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Influence of maternal factors on retinopathy of prematurity: A cross-sectional Study from a tertiary care centre

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a serious condition affecting premature infants and identifying maternal risk factors is essential for its prevention. This study aimed to identify maternal risk factors associated with ROP in preterm newborns at a tertiary care center.

Materials and Methods: This cross-sectional study was conducted between August 2021 and September 2022 at a tertiary care center. All preterm and low birth weight neonates attending the ROP clinic or admitted to the neonatal intensive care unit (NICU) were included, while term neonates and those weighing ≥2.5 kgs with anterior segment/posterior segment pathology other than ROP were excluded. Data on maternal and neonatal characteristics were obtained and inferential analysis was conducted using the chi-square test and Student's t-test.

Results: Out of 410 preterm newborns included, 109 were diagnosed with ROP, indicating an institutional incidence of 26.58%. Advanced maternal age, low socio-economic status, urinary tract infection, chorioamnionitis, multiple pregnancy, pre-eclampsia, maternal anemia, history of asthma and steroid use during pregnancy were significantly associated with ROP.

Conclusion: This study highlights the importance of addressing modifiable maternal risk factors to reduce the incidence of ROP in premature infants. Screening for ROP should be prioritized for neonates born to mothers with these risk factors to improve visual outcomes.

1. Introduction

Retinopathy of Prematurity (ROP) is a condition that affects premature infants with low birth weight (less than 1500 g) and is caused by the effects of oxygen supplementation, which is used to save the lives of these infants. Normally, the blood vessels in the retina, located at the back of the eye, develop and grow from the optic nerve head towards the outer edge of the retina, called the ora-serrata. This process begins at around 16 weeks of intra-uterine life and is completed around 40 weeks of intra-uterine life. However, in premature infants, this process may be disrupted due to their early birth, resulting in incomplete or delayed development of retinal blood vessels. Specifically, the nasal side of the ora-serrata is usually reached at around 36 weeks of intra-uterine life, while the temporal side is typically reached at around 40 weeks of intra-uterine life. The use of oxygen supplementation in premature infants can further contribute to the development of ROP by affecting the delicate balance of oxygen in the retina, leading to abnormal blood vessel growth and potential damage to the retina. [1,2]

Many surveys have been conducted worldwide to understand its occurrence and have shown varying incidence rates of ROP. For example, the incidence of ROP was

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reported as 12.6% in the United Kingdom in 2011, 16.4% in the United States of America between 2000-2012, 36.6% in Taiwan between 2002-2011, 29.8-31.7% in South Korea between 2007-2018, 21.9% in the Netherlands in 2009, 9.3% in Switzerland between 2006-2015, 15.9% in Shanghai between 2012-2016 and 12.8% in Southwest China between 2009-2012. In comparison, India has shown a higher incidence of ROP ranging from 26.6% to 49% between 1993-2013.[3,4]

Studies have shown that not all premature low-birth weight babies exposed to oxygen develop Retinopathy of Prematurity (ROP), which has led researchers to investigate the role of maternal factors and any protective factors in the development of ROP in preterm newborns. The placenta plays a crucial role in supplying oxygen and nutrients to the developing fetus and any disruptions in the remodeling process of the uterine arteries can lead to fetoplacental insufficiency, where the placenta gradually loses its ability to deliver adequate oxygen and nutrients to the fetus. This can result in a hypoxic environment, leading to decompensated hypoxia, acidosis and altered fetal metabolism. Maternal risk factors can also affect the presence of angiogenesis and vascular endothelial growth factor (VEGF), which are associated with ROP development. Studies have also shown that maternal factors such as maternal age, anemia, smoking, preeclampsia, mode of delivery, multiple pregnancies, infections during pregnancy and the use of certain medications can impact the fetus's ability to receive enough oxygen and nutrients through the placenta. Socioeconomic factors, such as maternal education and economic support, may also impact the overall well-being of the mother and fetus.[5–7] Most of these studies regarding ROP are done abroad and there are limited studies from India. Therefore, our study aims to identify maternal risk factors that contribute to the development of ROP in preterm newborns at a tertiary care center.

2. Material and Methods

2.1. Study design, setting and duration

This cross-sectional study was carried out between August 2021 and September 2022 in the Department of Ophthalmology in collaboration with the Department of Pediatrics of Gandhi Medical College and associated Hamidia Hospital, Bhopal, Madhya Pradesh.

2.2. Inclusion criteria and exclusion criteria

All preterm neonates (gestational age <37 weeks) and low birth weight neonates (birth weight <2.5 kgs) attending the ROP clinic or admitted to the neonatal intensive care unit (NICU) and those whose mothers gave consent were included. While all the term neonates (gestational age ≥37 weeks) and weighing ≥2.5 kgs at birth, with anterior segment/posterior segment pathology other than ROP were excluded.

2.3. Sample size and sampling

All eligible participants attending the ROP clinic and NICU during the study period were included in the study consecutively. Therefore, a total of 410 eligible preterm neonates, after considering the inclusion and exclusion criteria, were included as final sample size for our study.

2.4. Ethical considerations

This study was approved by the Institutional Ethics Committee, Gandhi Medical College, Bhopal. Written and informed consent was obtained from parents along with a thorough explanation of the study in the participant's native language.

2.5. Data collection

After obtaining consent, a history was obtained, with all the questions provided to elicit relevant or helpful information for the research. Data on the socio-demographic characteristics, gestational age, birth weight, maternal age, delivery method, previous birth interval, term births, preterm births, number of miscarriages, number of multiple births, blood transfusions and other maternal risk factors obtained from the parents/guardian of the premature infant with ROP through interview and from already obtained investigation's reports and medical records during the period of pregnancy on a predesigned proforma.

2.6. Data analysis

Data were analyzed using IBM SPSS software, version 26.0 (IBM Corp., Armonk, NY). Quantitative data were presented as the means ± standard deviation (SD), whereas qualitative data were presented as frequency and percentages. Inferential analysis was conducted using the chi-square test for categorical variables and the Student's t-test for continuous variables. A p-value of <0.05 was considered significant throughout.

3. Results

A total of 410 preterm newborns were included during the study period, out of which 109 newborns were diagnosed with ROP and showed an institutional incidence of 26.58% with male (65.1%) preponderance, however, it was not statistically significant (Table 1).

Tables 2 and 3 shows the sociodemographic characteristics of mothers and the distribution of maternal risk factors, respectively. We also found a significant association between maternal anemia and asthma with presence of ROP (Table 4).

Table 1: Incidence of ROP across gender (N=410)

Gender	Present(N=109)		Absent (N=301)		p-value
	Frequency	%	Frequency	%	
Male	71	65.1%	171	56.8%	0.130
Female	38	34.9%	130	43.2%	

Table 2: Maternal socio-demographic factors and association with ROP

Socio-demographic Factors		ROP Present (N=109)		ROP Absent (N=301)		p-value
		No.	%	No.	%	
Maternal age (in years)	<20	12	11.0%	84	27.9%	0.050
	20-25	42	38.5%	142	47.2%	0.120
	26-30	27	24.8%	70	23.3%	0.749
	31-35	17	15.6%	3	1.00%	<0.001*
	>35	11	10.1%	2	0.7%	<0.001*
Mean maternal age		25.72±4.65		24.71±4.39		0.045*
Maternal education level	Primary	7	6.4%	19	6.3%	0.937
	Middle	62	56.9%	165	54.8%	
	High	28	25.7%	82	27.2%	
	Higher	10	9.2%	25	8.3%	
	Graduation	2	1.8%	10	3.3%	
Occupation	Housewife	84	77.1%	232	77.1%	0.990
	Working	25	22.9%	69	22.9%	
Household size	>5 members	79	72.5%	223	74.1%	0.744
	1-5 members	30	27.5%	78	25.9%	
Marital status	With Partner	108	99.1%	299	99.3%	0.790
	Separated	1	0.9%	2	0.7%	
Socioeconomic status	Lower-middle	23	21.1%	89	29.6%	0.040*
	Upper-lower	32	29.3%	90	29.9%	
	Lower	54	49.5%	122	40.5%	
Area of residence	Urban	34	31.2%	99	32.9%	0.745
	Rural	75	68.8%	202	67.1%	

*Statistically significant

In the group where Retinopathy of Prematurity (ROP) was present, 5.5% of mothers had a history of steroid use, while in the group where ROP was absent, only 26.6% of mothers had a history of steroid use. The p-value was found to be statistically significant at <0.001, indicating that there is a lower incidence of ROP associated with antenatal steroid use. No significant associations were found between the incidence of ROP and the use of Metformin, Insulin, Betablocker, Cephalosporin, Doxilamine succinate, Antihistamine, Paracetamol, Ondansetron, Iron supplements, Folic acid, $MgSO_4$ and Tobacco.

4. Discussion

The institutional incidence of ROP in our study was 26.58%, with a higher prevalence in males at 65.1%. However, the incidence of ROP has shown variation in the literature.[8,9] A study conducted by Le et al. also found a male predominance, with 59% of patients being males and 41% being females, which is consistent with the findings of our present study.[10] In line with previous research, our study did not find any significant association between gender and the incidence of ROP.[7,11,12] However, there have been other studies that have reported male sex as a significant risk factor for the development of severe ROP compared to females.[13,14]

In our study, the mean age of mothers whose neonates developed Retinopathy of Prematurity (ROP) was 25.72±4.65 years, while the mean age of mothers whose neonates did not develop ROP was 24.71±4.39 years and this difference was statistically significant. Furthermore, we observed that the incidence of ROP was significantly higher among neonates born to mothers who were over 30 years old. These findings are in agreement with a study conducted by Wu et al., which also reported an association between higher maternal age and the development of ROP.[15]

The majority of mothers in our study were from a lower socio-economic class and we observed a significant association between socioeconomic status and the presence of Retinopathy of Prematurity (ROP) among neonates (p = 0.004). This suggests a higher incidence of ROP among neonates born to mothers from lower socioeconomic class. One possible explanation for this finding is that families from higher socio-economic classes may prefer

Table 3: Pregnancy-related maternal factors and ROP

Maternal Factors		ROP Present (N=109)		ROP Absent (N=301)		p-value
		No.	%	No.	%	
Previous history of premature birth	Absent	90	82.6%	262	87.0%	0.250
	Present	19	17.4%	39	13.0%	
Previous pregnancy loss	Absent	103	94.5%	277	92.0%	0.390
	Present	6	5.5%	24	8.0%	
Parity	Multiparous	38	34.9%	84	27.9%	0.170
	Primiparous	71	65.1%	217	72.1%	
Urinary tract infection	Absent	94	86.2%	293	98.0%	<0.001*
	Present	15	13.8%	8	2.0%	
Chorioamnionitis	Absent	99	90.8%	295	92.1%	0.001*
	Present	10	9.2%	6	1.9%	
Multiple pregnancies	Absent	92	84.4%	284	94.4%	0.001*
	Present	17	15.6%	17	5.6%	
Mode of delivery	LSCS	20	18.4%	30	10.0%	0.020*
	NVD	89	81.6%	271	90.0%	
Gestational hypertension	Absent	91	83.5%	249	82.7%	0.867
	Present	18	16.5%	52	17.3%	
Gestational diabetes mellitus	Absent	84	77.1%	254	84.4%	0.080
	Present	25	22.9%	47	15.6%	
Pre-eclampsia	Absent	103	94.5%	231	76.7%	<0.001*
	Present	6	5.5%	70	23.3%	
Eclampsia	Absent	105	96.3%	293	97.3%	0.590
	Present	4	3.7%	8	2.7%	
Prolonged labor	Absent	96	88.1%	262	87.0%	0.780
	Present	13	11.9%	39	13.0%	

*Statistically significant, LSCS- lower segment caesarean section, NVD-normal vaginal delivery

Table 4: Maternal health related factors and association with ROP

Maternal Factors		ROP Present (N=109)		ROP Absent (N=301)		p-value
		No.	%	No.	%	
Anemia	Absent	26	23.9%	276	91.7%	0.030*
	Present	83	76.1%	25	8.3%	
Hypothyroidism	Absent	100	91.7%	290	96.3%	0.050
	Present	9	8.3%	11	3.7%	
Cardiac disorder	Absent	106	97.2%	296	98.3%	0.480
	Present	3	2.8%	5	1.7%	
Asthma	Absent	100	91.7%	293	97.3%	0.012*
	Present	9	8.3%	8	2.7%	

*Statistically significant

private hospitals for healthcare services, while lower socio-economic class families may lack the financial means to access private healthcare and therefore seek care at government hospitals. This could account for the higher proportion of lower socio-economic class mothers in our study population. These findings highlight the need to consider socioeconomic factors in the assessment and management of ROP, as they may impact the risk and outcomes of this condition.

Our result showed that 13.76% of mothers whose neonates developed retinopathy of prematurity (ROP) had a history of urinary tract infection (UTI) during pregnancy, while only 2.66% of mothers without ROP reported a history of UTI. Similar to the result of other studies this difference was statistically significant and suggested a higher incidence of ROP among neonates born to mothers who had UTI.[16] This present study also found a higher incidence of ROP in mothers with a history of chorioamnionitis, which is justifiable given that the mothers in this study were from a lower socioeconomic class residing in a rural area with limited awareness and healthcare facilities. Villamor Martinez et al. also reported a positive association between chorioamnionitis and ROP.[17] Chorioamnionitis causes an inflammatory response in the fetus and leads to the production of cytokines that directly alter retinal angiogenesis. These factors make the

developing retina more sensitive to the effects of postnatal oxygen and the circulatory instability and fluctuation of oxygen saturation caused by infection or inflammation may alter retinal perfusion and increase retinal damage, leading to ROP. The present study also found a significant association between a history of multiple pregnancy and the development of ROP, which is consistent with the findings of Motta et al. and Sood et al.[18,19] Multiple pregnancy is associated with lower gestational age and birth weight, which can lead to prematurity and dilutional anemia in newborns, contributing to the development of ROP. Interestingly, the present study found that among neonates who developed ROP, only 5.5% of mothers had a history of pre-eclampsia, whereas 23.25% of mothers whose neonates did not develop ROP had a history of pre-eclampsia. This association was statistically significant and suggests that pre-eclampsia may lower the incidence of ROP. In mothers with pre-eclampsia, there is a higher level of anti-angiogenic factors and lower level of vascular endothelial growth factor (VEGF) in amniotic fluid, which may offer protection against ROP. Shulman et al. and Alshaikh et al. also showed a protective association between pre-eclampsia and ROP development, which is similar to the findings of the present study.[20,21]

In this study, we also examined the distribution of maternal health factors in relation to the development of retinopathy of prematurity (ROP) in newborns. We observed that a significantly higher percentage of mothers with newborns who developed ROP had anemia compared to mothers with newborns who did not develop ROP. This finding was consistent with a study by Dai et al. who reported a higher incidence of ROP in preterm newborns of mothers with anemia.[22] The prevalence of asthma was found to be 8.30% in mothers of neonates with retinopathy of prematurity (ROP), while it was only 2.70% in mothers of neonates without ROP. This significant association indicates a higher incidence of ROP in newborns whose mothers have asthma. Asthma is known to cause hyperventilation, leading to respiratory alkalosis, compromised oxygen supply, reduced uterine blood flow and fetal hypoxia, which could explain the observed association between ROP and asthma. The study by Mendola et al. also supports our findings, as they concluded that maternal asthma is associated with prematurity and indirectly affects the development of ROP.[23] Our study highlights the importance of considering maternal asthma as a risk factor for ROP and emphasizes the need for early screening and intervention in such cases. This research finding could potentially contribute to the development of preventive measures and management strategies for ROP.

The prevalence of gestational hypertension, gestational diabetes mellitus and eclampsia in mothers of neonates with retinopathy of prematurity (ROP) was 16.5%, 22.9% and 3.7%, respectively, compared to 17.3%, 15.6% and 2.7% in mothers of neonates without ROP. However, these differences were not statistically significant, indicating no association between these factors and the incidence of ROP. This finding is consistent with a previous study by Kuriakose et al.[24] These findings suggest that gestational hypertension, gestational diabetes mellitus and eclampsia may not be significant risk factors for ROP and other factors may play a more critical role in its development. However, further research is needed to confirm these findings and explore other potential risk factors for ROP.

Although our study had a large sample size, it may have limitations as it was conducted at a tertiary care center, which may not reflect the general population. Therefore, further studies with a larger sample size are needed to investigate maternal risk factors associated with retinopathy of prematurity (ROP). Additionally, to improve ROP screening, more screening centers should be established to provide screening to a larger number of newborns, particularly those whose parents reside in peripheral areas. These efforts would help to overcome the challenges of ROP screening and ensure that more infants receive appropriate care.

5. Conclusion

Our study found that advanced maternal age, lower socio-economic status, history of urinary tract infection, chorioamnionitis, multiple pregnancy, pre-eclampsia, maternal anemia and history of asthma were significantly associated with retinopathy of prematurity (ROP). These findings suggest the need to prioritize efforts to improve modifiable maternal risk factors to reduce the incidence of ROP. Additionally, screening for ROP should be given high priority for neonates born to mothers with these risk factors. By addressing these issues, we can potentially reduce the burden of ROP and improve the visual outcomes of premature infants.

6. Source of Funding

None.

7. Conflict of Interest

None.

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