showed that being SGA had significant correlation with any stage of ROP (odds ratio: 4.98, $P = 0.02$). **Conclusion:** This study showed that BW serves an effective role at any stage of ROP development in discordant twin pairs; however, no significant difference in terms of Type 1 ROP.

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Retinopathy of prematurity (ROP) is a serious vasoproliferative disorder in the incompletely vascularized retina of premature infants. It currently represents the leading avoidable cause of childhood blindness and visual impairment, especially in developing countries.[1-3] Several risk factors have been demonstrated to be associated with the development of ROP including low birth weight (BW), early gestational age (GA), being small for GA (SGA), multiple pregnancies, uncontrolled oxygen supplementation, mechanical ventilation, sepsis, apnea, anemia, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), and blood transfusions.[4-6]

The risk of preterm birth and low BW increases in multiple pregnancies.[7-9] In approximately one-fourth of twin pregnancies, a minimum of 15% discordance has been determined between BWs.[10] It is assumed that any differences of <15% between BWs are considered physiological and the result of individual genetic differences.[11,12] Breathnach *et al*.[11] found that the threshold for growth discordance is 18% for twin pairs without twin-twin transfusion syndrome in a large multicenter prospective study. The results of studies about the relationship between inter-twin BW discordance and ROP are contradictory.[13-16] One reason for this is that BW discordance rates in these studies are different.

Low weight at birth has been known as one of the most important known risk factors for the development of ROP. However, the BW of premature babies is strongly associated with GA and which risk factor is more important in developing ROP remains unknown. Since twin pairs with discordance in terms of BW share both the same prenatal risks and have equal GA, discordant twins constitute an appropriate group to investigate the specific effect that BW has on the development of ROP.

The present study aims to investigate the effect of BW on any and severe stages of ROP development in twin pairs with at least 18% discordance in terms of BW.

Methods

This study was performed in accordance with the principles outlined in the Declaration of Helsinki, following approval by the Hospital Ethics Committee. A retrospective review was conducted on medical records of twin pairs with a GA ≤32 weeks, who were screened for ROP between March 2010 and May 2016. The difference between BWs was calculated separately for each twin pair using the following formula:

(BW of higher BW twin − BW of lower BW twin)/BW of higher BW twin × 100.

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The criterion for BW discordance was defined as BW differences between the higher and the lower twin of ≥18%.[11] Twins with congenital eye anomaly or twin-to-twin transfusion syndrome were excluded from the study.

Twins were separated into the following two groups: the twin with the lower BW from each pair and their cotwin with the higher BW. The BWs of preterms, hospitalization periods, development of any stage or zone of ROP, and type 1 ROP, laser treatment, and the presence of perinatal risk factors that may affect ROP development were noted from the medical records for both groups. Perinatal risk factors that may affect ROP development included being SGA, respiratory distress syndrome, NEC, IVH, PDA, period under mechanical ventilation (days), period under nasal continuous positive airway pressure (CPAP) (days), period under free oxygen treatment (days), presence of sepsis, and need for two or more blood transfusions. SGA was defined as BW below the 10th percentile for the GA using the Fenton growth chart for prematurity infants.

Screening examinations for ROP were conducted 4 weeks after birth in preterms older than 27 weeks and in the 30th or 31st week in extremely premature cases (GA ≤27 weeks) depending on the clinical state of the infant.[17] For pupil dilatation, 2.5% phenylephrine (Mydfrin, Alcon, USA) and 0.5% tropikamid (Tropamide, Bilim İlaç, Turkey) were instilled twice. Topical anesthesia was performed with 0.5% proparacaine hydrochloride (Alcaine, Alcon, USA) and was instilled immediately before the examination. All examinations were performed with binocular indirect ophthalmoscopy using a pediatric eye speculum and scleral depressor. The severity of ROP was graded according to the revised international classification of ROP.[18] Control examinations of infants were planned according to both the presence and severity of ROP.

Preterms diagnosed as type 1 ROP (high-risk prethreshold) according to the criteria for the early treatment of retinopathy of premature (ETROP) study group (Zone 1 any stage of ROP with plus disease; Zone 1, Stage 3 ROP without plus disease; and Zone 2, Stage 2 or 3 ROP with plus disease), were treated with laser photocoagulation.[19] Laser photocoagulation was performed using an 810-nm diode laser (İridex, Oculight SL, USA) to the entire avascular retina under remifentanil sedoanalgesia in the neonatal intensive care unit.[20]

Preterms diagnosed as type 2 ROP (low-risk prethreshold) (Zone 1, Stage 1 or 2 ROP without plus disease, and Zone 2, Stage 3 ROP without plus disease) spontaneously regressed without being treated and were followed up with close observations until vascularization was completed.

Statistical analysis was performed using SPSS Version. 21.0 for Windows (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Continuous variables are presented as mean ± standard deviation (SD); categorical variables are defined as numbers and percentages. Pearson's Chi-square test and Fisher's exact test were used for categorical variables. After evaluating whether the data followed a normal distribution by performing both Kolmogorov–Smirnov and Shapiro–Wilk tests, differences between means were carried out by using a *t*-test for normally distributed data and the Mann–Whitney U-test for data that were not normally distributed.

Multivariate logistic regression analysis was performed to evaluate the potential role of other risk factors to predict any stage of ROP as a binary outcome. For this purpose, variables such as BW, being SGA, days on nasal CPAP, total days on oxygen, PDA, need for transfusion (≥2) and length of stay in the hospital (which were statistically significant in previous univariate logistic regression analyses) were included in the model. The enter method was used for logistic regression analysis. The Nagelkerke R-square index was then used to explanatory variance of the model.

Results

Fifty-six discordant twin pairs (112 preterms) who were diagnosed with a minimum of 18% discordance between their BWs were identified from reviewed records. Of these 56 twin pairs, 3 twin pairs (6 preterms), in whom twin-to-twin transfusion was determined, and 1 twin pair (2 preterms), one of whom had an iris and choroidal coloboma, were excluded from the study, thus accounting for 8 preterms being excluded overall. Evaluation in the present study was conducted in 52 discordant twin pairs (104 preterms). Fifty-five female and 49 male preterms were included in this study. The mean GA (mean ± SD) was 30 ± 2.0 weeks (26–32 weeks), and the mean BW (mean ± SD) was 1331 ± 385 g (490–2350 g). The mean discordance rate (mean ± SD) in terms of BW between twin pairs of the whole group was 31.3 ± 10.9 (18%–70%). In the smaller twin group, 19 infants (36.5%) were SGA. There was no SGA infant in the larger twin group. The difference in the number of SGA infants between the two groups was statistically significant ($P = 0.001$; Fisher's exact test).

Mean BW of preterms, gender, the rate of any stage of ROP, the rate of type 1 ROP development and perinatal risk factors, and statistical comparisons in both groups are shown in Tables 1 and 2, respectively. Although a statistically significant difference was observed between the groups in terms of length of hospital stay, no differences were found between groups in terms of other perinatal risk factors. When groups were evaluated in terms of ROP development, a statistically significant difference was observed in terms of any stage of ROP development ($P = 0.02$; Pearson's Chi-square); however, no difference was observed in type 1 ROP development ($P = 0.17$; Fisher's exact test).

The rate of any stage ROP and type 1 ROP were 24.0% ($n = 25$) and 4.8% ($n = 5$) in the whole group, respectively. Comparative demographic data of twin preterms diagnosed with type 1 (high-risk prethreshold) and Type 2 (low-risk prethreshold) ROP according to the ETROP study and ROP screening results are shown in Table 3. Fundus images of one of the twin pairs are shown in Fig. 1. In 15 of 52 twin pairs (28.8%), lower BW infants demonstrated higher stages of ROP than their larger-sized siblings. In three twin pairs (5.7%), higher stages of ROP were observed in higher BW twins than in their smaller-sized siblings. In one twin pair (1.9%), the same stage of ROP was determined. Preterms requiring treatment were evaluated in terms of BW and GA and were ≤1000 g and ≤27 weeks, respectively.

Multivariate logistic regression analysis of the 104 infants indicated that only being SGA (odds ratio [OR]: 4.983; 95% confidence interval 1.346–18.446, $P = 0.022$) was independent risk factor for any stage ROP. Other risk factors had no

significant effect. The results of logistic regression analysis exploring the relationship between development of any stage ROP and perinatal risk factors are shown in Table 4.

Discussion

The evaluation in the present study was conducted in 52 twin pairs who were diagnosed with a minimum of 18% discordance between their BWs. This study showed that BW serves an effective role at any stage of ROP development in twin pairs, but no statistically significant difference was determined between groups in terms of type 1 ROP development. Multivariate regression analysis indicated that being SGA was independently associated with any stage of ROP in discordant twins.

Fellows *et al*.[16] demonstrated that among twin pairs with a minimum of 15% discordance, 38% of infants with lower BW had a more advanced stage of ROP, whereas 23% of infants with higher BW had a more advanced stage of ROP. The authors determined a requirement for laser treatment in two babies in twin pairs with higher BW and observed that other twin pairs with lower weight progressed to spontaneous regression. This is in agreement with the present study, as a more advanced stage of ROP was observed in infants who were smaller in size in 28.8% (15 twin pairs) of the 52 twin pairs and in infants who were larger in size in 5.7% (3 twin pairs), while the same stage of ROP was observed in 1.9% (1 twin pair). One of the larger preterms diagnosed with advanced stage ROP underwent a shunt operation twice because of hydrocephaly, and two others underwent longer oxygen treatment than their twins who were kept under mechanical ventilation because of respiratory distress syndrome. As emphasized by Fellows *et al*. during ROP screenings in twin preterms, the infant with the higher BW may develop a more advanced stage of ROP, and clinical risk factors should be considered when screening ROP.

Table 1: Demographic data and retinopathy of prematurity results of between the smaller and larger twin groups in terms of birth weight

	Smaller (*n*=52)	Larger (*n*=52)	*P*
Birth weight (g), mean±SD (range)	1093±259 (490-1610)	1570±341 (900-2350)	<0.001*
Small for gestational age, *n* (%)	19 (36.5)	0	<0.001†
Gender, *n* (%)			
Male	20 (38.5)	29 (61.5)	0.07‡
Female	32 (55.8)	23 (44.2)	
Any stage ROP, *n* (%)	18 (34.6)	7 (13.4)	0.02‡
Type 1 ROP, *n* (%)	4 (7.7)	1 (1.9)	0.17†

*Mann–Whitney U-test, †Fisher's exact test, ‡Pearson's Chi-square test. ROP: Retinopathy of prematurity

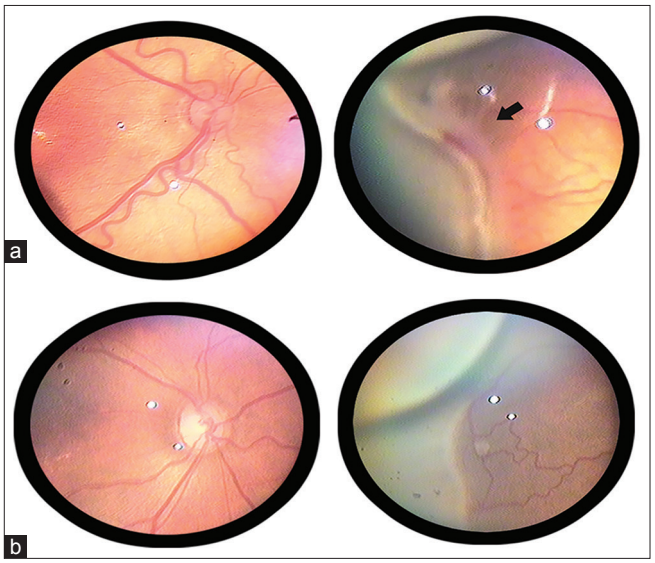

Figure 1: Representative fundus images of one of the twin pairs in the study. (a) Fundus images of right eye of smaller twin born at 26 weeks' gestation with a birth weight of 910 g taken at 37 weeks postmenstrual age showing Stage 3 retinopathy of prematurity with extraretinal fibrovascular proliferation (black arrow) in Zone 2 with plus disease suggestive of "Type 1 retinopathy of prematurity". (b) Fundus images of the right eye of larger twin born at 26 weeks' gestation with a birth weight of 1170 g taken at 37 weeks postmenstrual age showing Stage 2 retinopathy of prematurity in Zone 2 without plus disease suggestive of "Type 2 retinopathy of prematurity"

Table 2: Perinatal risk factors between the smaller and larger twin groups in terms of birth weight

	Smaller (*n*=52)	Larger (*n*=52)	*P*
Length of stay in the hospital (days), mean±SD (range)	56±26 (8-137)	39±27 (2-147)	<0.001*
Days on MV, mean±SD (range)	1±2 (0-14)	1±3 (0-15)	0.42*
Days on nasal CPAP, mean±SD (range)	3±3 (0-15)	2±2 (0-12)	0.91*
Days on supplemental O_2, mean±SD (range)	8±12 (0-56)	8±9 (0-40)	0.99*
Total days on O_2, mean±SD (range)	11.9±14.8 (0-71)	11.3±12.6 (0-67)	0.68*
Respiratory distress syndrome, *n* (%)	39 (75.0)	37 (71.2)	0.65†
Apnea, *n* (%)	23 (44.2)	21 (40.4)	0.70†
Patent ductus arteriosus, *n* (%)	15 (28.8)	13 (25.0)	0.66†
Sepsis, *n* (%)	6 (11.5)	3 (5.8%)	0.30‡
Necrotizing enterocolitis, *n* (%)	2 (3.8)	1 (1.9)	0.60‡
Intraventricular hemorrhage, *n* (%)	5 (9.6)	2 (3.8)	0.24‡
Transfusion (≥2), *n* (%)	20 (38.5)	10 (19.2)	0.47†

*Mann–Whitney U-test, †Pearson's Chi-square test, ‡Fisher's exact test. MV: Mechanical ventilation, CPAP: Continuous positive airway pressure

Table 3: Comparative demographic data and retinopathy of prematurity examination results of the twin pairs diagnosed with Type 1 retinopathy of prematurity (high-risk pre-threshold) and Type 2 retinopathy of prematurity (low-risk prethreshold) according to Early Treatment for Retinopathy of Prematurity study

Patients	Gender	BW (g)	GA (week)	Discordance rate (%)	ROP status	Treatment status
Twin 1	Female	1370	29	24	Type 2 ROP	Regression
	Male	1030	29		No ROP	-
Twin 2	Male	1400	27	28	Zone 3 Stage 1	Regression
	Female	1000	27		Type 1 ROP	Laser
Twin 3	Male	1170	26	22	Type 2 ROP	Regression
	Female	910	26		Type 1 ROP	Laser
Twin 4	Female	1070	26	28	Type 1 ROP	Laser
	Male	770	26		Type 1 ROP	Laser
Twin 5	Female	880	29	34	Type 1 ROP	Laser
	Female	1340	29		Zone 2 Stage 1	Regression
Twin 6	Male	910	26	18	No ROP	-
	Female	740	26		Type 2 ROP	Regression
Twin 7	Male	1935	32	24	Type 2 ROP	Regression
	Female	1470	32		No ROP	-

BW: Birth weight, GA: Gestational age, ROP: Retinopathy of prematurity

Table 4: Results of the multivariate logistic regression analysis exploring the relationship between development of any stage retinopathy of prematurity and perinatal risk factors

	P	OR	95% CI
Birth weight	0.501	1.001	(0.99-1.00)
Small for gestational age	0.022	4.983	(1.32-18.44)
Length of stay in the hospital (days)	0.521	0.656	(0.98-1.04)
Days on nasal CPAP	0.099	0.216	(0.03-1.33)
Total days on O_2	0.247	1.030	(0.98-1.08)
Patent ductus arteriosus	0.263	-0.725	(1.18-2.37)
Transfusion (≥2)	0.658	0.703	(0.14-3.34)

OR: Odds ratio, CI: Confidence of interval, CPAP: Continuous positive airway pressure

In our study, the number of SGA infants in the smaller twin group was statistically higher than that of the larger twin group. Multivariate logistic regression analysis of the 104 infants indicated that being SGA (OR: 4.983 $P = 0.004$) had significant correlation with any stage of ROP. Some studies suggest that being born SGA increases the risk for the development of any stage and severe stage ROP in preterm babies.[21,22] Factors that are considered an increased risk for development of ROP in SGA babies include chronic uterine hypoxia, abnormal growth factor levels, nutrient restriction, and antioxidant deficiency.[22,23] It is showed that umbilical cord serum Insulin-like growth factor 1 (IGF 1) concentrations are lower at preterm birth and following intrauterine growth restriction.[24] Low serum IGF-1 levels in premature infants in the postnatal period are known to increase the risk and severity of ROP.[25,26] Anaya-Alaminos *et al*.[13] demonstrated that advanced stage ROP was statistically higher in the lower BW twins than their larger-sized siblings. They showed that the nonvascularized area of the temporal retina was significantly larger in the lower BW group at the first ROP examination. Thus, the larger avascular retina may be a greater hypoxic stimulus for the subsequent release of angiogenic factors that cause the development of severe ROP. We did not have a chance to assess the size of the avascular area as this was a retrospective study.

Two previous twin-paired studies reported that GA, namely, maturity, serves a more effective role than BW in both ROP development and treatment indication.[14,15] Wang *et al*.[14] set the discordance rate at 15%, and in the second study by Woo *et al*.[15], no minimum value for the discordance rate was required. In the current study, however, BW played a statistically significant role in the ROP development in particular. The difference observed in the present study and other previous studies may be accounted for by the difference in discordance rates. The mean discordance rate (mean ± SD) in terms of BW between twin pairs of the whole group was 31.3 ± 10.9 (18%–70%) in this study. Because of our study's mean discordance rates are high, BW played a statistically significant role in the ROP development in particular. Furthermore, previous studies stated that the lower the infants' BWs are, the higher the perinatal risk factors; however, it is difficult to evaluate the individual effect of BW on ROP. In the present study, no statistically significant difference was determined between the two groups in terms of perinatal risk factors, except for hospitalization period. When the whole group was evaluated, it was determined that preterms diagnosed with type 1 ROP were in the extremely premature (≤27 weeks) or extremely low BW (≤1000 g) preterm group.

A limitation of the study was that prenatal risk factors could not be obtained from the twins' medical records included in the study, as it is a retrospective study. Therefore, the effect of prenatal risk factors on both discordance and ROP development could not be evaluated at this stage. Furthermore, since twin pairs with discordance in terms of BW are a special group, the evaluation was performed on a relatively small sample size which was retrieved from one neonatal care center. No statistically significant difference was determined between the groups in terms of type 1 ROP development probably

because the type 1 ROP development rate was low in the whole group (4.8%). However, similar perinatal risk factors between the groups seem to a strength side of our study.

Conclusion

Lower BW twin pairs have an increased risk for any stage of ROP as compared to the twin sibling. In particular, it was seen that being SGA was independently associated with any stage of ROP in discordant twins**.** In higher BW twin pairs, a more advanced stage of ROP could potentially develop because of clinical risk factors.

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Conflicts of interest

There are no conflicts of interest.

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