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STUDY OF FETAL HEMOGLOBIN WITH GESTATIONAL AGE, BIRTH WEIGHT AND RETINOPATHY OF PREMATURITY IN PRETERM INFANTS

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Abstract

Introduction: The objective of this study was to find an association of fetal hemoglobin (HbF) with gestational age, birth weight and retinopathy of prematurity (ROP) in preterm infants.

Methods*: Observational prospective study. We included a total of 410 preterm infants with <36 gestational weeks and <2.5 kg birth weight, at a tertiary care hospital of central India for a period of one year. All infants were divided into 3 groups based on gestational age and 4 groups based on birth weight. Fetal hemoglobin and ROP were compared between these groups. The infants were then categorized into ROP and no ROP groups based on International Classification for Retinopathy of Prematurity (ICROP), 2021. The relationship between gestational age, birth weight, fetal hemoglobin and ROP was evaluated.*

Results*: A total of 410 preterm infants were included out of which 110 infants had ROP. Fetal Hb concentration was higher in 33-36 weeks when compared to lower gestational age showing a positive corelation with gestational age. Similarly, fetal Hb concentration was higher in birth weight 1.5-2 kg compared to lower birth weight showing a positive corelation. Infants with ROP had a significantly lower concentration of HbF, with gestational age and birth weight groups compared to infants without ROP. There was inverse correlation between HbF and severity of ROP.*

Conclusions*: Lower gestational age, lower birth weight and lower concentration of HbF was found significantly associated with the development of ROP in preterm infants. Preterm infants have a positive corelation between fetal hemoglobin and gestational age/birth weight.*

Keywords: Retinopathy of Prematurity, Gestational age, Birth weight, Fetal Hemoglobin, preterm infants
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INTRODUCTION

Retinopathy of Prematurity (ROP) is a serious vaso-proliferative disorder that affects the retina of premature infants. Low gestational age and low birth weight are the major risk factors for development of retinopathy of prematurity.[1,2]

Both factors are related to the immaturity extent of retinal neural and vascular development at birth. Lower gestational age increases the duration of infant exposure to postnatal insults, ultimately contributing to retinopathy of prematurity.[2] Lower the gestational age and birth weight, the more loss of factors responsible for intrauterine environment for the fetus.[2] The low concentration of factors responsible for development that are normally available in utero prevent the immature retina of preterm infants from normal vascularization, which can precipitate the disease.[2-7] Identifying the postnatal factors that affect the risk and course of ROP, might allow the ophthalmologists and neonatologists to attempt for prevention of the disease and limits comorbidities as well.

Fetal hemoglobin (HbF) is the normal hemoglobin present in the fetus and absent in the adults.[8] It is primarily produced by liver and spleen, whereas adult hemoglobin is produced is produced by bone marrow. It is produced by erythroid precursor cells from 10 to 12 weeks of pregnancy to the first six months of postnatal life.[9-11] HbF is predominant in neonates at birth. It is the oxygen carrier protein involved in transporting oxygen from mother's bloodstream to fetus organs. It has an oxy-hemoglobin curve that may affect systemic oxygenation and the development of ROP.[12] Though gestational age and birth weight are related to ROP, whether fetal hemoglobin is also related to gestational age, birth weight and ROP in preterm infants and can be used to assess the maturity status of the infants and hence probability of development of ROP. Hence, this study was conducted to find an association of fetal hemoglobin with gestational age, birth weight and retinopathy of prematurity in preterm infants.

METHODS

This was a hospital based observational prospective study done in Department of Ophthalmology, in a tertiary care hospital of central India from for a period of one year. This study was conducted following the declaration of Helsinki. Ethics committee approval was obtained from the Institutional Ethics committee of Gandhi medical college, Bhopal. Informed and written consent was taken from the parents of neonates. All preterm infants of <36 weeks of gestation and <2.5 kg birth weight, referred from Department of paediatrics, Ophthalmology OPD or elsewhere, attending 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. Neonates with any congenital abnormality were also excluded from this study. Demographic history was taken including the gender, gestational age and birth weight. Dilated fundoscopy examination was done by indirect ophthalmoscope as per the ROP screening guidelines. ROP was classified according to the International Classification of Retinopathy of Prematurity (ICROP), 2021. Follow up and treatment of ROP infants was scheduled as per the Early Treatment of Retinopathy of Prematurity guidelines. Counselling of the parents was done regarding the timely follow up visits and need for periodic review was suggested. 3 ml of blood sample was withdrawn from baby's peripheral vein in EDTA tube and was sent to the pathology laboratory for fetal hemoglobin level estimation, which was measured with high performance liquid chromatography.

Fetal hemoglobin concentration was divided into three groups i.e <30%, 30-60% and >60%. Gestational age, gender and birth weight of the infants was studied and compared in these groups and their association was evaluated.

On the basis of gestational age, infants were categorized into three sub-groups i.e <28 weeks (extreme preterm), 29-32 weeks (early preterm) and 33-36 weeks (late preterm). Birth weight was categorized into four sub-groups i.e <1 kg (extremely low birth weight), 1-1.5 kg (very low birth weight), 1.5-2 kg (moderately low birth weight) and 2-2.5 kg (low birth weight). On the basis of dilated fundoscopy findings, the neonates were divided into ROP and no ROP groups. The concentration of fetal hemoglobin was compared in both these groups. The concentration of fetal Hb was also compared with different stages of ROP among the infants who developed ROP. The collected data were compiled in a Microsoft Excel sheet and subsequently statistically analysed. Descriptive and inferential statistical analyses were carried out in the present study. Results on continuous measurements are present on Mean ± SD (Min.-Max.) and results on categorical measurements are presented in Number (%). The statistical software SPSS version 20 (The Standard Protocol for Social Sciences) was used for the analysis.

RESULT

A total of 410 preterm infants were included in this study. Out of 410 infants, 110 infants had developed ROP. Male infants were 235 (57.3%) while female infants were 175 (42.7%). Gender wise distribution of study subjects with fetal hemoglobin concentration are shown in table 1. In this study male preponderance was observed but statistical analysis showed an insignificant difference between male and female with respect to fetal Hb levels (P >0.05).

Table 1: Gender wise distribution of Study subjects with Fetal Hemoglobin (%) levels

Gender	Fetal Hemoglobin (%)			Total	χ^2	P Value
	<30	30-60	>60			
Female	4 (40.0)	61 (38.9)	110 (45.3)	175 (42.7%)	1.634	0.4418
Male	6 (60.0)	96 (61.1)	133 (54.7)	235 (57.3%)		
Total	10 (2.4)	157 (38.3)	243 (59.3)	410		

Table 2: Distribution of Gestational Age of Study subjects with Fetal Hemoglobin (%) levels

Gestational Age	Fetal Hemoglobin (%)			Total	χ^2	P Value
	<30	30-60	>60			
<28 weeks	1 (10.0)	15 (9.6)	5 (2.1)	21 (5.1%)		
29-32 weeks	3 (30.0)	65 (1.4)	80 (32.9)	148 (36.1%)	17.090	0.0019
33-36 weeks	6 (60.0)	77 (49.0)	158 (65.0)	241 (58.8%)		
Total	10 (2.4)	157 (38.3)	243 (59.3)	410		

Fetal hemoglobin was also compared between preterm infants of different birth weight groups. It was observed that higher the birth weight of the babies, more was the fetal Hb levels, showing a statistically positive significant association between birth weight and fetal Hb levels (P <0.05). (Table 3) The fetal hemoglobin concentration in all the birth weight group of infants up to 2 kg were higher in no ROP groups compared to ROP groups. (Figure 2)

Figure 1: Distribution of gestational age of study subjects with fetal hemoglobin (%) levels with respect to ROP status

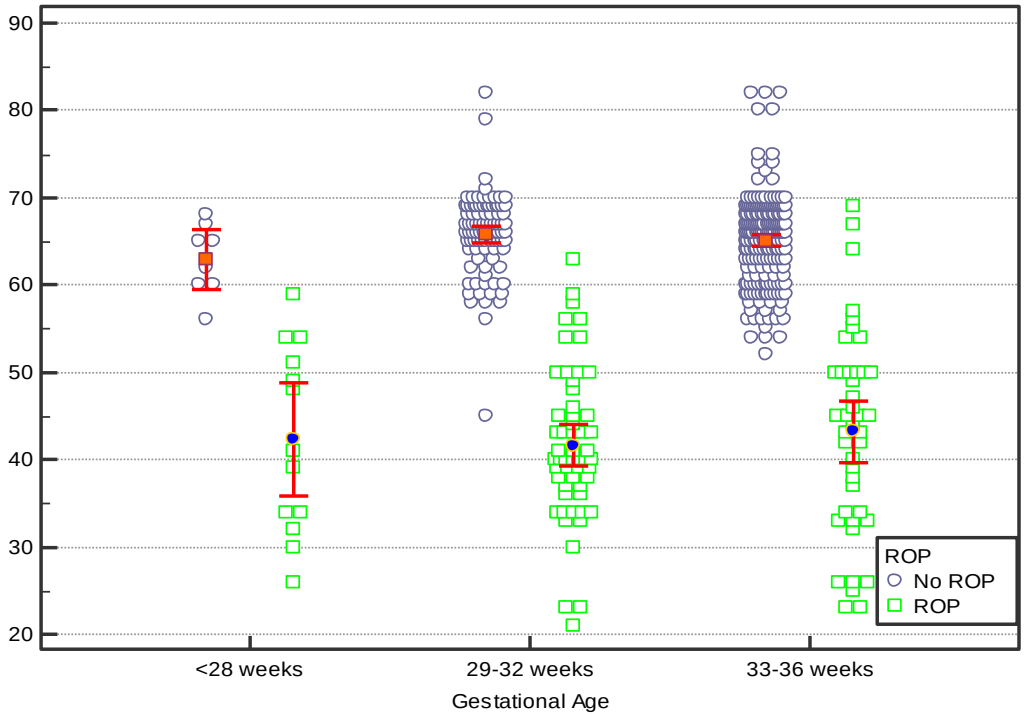
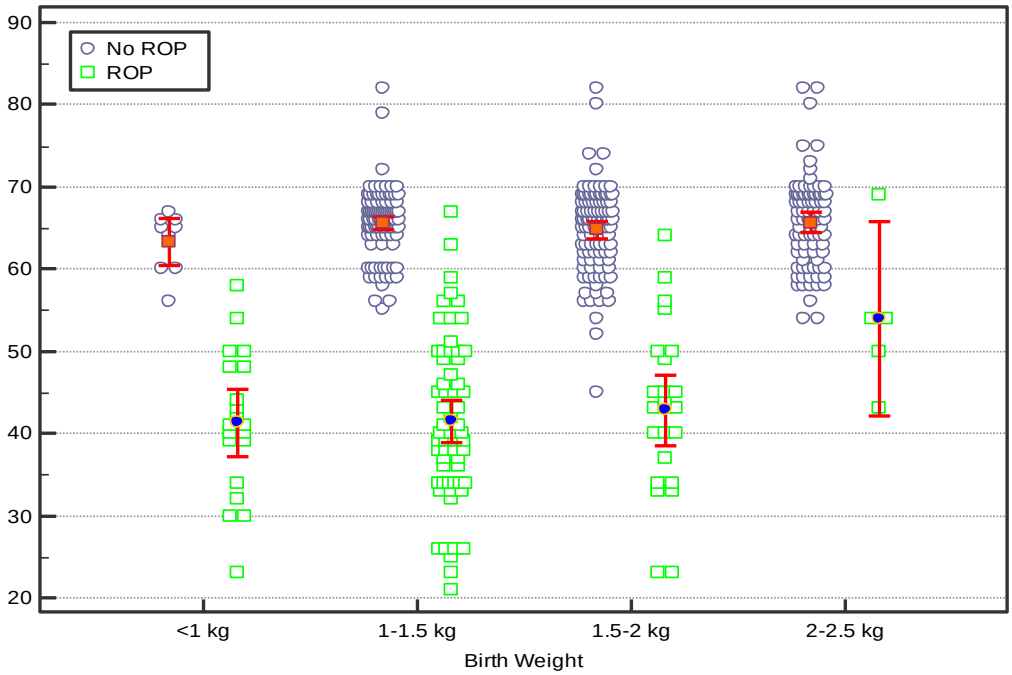


Table 3: Distribution of birth weight in study subjects with Fetal Hemoglobin levels (%)

Birth Weight	Fetal Hemoglobin (%)			Total	χ^2	P Value
	<30	30-60	>60			
<1 kg	1 (10.0)	22 (14.0)	6 (2.5)	29 (7.1%)		
1-1.5 kg	7 (70.0)	70 (44.6)	83 (34.2)	160 (39.0%)	36.082	< 0.0001
1.5-2 kg	2 (20.0)	42 (26.8)	85 (35.0)	129 (31.5%)		
2-2.5 kg	0 (0.0)	23 (14.6)	69 (28.4)	92 (22.4%)		
Total	10 (2.4)	157 (38.3)	243 (59.3)	410		

Figure 2: Distribution of birth weight of study subjects with fetal hemoglobin (%) levels with respect to ROP status



The infants were then categorized into ROP and no ROP groups based on International Classification for Retinopathy of Prematurity (ICROP), 2021. The relationship between fetal hemoglobin and ROP was evaluated. Fetal hemoglobin and ROP were compared between these groups (Table 4). All 10 (9.1%) babies were observed to be ROP positive in lower levels of fetal Hb (<30%) and majority of the babies that did not develop ROP had higher levels of fetal Hb (>60%). Hence the concentration of fetal Hb was significantly associated with development of ROP (P <0.05).

Table 4: Distribution of Fetal Hemoglobin (%) of Study Subjects with ROP

Fetal Hemoglobin (%)	No ROP	ROP	Total	χ^2	P Value
<30%	0 (0.0)	10 (9.1)	10 (2.4%)		
30-60%	61 (20.3)	96 (87.3)	157 (38.3%)	199.959	< 0.0001
>60%	239 (79.7)	4 (3.6)	243 (59.3%)		
Total	300 (73.2)	110 (26.8)	410		

Among those infants who developed ROP, fetal hemoglobin was also evaluated and compared between different stages of ROP for determining the severity (table 5). It was observed that the concentration of fetal Hb was significantly associated with staging or severity of the disease (P <0.05). Higher the concentration of fetal Hb, lower was the staging of ROP.

Table 5: Distribution of severity of ROP in Study Subjects with Fetal Hemoglobin (%) levels

Staging of	Fetal Hemoglobin (%)				χ^2	P Value
ROP	<30	30-60	>60	Total		
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%)		

DISCUSSION

In this study, there was no significant difference in gender with respect to fetal hemoglobin levels. We observed a positive association of gestational age with fetal Hb concentration in preterm infants. Maximum fetal Hb concentration was seen in infants with gestational age of 33-36 weeks. Only few landmark studies have been reported between fetal hemoglobin and gestational age of preterm infants. Most of the studies of fetal hemoglobin are in comparison with preterm, term and post-term infants. Roy SK et al (2021) conducted a comparative study of 90 neonates which included preterm, term and post-term babies of different birth weights. They found HbF levels to be significantly higher in preterm newborns compared to term and post-term newborns. They concluded a negative correlation between gestational age and fetal hemoglobin concentration.[13] The higher levels of fetal hemoglobin percentage in different series of studies are due to different methods employed for estimation of fetal hemoglobin, method of collection of blood samples and associated maternal diseases responsible for intrauterine anoxia in fetus. Thus, the level of fetal hemoglobin estimation can be considered an important criterion for evaluation of gestational age, maturity and hence development of retinopathy of prematurity. Fetal hemoglobin has been compared with other methods for assessment of maturity and gives the same precision in estimation of gestational age.[14] Fetal hemoglobin concentration at postmenstrual age however is unaffected by gestational age at birth.[15]

In our study, we also observed a positive correlation between birth weight and fetal hemoglobin concentration. The fetal Hb concentration was found to be higher in infants with birth weight of 1.5-2 kg. Roy SK et al (2021) conducted a comparative study of 90 neonates of different birth weights and found HbF levels to be significantly higher in infants with birth weight <2.5 kg as compared to =/>2.5 kg which included preterm, term and post-term infants.13

The difference in results among various series may be due to nutritional, racial and geographical variation as well as due to difference in the method of collection of blood and estimation of fetal hemoglobin. Wilson K, et al (2017) conducted a retrospective cohort analysis of 159,215 infants for postnatal prediction of gestational age using newborn fetal hemoglobin levels. The study concluded that models derived from a combination of hemoglobin ratios and birth weight were more precise at predicting gestational age than models limited to the birth weight of the infants.[16]

We also observed in our study that the mean HbF percentage was significantly lower in the ROP group than in the neonates that did not develop ROP. The fetal hemoglobin concentration had a negative correlation with retinopathy of prematurity in all the gestational age groups and birth weight groups of preterm infants. Those infants who had ROP, had a significantly lower amount of HbF compared to those who did not develop ROP. The inverse correlation between concentration of fetal Hb and severity of the disease was observed. Similar results were observed in a study done by Bhatti R.A, et al (2005), who conducted a prospective study of 14 preterm infants and studied the role of fetal hemoglobin on the development and progression of ROP. The study concluded that a higher level of fetal hemoglobin could be protective against the progression of ROP.[17] There is physiological evidence supporting left shift of the oxyhemoglobin dissociation curve with increasing HbF percentage. HbF has a higher affinity for oxygen due to its decreased binding to 2,3 DPG.9,18 This unique property of HbF confers advantage to oxygen delivery in the preterm infant. It is therefore biologically plausible that a lower HbF concentration provides greater oxygen delivery to the developing retina.[18] Evidence of this effect has been found in our study.

Mortality and morbidity are inversely related with the gestational age, prematurity being one of the most important causes of prenatal mortality. Similarly post maturity also constitutes a risk for fetal life by increasing still births, fetal distress and neonatal death.[19] In the present study the results suggested that fetal hemoglobin could provide significant information as an index of maturity and thus the status of retinopathy of prematurity.

There are few limitations of the study like less sample size. Larger cohort studies with more sample size are needed to investigate the detailed correlation between fetal hemoglobin with different gestational age and birth weight of the neonates.

CONCLUSION

Based on our study outcomes, we conclude that preterm infants have a positive corelation between gestational age and fetal hemoglobin, and also between birth weight and fetal hemoglobin. Infants with ROP had a significantly lower concentration of HbF, with gestational age and birth weight groups compared to infants without ROP. Lower gestational age, lower birth weight and lower concentration of HbF was found significantly associated with the development of ROP in preterm infants.

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