·Clinical Research·

Birth weight and gestational age on retinopathy of prematurity in discordant twins in China

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Abstract

• AIM: To assess the relative effect of birth weight and gestational age on retinopathy of prematurity (ROP) using preterm twin pairs discordant for birth weigh in a tertiary neonatal intensive care unit in China.

• METHODS: Fifty -six discordant twin pairs of 112 preterm infants were retrospectively analyzed. The twin pairs were divided into two subgroups based on birth weight in each pair. The occurrence of ROP and severe ROP requiring treatment were compared between the lower birth weight infants and their co -twins with the higher birth weight. Some neonatal morbidities related to prematurity and neonatal characteristics were also compared between the twin pairs.

• RESULTS: Based on the univariate analysis, gestational age and birth weight were significantly associated with the occurrence and progression of ROP. But no significant differences in ROP between larger and smaller infants were observed in the twin -paired analysis. The incidence of neonatal morbidities regarding respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), sepsis and neonatal characteristics regarding gender distribution, one - and five -minute Apgar score, postnatal steroid treatment, blood transfusion, supplemental oxygen therapy, and mechanical ventilation were not different between the twins. However, gestational age of ≤28wk was significantly associated with significantly higher rates of ROP and severe ROP.

• CONCLUSION: Gestational age is a better predictor of ROP than birth weight in the twin-paired study.

• KEYWORDS: retinopathy of prematurity; gestational age; birth weight
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INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially avoidable cause of blindness in children, particularly in middle-income countries and cities of Asia [1-4]. Survival rates have increased and these infants are more likely to develop severe ROP that requires treatment[2-5]. ROP is a multifactorial disorder which correlates inversely with gestational age and birth weight[1,2]. Low gestational age and low birth weight are the strongest and most consistently identified risk factors[1,6,7]. Low birth weight is closely correlated to low gestational age, the respective effect on the pathogenesis of ROP and the dominance of the two factors are still unclear. Birth weight is sometimes assumed to be a quality of growth and is strongly related to infant survival [8]. Gestational age, on the other hand, determines the status of health state: (*i.e.* maturity). Which of these is a more important risk factor of ROP? It is practically impossible in the setup of commonly run clinical studies to evaluate the independent effects of these two factors on ROP. Twins are exposed to an identical intrauterine environment for an equal period of time; and they have the same gestational age but different birth weights. It is thus possible to study the exact effect of birth weight on ROP after excluding the effect of gestational age by a twin study. In studies on twin preterm infants, a lower birth weight may not pose a greater risk for more severe ROP [9]. Birth weight discordance (defined as difference of ≥15% in the birth weight of two twins) has been reported as a special risk factor for severe ROP in both the twin sibling [10]. However, another recent study has failed to prove the difference in ROP

spectrum between twins with discordant birth weight and set of twins with no birth weight discordance[9].

This study aimed to evaluate the influence of birth weight on ROP, independent of gestational age, among patients attending a neonatal center in Beijing. To eliminate the effect of gestational age, we used a twin-paired analysis between the preterm twins with different birth weight.

SUBJECTS AND METHODS

Subjects This was a retrospective cohort study of twin deliveries at neonatal intensive care units (NICUs) of Bayi Children's Hospital affiliated to the General Hospital of Beijing Military Command of the PLA, Beijing from January 1, 2012 to June 30, 2012. Twin pairs both of whom survived until the 45th postconceptional week (PCA: defined as gestational age at birth plus weeks of life) and underwent ROP screening examinations. Twin pairs with the same birth weight, or with one or both members being stillborn, or having major congenital malformation were excluded. Neonatal characteristics (gestational age at birth, birth weight, gender, one- and five-minute Apgar score, postnatal steroid therapy, surfactant treatment, blood transfusion, oxygen therapy, and mechanical ventilation); and neonatal morbidities [sepsis, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH)] were available in all cases. Data collection confirmed to all local laws and was conducted according to the principles of the Declaration of Helsinki.

Methods of Screening Examination Infants born between ≤34wk or weighting ≤2000 g who had an unstable clinical course were referred for ROP screening. The infants were examined at 4-6wk chronological age or 32wk corrected age to the 45th PCA. Pupils were dilated using 0.5% phenylephrine and 0.5% tropicamide, instilled four times at an interval of 15min. The fundus was examined with a binocular indirect ophthalmoscope and +28D lens, lid speculum, and scleral depressor approximately 45min after the first instillation. A drop of 0.4% oxybuprocaine was used for topical anesthesia. Infants were monitored until a diagnosis of ROP was established or an eye examination showed vascularization into Zone 3. If ROP developed, then parents were asked to sign a consent form to allow the more frequent examinations necessary to track the course and severity of ROP. ROP findings were classified according to the international classification for ROP (ICROP) [11]. Threshold ROP is defined as stage Ⅲ disease in zones 1 or 2 with at least 5 contiguous or 8 cumulative clock hours of extraretinal fibrovascular proliferation in the presence of plus disease [12,13]. Pre-threshold ROP type Ⅰ was zone 1 ROP of any stage with plus disease or stage Ⅲ without plus disease; zone 2 stage Ⅱ and stage Ⅲ with plus disease but less than required threshold clock hours [13]. Follow-up examinations were performed at 1-3wk intervals, depending on the findings of each examination. Infants with normal vascularization of the retina to the periphery were not re-examined. Infants were diagnosed as pre-threshold ROP type Ⅰ were treated or followed up after discussions with their parents [14]. Infants who were diagnosed as threshold ROP and pre-threshold ROP type Ⅰ received laser treatment. The main outcome measures of ROP were the occurrence of any stage of ROP, severe ROP requiring treatment. All of the examination and treatment were approved by our hospital ethics committee.

We first examined the associations between gestational age, birth weight, and ROP on individual twin data. To evaluate the independent effect of birth weight on ROP, we divided the twin pairs into two subgroups based on birth weight in each pair, namely a larger and a smaller subgroup and within-pair analysis was subsequently conducted. Then, we compared the spectrum of ROP in difference of ≥15% in the birth weight of twin pairs and those with birth weight discordance <15%. Finally, to evaluate the influence of gestational age on ROP, gestational age was categorized as ≤28wk and >28wk in 112 infants and the incidence of ROP and severe ROP were compared between the two group (The previous studies reported that the mean gestational age of treated ROP were 28.06wk [15], so we choose 28wk as the cutoff point).

Statistical Analysis All statistical analysis were performed using the statistical package for the social sciences (SPSS), version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Univariate analysis was conducted for unpaired data with the Independent-Sample t-test, Mann-Whitney U-test, χ^2-test, or Fisher's exact test. A Pearson correlation analysis was used to evaluate the correlation between the gestational age and birth weight. Univariate paired comparisons between the larger infant from the twin pair and the smaller infant from the same pair were performed using the McNemar test and paired t-test. Chi-squared test was used for count data analysis. All reported P-values are two-sided, and P-values <0.05 were considered statistically significant.

RESULTS

Patient and Database Characteristics During the study period, a total of 56 twin premature pairs were delivered at our neonatal intensive care units (NICUs). The mean gestational age of the cohort was 30.7 ±1.71wk (range

Table 1 Paired comparisons of clinical feature and perinatal outcomes between larger and smaller infants of 56 twin pairs *n* (%)

Factors	Smaller infant (*n*=56)	Larger infant (*n*=56)	*P*
BW (g, mean±SD)	1475.22±364.32	1645.54±357.07	<0.001
BW≤1500 g	31 (55.36)	21 (37.50)	0.058
ROP	12 (21.42)	9 (16.07)	0.468
Severe ROP	3 (5.36)	5 (8.93)	0.463
Neonatal morbidities			
Respiratory distress syndrome	26 (46.43)	28 (50.00)	0.705
Patent ductus arteriosus	18 (32.14)	23 (41.07)	0.372
Intraventricular hemorrhage	8 (14.29)	9 (16.07)	0.792
Sepsis	3 (5.36)	4 (7.14)	0.696
Neonatal characteristics			
Female infant	29 (51.79)	21 (37.50)	0.128
1-min Apgar score <7	8 (14.29)	2 (3.57)	0.098
5-min Apgar score <7	4 (7.14)	3 (5.36)	0.696
Dexamethasone treatment	32 (57.14)	30 (53.57)	0.704
Surfactant treatment	23 (41.07)	29 (51.79)	0.256
Blood transfusion	38 (67.86)	31 (55.36)	0.174
Oxygen therapy	35 (62.50)	28 (52.17)	0.182
Mechanical ventilation	26 (46.43)	22 (39.28)	0.445

BW: Birth weight; ROP: Retinopathy of prematurity.

26.0-33.0wk), and the mean birth weight was 1529±334.20 g (range 760-2160 g). Fifty (44.64%) were females. The prevalence of any stage ROP in our sample was 21/112 infants (18.75%), including 15 with mild ROP (13.39%, stage Ⅰ, Ⅱ) and 6 with severe ROP (5.36%, stage Ⅲ). There were no cases with stage 4 or 5 ROP. The incidence of ROP severe enough to require treatment in this study was 8/112 patients (7.14%).

Gestational Age and Birth Weight on Retinopathy of Prematurity Univariate analysis of all the infants showed the following: the mean gestational age of the 21 infants with ROP was 28.56wk (SD 1.82) and was significantly earlier than those with no ROP (31.35±1.54wk, P<0.001). The mean gestational age of severe ROP requiring treatment was 27.75±1.58wk and was significantly earlier than the others (31.10±1.71wk, P<0.001). Birth weight, on the other hand, was also significantly less in the ROP infant group as compared to the non-ROP group (1104.44 g *vs* 1671.28 g, P <0.001). The mean birth weight of the 8 infants with severe ROP requiring treatment was 1073.73±232.70 g and was significantly less than the others (1606.79±345.69 g, P <0.001). Both of the gestational age and birth weight were important risk factors of ROP. As gestational age and birth weight were highly correlated (r=0.993, P<0.001), the two variables could not be considered independently predictive of the occurrence and progression of ROP. Therefore, the within-pair analysis was conducted to determine the effect of birth weight on ROP, independent of other factors that influence its value (including gestational age).

Independent Effect of Birth Weight on Retinopathy of Prematurity To evaluate the independent effect of birth weight on ROP, we divided the twin pairs into two subgroups based on birth weight in each pair, namely a larger and a smaller subgroup. The mean difference in birth weight between the two groups was 160.0 g (P<0.001), and the mean birth weight discordance within twin pairs was 10.26%. The birth weight of the smaller infant (1475.22±364.32 g) was lighter than the larger infants (1645.54±357.07 g, P< 0.01). The proportion of infants with a birth weight ≤1500 g was lower in the larger twin group than that in the smaller twin group, but there was no significant difference (37.50% *vs* 55.36%, P=0.058). The incidence of ROP and severe ROP in larger infants was 16.07% and 8.93% respectively, and that in smaller infants was 21.42%, 5.36% respectively. There were no differences in the occurrence and progression of ROP between larger and smaller infants (P>0.05, Table 1). No differences were found between twin pairs regarding other perinatal morbidities including RDS, PDA, IVH and sepsis. Other clinical characteristics, such as gender distribution, one- and five-minute Apgar score postnatal steroid treatment, blood transfusion, supplemental oxygen therapy, and mechanical ventilation were not significantly different between the two groups (P>0.05, Table 1).

In our study, seven twins (17.07%) had ROP among 41 twin pairs with birth weight discordance <15% and six twins (40.00%) had ROP among 15 pairs with discordance ≥15%.

There was no difference in ROP spectrum between twins with birth weight discordance ≥15% and set of twin with birth weight discordance <15% (P=0.072). In every case, their twin siblings had mild or no ROP. Eight twins had ROP and only two twins (15.38%) had the same ROP outcome. There were five twin pairs who were found ROP in one eye and were not found ROP in the other eye. Forty-three twin pairs had no ROP. Five (38.46%) lower birth weight infants had higher grades of ROP than their twin and six (46.15%) heavier birth weight twins had higher grades of ROP than their smaller siblings. Four infants reached threshold, and four were prethreshold. In 56 discordant twins, the lower birth weight may not pose a greater risk for more severe ROP as compared to the twin sibling.

Independent Effect of Gestational Age on Retinopathy of Prematurity Eleven (68.75%, 11/16) infants born at ≤28wk had ROP and only 10 (10.42%, 10/96) infants born at >28wk (χ^2=30.632, P<0.001). Six (37.50%) infants born at ≤28wk had severe ROP requiring treatment and only 2 (2.08%) infants born at >28wk had severe ROP requiring treatment (χ^2=20.807, P<0.001). The birth weight in infants born at ≤28wk (1063.13±161.57 g) was lighter than in infants born at >28wk (1665.07±309.77 g, P<0.01). The proportion of infants with a birth weight ≤1000 g was significantly higher in infants born at ≤28wk (31.25%, 5/16) than in infants born at >28wk (1.04%, 1/96) (χ^2=19.085, P<0.001). Thus, gestational age is a better predictor of ROP than birth weight.

DISCUSSION

The results of previous studies regarding incidence and risk factors for ROP have varied widely. The most widely cited incidence data were obtained from the multicenter CRYO-ROP trial, which reported a 83.4% incidence of ROP among infants born at ≤28wk, and a 81.6% incidence in infants <1000 g birth weight [13]. The early treatment for retinopathy of prematurity cooperative group (ETROP) reported an incidence of ROP of 89.0% among infants who born at ≤28wk and an incidence of ROP of 68% among infants of <1251 g [14]. All studies of risk factors for ROP identified a measure of immaturity or the infant's size as having the greatest association with risk of ROP [16-18]. As gestational age is a major contributor of birth weight and these two factors closely correlate, which is the more important risk of ROP between these two factors is still unknown. It is impossible to evaluate the independent effects of gestational age and birth weight on ROP in the usual clinical study. As discordant twins with the equal gestational age and different birth weight, we may expect that the exact effect of birth weight on ROP could be determined by a twin study. Most prenatal factors related to the development of ROP could be made equivalent between the two groups with different birth weight. Therefore, the true influence of birth weight or intrauterine growth on ROP could be determined. The twin-paired analysis between the twins with different birth weight showed that birth weight is not significantly associated with the occurrence or severity of ROP while gestational age is. The independent effect of birth weight on other perinatal morbidities including RDS, PDA, IVH, sepsis, gender distribution, Apgar score <7 at 1min, 5min, postnatal steroid treatment, blood transfusion, supplemental oxygen therapy, and mechanical ventilation could also be evaluated in this twin-paired study.

In our study, the lower birth weight may not pose a greater risk for more severe ROP as compared to the twin sibling. Most studies also showed that birth weight per se is not associated with the occurrence or severity of ROP while gestational age is [6,19,20]. Birth weight discordance has been reported as a special risk factor for severe ROP in both the twin sibling [10]. However, another recent study has failed to prove the difference in ROP spectrum between twins with birth weight discordant and set of twins with no birth weight discordance [9]. We compared the incidence of ROP among twins with a difference of ≥15% in birth weight and those with birth weight discordance <15% was and found no statistically significant difference. Birth weight discordance is also not associated with the occurrence of ROP. The mean birth weight discordance of twin pairs was 10.26% and as the number of significantly discordant twins (discordance ≥15%) was 15 pairs out of 56 pairs (26.79%). Six twins (40.0%) of significantly discordant twins got ROP, three (50%) lower birth weight infants had higher grades of ROP and one (16.67%) heavier birth weight twins had higher grades of ROP and two twins (33.33%) had the same ROP outcome. Although analysis on the subgroup of discordant twins did not yield significant changes in our result, additional research including larger number of twin infants with extreme discordance is required in future.

In our study, birth weight was not directly associated with stage or severity of ROP in preterm twins. This indicates that maturity is more important in the pathogenesis of ROP than intrauterine growth. Limitations of the current study include the relatively small sample size which was retrieved from one neonatal care center and has limitations in generalizing this result to the population. Larger multicenter studies are needed to confirm our findings.

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