

Original Research Article

PREVALENCE OF RETINOPATHY OF PREMATURITY ASSOCIATED WITH HIGH RISK PREGNANCY: A RETROSPECTIVE COHORT STUDY IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a potentially blinding retinal vascular disorder affecting premature infants. Its occurrence is influenced by gestational age, birth weight, oxygen exposure, respiratory morbidity, and other perinatal factors. High-risk pregnancies may contribute indirectly through prematurity and neonatal complications. **Aims and objectives:** The study aimed to determine the prevalence of ROP among infants born from high-risk pregnancies and assess the association between maternal pregnancy-related risk factors and ROP occurrence.

Materials and Methods: An institution-based retrospective cohort study was conducted at Medical College and Hospital, Kolkata, from January 2018 to June 2019, involving 292 babies presenting to RIO OPD or admitted in SNCU and their mothers.

Results: Among 292 infants, 64.7% were delivered by Caesarean section and 61.0% were male. ROP occurred in 73.6%, with Type 1 ROP in 38.7% and Type 2 in 34.9%. Mean gestational age was 32.10 ± 2.34 weeks and birth weight 1447.11 ± 282.20 g.

Conclusion: ROP represents an important ocular complication among premature neonates born following high-risk pregnancies. Early identification of high-risk infants, appropriate neonatal care, and timely ROP screening are essential to reduce the risk of severe disease and preventable childhood visual impairment. Previous Indian studies similarly demonstrate that low gestational age, low birth weight, respiratory morbidity, and oxygen exposure are important determinants of ROP.

Keywords: Retinopathy of prematurity; preterm neonate; high-risk pregnancy; birth weight; gestational age; oxygen therapy; neonatal risk factors.

INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially blinding vasoproliferative disorder of the developing retinal vasculature that primarily affects premature and low-birth-weight infants. It is an important cause of preventable childhood blindness worldwide. Initially recognized mainly as a problem in industrialized countries, the epidemiological burden of ROP has increasingly shifted toward middle-income and developing countries because of

improvements in neonatal care and increased survival of premature infants.^[1,2] The characteristics of infants developing severe ROP also vary according to the level of socioeconomic development and neonatal-care facilities, highlighting the importance of appropriate screening strategies for different populations.^[2] India has witnessed a substantial decline in infant mortality with improvements in neonatal intensive care and survival of preterm and low-birth-weight infants. As more premature infants survive, the prevention of long-term disability has

become an important component of neonatal healthcare. National child-health programmes have incorporated screening and early intervention for conditions that can result in childhood disability, including vision-threatening disorders.^[3] Globally, prematurity remains a major public-health problem, with a large proportion of preterm births occurring in low- and middle-income countries.^[4] Therefore, prevention of ROP-related visual impairment has considerable public-health significance. The burden of ROP in India is substantial and varies according to the characteristics of the neonatal population, gestational age, birth weight and quality of neonatal care. Earlier Indian studies conducted in neonatal care units demonstrated a significant incidence of ROP among premature infants and emphasized the importance of systematic ophthalmological screening in high-risk neonates.^[7-9] The disease has also been reported among Indian infants with birth weights above traditionally recognized screening thresholds, indicating that clinically significant ROP may occur even among relatively heavier premature infants.^[10,11] Consequently, screening based exclusively on very low birth weight may fail to identify some infants at risk of ROP in developing-country settings. Timely detection and appropriate management are essential because progression to severe ROP can result in retinal detachment and permanent visual impairment. Protocol-based screening and management have demonstrated improved outcomes, particularly in severe disease involving the posterior retina.^[12] Prevention of blindness from ROP therefore requires systematic screening, regular follow-up and timely treatment of infants who develop sight-threatening disease.^[13] The development of ROP is multifactorial. Low gestational age and low birth weight are among the most consistently recognized risk factors. Other neonatal factors, including oxygen exposure, respiratory distress, mechanical ventilation, sepsis, apnea and other complications associated with prematurity, may contribute to abnormal retinal vascular development. However, the pattern of ROP may differ between neonatal units according to the population characteristics and level of neonatal care. Importantly, ROP has also been reported from rural and level-II neonatal intensive-care units, demonstrating that the disease is not restricted to sophisticated urban tertiary-care centres.^[14,15] The study aimed to determine the prevalence of ROP among infants born from high-risk pregnancies and assess the association between maternal pregnancy-related risk factors and ROP occurrence.

MATERIALS AND METHODS

Study design- Institution based Retrospective Cohort Study.

Place of Study: Medical College and Hospital, Kolkata.

Study period- One and half year (1st January 2018 – 30st June 2019).

Study population- Babies presenting at OPD of RIO, Kolkata & admitted in SNCU and their mothers.

Sample size- A total of 292 patients.

Inclusion Criteria

- All viable preterm babies eligible for ROP screening according to established screening guidelines.
- Babies with GA ≤ 35 weeks and/or birth weight < 1200 g.
- Infants with BW > 1700 g or GA > 34 weeks considered at risk for ROP at the discretion of the pediatrician.
- All viable babies detected with ROP during the study period.

Exclusion Criteria

- Babies with organic ocular diseases other than ROP.
- Infants with significant central nervous system (CNS) disorders, including cerebral palsy.
- Infants with significant cardiovascular system (CVS) disorders, including congenital heart disease (CHD).
- Infants with incomplete or insufficient medical records for assessment.

Study Variable:

- Gestational age
- Birth weight
- Maternal age
- Sex of the baby
- Mode of delivery
- High-risk pregnancy factors
- Presence or absence of ROP
- Stage/type of ROP
- ROP treatment modality
- Spontaneous regression of ROP
- Neonatal outcome

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 27.0 and GraphPad Prism version 5. Continuous variables were expressed as mean $\pm$ standard deviation, while categorical variables were presented as frequency and percentage. Independent and paired t-tests were used for comparison of numerical variables. One-way ANOVA was applied for comparison among multiple groups. Categorical variables were analyzed using Chi-square test or Fisher's exact test. Non-parametric data were analyzed using Mann-Whitney U test. Pearson correlation analysis was used to assess relationships between variables, and logistic regression was performed to identify associated risk factors. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Table 1: Distribution of Study Participants According to Mode of Delivery, Sex, and ROP Detection

Mode of Delivery	Caesarean	Frequency, n (%)	ROP detected, n (%)
	Normal delivery	189 (64.7%) 103 (35.3%)	149 (78.8%) 66 (64.1%)
Sex	Female	114 (39.0%)	82 (71.9%)
	Male	178 (61.0%)	133 (74.7%)

Table 2: Association of Mode of Delivery and High-Risk Pregnancy Status with ROP

Mode of Delivery	Caesarean (Exposed group)	ROP, n (%)	No ROP, n (%)
	Normal delivery (Non-exposed group)	149 (80.1%) 66 (64.1%)	37 (19.9%) 37 (35.9%)
High-risk Pregnancy Status	Exposed group (Any history of high-risk pregnancy)	135 (77.1%)	40 (22.9%)
	Non-exposed group (No history of high-risk pregnancy)	44 (67.7%)	21 (32.3%)

Table 3: Distribution of ROP According to Sex and Mode of Delivery

Sex	Category	Frequency	ROP detected, n (%)
	Male	178	133 (74.7%)
Mode of delivery	Female	114	82 (71.9%)
	Caesarean	189	149 (78.8%)
	Normal delivery	103	66 (64.1%)

Table 4: Distribution of Gestational Age, Maternal Age, and Birth Weight Among Study Participants

	Mean	SD	Minimum	Maximum	Median
GA at Birth in week	32.0959	2.3443	27	39	32
Mother's Age in Years	23.9452	5.2127	17	37	22
BW in gm	1447.11	282.196	850	2600	1460

Table 5: Distribution of Study Participants According to Presenting Stage of ROP

Presenting Stage of ROP	Frequency, n (%)
No ROP	74 (25.3%)
Dead	3 (1.0%)
Type 1 ROP	113 (38.7%)
Type 2 ROP	102 (34.9%)

Table 6: Distribution of Treatment Modalities According to Maternal High-Risk Pregnancy Factors

Maternal high-risk pregnancy factor	Anti-VEGF, n (%)	Laser photocoagulation, n (%)	No ROP, n (%)	Spontaneous regression, n (%)
Diabetes mellitus	2 (8.3%)	12 (50.0%)	2 (8.3%)	8 (33.3%)
Maternal hypertension	11 (37.9%)	6 (20.7%)	6 (20.7%)	6 (20.7%)
Multiple pregnancy	3 (8.1%)	9 (24.3%)	10 (27.0%)	15 (40.5%)
Multiple pregnancy with assisted pregnancy	3 (25.0%)	4 (33.3%)	2 (16.7%)	3 (25.0%)
None	7 (10.8%)	5 (7.7%)	21 (32.3%)	32 (49.2%)
Others	7 (28.0%)	5 (20.0%)	6 (23.1%)	8 (30.8%)
PROM + Sepsis	8 (17.0%)	6 (12.8%)	15 (31.9%)	18 (38.3%)

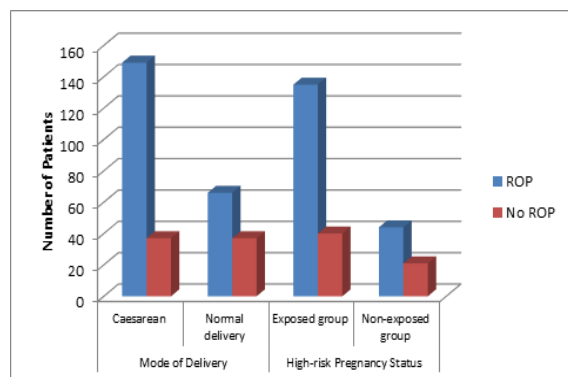


Figure 1: Association of Mode of Delivery and High-Risk Pregnancy Status with ROP

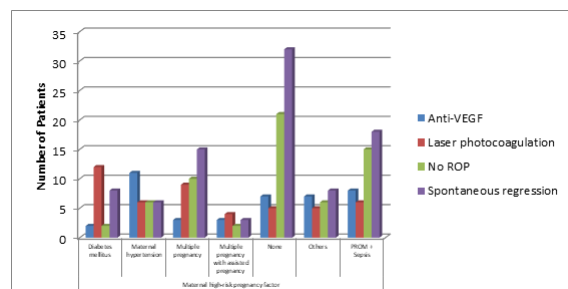


Figure 2: Distribution of Treatment Modalities According to Maternal High-Risk Pregnancy Factors

Mode of Delivery and Sex-wise Distribution of Study Participants

Among the 292 study participants, 189 (64.7%) infants were delivered by Caesarean section, whereas 103 (35.3%) were delivered by normal vaginal

delivery. ROP was detected in 149 (78.8%) infants delivered by Caesarean section and 66 (64.1%) infants delivered by normal vaginal delivery. Regarding sex, 178 (61.0%) infants were male and 114 (39.0%) were female. ROP was detected in 133 (74.7%) male and 82 (71.9%) female infants.

Interpretation:

The study population was predominantly composed of infants delivered by Caesarean section and male infants. The occurrence of ROP was higher among Caesarean-delivered infants compared with those delivered vaginally. A slight male predominance in ROP occurrence was also observed.

Association of Mode of Delivery and High-Risk Pregnancy Status with ROP

Results:

Among infants delivered by Caesarean section, 149 (80.1%) had ROP compared with 66 (64.1%) among those delivered by normal vaginal delivery. The relative risk for ROP among Caesarean-delivered infants was 1.25, indicating a positive association between Caesarean delivery and ROP. Regarding maternal pregnancy risk, ROP was detected in 135 (77.1%) infants born following high-risk pregnancies compared with 44 (67.7%) infants from non-high-risk pregnancies. The relative risk was 1.14, suggesting a higher risk of ROP among infants born following high-risk pregnancies.

Interpretation:

ROP was more frequently observed among infants delivered by Caesarean section and among those born following high-risk pregnancies. The relative risks indicate that both Caesarean delivery and high-risk pregnancy status were associated with an increased occurrence of ROP in the study population.

Sex and Mode of Delivery-wise Distribution of ROP

Results:

Among the 292 study participants, 133 (74.7%) male infants developed ROP compared with 82 (71.9%) female infants. According to mode of delivery, ROP was detected in 149 (78.8%) infants delivered by Caesarean section and 66 (64.1%) infants delivered by normal vaginal delivery. Thus, ROP was slightly more frequent among male infants and was considerably more common among infants delivered by Caesarean section.

Interpretation:

The occurrence of ROP showed a slight male predominance, although the difference between males and females was relatively small. In contrast, a greater proportion of ROP was observed among Caesarean-delivered infants compared with those delivered by normal vaginal delivery.

Gestational Age, Maternal Age, and Birth Weight-wise Distribution of Study Participants

Results:

The mean gestational age at birth among the 292 study participants was 32.10 ± 2.34 weeks, with a range of 27–39 weeks and a median of 32 weeks. The mean maternal age was 23.95 ± 5.21 years, ranging from 17–37 years, with a median age of 22 years. The

mean birth weight was 1447.11 ± 282.20 g, ranging from 850–2600 g, with a median birth weight of 1460 g.

Interpretation:

The study population predominantly consisted of preterm infants with relatively low birth weight. The relatively low mean gestational age and birth weight indicate that the participants represented a population at increased risk for the development of ROP. The mothers were generally young, with a mean maternal age of approximately 24 years.

Presenting Stage-wise Distribution of ROP

Results:

Among the 292 study participants, 74 (25.3%) infants had no ROP, while 215 (73.6%) had documented ROP. Among infants with ROP, 113 (38.7%) had Type 1 ROP and 102 (34.9%) had Type 2 ROP. Three infants (1.0%) died during the study period. Type 1 ROP was slightly more frequent than Type 2 ROP among the study participants.

Interpretation:

The prevalence of ROP in the study population was approximately 73.6%, indicating a substantial burden of the disease. Type 1 ROP was slightly more common than Type 2 ROP. Approximately one-fourth of the infants had no ROP, while a small proportion of infants died during the study period.

Maternal High-Risk Pregnancy Factor-wise Distribution of ROP Treatment Modalities

Results:

Among infants born to mothers with diabetes mellitus, 2 (8.3%) received anti-VEGF therapy, 12 (50.0%) underwent laser photocoagulation, 2 (8.3%) had no ROP, and 8 (33.3%) showed spontaneous regression. Among infants born to mothers with hypertension, 11 (37.9%) received anti-VEGF therapy, 6 (20.7%) underwent laser photocoagulation, 6 (20.7%) had no ROP, and 6 (20.7%) showed spontaneous regression. In multiple pregnancies, anti-VEGF therapy, laser photocoagulation, no ROP, and spontaneous regression were observed in 3 (8.1%), 9 (24.3%), 10 (27.0%), and 15 (40.5%) infants, respectively. Among assisted multiple pregnancies, the corresponding proportions were 25.0%, 33.3%, 16.7%, and 25.0%. Among infants born to mothers with PROM and sepsis, 8 (17.0%) received anti-VEGF therapy, 6 (12.8%) underwent laser photocoagulation, 15 (31.9%) had no ROP, and 18 (38.3%) showed spontaneous regression.

Interpretation:

The distribution of ROP treatment modalities varied according to the maternal high-risk pregnancy factor. Laser photocoagulation was particularly common among infants born to mothers with diabetes mellitus, whereas anti-VEGF therapy was more frequently observed among infants born to mothers with hypertension. Spontaneous regression was relatively common in multiple pregnancies and among infants associated with PROM and sepsis, indicating variation in disease severity and treatment requirements across different maternal risk factors.

DISCUSSION

The present study included 292 infants and demonstrated a high burden of retinopathy of prematurity (ROP), with 215 (73.6%) infants developing ROP. The study population was predominantly composed of preterm and relatively low-birth-weight infants, with a mean gestational age of 32.10 ± 2.34 weeks and mean birth weight of 1447.11 ± 282.20 g. These characteristics are important because prematurity and low birth weight are among the major determinants of abnormal retinal vascular development and subsequent ROP. In the present study, Caesarean section was the predominant mode of delivery, accounting for 189 (64.7%) infants, whereas 103 (35.3%) were delivered by normal vaginal delivery. ROP was detected in 149 (78.8%) infants delivered by Caesarean section compared with 66 (64.1%) infants delivered vaginally. Thus, a higher proportion of ROP was observed among Caesarean-delivered infants. However, this finding should be interpreted cautiously because the association between mode of delivery and ROP is not consistent across the literature. Sumual, Sutanto and Chandra conducted a systematic review and meta-analysis involving five cohort studies and 2048 infants and reported that the unadjusted odds of ROP were lower following Caesarean delivery; however, after adjustment for confounding factors, the association was no longer statistically significant.^[16] The authors suggested that differences in gestational age, birth weight and other clinical variables may account for the apparent association between mode of delivery and ROP.^[16] Therefore, the higher frequency of ROP among Caesarean-delivered infants in the present study may reflect the underlying obstetric and neonatal characteristics that necessitated Caesarean delivery rather than a direct causal effect of the delivery method itself. In the present study, 178 (61.0%) infants were male and 114 (39.0%) were female. ROP was detected in 133 (74.7%) male infants compared with 82 (71.9%) female infants, indicating a slight male predominance. This observation is consistent with the findings of van Westering-Kroon, Huizing, Villamor-Martínez and Villamor, who performed a systematic review and meta-analysis involving more than 625,000 infants and reported that male preterm infants had a higher risk of severe ROP, with a relative risk of 1.14.^[18] The authors proposed that the greater vulnerability of male preterm infants may be related to increased oxidative stress, respiratory morbidity, sepsis and other complications of prematurity.^[18] Nevertheless, the difference between male and female infants in the present study was relatively small, suggesting that sex may act as a modifying factor rather than being an independent major determinant of ROP. The present study further demonstrated an increased occurrence of ROP among infants born following high-risk pregnancies. ROP was detected in 135

(77.1%) infants in the high-risk pregnancy group compared with 44 (67.7%) infants in the non-high-risk group, with a relative risk of 1.14. This finding suggests that maternal and pregnancy-related complications may contribute to the risk of ROP. Karkhaneh et al., in a systematic review and meta-analysis of neonatal and maternal risk factors, demonstrated that several maternal and neonatal conditions were associated with ROP, highlighting the multifactorial nature of the disease.^[19] Maternal complications may increase the risk of prematurity, fetal growth abnormalities and neonatal instability, thereby indirectly increasing the risk of retinal vascular disease. In the present study, the mean gestational age was 32.10 ± 2.34 weeks, with a range of 27–39 weeks and a median of 32 weeks. The mean birth weight was 1447.11 ± 282.20 g, ranging from 850–2600 g, with a median of 1460 g. These findings indicate that the study population consisted predominantly of premature infants with relatively low birth weight, representing a population at considerable risk for ROP. Wu et al. demonstrated that the risk of ROP increases substantially with decreasing gestational age and emphasized gestational age as an important factor for risk stratification.^[20] The relatively low gestational age in the present study therefore provides an important explanation for the high prevalence of ROP. Similarly, the relatively low mean birth weight indicates that a large proportion of infants had immature retinal vascular development at birth. Premature birth interrupts the normal process of retinal vascularization, leaving substantial areas of the retina avascular. Following premature delivery, exposure to the extrauterine environment and fluctuations in oxygenation can disturb normal retinal vascular development, followed by hypoxia-induced pathological neovascularization. The combination of low gestational age and low birth weight in the present study therefore represents an important biological basis for the high frequency of ROP. Regarding the stage of disease, 74 (25.3%) infants had no ROP, whereas 215 (73.6%) had documented ROP. Among the total study population, 113 (38.7%) had Type 1 ROP and 102 (34.9%) had Type 2 ROP, while three (1.0%) infants died during the study period. The prevalence of ROP observed in the present study was therefore considerably high. This may be related to the high-risk characteristics of the study population, particularly the predominance of preterm infants with relatively low birth weight. Variation in ROP prevalence between studies may also occur because of differences in gestational-age distribution, birth-weight criteria, neonatal intensive-care practices, oxygen exposure, referral patterns and screening protocols. The high proportion of Type 1 ROP in the present study is clinically important because Type 1 disease represents ROP requiring treatment to prevent progression and unfavorable structural outcomes. The Early Treatment for Retinopathy of Prematurity Cooperative Group demonstrated that early treatment of high-risk ROP

significantly reduced unfavorable outcomes compared with conventional treatment thresholds.^[20]

In the present study, treatment requirements also varied according to maternal high-risk pregnancy factors. Among infants born to mothers with diabetes mellitus, laser photocoagulation was the most frequently used treatment modality, being performed in 12 (50.0%) infants, while 2 (8.3%) received anti-VEGF therapy and 8 (33.3%) showed spontaneous regression. Among infants born to mothers with hypertension, anti-VEGF therapy was used in 11 (37.9%), laser treatment in 6 (20.7%), and spontaneous regression occurred in 6 (20.7%). In multiple pregnancies, spontaneous regression was observed most frequently, occurring in 15 (40.5%) infants, while 9 (24.3%) underwent laser photocoagulation. Among infants from assisted multiple pregnancies, laser treatment was required in 33.3% and anti-VEGF therapy in 25.0%. In infants associated with PROM and sepsis, spontaneous regression occurred in 18 (38.3%), whereas 8 (17.0%) received anti-VEGF therapy and 6 (12.8%) underwent laser photocoagulation. These differences indicate variation in disease severity and clinical course among infants associated with different maternal risk factors. However, treatment modality should primarily be interpreted in relation to retinal disease characteristics rather than the maternal risk factor alone. The use of laser and anti-VEGF therapy in the present study reflects contemporary approaches to the management of treatment-requiring ROP. Laser photocoagulation remains an established treatment option, while anti-VEGF therapy is increasingly used, particularly for posterior or severe disease. The Early Treatment for Retinopathy of Prematurity Cooperative Group emphasized the importance of early treatment for high-risk disease, supporting the need for prompt identification and intervention in infants with Type 1 ROP.^[20]

CONCLUSION

The present study concludes that retinopathy of prematurity (ROP) is an important ocular complication among preterm and low-birth-weight infants. ROP was more frequently observed among Caesarean-delivered and male infants and those born following high-risk pregnancies. Prematurity and low birth weight were important characteristics associated with ROP development. Type 1 ROP was slightly more common than Type 2 ROP. Treatment modalities varied according to disease severity and included laser photocoagulation and anti-VEGF therapy, while some infants showed spontaneous regression. Early identification, timely screening, regular follow-up and prompt treatment of high-risk infants are essential to prevent severe visual impairment and childhood blindness.

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