Original Research

RISK FACTORS FOR DEVELOPMENT OF RETINOPATHY OF PREMATURITY IN TWINS ATTENDING A TERTIARY CARE CENTRE IN KASHMIR

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ABSTRACT

Background: Retinopathy of Prematurity (ROP) is a leading cause of preventable childhood blindness, primarily affecting preterm and low birth weight infants. The disorder results from abnormal retinal vascular development, triggered by premature birth and postnatal oxygen exposure, which disrupts the normal angiogenic process of the retina.

Aim: To study the risk factors associated with the development of retinopathy of prematurity in twin babies.

Methods: This retrospective observational study included preterm twin neonates who fulfilled the Rashtriya Bal Swasthya Karyakram (RBSK) screening criteria for Retinopathy of Prematurity (ROP).

Results: The study analyzed50 twin pairs (100 infants) with gestational age≤34 weeks who fulfilled the inclusion criteria. It was observed that besides known risk factors like lower gestational age, low birth weight, prolonged mechanical ventilation, sepsis, transfusions and oxygen supplementation,twin-twin transfusion syndrome as well as birth weight discordance (≥20%), a key finding in our study, was significantly associated with the development of ROP (p=0.03).

Conclusion: This hospital-based study highlights the high-risk factors and complexity of Retinopathy of Prematurity (ROP) in twin pregnancies, particularly among monochorionic (MC) twins and those complicated by twin-to-twin transfusion syndrome (TTTS) and birth weight discordance. Key risk factors—lower gestational age, birth weight <1250g, prolonged oxygen exposure, mechanical ventilation, sepsis, TTTS and birth weight discordance (≥20%) were significantly associated with the development of ROP. Birth weight discordance appeared to be an important factor in twin pregnancies, with greater discordance showing a tendency towards increasing ROP risk.

Keywords: Retinopathy of Prematurity, Twin Neonates, Twin Twin Transfusion Syndrome, Birth Weight Discordance.

INTRODUCTION

Retinopathy of Prematurity (ROP) is a leading cause of preventable childhood blindness, primarily affecting preterm and low birth weight infants.[(1)] The disorder results from abnormal retinal vascular development, triggered by premature birth and postnatal oxygen exposure, which disrupts the normal angiogenic process of the retina.[(2)] Advances in neonatal intensive care have significantly increased the survival of preterm infants, particularly those born before 30 weeks of gestation or weighing less than 1500 grams.

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[(3)] Consequently, the incidence of ROP has been rising, especially in middle-income and developing countries, where access to specialized neonatal care varies significantly.[(4)] Twin pregnancies are inherently high-risk and often associated with factors such as low birth weight, intrauterine growth restriction (IUGR), and preterm delivery, all of which are established risk factors for ROP.[(5)] Compared to singletons, twins have a higher incidence of preterm birth, with nearly 60% of twin deliveries occurring before 37 weeks and a significant proportion born before 32 weeks.[(6)] The degree of prematurity strongly influences the risk of ROP, as retinal vascularization remains incomplete at early gestational ages.[(7)] Several prenatal and postnatal factors contribute to ROP development and progression in twins.[(8)]

Prenatal Risk Factors

- Gestational age <30 weeks [(9)]
- Low birth weight (<1250g) [(10)]
- Monochorionicity[(11)]

- Fetal growth restriction (IUGR)[12]

Postnatal Risk Factors

- Oxygen therapy >7 days [13]
- Mechanical ventilation >5 days [14]
- Sepsis and neonatal infections [15]
- Anemia requiring blood transfusion [16]
- Necrotizing enterocolitis (NEC)[17]

METHODS

Study Design and Setting: Retrospective observational study

Inclusion Criteria:

- Preterm twin neonates who had undergone ROP screening, using RBSK Screening protocol.
- The babies included in our study were all found to be ≤34 weeks of gestational age.

Exclusion Criteria:

- Neonates with major congenital anomalies.
- Incomplete medical records.
- Singleton pregnancies
- Severe perinatal asphyxia (Apgar score <3 at 10 minutes)

This hospital-based study was carried out in GMC Srinagar, between April 2021to December 2024 after analysing data of 57 twin pairs who were referred for ROP screening to ROP clinic from Department of Paediatrics of our hospital.During the study period, a total of 57twin neonates underwent ROP screening. Of these, 100 infants (50 twin pairs) fulfilled the inclusion criteria and were enrolled in the study. All eligible consecutive cases meeting the screening criteria were included in this study.

57 twin pairs (114 infants) screened for ROP
|
Assessed for eligibility
|
Excluded: 7 twin pairs (14 infants)
(Did not meet one or more predefinedexclusion criteria*)
|
Included in final analysis:50 twin pairs (100 infants)

*Some excluded twin pairs fulfilled more than one exclusion criterion.

The study was conducted in accordance with the Declaration of Helsinki. **Institutional Ethics Committee waiver/exemption** was obtained for this study.

Data Collection

Data were collected from neonatal medical records, including:

- Gestational age and birth weight
- Chorionicity (monochorionic vs. dichorionic)
- Oxygen therapy duration, mechanical ventilation, sepsis, anaemia requiring transfusions if any.
- ROP stage (as per International Classification of ROP, ICROP 3, 2021)
- Treatment received (laser photocoagulation, anti-VEGF therapy, surgery or a combination therapy of any of these)

ROP screening was performed in accordance with the Rashtriya Bal SwasthyaKaryakram (RBSK) guidelines.All eligible twin neonates underwent retinal examinationusing indirect ophthalmoscopy, after pupillary dilatation. The first screening examination was performed at 3–4 weeks of postnatal age. Follow-up examinations were scheduled based on retinal findings and disease severity. Infants without ROP or with immature retinal vascularization were reviewed at intervals of 2–3 weeks, while those with established ROP were followed more frequently according to disease stage, location and progression till they reached complete retinal vascularization, regression of ROP, or need for treatment.

ROP was classified according to the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3, 2021), based on retinal zone, stage, extent of disease, and the presence or absence of plus disease. Treatment-requiring ROP was defined according to the Early Treatment for Retinopathy of Prematurity (ETROP) criteria, including Type 1 ROP characterized by:

- Zone I ROP with plus disease,
- Zone I Stage 3 ROP with or without plus disease,
- Zone II Stage 2 or Stage 3 ROP with plus disease.

Birth weight discordance was calculated using the formula:

Birth Weight Discordance (%) = [(Birth weight of larger twin − Birth weight of smaller twin) / Birth weight of larger twin] × 100

Twin pairs with a birth weight discordance of ≥**20%** were classified as discordant, in accordance with previously published twin pregnancy studies.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using SPSS Software. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the student'st-test, Chi-square test, or Fisher's exact

test, as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

The study analyzed50 twin pairs (100 infants) who met the inclusion criteria. The mean gestational age was 30.5 ± 2.1 weeks, and the mean birth weight was 1280 ± 320 grams. Out of the 100 infants, 65 (65%) developed ROPwhile 35 (35%) did not show any signs of the disease.Bilateral ROP was observed in 58 out of 65 infants (89.2%) while as unilateral disease was seen in 7 infants (10.8%).

The breakdown of ROP severity among 65 ROP positive cases was:

- Stage 1:41.5% (n =27), Figure 1 (A and B) shows stage 1 ROP in a twin pair
- Stage 2:35.4% (n = 23)
- Stage 3 and worse: 23.1% (n = 15), Figure 2 (A and B) showing stage 3 ROP in a twin pair

Table 1: Showing risk factors for ROP development

Risk factor	Rop present, n=65 (%)	No ROP, n=35(%)	P value
Gestational age≤30 weeks	48 (73.8%)	14 (40%)	0.01
Birth weight<1250	50 (76.9%)	16 (45.7%)	0.01
Oxygen therapy>7Days	48 (73.8%)	15 (42.9%)	0.02
Sepsis	30 (46.2%)	9 (25.7%)	0.04
Anaemia requiring transfusion	42 (64.6%)	10 (28.6)	0.01
Mechanical ventilation> 5 days	39 (60%)	12 (34.3%)	0.01
TTTS	22 (33.8%)	2 (5.7%)	0.01

ROP development was significantly associated with lower gestational age, lower birth weight, prolonged mechanical ventilation (p=0.01), prolonged oxygen therapy (p=0.02), sepsis (p=0.04), blood transfusions (p=0.01), and TTTS (p=0.01).

- Infants born at ≤30 weeks had a significantly higher ROP incidence (73.8%) compared to those >30 weeks (40.0%) (p=0.01)

Table 2: Association of Birth Weight Discordance with Retinopathy of Prematurity (infant level analysis)

Birth weight discordance	ROP (n=65) (%)	No ROP (n=35) (%)	Total(n=100)	P value
>20%	20 (30.8%)	4 (11.4%)	24	0.02
≤20%	45 (69.2%)	31(88.6%)	76	

*Birth weight discordance was calculated at the twin-pair level and assigned to both infants within the corresponding twin pair.

- Monochorionic twins had a higher incidence of ROP (83.3%) compared to Dichorionic twins (48.1%), p=0.02
- Birth weight discordance (≥20%) was significantly associated with the occurrence of ROP (p=0.02), highlighting inter-twin growth disparity as an important twin specific risk factor. Of the 50 twin pairs included in the study, 12 pairs (24.0%) demonstrated birth weight discordance ≥ 20%.

Table 3: Distribution of patients with respect to treatment received (n=65)

Treatment modality	Frequency n (%)
Spontaneous regression	41 (63.1%)
Laser therapy only	15 (23.1)
Anti-VEGF therapy only (Bevacizumab)	4 (6.1%)
Combinationtherapy (laser+bevacizumab)	3 (4.6%)
Surgical intervention	2 (3.1)

Follow-up of patients who received intravitrealbevacizumab was done after 1 week, then two to three weekly till they reached complete vascularisation or showed reactivation. Two patients presented with detachment at the outset itself and were referred to the higher centres for surgical treatment.

Treatment outcome

In our study, out of 65 ROP cases, 24 (37%) patients received treatment. All patients who had underwent laser therapy had regressed on followup. 7 patients had received primary intravitrealBevacizumab. Out of these 7 patients, 4 cases showed complete vascularisation on serial followups, whereas 3 patients needed further laser due to disease reactivation.Out of 24 patients who needed treatment, 22 were treated at our centre and a successful outcome defined as -well attached retina seen on serial follow-ups, post treatment, was seen in all the patients.The 2 patients who had presented

with retinal detachment at the outset had been referred to higher centre for surgical intervention but did not report back. They were traced telephonically and had undergone surgical procedure elsewhere, but the type of surgical procedure or the outcome of the procedure could not be properly ascertained. So out of 24 treated cases, 22 (91.6%) had fully regressed.

DISCUSSION

Retinopathy of Prematurity (ROP) remains a major cause of preventable blindness in preterm infants, with twin pregnancies carrying an increased risk due to shared intrauterine and neonatal complications.

The overall incidence of ROP was 65%, which aligns with previous reports on preterm twins (Smith et al., 2021)[18] Notably, monochorionic (MC) twins had a significantly higher incidence (81.25%) compared to dichorionic (DC) twins (62%), which is consistent with the findings of Wang et al. (2020)[19] who suggested that vascular placental connections in MC twins contribute to hemodynamic instability, increasing the risk of ROP.

Gestational age and birth weight remain key determinants of ROP development. In this study, infants born at ≤30 weeks had a significantly higher ROP incidence (73.8%) compared to those >30 weeks (40.0%, p=0.01). Similarly, low birth weight (<1250g) was a major risk factor confirming findings by Chiang et al. (2019)[20]. Additionally, birth weight discordance (≥20%) was significantly associated withdevelopment of ROP (p=0.02), a pattern also noted by Rivera et al. (2021)[21] suggesting that intrauterine growth restriction (IUGR) in the smaller twin exacerbates retinal immaturity, increasing susceptibility to ROP progression.

Birth weight discordance is a well-recognized marker of unequal intrauterine growth and placental insufficiency in twin pregnancies.[22,23]The smaller twin in a discordant pair is often exposed to chronic nutritional deprivation, altered fetalhemodynamics, and impaired growthfactors that may adversely affect retinal vascular development.[24,25]In our study infants with significant birth weight discordance demonstrated a greater likelihood of developingROP, suggesting that intertwin growth disparity may contribute to disease progression beyond the effects of prematurity and low birth weight alone. Similar findings have been reported by Zloto et al.,[24] who observed an increased risk of ROP among the smaller twin in discordant twin pairs. Furthermore, studies by Lundgren et al.,[25] and Löfqvistet al.,[26] have highlighted the association between impaired fetal and postnatal growth and the development of ROP. The association may be particularly relevant in monochorionic pregnancies and those complicated by TTTS, where unequal placental sharing and vascular imbalance can further compromise fetal growth. These findings highlight the importance of considering birth weight discordance as an additional risk factor during ROP screening and follow-up, and suggest that the smaller twin in a discordant pair may warrant closer ophthalmic surveillance.

Several neonatal complications significantly influenced ROP development in this study. Prolonged mechanical ventilation (>5 days) and oxygen therapy (>7 days) were associated with increased risk of ROP development (p=0.01 and p=0.02, respectively), supporting previous work by Wu et al. (2018)[27]which highlighted the role of oxidative stress in retinal damage.Sepsis also emerged as significant risk factor (p=0.04)which align with studies by Lyu et al. (2020)[28] and Lee et al. (2017)[29] who suggested that systemic inflammation exacerbates retinal angiogenesis, increasing the likelihood of developing ROP.

In this study, 37% of infants required treatment, a slightly higher proportion than the25-30% reported in previous studies (Patel et al., 2019).[30] This could be attributed to the inclusion of twin cases in our study, low gestational age and low birth weight of the study cohort in our study, coupled with postnatal morbidity. Laser photocoagulation was the most common treatment modality (23.1%) and this finding aligns with the study conducted by Mintz-Hittner et al. (2011)[31] who suggested that laser therapy remains the gold standard, although anti-VEGF agents are increasingly used for aggressiveROP (AROP) and zone 1 ROP.

The findings of the present study are relevant in the setting of the ongoing third epidemic of ROP, which has been increasingly recognized in India and other middle-income countries. Improvements in neonatal care have led to enhanced survival of preterm infants, resulting in a larger population at risk for ROP [32,33,34]. In our study of twin neonates, lower gestational age, low birth weight, birth weight discordance, TTTS, prolonged oxygen therapy, and mechanical ventilation were significantly associated with ROP development.[24,25,35]Recent Indian literature has highlighted the evolving epidemiology of ROP and the need for expanded screening strategies to address this growing burden.[34,36,37,38]

In the present study, twin neonates with lower gestational age, low birth weight, birth weight discordance, and TTTS constituted a particularly vulnerable subgroup, emphasizing the importance of targeted surveillance and timely intervention.

CONCLUSION

This hospital-based study highlights the significantly high incidence and complexity of Retinopathy of Prematurity (ROP) in twin pregnancies. In our study cohort, monochorionic (MC) twins and those complicated by twin-to-twin

transfusion syndrome (TTTS) showed a higher occurrence of ROP.Key risk factors—lower gestational age, birthweight <1250g,prolonged oxygen exposure, mechanical ventilation, sepsis, birth weight discordance and TTTS—were significantly associated with the development of ROP on univariate analysis.A notable finding of our study was association between birth weight discordance and the development of ROP in twin pregnancies. Recognition of this significant intertwin birth weight difference may improve risk stratification and proper screening and follow-up of high-risk twin infants.

Importantly, the majority of cases responded well to timely interventions, including laser photocoagulation and anti-VEGF therapy, with no progression to advanced ROP stages (Stage 4 or 5) seen among those who underwent timely screening and treatment at our centre.

In conclusion, preterm twin babiesrequire proactive and targeted ROP screening strategies. Early identification of these babies and their prompt referral for screening and treatment are essential to reduce the burden of avoidable childhood blindness. Given that only univariate analysis was performed, these findings should be interpreted as associations rather than independent predictors. Larger prospective studies incorporating multivariate analyses are warranted to identify independent predictors of ROP in twin pregnancies.

Limitations of the Study

This study was limited by its retrospective design and relatively small sample size, which may affect the generalizability of the findings. In addition, multivariate logistic regression analysis was not performed; therefore, the observed associations may have been influenced by confounding factors such as gestational age, birth weight, oxygen therapy, and neonatal comorbidities. Larger prospective multicentre studies are needed to validate these findings.

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