

Discordant ROP (Retinopathy of prematurity) development in twins less than 32 weeks of gestational age

Musa Silabli¹, Mehmet Tekin², Ali Kal³, Mahmut Oğuz Ulusoy³, Zeynel Gokmen¹

¹Department of Pediatrics, Division of Neonatology, Baskent University, Konya, Turkey; ²Department of Pediatrics, Baskent University, Konya, Turkey; ³Department of Ophthalmology, Baskent University, Konya, Turkey.

Abstract. *Background and aim:* Retinopathy of prematurity (ROP), is a vasoproliferative disorder of the immature retina and a major cause of preventable blindness in childhood. Although the development of ROP is multifactorial, the principal reasons are lower gestational age and lower birth weight. However, in twins their gestational ages were the same, ROP development can be discordant. This study aims to evaluate the etiologic factors of discordant ROP development in twins. *Methods:* We reviewed the last 5 years' records and found the twins whose discordant ROP development. This discordance was; 1. Different stages of ROP, 2. One sibling treated the other is not, 3. One sibling has aggressive posterior ROP the other is not, 4. One sibling has more influenced area as zones the other is not. We documented some data of these twins, as birth order, birth weight, resuscitation at birth, morbidities, the number of hemotransfusion, age of regaining birth weight, relative weight gain at 28 weeks. *Results:* We evaluated a total of 26 cases of 13 twins. The mean gestational age and birth weight of the entire study group were 27.7 ± 2 , and 1053 ± 364 grams, respectively. We found that more transfused preterm baby in twins is more likely to show severe ROP. Sepsis and the duration of mechanical ventilation may be risk factors for more severe ROP in twins. *Conclusion:* We can reduce discordant retinopathy in less than 32-weeks premature twins by using methods such as cord milking and by improving non-invasive ventilation modalities. (www.actabiomedica.it)

Key words: Prematurity, Discordant Retinopathy of prematurity, Morbidities, Twin

Introduction

ROP is a vasoproliferative disease that is one of the leading causes of preventable blindness in childhood, specific to premature babies (1-3). While ROP is the problem of preterm babies born under 28 weeks in developed countries, it is reported that severe ROP develops up to 34 weeks in developing countries (4). Recent technical advancements in the neonatal intensive care units have markedly improved the survival rates of extremely premature infants and therefore the incidence of ROP increased worldwide (5). Although many etiological factors have been described in the development of retinopathy of prematurity, the best-known risk factors are low birth weight and low gestational weeks (6,7).

The fact that multiple pregnancies are a risk factor for ROP, is still a controversial issue. The risk of preterm birth and lower gestational age increases in multiple pregnancies. Multiple pregnancies cause premature birth and low birth weight. In preterm babies, ROP is observed more, as expected (8). However, few published articles say that multiple pregnancies are not a risk factor for ROP (9-11). Also, low birth weight has been shown as an independent risk factor for ROP in studies with discordant twins (12). There is also a case report with laser photocoagulation requiring ROP because of intrauterine transfusion which causes hyperoxia-hypoxia fluctuations in the anemic fetus (13).

There are few studies in this field. In this study, we aimed to investigate the causes of discordant ROP in twins less than 32 gestational weeks.

Methods

This retrospective study was conducted in Baskent University Konya Hospital. Patient records were examined, from 2015 to 2020, retrospectively. The data of this study were extracted from our 2 premature studies, which were previously approved by the Baskent University Ethics Committee (project no: KA15/76, KA19/70). There is no separate ethics committee approval for this study. Informed consent was not obtained since it was a retrospective study. Twins born at less than 32 weeks and survivors were included in the study. Among them, those with discordant ROP were included in the study. The eye examinations for ROP were performed starting at either 4week chronological age or 31week postmenstrual age, whichever was later. Retinopathy of prematurity was classified using the International Classification for Retinopathy of Prematurity (14). Discordant ROP was described as follows: 1. Different stages of ROP, 2. One sibling treated the other is not, 3. One sibling has aggressive posterior ROP, the other is not, 4. One sibling has more influenced by ROP as zones the other is not. Of those with mild symptoms or not developing ROP as Group 1, the others were classified as Group 2. We documented some data of these twins, as birth order, birth weight, resuscitation at birth, respiratory distress syndrome (RDS), surfactant use, mechanical ventilation duration,

patent ductus arteriosus (PDA) requiring treatment, intraventricular hemorrhage (IVH), sepsis, necrotizing enterocolitis, BPD, number of packed red blood cells (pRBC), age of regaining birth weight, relative weight gain on 28th day. Descriptive statistics of scale variables were presented as mean \pm standard deviation (SD) or median (range) as appropriate. Demographic and clinical continuous variables were compared using the 2-independent Student's t-test for normally distributed values and the Mann-Whitney U test for non-normally distributed values. Categorical variables were compared using Fisher's exact test. For all tests, the level of statistical significance was set at $p=0.05$. SPSS 25 was used for all data analysis.

Results

A total of 26 cases of 13 twins were evaluated. The mean gestational age and birth weight of the whole study group were 27.7 ± 2 , and 1053 ± 364 grams, respectively. While 53.8% of pregnant women were administered antenatal steroids, 23% had preeclampsia, 15% had gestational diabetes, 7.7% had chorioamnionitis, and 65% pregnancy had occurred via in-vitro fertilization (Table 1). While 8 of 26 participants did not develop ROP, Stage 1 ROP was detected in 11, stage 2 in 4, stage 3 ROP in 3. Plus disease was present

Table 1. Demographic properties of the Group 1 and Group 2

	Group1 (n=13)	Group2 (n=13)	P-value
Gender, male; n (%)	7 (53)	2(15)	.097
Birth weight; median (min-max)	1010(700-1800)	910(570- 1700)	.169
Mechanical ventilation day; median (min-max)	0(0-0)	0(0-6)	.091
Non-invasive mechanical ventilation day; mean \pm SD	13,4 \pm 7	19,5 \pm 12	.150
Total oxygen exposure; mean \pm SD	36,7 \pm 25	49,3 \pm 30	.266
RDS; n (%)	10(76)	9(69)	1
The need for surfactant; n (%)	10(76)	9(69)	1
PDA requiring treatment; n (%)	3(23)	0	.220
IVH (>grade 2); n(%)	1(7)	3(23)	.593
Proven Sepsis; n (%) (6 (46)	11(84)	.091
BPD (any stage);n (%)	8(61)	9(69)	1
NEC (>stage 2); n (%)	0	1(7)	1

Table 1 (Continued)

Table 1. Demographic properties of the Group 1 and Group 2 (*Continued*)

	Group1 (n=13)	Group2 (n=13)	P-value
Birth order (second); n (%)	4(30)	9(69)	.115
The age of regaining birth weight	17,3 ± 4	19,4 ± 7	.435
Relative weight gain at 28 th day	217±116	164±137	.348
The number of pRBC; median (min-max)	0(0-2)	2(0-2)	.019
PDA requiring treatment;n (%)	3 (23)	0	.220
SGA; n (%)	1(7)	4(30)	.322
Resuscitation at birth; n(%)	1(7)	2(15)	1

Abbreviations: RDS: Respiratory distress syndrome, PDA: Patent ductus arteriosus, IVH: Intraventricular hemorrhage, BPD: Bronchopulmonary dysplasia, NEC: Necrotising enterocolitis, pRBC: Packed red blood cell, SGA: Small for gestational age.

Table 2. ROP stages according to the groups

	Group1	Group2	P values
Non-rop, n (%)	8 (100)	0	.002
Non rop + stage 1, n (%)	12 (63)	7 (36)	.073
Stage 2 and above, n (%)	1 (14)	6 (86)	.073
Plus disease, n (%)	2(25)	6 (75)	.202
Laser requiring ROP, n(%)	2(25)	6 (75)	.202

Abbreviations: ROP: Retinopathy of prematurity, Group 1: Mild disease or no, Group 2: Severe disease

in 15.4% between twins (Table 2, Table 3). Laser photocoagulation treatment was required in 8 cases. No cases developing APROP were detected in the groups during follow-up. There are no significant differences between groups regarding gender, birth order, and birth weights (Table 1). Also, secondary morbidities including RDS, IVH, NEC, proven sepsis, BPD any stage, invasive mechanical ventilation duration, total exposure to oxygen, PDA requiring treatment did not differ between the groups. Although not statistically significant, mechanical ventilation duration and proven

Table 3. Baseline characteristics of twins developing variable severity of ROP

	Group1 (mild or no)			Group2 (more severe)	
	Gestational week	Birth weight (gram)	Stage	Birth weight	Stage
1	27	700	No ROP	710	Stage 1
2	28	810	Stage 1	1010	Stage 3 + zone2
3	27	1060	No ROP	910	Stage 3 + zone2
4	30	1800	No ROP	600	Stage 1
5	25	940	No ROP	980	Stage 1
6	28	820	Stage 1	950	stage 3 + zone 2
7	30	1660	No ROP	950	Stage 1
8	30	1550	No ROP	1530	Stage 2 + zone 2
9	32	1700	No ROP	1730	Stage 1
10	25	1010	No ROP	910	Stage 1
11	27	1020	Stage 1 +	570	Stage 2 + zone 2
12	27	790	Stage 2 + zone 2	820	Stage 2+ zone1-2
13	28	1010	Stage 1	860	Stage 1

+: Plus disease, ROP: Retinopathy of prematurity

Table 4. ROP stages and progression according to the birth weight discordance (15% discrepancy in birth weight)

	Discordant birth weight (5 pairs) (n=10)	No birth weight discordance (8 pairs) (n=16)	P value
No ROP; n (%)	2(20)	6(37,5)	.420
ROP that needs laser photocoagulation; n (%)	3 (30)	5(31,3)	.648
Other stages of ROP (rop developed but regressed spontaneously); n (%)	5 (62,5)	5 (50)	.664

Abbreviations: ROP: Retinopathy of prematurity

sepsis rates were slightly higher in Group 2. Only, the number of p RBC was statistically significantly higher in group 2 ($p=.019$) (Table 1). In discordant twins as birth weights, we did not find significant differences in terms of severity of ROP (Table 4). Also, there were no significant differences between the groups in terms of the age of regaining birth weight and relative weight gain on the 28th day of life.

Discussion

In this study, only the given more packed RBC had an unfavorable effect on discordant ROP in twins. Additionally, more invasive mechanical ventilation duration and culture-positive proven sepsis may contribute to develop the discordant ROP in twins. One of the results of this study is that it should be kept in mind that ROP can develop between twins at different stages, despite the same perinatal environment and exposure. Here, of course, the question arises about whether postnatal factors are important determinants of this event.

There are no publications, except for only a few studies and case reports evaluating the development of discordant ROP in twins. In a retrospective Indian study, which developed asymmetric ROP in 11 pairs of 45 twins in different zones and requiring different treatment options and where risk factors were examined, the weight difference in 4 of 11 pairs was more than 15% (15). Although they did not find a significant difference in birth weight between the subjects who developed asymmetric ROP and the other group who did not develop asymmetric ROP, interestingly, they reported that their heavier babies of twins developed more severe ROP. We have followed 65 pairs

of twin premature babies in the last 5 years. Thirteen pairs of these were below 32 weeks gestational age and had a discordant ROP. In our study group, there was a difference of more than 15% between the weight of 5 twin pairs. Severe ROP was observed in the baby who was lighter in 3 of the 5 twin pairs. Of the 3 twin pairs, while the lighter in weight of two twin pairs required laser treatments, the difference in weight did not make a difference in 1 pair, and laser treatment was required in both of them. One of them was 1020 gr, and the other one was 570 grams. In contrast to this study, the results of our study tended to have a more severe course of ROP in the lighter twin. In another study in India by Snahgi et al. who investigated the risk factors to evaluate intersibling variability of ROP in twins, they found that twins had an 80% intersibling variability of ROP (19). In our study, this rate was 50%. Although there is no significant difference in risk factors for discordant ROP development between twins in their study, they observed that the second birth order was more in the more severe observed ROP group. Similar to the study by Sangi et al., we observed that the number of babies born in the second-order was approximately 2 times higher in the group of observed severe ROP. However, this difference had no statistical significance level. Similar to the results in the same study, in terms of discordance birth weight did not make any difference between twins in terms of ROP severity.

In a study by Fellows et al. who investigated ROP in discordant twins, they found that thirty-eight percent of the lower birthweight infants had higher grades of ROP than their twin. Twenty-three percent of the heavier birthweight twins had higher grades of ROP than their smaller siblings (12). Similar to our results, the study also found that the lower-weight

twin was more likely to develop more severe ROP. In a premature twin ROP study from Korea, they found that birth weight was the most important risk factor for intersibling difference of ROP (16). However, their discordant ROP description was a little different from ours. Also, a study found results in the opposite direction of this result. In a study in which 56 discordant twins were examined, it was shown that birth week was a more influential factor in ROP severity than birth weight (20). In this study, the group was selected from premature babies below at 34 gestational weeks and 2000 g. In fact, they showed that gestational week was a more determining factor on ROP than birth weight, as they showed that the difference in ROP development was more pronounced under 28 weeks. In a case report published in Australia, they had to undergo intrauterine transfusion to the baby with anemia, which they followed up with the diagnosis of twin-to-twin transfusion syndrome, and they detected severe ROP in one of the twins at 40 weeks and self-regressing ROP in the other sibling (13). Stated that ROP disease requiring laser in the anemic baby was hypothesized that the immature retina was affected by these fluctuations because of hypoxia and hyperoxia in the intrauterine period and related it to transfusion. Our study also provided findings to support this. The number of transfusions seems to have an effect on the development of ROP at different stages between twins. Studies examining the relationship between weight gain, somatic growth factors such as Insulin-like growth factor-1 and ROP have shown an inverse relationship between weight gain and ROP (17,18). However, the studies were not specific to twin premature babies. We did not find a difference between weight gain and ROP severity in our study. We think this result is affected by the small sample size. It is known that smaller gestational age is associated with slower weight gain. If there was a larger sample size, the significance could arise with stratified classification. We think that this is the main reason why we did not find the differences between groups regarding weight gain.

Our study had some limitations. The first was that it was a retrospective study. A prospective study can contribute more to science. Second, the sample size and the small number of cases that were retrieved from one neonatal care center and have limitations in

generalizing this result to the population. Discordant ROP description can be made more clearly or more accurately or disease severity score can be described or improved. Larger multicenter studies are needed to confirm our findings.

For the future, the subject of research may be to investigate the risk factors for concordant ROP and discordant ROP.

In conclusion, the number of transfusions, invasive mechanical ventilation duration, and oxygen exposure seem to be the most important risk factors in observed discordant ROP in twins less than 32 weeks of gestation. Prevention to reduce these exposures, such as late cord clamping or cord milking, placental transfusion practices such as late cord clamping for donor fetuses in twins with discordant weight, or less invasive respiratory support strategies and gentle ventilation modalities, can reduce the development of discordant ROP.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This research involved humans. However, since this retrospective study was performed using a hospital database with de-identified patients; the risk was minimal for the participants. Patient identity and private images were not shared by paying attention to ethical rules.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:

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Musa Silahli, MD

Neonatal Intensive Care Unit,
Baskent University, Faculty of Medicine,
Department of Pediatrics,
Division of Neonatology, Konya, Turkey
Saray Cd., Hoca Cihan Mah.

No: 1 Selçuklu /Konya/Turkey

Phone: +90 534 296 1110

E-mail: msilahli@gmail.com