Original Article

Role of fetal hemoglobin in the development and progression of retinopathy of prematurity in preterm infants

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Purpose: The objective of this study was to find the association between fetal hemoglobin (HbF) concentration and retinopathy of prematurity (ROP) in preterm infants. **Methods:** In this observational, prospective, longitudinal study, a total of 410 preterm infants with <36 gestational weeks and <2.5 kg birth weight, who were attending ROP clinic in a tertiary care hospital of central India for 1 year duration were included. Dilated fundus examination was done as per ROP screening guidelines, and ROP was staged as per international classification for retinopathy of prematurity (ICROP) classification, 2021. HbF (%) was measured with high-performance liquid chromatography, and data was analyzed statistically. The relationship between HbF (%) and ROP was evaluated. Those infants who had ROP were further divided into treatment-requiring and non–treatment-requiring groups and HbF was compared in these groups at the first visit and after 1-month follow-up period. The outcome of ROP was studied with HbF levels. **Results:** A total of 410 preterm infants were included, out of which 110 infants had ROP (26.8%). Infants with ROP had significantly lower percentage of HbF with gestational age groups and birth weight groups, compared to infants without ROP. Higher percentage of HbF was associated with a lower prevalence of ROP. Higher concentration of HbF was found in the ROP infants who regressed spontaneously without treatment and less concentration was found in those who progressed to a severe disease and those who required treatment. The predictive ability of HbF (%) was 0.976 for ROP. **Conclusion:** Low fraction of HbF was found to be significantly associated with the development and progression of ROP.

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Retinopathy of prematurity (ROP) is a vascular disease affecting primarily the premature retina, which can lead to severe visual impairment and blindness.[1] ROP is a multifactorial disease. The various risk factors associated with ROP have been studied abundantly and are low birth weight, prematurity, supplemental oxygen, apnea, sepsis, respiratory distress syndrome, asphyxia, and blood transfusion.[2,3] Oxygen supplementation given in the initial weeks of postnatal life has been considered an important risk factor for the development of ROP, but not all low-birth-weight and preterm babies who are exposed to oxygen develop ROP. There are multiple biochemical markers that can affect the development and clinical course of ROP. One such factor is fetal hemoglobin (HbF), whose role has been evaluated in ROP in recent years.

Fetal hemoglobin is predominantly present in neonates at birth. HbF is the main oxygen carrier protein in the human fetus. It is found in fetal red blood cells and is involved in transporting oxygen from the mother's bloodstream to organs and tissues in the fetus.[4] The switch to produce an adult form of hemoglobin (HbA) starts at around 40 weeks of gestation, which is close to the expected time of term birth. Fetal hemoglobin differs from adult hemoglobin in its ability to bind to oxygen with greater affinity than the adult form, giving the developing fetus better access to oxygen from the mother's bloodstream.[5] HbF can carry 30% more oxygen than HbA. HbF oxygen dissociation curve is left sided in comparison to HbA, which denotes HbF having a higher affinity for oxygen at all partial pressures, thus ensuring that oxygen is transferred to the fetus from the maternal blood across the placenta.[5] This study was conducted to evaluate the role of HbF in preterm low-birth-weight infants exposed to oxygen, with respect to the development of ROP.

Methods

We conducted a hospital-based, observational, prospective, longitudinal study in the department of ophthalmology of a tertiary care center in central India for a period of 1 year. This study was conducted following the tenets of the Declaration of Helsinki. Ethics committee approval was obtained from the institutional ethics committee. Informed and written consent was taken from the parents of all neonates. All preterm infants of <36 weeks of gestational age and <2.5 kg birth weight, referred from the department of pediatrics, ophthalmology outpatient department (OPD), or elsewhere, attending the ROP clinic were included in this study. Term, post-term neonates and neonates with any ocular abnormality other than ROP were excluded from this study. Detailed demographic history including the

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gestational age, birth weight, and gender was taken. Dilated fundus examination was done as per ROP screening guidelines, and ROP was staged according to the International Classification of Retinopathy of Prematurity, 2021. Follow-up and treatment of ROP in infants was scheduled as per the Early Treatment of Retinopathy of Prematurity guidelines. Counseling of parents was done regarding the timely follow-up, and the need for periodic review was suggested. The blood sample was withdrawn from baby's peripheral vein and was sent to the pathology laboratory for fetal hemoglobin level estimation, which was measured with high-performance liquid chromatography. Fetal hemoglobin of infants was estimated at gestational age 30 weeks and after a period of 1 month, that is, 34 weeks.

On the basis of dilated fundus findings, the neonates were divided into ROP and no ROP groups. The percentage of fetal hemoglobin was studied in both the groups and was evaluated for their correlation. Fetal hemoglobin levels were evaluated in different gestational age groups in both ROP and no ROP study subjects. Similarly, HbF was also evaluated for different birth weight groups in both ROP and no ROP study subjects. Neonatal risk factors were also studied with respect to ROP. In those infants who had ROP, HbF was estimated for different zones 1–3 and stages 1–5, corresponding to the location and severity of ROP. Those infants who had ROP were further divided into treatment-requiring groups and non–treatment-requiring groups and fetal hemoglobin was compared in these groups. On follow-up after a month, fetal hemoglobin was also compared between the study subjects showing progression, spontaneous regression, and regression after treatment. The collected data were compiled in a Microsoft Excel sheet and subsequently statistically analyzed. Descriptive and inferential statistical analyses were carried out in the present study. Results of continuous measurements are presented as mean ± standard deviation (SD) (Min.–Max.), and results of categorical measurements are presented as number (%). The statistical software Statistical Package for the Social Sciences (SPSS) version 20 and MedCalc 19.5 were used for the analysis.

Results

A total of 410 preterm infants were included in this study. There were 235 (57.3%) male infants and 175 (42.7%) female infants. The neonates were divided into two groups – ROP and no ROP – on the basis of fundus findings. Among 410 infants, 110 (26.8%) infants had ROP, while 300 infants (73.2%) did not develop ROP.

Fetal hemoglobin percentage values in relation to different gestational age groups in infants with and without ROP were evaluated and are displayed in Fig. 1. Infants with ROP displayed significantly lower fetal hemoglobin percentage with gestational age groups, compared to infants without ROP, which was statistically significant. Fetal hemoglobin percentage in relation to different birth weights in infants with and without ROP were evaluated and are displayed in Fig. 2. Infants with ROP displayed significantly lower fetal hemoglobin percentage with birth weight compared to infants without ROP, which was statistically significant. The fraction of HbF (%) in ROP and no ROP groups is displayed in Fig. 3. Higher fraction of HbF (%) was associated with a lower prevalence of ROP, which was statistically significant ($P < 0.05$).

The relation of neonatal risk factors with development of ROP is shown in Table 1. History of neonatal intensive care unit (NICU) hospitalization for less than a week was observed in 98 (32.7%) babies among the no ROP group patients and in 95 (86.4%) babies among the ROP group patients. NICU

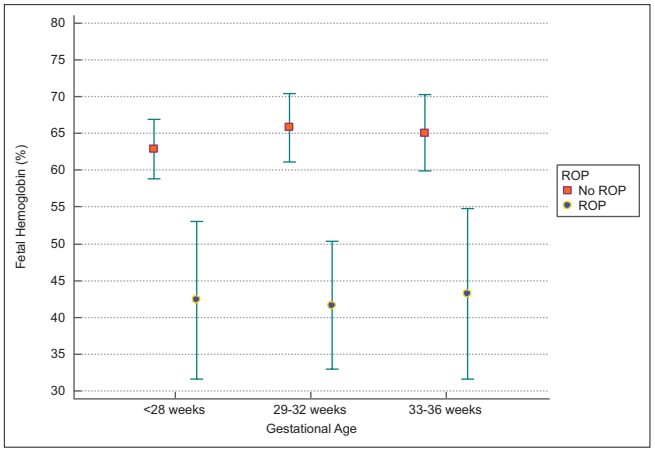

Figure 1: Fraction of HbF (%) with gestational age in study subjects with ROP and without ROP. ROP = retinopathy of prematurity

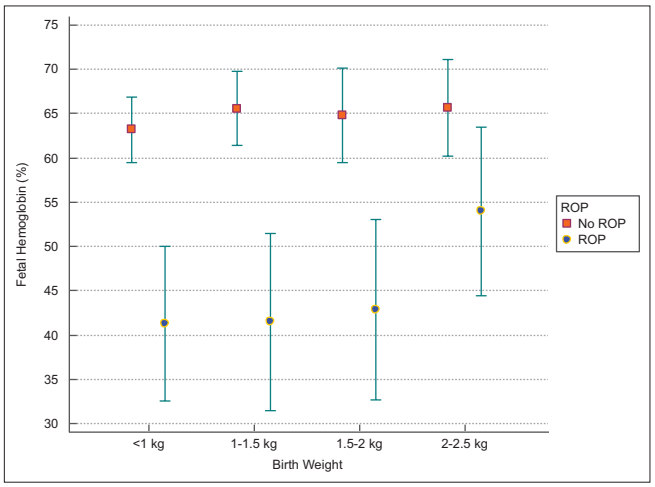

Figure 2: Fraction of HbF (%) with birth weight in study subjects with ROP and without ROP. ROP = retinopathy of prematurity

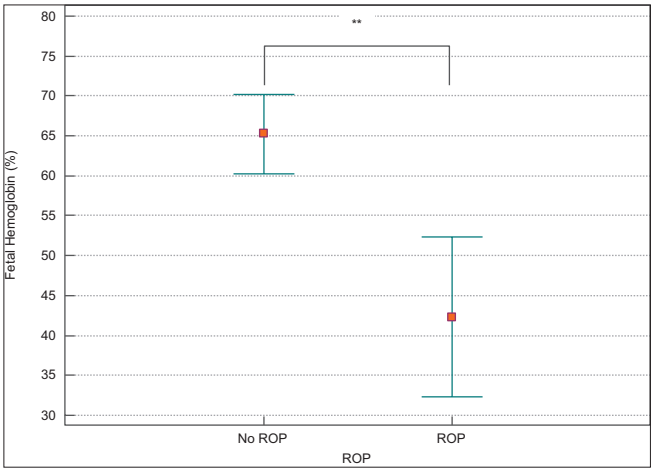

Figure 3: Fraction of HbF (%) in the study subjects with ROP and without ROP. ROP = retinopathy of prematurity

stay for more than a week was observed in 202 (67.3%) babies from the no ROP group and 15 (13.6%) babies from the ROP group, and the difference was statistically significant. Similarly, oxygen supplementation for less than a week was observed in 98 (32.7%) babies from the no ROP group and 95 (86.4%) babies from the ROP group. Oxygen supplementation for more than a week was observed in 202 (67.3%) babies from the no ROP group and 15 (13.6%) babies from the ROP group, and the difference was also statistically significant. Respiratory distress syndrome history was observed in 104 (34.7%) babies from the no ROP group and 92 (83.6%) babies from the ROP group, and the difference was statistically significant. History of sepsis was present in 26 (8.7%) babies from the no ROP group and 39 (35.5%) babies from the ROP group, showing statistical significance. Bilirubinemia was found to be statistically insignificant with the development of ROP in our study.

The location of ROP in terms of zones among the infants who developed ROP was studied in relation to fetal hemoglobin levels. Table 2 shows the zone-wise concentration of HbF in infants who developed ROP. Higher HbF concentration was found in zone 2 ROP; however, the zone-wise location of ROP was statistically insignificant with HbF levels. The severity of ROP in terms of the stages of infants who developed ROP was also studied in relation to fetal hemoglobin levels. Table 3 shows stage-wise concentration of fetal Hb who developed ROP (n = 110). In this study, it was observed that the concentration of fetal Hb was significantly associated with the staging of the disease ($P < 0.05$). Higher the concentration of fetal Hb, lower was the staging of ROP. Fig. 4 shows RetCam fundus imaging of ROP stages 1, 2, 3, and 4A.

Those infants who had ROP (n = 110) were further divided into treatment-requiring groups and non–treatment-requiring groups based on severity of the disease, and fetal hemoglobin was compared in these groups. Table 4 shows the relation of severity of ROP in terms of treatment in relation to fetal Hb levels. Among 110 ROP babies, 33 babies did not require treatment and 77 babies required treatment. Among the no treatment group babies, most of the cases had stage 1 disease; fetal Hb concentration of 30%–60% and spontaneous regression were seen. Among the treatment group babies, most of the cases of ROP had stage 3 disease and majority of the cases had fetal Hb concentration of 30%–60%.

On follow-up after a month, fetal hemoglobin was compared among the study subjects showing progression, spontaneous regression, and regression after treatment. Table 5 shows the relation of fetal Hb (%) with the outcome on follow-up of ROP after a month. Ten cases showed progression of ROP on serial examination, of which all the cases had fetal Hb of <60%. Sixty-seven cases showed regression of ROP after treatment, of which majority (89.6%) had fetal HbF of 30%–60%. Thirty-three cases showed spontaneous regression of ROP and had fetal Hb concentration of 30%–60%.

The predictive ability (area under the curve) of fetal hemoglobin % was 0.976 for ROP, with $P < 0.001$ and 95% Confidence Interval

Table 1: Distribution of neonatal risk factors in study subjects with ROP

Neonatal risk factors	Presence	No ROP	ROP	Total	χ^2	P
Duration of NICU stay <1 week	No	98 (32.7)	95 (86.4)	193 (47.1%)	92.922	<0.0001
	Yes	202 (67.3)	15 (13.6)	217 (52.9%)		
Duration of NICU stay >1 week	No	202 (67.3)	15 (13.6)	217 (52.9%)	92.922	<0.0001
	Yes	98 (32.7)	95 (86.4)	193 (47.1%)		
Oxygen supplementation required <1 week	No	98 (32.7)	95 (86.4)	193 47.1%)	92.922	<0.0001
	Yes	202 (67.3)	15 (13.6)	217 (52.9%)		
Oxygen supplementation required >1 week	No	202 (67.3)	15 (13.6)	217 (52.9%)	92.922	<0.0001
	Yes	98 (32.7)	95 (86.4)	193 (47.1%)		
RDS	No	196 (65.3)	18 (16.4)	214 (52.2%)	77.165	<0.0001
	Yes	104 (34.7)	92 (83.6)	196 (47.8%)		
Sepsis	No	274 (91.3)	71 (64.5)	345 (84.1%)	43.190	<0.0001
	Yes	26 (8.7)	39 (35.5)	65 (15.9%)		
Raised bilirubin level	No	287 (95.7)	102 (92.7)	389 (94.9%)	1.428	0.2322
	Yes	13 (4.3)	8 (7.3)	21 (5.1%)		
	Total	300 (73.2)	110 (26.8)	410		

NICU=Neonatal intensive care unit, ROP=Retinopathy of prematurity, RDS= Respiratory distress syndrome

Table 2: Distribution of location of ROP in study subjects with different fetal hemoglobin (%) levels

Location of ROP	Fetal hemoglobin (%)			Total	χ^2	P
	<30	30–60	>60			
Zone 1	0 (0.0)	22 (22.9)	2 (50.0)	24 (21.8%)		
Zone 2	6 (60.0)	50 (52.1)	1 (25.0)	57 (51.8%)	5.153	0.2720
Zone 3	4 (40.0)	24 (25.0)	1 (25.0)	29 (26.4%)		
Total	10 (9.1%)	96 (87.3%)	4 (3.6%)	110		

ROP=Retinopathy of prematurity

Table 3: Distribution of severity of ROP in study subjects with different fetal hemoglobin (%) levels

Staging of ROP	Fetal hemoglobin (%)			Total	χ^2	*P*
	<30	30–60	>60			
Stage 1	0 (0.0)	35 (36.5)	2 (50.0)	37 (33.6%)		
Stage 2	1 (10.0)	16 (16.7)	1 (25.0)	18 (16.4%)		
Stage 3	8 (80.0)	41 (42.7)	1 (25.0)	50 (45.5%)	21.474	0.0439
Stage 4	1 (10.0)	3 (3.1)	0 (0.0)	4 (3.6%)		
Stage 5	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.9%)		
Total	10 (9.1%)	96 (87.3%)	4 (3.6%)	110		

ROP=Retinopathy of prematurity

Table 4: Distribution of severity of ROP in terms of requirement of treatment, with fetal hemoglobin (%) levels

Severity of ROP	ROP (*n*=110)							
	No treatment required (*n*=33)				Treatment required (*n*=77)			
	Fetal hemoglobin (%)							
	<30	30–60	>60	Total	<30	30–60	>60	Total
Stage 1	0 (0.0)	25 (83.3)	2 (100.0)	27 (81.8%)	0 (0.0)	10 (15.2)	0 (0.0)	10 (13.0%)
Stage 2	1 (100.0)	4 (13.4)	0 (0.0)	3 (9.1%)	0 (0.0)	12 (18.1)	1 (50.0)	13 (16.9%)
Stage 3	0 (0.0)	1 (3.3)	0 (0.0)	1 (3.0%)	8 (88.9)	40 (60.6)	1 (50.0)	49 (63.6%)
Stage 4	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.5)	3 (4.5)	0 (0.0)	4 (5.2%)
Stage 5	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.3%)
Total	1 (3.0)	30 (90.9)	2 (6.1)	33	9 (11.7)	66 (85.7)	2 (2.6)	77
	χ^2	10.674	*P*	0.0990	χ^2	20.694	*P*	0.0550

ROP=Retinopathy of prematurity

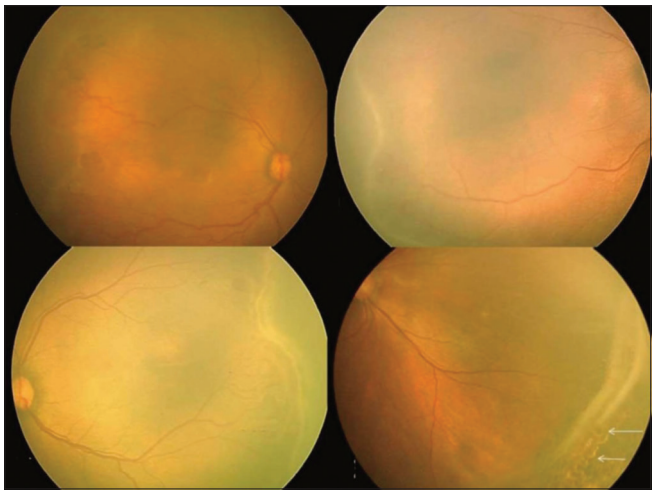

Figure 4: RetCam fundus imaging of ROP stage 1, 2, 3, and 4A. ROP = retinopathy of prematurity

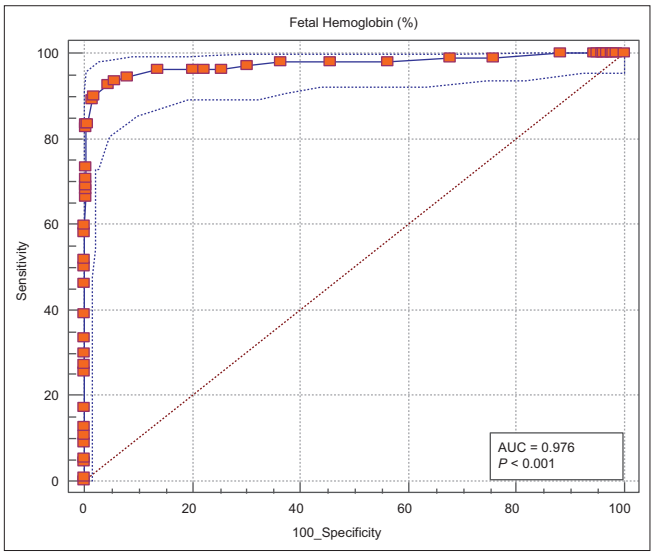

Figure 5: ROC curve for ROP and fraction of HbF (%). AUC = area under the curve, ROC = receiver operating characteristic, ROP = retinopathy of prematurity

0.956–0.988, as shown in Fig. 5. The optimum criterion was ≤ 55. The various coordinates of receiver operating characteristic (ROC) curve are shown in Table 6. The sensitivity and specificity curves for ROP and fetal hemoglobin % are shown in Fig. 6.

Discussion

There are an estimated 15 million babies born prematurely each year worldwide.[6] Decline in neonatal mortality and increased survival of extremely preterm infants contribute to increase in ROP incidence. ROP is proliferative retinopathy occurring at the confluence of the normal vascularized retina and the peripheral avascular retina and is a significant contributor to preventable childhood blindness.[7-9] Low birth weight, prematurity, oxygen supplementation, a short gestational period, history of blood transfusion, respiratory distress syndrome, and sepsis are the major risk factors for the development of ROP.[10,11]

Table 5: Distribution of outcome of ROP in study subjects with different fetal hemoglobin (%) levels

Fetal hemoglobin (%)	Progression/regression on follow-up			Total	χ^2	*P*
	Progression	Treatment regressed ROP	Spontaneous regression			
<30%	4 (40.0)	4 (6.0)	1 (3.0)	9 (8.2%)		
30%–60%	6 (60.0)	60 (89.6)	30 (90.9)	96 (87.3%)	15.409	0.0039
>60%	0 (0.0)	3 (4.5)	2 (6.1)	5 (4.5%)		
Total	10 (9.1)	67 (60.9)	33 (30.0)	110		

ROP=Retinopathy of prematurity

Table 6: Criterion value and coordinates of ROC

Parameters	Value
AUC	0.976
95% Confidence interval	0.956–0.988
Significance level *P* (area=0.5)	<0.0001
Optimal criterion	≤55
Sensitivity	90.00
Specificity	98.00

AUC=Area under the ROC curve, ROC=receiver operating characteristic

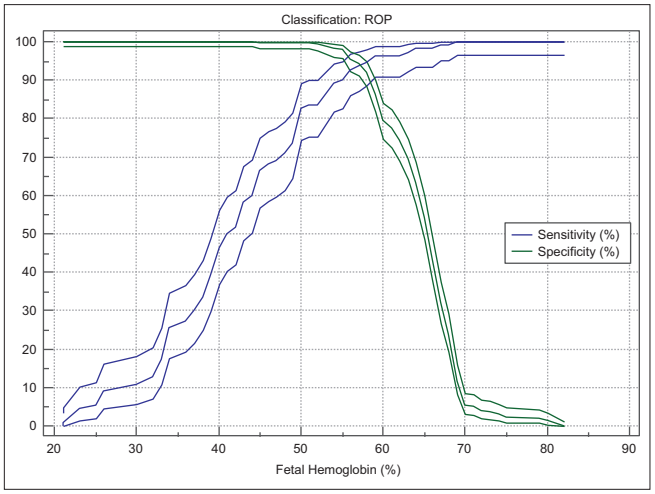

Figure 6: Sensitivity and specificity curves for ROP and HbF (%). ROP = retinopathy of prematurity

In our study, it was observed that infants with ROP had lower fetal hemoglobin concentration in all gestational age groups and birth weight groups compared to infants without ROP. It was also observed that the concentration of fetal Hb was significantly associated with the development of ROP. The difference in fraction of HbF between the infants of ROP and no ROP groups was statistically significant. The probability of ROP was inversely related to fetal hemoglobin levels. Higher the fetal Hb value, lower were the chances of developing ROP. The relationship between low HbF levels and ROP was independent of gender, gestational age, and birth weight of infants. The potential causal mechanism in ROP development involving low HbF levels thus play a role during early postnatal development. In our study, infants with prolonged oxygen supplementation, prolonged NICU hospitalization, respiratory distress syndrome, and a higher proportion of culture-proven sepsis were found to be statistically significant with the development of ROP. Also, the concentration of HbF was significantly associated with severity of the disease. An inverse correlation between the concentration of fetal Hb and the staging of the disease was observed. Higher the concentration of fetal Hb, lower was the staging of the disease. In this study, the relation of fetal Hb (%) with the outcome of ROP on follow-up was evaluated. More concentration of HbF was found in the ROP infants who regressed spontaneously without treatment, and less concentration of HbF was found in those who progressed to a severe disease and those who required treatment. Hence, HbF can also be considered a predictor for the progression of ROP. The predictive ability (area under the curve) of fetal hemoglobin % was 0.976 for ROP, and high sensitivity and specificity curves were observed. It can be concluded that the probability of developing ROP and its progression is less with increased concentration of fetal Hb, and therefore, fetal Hb is protective.

For a better understanding of oxygenation of retina and development of ROP, it is important to understand the role of HbF and HbA. HbF comprises around 70%–90% of the total hemoglobin *in utero* and at term birth.[12] The unique properties of HbF confer advantage to oxygen delivery in preterm infants, compared to HbA. HbF has a higher oxygen affinity at all partial pressures then HbA due to its decreased binding to 2,3-diphosphoglycerate.[12] This results in a shift of oxyhemoglobin dissociation curve toward the left and lowering of the arterial partial pressure of oxygen required for the release of oxygen to fetal tissues. Moreover, the oxyhemoglobin dissociation curve of HbF is steeper than that of HbA, which results in a greater oxygen unloading to the fetal tissues in response to small decrease in arterial partial pressure of oxygen.[12] It has been suggested that replacing fetal hemoglobin by adult hemoglobin (HbA) may lead to high oxygen exposure to the developing retina as a result of lower HbF, thereby increasing the risk of development of ROP.[12,13] The retina is the part of the central nervous system, and higher fractions of HbF in preterm infants have beneficial effects in the brain, such as increased oxygen transport as a result of specific oxygen-carrying properties of HbF.[14]

Some studies have shown a strong correlation between the fetal hemoglobin and ROP. Bhatti *et al*.[15] conducted a prospective study to find the effect of fetal hemoglobin levels on the development and progression of ROP. Among 14 babies screened with birth weight <1000 g and <29 weeks of gestational age, fetal hemoglobin was measured at 29, 32, 35, and 38 weeks, and seven (50%) out of 14 babies developed ROP and required laser treatment. They found HbF to be statistically different between the groups that needed and did not need treatment. They reported that infants with lower HbF levels had higher risk to develop severe ROP and this risk increased as gestational age increased in nontreatment

groups, while HbF was comparatively higher with low risk in treatment groups. The study concluded that fetal hemoglobin could be protective against the development and progression of ROP. Similarly, Hellstrom *et al*.[16] conducted a retrospective observational cohort study to clarify if the degree of loss of HbF was associated with later ROP. A total of 452 infants born in <30 gestational weeks were included, out of which 385 infants had final ROP. The relation between the mean fractions of HbF % and ROP was evaluated. They reported that the fraction of HbF % was inversely associated with the severity of ROP. The study concluded that early low fraction of HbF was independently associated with abnormal retinal neurovascular development in the very preterm infant. Hence, it can be postulated that HbF (%) is a good predictor for the development of ROP in preterm babies.[16] Our findings are also supported by previous studies, which stated that lower level of fetal hemoglobin may decrease the oxygen-carrying capacity of tissues, and hypoxia might hinder the process of retinal vascularization and spontaneous regression.[13]

The Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial (SUPPORT) has shown the challenges of oxygen management in preterm neonates.[17] It was observed that despite proper monitoring and regulation of oxygen supplementation, preterm neonates experienced increased episodes of intermittent hypoxemia in the initial weeks of life.[17] Intermittent hypoxemia is associated with exacerbation of retinal neovascularization and neurological impairment in preterm neonates.[18-20] Since fetal hemoglobin shows better delivery of oxygen to tissues during hypoxia, we hypothesize that preterm infants with higher fetal hemoglobin levels will have a protective effect against these episodes of intermittent hypoxemia, and are, therefore, less susceptible for the development of ROP.

Limitation of this study includes its small sample size. Further studies with larger sample size need to be done on the correlation of fetal hemoglobin and other protective biomarkers with ROP.

We plan to study factors which influence fetal hemoglobin levels, oxygenation, and whether increasing fetal hemoglobin levels through blood transfusion can improve the outcomes of oxygenation in preterm babies and development of ROP.

Conclusion

Low fraction of fetal hemoglobin was independently associated with the development of ROP in preterm infants. Conversely, maintaining a higher level of fetal hemoglobin may be protective against the development of ROP.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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