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Original Research Article

Retinopathy of prematurity: A comparative analysis of multiple births versus singleton premature births

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Abstract

Background: Retinopathy of prematurity (ROP) is a significant cause of childhood blindness, with prematurity and low birth weight as major risk factors. The role of multiple gestations in influencing the incidence and severity of ROP, however, remains uncertain.
Aims: To find out incidence of retinopathy of prematurity (ROP) in premature infants born as a result of multiple pregnancy vs single pregnancy and to assess the severity of ROP in the both groups.
Materials and Methods: A prospective observational study carried out in Ophthalmology department of a tertiary care institute of central India. Total 603 premature babies of gestational age 24 weeks - 37 weeks were screened for ROP of which 96 were from multiple pregnancy and 507 were singletons. Indian guidelines were used in screening and for follow-up of the premature babies. Statistical analysis used: chi-square test and SPSS software.
Results: Incidence ROP in multiple birth premature neonates was found to be 31.25% as compared to 14.3% of singletons (statistically significant, p=0.000057). None of the groups shows statistically significant findings in severity of ROP (stage ≥3) over the other (p=0.218239).
Conclusion: Premature infants born as a result of multiple pregnancy are at a significantly higher risk of ROP than the single born infants. Risk factors like blood transfusion and respiratory distress were found to be statistically significant, leading to ROP in multiple-born vs singletons.

Keywords: Retinopathy of prematurity, Singleton premature birth, Multiple births.

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1. Introduction

Retinopathy of prematurity (ROP) is an eye disorder characterised by neurovascular disruption in the immature retina and is known to lead to visual impairments and blindness.[1-4] Low birth weight and prematurity are strongly associated with an increased risk of the disease.[5] In India, the incidence of ROP is between 38 and 51.9% in low-birth-weight infants.[6-7] Several risk factors are known till date to be associated with the development of ROP.[8-12]

The primary risk factors associated with ROP include gestational age, birth weight, oxygen exposure, and the presence of comorbidities such as intraventricular hemorrhage and respiratory distress syndrome.[5] Multiple pregnancy is mostly associated with premature birth and also low birth weight.[12] Whilst multiple pregnancy is known to be related to premature birth there is a paucity of studies suggesting consistency in results for the relation between multiple births and retinopathy of prematurity.

Multiple pregnancies are increasingly common due to advancements in reproductive technology, and they are known to be associated with a higher incidence of premature births and low birth weights, both of which are significant risk factors for ROP.[10] Despite the established links between

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prematurity and ROP, the relationship between multiple births and the incidence or severity of ROP remains controversial, with studies yielding varying results. Some research indicates that twins may have higher incidences of ROP compared to singletons,[13] while others suggest that singletons may be at greater risk for severe forms of the disease.[14]

Given these discrepancies in the literature, our study aimed to assess the incidence and severity of ROP in multiple birth infants compared to those born as singletons. This research seeks to provide more clarity on how the dynamics of multiple births influence the risk of developing this vision-threatening condition.

Although prematurity and low birth weight are well-established risk factors for retinopathy of prematurity (ROP), the independent contribution of multiple gestations remains unclear. Prior studies have reported conflicting evidence, with some suggesting a higher incidence among twins and others indicating greater severity in singletons. The inconsistency in available literature, coupled with a paucity of large-scale comparative data from Indian settings, highlights a critical research gap. Our study was therefore designed to specifically evaluate the incidence and severity of ROP in multiple births versus singletons in a tertiary care center of central India, aiming to provide clarity in this underexplored domain.

2. Materials and Methods

A prospective cross-sectional comparative observational study was conducted in a tertiary care centre of central India from January 2018 to June 2019, i.e. 18 months. The study was conducted after due permission from the institutional ethics committee.

Inclusion criteria included all premature infants born less than 37 weeks gestational age admitted in the paediatric NICU and those premature infants reported to our centre for ROP screening with gestational age less than 37 weeks. All infants >37 weeks gestational age were excluded from the study. All preterm babies were screened and followed up according to Indian screening guidelines.[7]

A detailed history was obtained from parents and available birth and NICU records and were recorded such as gestational age, birth weight, multiple delivery etc. in the pre-formed proforma. The screening was done after obtaining proper written consent from the parents of the babies. The initial ocular examination carried out without pupillary dilatation. Then after dilatation, fundus examination was done with an indirect ophthalmoscope and +28/20 diopter lens, aided with scleral depression.

Parents were explained about the procedure. Initial ocular examination was carried without dilating pupil. Examination of the anterior segment was done for any pathology in the anterior segment. One drop each of 2.5% phenylepherine and 0.5% tropicamide instilled at an interval of 15 minutes, and lids were opened with the use of eye speculum. Fundus examination was performed with an indirect ophthalmoscope and a 20D or 28D lens. Posterior pole examination without depression for plus disease. Sclera depression is used to examine the temporal retina followed by the nasal retina, to establish the proximity of the retinal vessels at the ora serrata after a complete examination, the speculum was removed gently, and antibiotic eye drops instilled.

The collected data was entered in the M.S. excel sheet and was then analysed using the chi-square test with/without Yates correction and SPSS software. A p value of ≤0.05 was considered statistically significant.

3. Results

A total of 603 premature infants were screened from January 2018 to June 2019.Total 96 premature infants were screened born from multiple pregnancy, and 507 premature infants were born singletons. **Table 1** shows the demographic details of the screened infants. No significant difference was seen in sex predisposition, gestational age and birth weight between single born infants and multiple born infants.

Table 1: Baseline characteristics of the study population

	Singletons	Multiple birth	p-value
Male: Female	281:226	47:49	0.24
Gestational age (weeks)	33.04(24-36)	32.98(28-36)	
Birth weight (grams)	1498.63(600-2900)	1502.96(850-2500)	

Of total screened premature infants, 103 (17.8%) were diagnosed with some stage of ROP. In the study, 30 out of 96 infants (31.25%) born from multiple pregnancy were having some stage of ROP, whereas in single born 73 out of 507 (14.3%) were having ROP. The number of singles born and infants born of multiple pregnancy were compared for the incidence of ROP. **Table 2** represents the finding; multiple birth premature infants are at much higher risk of developing ROP compared with single born premature infants ($p<0.05$).

Table 2: Incidence of ROP in premature infants born as single pregnancy vs multiple pregnancy

	Singletons	Multiple birth	Chi square value	p value
No ROP	434	73	16.1834	0.000057 (highly significant)
ROP	66	30		
Total	507	96		

p values related to comparison of numbers of singleton premature infants vs premature infants born as multiple

pregnancy using chi-square test; p values <0.05 were considered significant.

Table 3 represents the fundus findings. ROP stage ≥3 was considered as severe ROP. The number of singleton infants were compared to multiple born for severity of ROP using chi-square analysis. There was no significant rise in severity found in multiple born compared to singletons ($p<0.05$).

In this study, the severity of ROP in multiple births was considered after comparison between small and large infant of a pair. In our study we found that 6 pairs of total 24 twin pairs (25%) had some stage of ROP. Three pair of twins are of equal size two (33%) of them shows equal stages of ROP in both the infants and one pair (16%) shows variability in ROP stage. In the other three pairs (50%) who are having one small and one large infant, smaller infant shows higher staging of ROP then the larger infant.

Table 4 shows risk factors associated with ROP in singletons versus multiple birth infants. In our study, oxygen supplementation, asphyxia, and sepsis were found to be statistically insignificant for causing ROP while blood transfusion and respiratory distress were found to be statistically significant leading to ROP in multiple born vs singleton s($p<0.05$).

4. Discussion

Retinopathy of prematurity primarily occurs in premature neonates, especially those with reduced gestational age or low birth weight. Despite extensive research establishing various ROP risk factors, few studies examine the comparative risk between multiple and singleton births, with current literature showing inconsistent results. We investigated ROP risk factors comparing multiple-birth infants to singletons.

Earlier studies show varying outcomes in ROP risk between multiple births and singletons, possibly due to sample size differences. The present study found higher ROP susceptibility in multiple-birth infants compared to singletons, though severity levels remained comparable between groups.

It is well known that multiple born infants are usually low birth weight infants and born prematurely which are again risk factors for developing retinopathy of prematurity.[12]

Our study demonstrated that multiple birth infants exhibited a significantly higher incidence of Retinopathy of prematurity (ROP) compared to single-born infants, with 31.25% of infants from multiple pregnancies diagnosed with ROP versus 14.3% in singletons ($p < 0.05$). This finding aligns with existing literature that suggests multiple pregnancies are a notable risk factor for developing ROP. For instance, a population-based study in Taiwan highlighted that twins had a markedly higher prevalence of ROP compared to singletons, with rates of 3.35% versus 0.25%.[13] This discrepancy is likely attributable to the generally lower birth weights and gestational ages observed in multiple birth infants, both recognized as primary risk factors for ROP.[2]

Notably, our findings did not indicate a statistically significant increase in the severity of ROP (Stages ≥3) among multiple births compared to singletons. This contrasts with a study conducted in Israel, which reported that singletons weighing less than 1500 grams were at higher risk for severe ROP compared to multiple births.[14] Such variability may be grounded in differences in study design, population characteristics, and the definitions used for severity assessment.

Table 3: Severity of ROP based on staging in both the groups

	Singletons (74)	**Multiple born (29)**	**Chi-square value**	**p-value**
Stage1-2 (Mild to moderate ROP)	19	11	1.5159	0.218239
Stage ≥3 (Severe ROP)	55	18		

Table 4: Shows risk factors associated with ROP in singletons vs multiple birth infants

Risk factor	**Single born**		**Multiple birth**		**Chi square value**	**p-value**
	Present	Absent	Present	Absent		
Oxygen supplementation	59	14	22	8	0.709	0.563
Blood transfusion	24	49	3	27	5.75	**0.016**
Asphyxia	3	70	2	28	0.301	0.583
RDS	43	30	12	18	3.053	0.08
Sepsis	19	54	2	28	4.91	**0.026**

Interestingly, when analyzing ROP severity within twin pairs, we found that smaller infants in a pair often had a higher stage of ROP compared to their larger counterpart, with 50% of twin pairs demonstrating this trend. This aligns with the work of Wang et al., which examined discordant twins and identified that lower gestational age and birth weight significantly predicted ROP but did not confirm substantial differences in ROP between larger and smaller pair members.[15,16] Our study's results corroborate this notion that while prematurity and low birth weight are critical factors, the intra-pair dynamics in multiple births may play a role in the heterogeneous presentation of ROP.

Additionally, the absence of increased severity in multiple pregnancies reflects a complex interaction of various factors, including neonatal care practices and screening protocols that might mitigate the risks for some populations. A study by Pejawar et al. highlighted that adherence to stringent screening guidelines could lead to earlier detection and management of ROP, potentially reducing the severity in at-risk groups.[6]

In the discussion of the study, the statistical insignificance of oxygen supplementation, asphyxia, and sepsis as risk factors for ROP, contrasted with the significant association of blood transfusion and respiratory distress with ROP in multiple births versus singletons, is crucial (**Table 4**). These findings should be considered in light of the broader context of ROP risk as found in the study that multiple birth infants are at a significantly higher risk of developing ROP compared to single-born infants, with a reported incidence of 31.25% in multiple births versus 14.3% in singletons ($p < 0.05$). This aligns with the data that multiple pregnancies often result in premature births and low birth weights,[12] both of which are well-established risk factors for ROP.[8] Although we did not find a significant increase in the severity of ROP in multiple births, understanding the specific risk factors that contribute to ROP development in this population remains vital for tailored screening and intervention strategies.

The present findings emphasize the need for individualized care strategies in managing premature infants, particularly in the context of multiple pregnancies. Given the higher risk of ROP in these infants, tailored screening regimens that consider both infant size and gestational age within the multiple birth context are essential for better outcomes.

5. Limitations of the Study

This study has several limitations that warrant consideration. It was conducted at a single tertiary center with a relatively limited number of multiple-birth infants, which may restrict the generalizability of the findings to broader populations. Although efforts were made to standardize the staging of retinopathy of prematurity (ROP), the assessment process inherently carries some degree of observer subjectivity, potentially introducing variability in classification. Furthermore, the cross-sectional design precludes establishing causal relationships between multiple gestation and the incidence or severity of ROP. In addition, certain unmeasured confounders, including variations in oxygen delivery protocols, nutritional supplementation, and neonatal intensive care practices, were not captured in the present analysis but may have influenced disease outcomes. These factors, combined with the modest sample size, highlight the need for larger multicenter studies with longitudinal follow-up to validate these findings and provide a more comprehensive understanding of ROP risk in multiple births.

6. Conclusions

Ultimately, this investigation reaffirms that infants born prematurely from multiple pregnancies face a considerably increased likelihood of developing retinopathy of prematurity (ROP) when contrasted with single-born premature infants. This finding underscores the vital importance of increased monitoring and specialized screening procedures for this particular group. Although the research did not reveal a substantial variation in ROP severity between infants from multiple births and single infants, this outcome highlights the intricate nature of the condition. It implies that elements beyond multiple gestation may exert a more significant influence on the advancement of the disease. Additional studies into the subtle relationships among factors such as gestational age, birth weight, and specific infant traits are vital to enhance risk assessment and improve treatment approaches. These insights advocate for ongoing research with larger, more varied participant groups to substantiate these conclusions, clarify the fundamental processes driving ROP development in multiple births, and, in the end, enhance visual results for all premature infants.

7. Source of Funding

None.

8. Conflict of Interest

None.

9. Ethical Approval

Ethical No.: 3848-50/MC/IEC/2018.

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