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ORIGINAL ARTICLES

Retinopathy of Prematurity: Discordance in Disease Expression Among Twin Infants

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Abstract

Background: Retinopathy of prematurity (ROP) is a significant cause of preventable childhood blindness. Twin births offer a unique opportunity to evaluate how individual neonatal factors contribute to ROP development, as co-twins typically share similar prenatal and perinatal environments.

Objective: To evaluate how individual neonatal risk factors contribute to ROP severity, differences, and treatment outcomes among preterm twin pairs managed under identical neonatal intensive care conditions.

Materials and Methods: This prospective observational study included 24 twin pairs and two singletons born at 27–34 weeks' gestation (birth weight 850–2650 g) and was screened in accordance with ICROP3 guidelines. Clinical variables, such as gestational age, birth weight, respiratory support, and metabolic stability, were compared within twin pairs. Discordance was defined as any inter-twin difference in ROP stage, severity, or treatment requirement. Treatment options included intravitreal injection, laser photocoagulation, and vitrectomy.

Results: Seven twin pairs (2.9 %) demonstrated discordant ROP. In each pair, one twin developed any stage of ROP, including aggressive (treatment-requiring) ROP, while the co-twin exhibited mild or no ROP. Discordant pairs were delivered at 28–31 weeks, with mean birth weights of 1496 ± 523g (affected) and 1322 ± 333g (unaffected). One twin pair had the same ROP stage, but regression occurred at different times. Despite similar durations of oxygen therapy, affected infants experienced more episodes of early respiratory instability and metabolic fluctuations. All affected infants required intravitreal anti-VEGF therapy; one needed supplemental laser for recurrence. Two progressed to stage 4 ROP requiring vitrectomy, with one developing secondary glaucoma.

Conclusion: The observed discordance underscores the need for further research with larger sample sizes, inviting the scientific community to contribute to the understanding of ROP variability in twins.

Keywords: retinopathy of prematurity, anti-VEGF, neonatal intensive care.

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder and remains a leading cause of preventable childhood blindness, occurring exclusively in premature infants [1–3]. In high-income countries, ROP predominantly affects infants born before 28 weeks' gestation, whereas in many low- and middle-income countries, such as Albania, severe forms of the disease have been reported in infants born up to 34 weeks [4].

Advances in neonatal intensive care have significantly increased the survival of extremely premature infants, thereby contributing to a global rise in ROP incidence [5]. Although numerous etiological factors have been associated

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with ROP, low birth weight and reduced gestational age remain the most critical risk determinants [6, 7].

Terry first identified ROP in 1942 and described the condition as *retrolental fibroplasia*, based on the initial impression that the primary abnormality involved proliferation of the embryonic hyaloid system extending into the retina.

The term "retinopathy of prematurity (ROP)" was introduced by Heath in 1951, providing a more accurate description of the disorder.

Also in 1951, Campbell proposed that the epidemic of blindness was caused by the toxic effects of unregulated oxygen administration in premature infants. She recommended avoiding supplemental oxygen unless the infant was cyanotic.

During the 1970s and 1980s, a second epidemic of ROP was observed, attributed to improved survival among extremely premature infants with very low birth weight.

In 1983, the International Classification of Retinopathy of Prematurity (ICROP) was established under John Flynn's leadership, providing a standardized framework for describing disease stages, zones, and severity.

In the early 1990s, it became apparent that an epidemic of ROP blindness was emerging in middle-income countries with developing neonatal intensive care, referred to as the third epidemic [7].

The role of multiple gestation as an independent risk factor for ROP remains uncertain. Multiple pregnancies are inherently associated with higher rates of preterm delivery and lower gestational age, both of which increase the likelihood of ROP [8].

As expected, premature infants from multiple gestations more often develop ROP. However, several studies have suggested that multiple gestation itself may not be an independent risk factor [9–11]. In addition, discordant twin studies indicate that low birth weight may be an independent predictor of ROP severity [12]. A case report has also described severe ROP requiring laser photocoagulation after intrauterine transfusion, presumably due to hyperoxia–hypoxia fluctuations experienced by the anemic fetus [13].

Given the limited evidence in this area, the present study aims to examine the factors underlying discordant ROP development in twins born before 32 weeks' gestation.

Materials and Methods

This retrospective study was conducted at two NICUs at the University Hospital Centers in Tirana. Medical records from September 2023 to September 2025 were reviewed. The dataset was derived from a previous study of premature infants, approved by the Ethics Committee of the University of Medicine Tirana, Albania.

The study population comprised surviving twin infants born before 32 weeks' gestation. Ophthalmologic screening for ROP was initiated at 4 weeks of chronological age or at 31 weeks of postmenstrual age, whichever came later. ROP staging and anatomic classification were based on the International Classification of Retinopathy of Prematurity [14].

Discordant ROP was defined as the presence of any of the following differences between siblings: (1) a difference in ROP stage; (2) the need for treatment in one infant but not the other; (3) the development of aggressive posterior ROP or plus disease (PD) in only one twin; or (4) more extensive zone involvement in one sibling.

Clinical data collected for each twin included birth order, birth weight, presence of respiratory distress syndrome (RDS), duration of mechanical ventilation, sepsis, and bronchopulmonary dysplasia (BPD).

Continuous variables were summarized as mean ± standard deviation (SD) or median (range), depending on the distribution. Normally distributed variables were compared using the independent-samples Student's t-test, whereas non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were examined using Fisher's exact test. A p-value of 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 25.

Results

Among the 308 screened infants, 26 (8.4%) developed ROP Type 1. In our sample of 50 twin infants, 3 (6%) developed ROP Type 1. The infants who met the inclusion criteria comprised 24 twin pairs and two singletons. The cohort's mean gestational age was 31.8 ± 2.1 weeks (27-34 weeks), and the mean birth weight was 1684 ± 430 g (850-2650 g) (Figure 1).

Of the 50 infants included in the study, eight twin pairs developed ROP, and seven twin pairs showed discordant disease expression. Among these, three infants developed advanced ROP: three had Stage 3 ROP, with two having Stage 3 ROP with plus disease (Figure 2). Additionally, Stage 1 ROP was identified in six infants (one twin pair had Stage 1 ROP), and Stage 2 ROP in one infant.

One twin pair exhibited concordant findings at the initial examination, with both infants presenting Stage 1 ROP. These cases underwent spontaneous regression; however, the time to complete resolution differed between the twins.

There were no significant differences between the twins who developed ROP by sex, birth order, or birth weight (Table 1). Additionally, secondary morbidities, including respiratory distress syndrome (RDS), sepsis, bronchopulmonary dysplasia (BPD), duration of invasive mechanical ventilation, and total oxygen exposure, did not differ significantly between groups.

Oxygen therapy duration during mechanical ventilation was 6 days (range: 3–20 days), with minimal variation between twins (mean difference < 12 hours). Among discordant twins, birth weight differences were not significantly associated with ROP severity (Table 2).

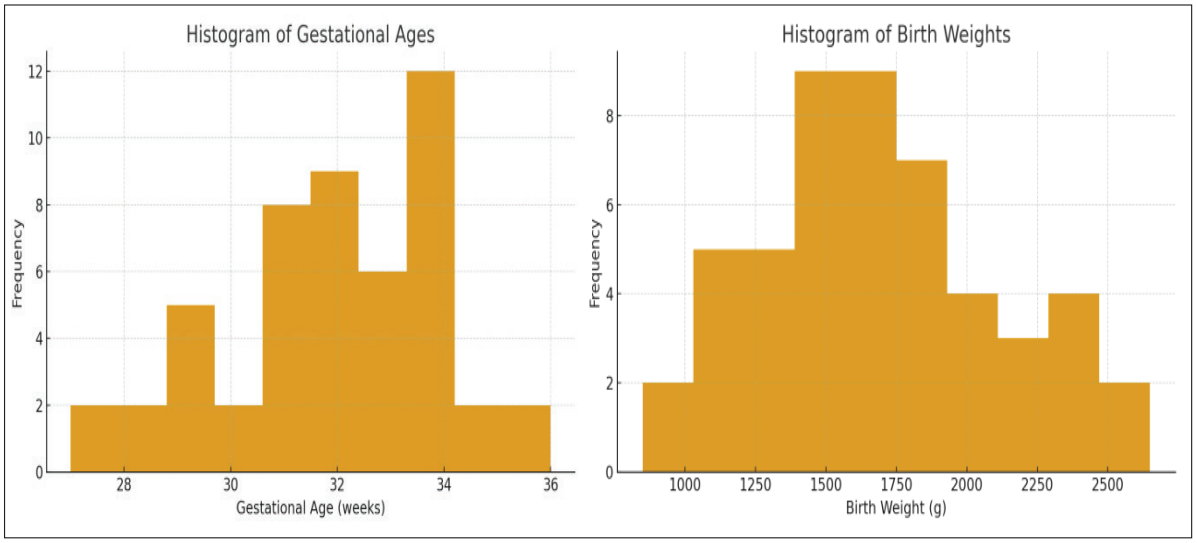

Figure 1. Histogram of GA and BW of twin babies

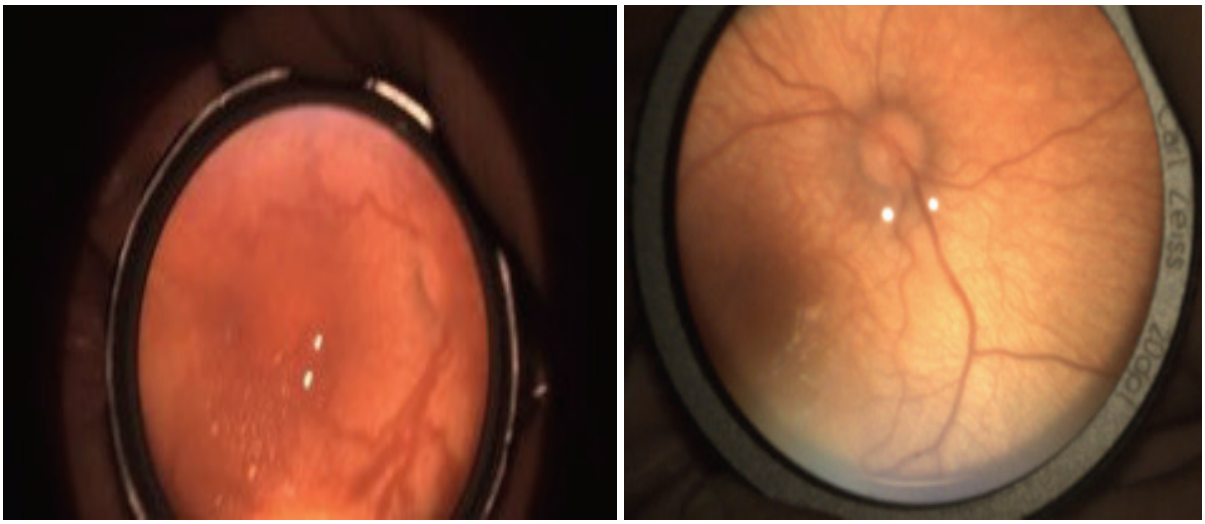

Figure 2. Discordant fundus findings between twins, with one infant developing ROP while the co-twin remained unaffected.

Nr.	Sex	Gestational week	Birth weight		Stage of ROP
			Affected	Discordant	
1	F	30-31	1430	1580	Stage 1
2	F	31-32	1500	1450	Stage 3, PD
3	M	27-28	1100	1100	Stage 3, PD
4	M	27-28	880	850	Stage 1
5	M	32-33	1100	1750	Stage 1
6	M	30-31	1050	1200	Stage 3
7	M	31-32	1400	1800	Stage 2/Stage 1
Twin pairs with the same stage of ROP					
1	F	33-34	2300	2400	Stage 1/Stage1

Table 1. Baseline characteristics of twins developing variable severity of ROP

Description	ROP	Non ROP
Gender (male)	6 (10)	17 (40)
Birth weight	1496 ± 523 (880-2400)	1322 ± 333 (850-2650)
Mechanical ventilation	6 days (3-20)	5 day (0-20)
Comorbidities	3 (10)	17 (40)
Requiring treatment	3 (10)	-

Table 2. Baseline Characteristics of the Study Population Stratified by ROP Status

The mean birth weight of infants with ROP was 1496 g, compared with 1322 g in those without ROP; the difference was not statistically significant ($p \approx 0.43$). After adjusting for clustering within twin pairs, the difference remained non-significant ($p > 0.6$). These results suggest that birth weight alone was not a significant predictor of ROP in this cohort.

Discussion

In this study, prolonged invasive mechanical ventilation and sepsis also appeared to contribute to intersibling differences in ROP severity, although these associations did not reach statistical significance. These findings highlight that ROP may progress differently between twins despite shared perinatal conditions, prompting consideration of whether postnatal exposures play a greater role than previously appreciated.

Although the incidence of ROP among twins was slightly lower (6%) than in the overall cohort (8%), the difference was not statistically significant, likely because of the small number of events. These findings suggest that twin status alone may not substantially alter the risk of ROP Type 1, but larger studies are needed to confirm this trend.

This study shows that retinopathy of prematurity (ROP) can develop asymmetrically in twins born and managed under similar clinical conditions, underscoring its multifactorial nature. Genetic susceptibility, oxygen regulation, inflammation, and microvascular dynamics collectively influence disease progression.

Previous studies have reported similar discordant cases among twins, often linked to placental sharing patterns, intrauterine nutrient transfer, or epigenetic variation in angiogenic pathways. Differences in VEGF expression and retinal sensitivity to hypoxia may explain variability even in controlled neonatal environments.

In this cohort, systemic instability, particularly oxygen fluctuations and infection episodes, was more common in the twin with advanced ROP, suggesting that even minor deviations in oxygen homeostasis may have lasting retinal consequences.

Although most severe cases responded to anti-VEGF therapy, two infants required surgery, and one developed postoperative glaucoma, underscoring the need for prolonged monitoring.

These findings highlight the importance of individualized screening in twins, as assuming symmetric disease expression may delay diagnosis and treatment for the more severely affected infant.

The literature on discordant ROP in twins is limited to a few retrospective studies and isolated case reports. An Indian study evaluating asymmetric ROP in 11 of 45 twin pairs found that four pairs had a birth weight difference greater than 15% [15]. Although no significant differences in birth weight were found between twins with and without asymmetric disease, the authors reported an unexpected finding: heavier twins sometimes exhibited more severe ROP (as in two cases in our study).

Another Indian study by *Sangi et al.* reported an 80% intersibling variability in ROP severity [19], whereas in our cohort, this rate was 50% (4 twin pairs of 8 total that developed ROP). Although the authors did not identify significant differences in clinical risk factors between discordant twins, they observed that the second-born twin was more likely to develop severe ROP.

We also noted a higher proportion of second-born infants in the more severe group, although the difference was not statistically significant. As in their study, birthweight discordance did not appear to affect ROP severity.

Fellows et al. also found that lower-birthweight infants more often developed higher grades of ROP, with 38% of smaller infants and 23% of larger infants showing more severe disease than their co-twins [12]. Their findings align with ours, indicating greater vulnerability among lighter twins, although the difference was not clinically significant.

A Korean study further emphasized birth weight as a principal determinant of intersibling variability [16]. Conversely, in another study, most twins with ROP exhibited severe intersibling variability. Birth weight and post-gestational neonatal risk factors were not predictive of more severe ROP in a twin sibling [20].

This study included infants up to 34 weeks' gestation and 2000 g birth weight. It demonstrated that differences in ROP severity were more pronounced among twins born before 28 weeks, suggesting that gestational maturity may influence discordance.

A case report from Australia described severe ROP in a twin who had undergone intrauterine transfusion for anemia associated with twin-to-twin transfusion syndrome. In contrast, the co-twin showed only regressing disease [13]. The authors proposed that fluctuating intrauterine oxygenation associated with transfusion may predispose the immature retina to severe ROP.

Although several studies have examined the role of

postnatal weight gain and growth factors, including insulin-like growth factor-1, in ROP pathogenesis [17, 18], none have specifically examined twins.

This study has several limitations. The small sample size limits the generalizability of the findings. The definition of discordant ROP could be refined, and future studies may benefit from incorporating detailed severity scoring systems. Larger, multicenter investigations are needed to validate the factors associated with discordant ROP.

Future research should also aim to distinguish risk factors for concordant versus discordant ROP, as this distinction may offer insights into differential disease progression among genetically and environmentally similar infants.

Conclusion

ROP progression in twins is not always parallel, even when prenatal and perinatal circumstances are closely shared. The discordant expression observed in our cohort suggests that postnatal factors, particularly respiratory instability, fluctuating oxygen requirements, and infectious episodes, play a critical role in determining individual susceptibility to disease progression.

These findings underscore the importance of evaluating each twin as an independent patient and remaining vigilant for early asymmetry in retinal vascular development. Strengthening respiratory management, minimizing oxygen variability, and optimizing infection control may help reduce the risk of discordant and severe ROP. Early detection and tailored interventions remain essential to preventing long-term visual impairment in this uniquely informative population.

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Ethical Approval: All procedures involving human participants were conducted in accordance with institutional and national research committee standards, as well as with the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments. Because this retrospective study utilized a hospital database with fully de-identified patient information, participant risk was minimal. No identifying data or clinical images were disclosed.

Conflict of Interest: The authors declare that they have no commercial or financial relationships that could be perceived as a potential conflict of interest regarding the submitted work.

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