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Prevalence and Factors Affecting Delayed Retinal Maturation among Preterm Babies

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Abstract:-

Background: Preterm babies are at risk for delayed retinal maturation including retinopathy of prematurity. This study intends to analyse the prevalence of delay in retinal maturation among preterm infants, in a tertiary care institution in north Kerala. The factors affecting retinal maturation are evaluated.

Methodology: Design- descriptive cross sectional; duration 6 months; inclusion - preterm infants with birth weight less than or equal to 1.5 kg and gestational age less than or equal to 32 weeks; sample size - 76; variables-maternal risk factors, age at birth, gender, birth weight, weight at 38 weeks and fetal risk factors.

Results: Male female ratio was 2.1:1.7, 51.3% had adequate retinal maturation, 23.7% had delayed retinal maturation and 25% had progressed to ROP. The mean birth weight was 1.22 kg (SD 0.223). The mean gestational age was 30.29days.The mean weight at 38 weeks was 1.801 kg. Maternal factors did not affect the outcome. Delay in retinal maturation and ROP were associated with lower gestational age (p 0.01), birthweight (p 0.09), male gender(p 0.04), mechanical ventilation (p 0.016), surfactant use (p 0.003), anemia of prematurity (p 0.09), blood transfusion (p 0.016), sepsis (p 0.091) and NEC (p0.026). Use of antenatal steroids (p 0.09), adequate gain in weight (p 0.113) and breastfeeding soon after birth(p 0.027) had a positive association with maturation.

Conclusion: Gestational age at birth, birth weight , male gender , hypoxia & need for assistive devices, nutritional factors, hemodynamic factors, CHD, PDA, use of surfactants , sepsis and NEC were associated with poor retinal maturation. Use of antenatal steroids, adequate gain in weight and breastfeeding soon after birth were protective.

Keywords:- *retinopathy of prematurity, delayed retinal maturation, preterm, fetal hypoxia, early breast feeding.*

I. INTRODUCTION

Preterm births have become a common happening and concern to the healthcare sector. Though the causes may be numerous,the fact that these infants are highly prone to numerous complications pertaining to the different systems is non-conflicting. Preterm infants lag behind in many developmental milestones, and also in retinal maturation. In a preterm infant, the retinal vessels are expected to vascularise the nasal retina by 32 weeks and temporal retina by 38 weeks. However, despite adequate care and management, a significant number of preterm infants do not acquire age appropriate retinal maturation. And this delay, if not recognized early, could even end up in the development of retinopathy of prematurity, a leading cause of blindness in the world.

Previous studies related to delayed retinal maturation, across the world, have pointed to smaller gestational age,(ie:-GA<32 weeks), birth weight<1.5kg, as some of the important risk factors among the preterms. Several other fetal factors like APGAR scores, oxygen therapy, neonatal sepsis, pulmonary disease, intraventricular haemorrhage, hyperbilirubinemia, anemia, blood transfusion etc and the maternal risk factors that complicated the pregnancy were also studied by different researchers across the globe.

This study aims to evaluate the proportion of various maternal and fetal factors among preterm babies with age appropriate retinal maturation, delayed maturation and ROP.

II. MATERIALS AND METHODS

A descriptive cross sectional study was conducted among preterm infants,who were in follow-up in ROP Clinic of Government Medical College Kozhikode, for a period of 6 months. The study was conducted after approval by the institutional ethics committee. There was no financial burden to the study participants. Only those preterm infants with birth weight less than or equal to 1.5 kg and gestational age less than or equal to 32 weeks were included in the study. The sample size of 76 was obtained by considering the prevalence of ROP in the population as 25.5% and using the formula 4PQ/d*d. The type of sampling was convenient sampling. The data required was collected by data collecting proformas,periodic examination of the retina of these babies and their discharge cards. The development of retina was studied in a periodical manner and the retinal maturity at 38 weeks were grouped as follows.

- Adequate maturation (on examination, the retina was found to be vascularized upto ora serrata.ie age-appropriate maturation attained)
- Delayed maturation (eyes showing vascularization in zone 2 only and incomplete vascularization in zone 3 were included in this group.ie age-appropriate maturation not attained)
- Retinopathy of prematurity

The study variables were grouped as maternal and fetal factors. The maternal factors considered were maternal age, type of delivery , anemia, GDM, GHTN, PROM, parity, placenta previa, abruptio placenta, abortion and hypothyroidism. The fetal factors studied were gestational age at birth, birth weight, gender, weight at 38 weeks, birth order, APGAR scores at 1 min and 5 min, oxygen therapy, hypoxia, neonatal sepsis, neonatal jaundice, intraventricular haemorrhage, neonatal depression, blood transfusion, postnatal weight gain, breastfed within 1 hour after birth, respiratory distress syndrome, necrotizing enterocolitis,

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meconium aspiration syndrome, meconium stained liquor, congestive cardiac failure, congenital heart disease, patent ductus arteriosus, transient tachypnea of newborn, apnea of prematurity, anemia of prematurity, fetal bradycardia, fetal tachycardia, fetal distress, administration of surfactants, administration of antenatal steroids, neonatal hypoglycemia and bronchopulmonary dysplasia

The statistical tests used for the analysis of data were chi square test, independent t test and anova test. "Statistical package for social sciences" /SPSS software (VERSION:18.0.0) was used for the analysis.

III. RESULTS

In this study, 76 preterm infants of birthweight less than 1.5 kg and gestational age less than 32 weeks were included. The retinal maturation was evaluated at 38 weeks and a retrospective evaluation of the factors they had in common, which were either protective or posing a risk to the maturation of retina were analysed.

There were 42 males and 34 females. 51.3% had adequate retinal maturation, 23.7% had delayed retinal maturation and 25% had progressed to ROP.

The mean birth weight of the preterm infants was 1.22 kg; SD 0.223. The birth weight of the babies were distributed between 0.71kg-1.6 kg. The mean gestational age of these infants was 30.29 [30 weeks 2 days]; (SD:1.88). It varied between 25 weeks 5 days to 33 weeks 3 days. The mean gestational age among ROP (28.88weeks;SD1.88) was lesser than those with delayed maturation (31.18wks;SD 1.80) and adequate maturation (30.57wks;SD1.57). This finding was statistically significant. (P value=0.000).

Lower birth weight was associated with delay in retinal maturation (p 0.253)[figure-1]. The mean weight at 38 weeks was 1.801 kg (STD:0.371), and it ranged between (1.2-2.56 kg). Lower weight at 38 weeks was associated with adequate maturation (p0.099)[figure-2]

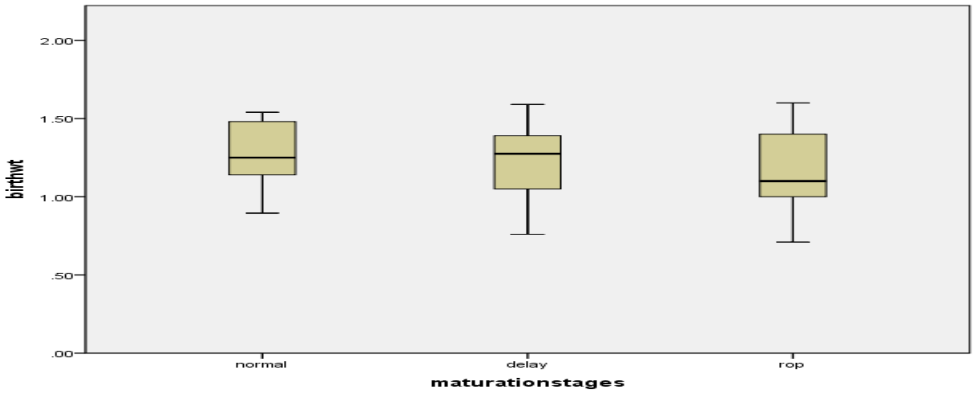

Fig. 1:birth weight Vs stages of retinal maturation.

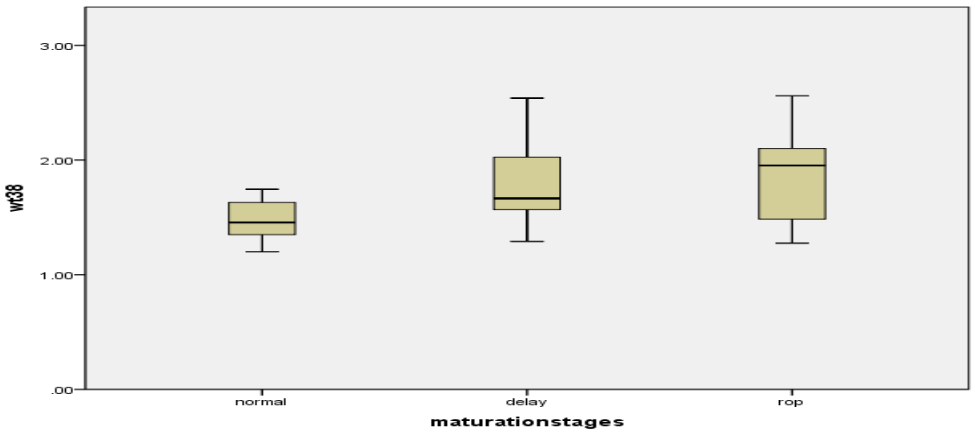

Fig. 2: weight at 38 weeks Vs stages of retinal maturation

The proportion of males among babies with ROP was 68.4% as compared to 38.5% with adequate maturation and 77.8% among delayed maturation. This finding was statistically significant (p 0.04). APGAR scores at 1 min and 5 min did not affect the retinal maturation.

77.6 pregnancies (n=59) were singleton and the remaining were twins. The mean maternal age was 27.04 years; SD:5.91. The maternal age ranged between 19-42 years. 41% of the mothers in the study were primigravida.25%,18%,9% were G2,G3 and G4 respectively. Sixty three percent of the pregnancies were preterm vaginal deliveries and 37% were LSCS.

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The maternal risk factors observed among the study group were anemia, gestational diabetes mellitus (GDM), Gestational Hypertension (GHTN), intrauterine growth retardation (IUGR), placenta previa, abruptio placenta, history of abortions , Premature rupture of membrane (PROM) and hypothyroidism.

The distribution of cases based on the presence of maternal risk factors is given in table 1

MATERNAL FACTORS	ADEQUATE MATURATION	DELAYED MATURATION	RETINOPATHY OF PREMATURITY	P VALUE
ANEMIA	N=6	N=4	N=0	0.125
	%=16.2	%=22.2	%=0	
GDM	N=15	N=5	N=7	0.729
	%=38.5	%=27.8	%=36.8	
GHTN/ECLAMPSIA/PRE-ECLAMPSIA	N=20	N=10	N=6	0.269
	%=51.3	%=55.6	%=31.6	
IUGR	N=15	N=8	N=4	0.285
	%=38.5	%=44.4	%=21.1	
PLACENTA PREVIA	N=2	N=0	N=3	0.134
	%=5.1	%=0	%=15.8	
ABRUPTIO PLACENTA	N=0	N=1	N=0	0.195
	%=0	%=5.6	%=0	
ABORTION	N=13	N=6	N=5	0.887
	%=34.2	%=33.3	%=27.8	
PROM	N=6	N=3	N=5	0.520
	%=15.4	%=16.7	%=27.8	
HYPOTHYROIDISM	N=6	N=3	N=0	0.181
	%=15.4	%=16.7	%=0	

Table 1- The distribution of cases based on the presence of maternal risk factors

Mothers of 31.6% of the ROP babies were having gestational hypertension/preeclampsia or eclampsia. The proportion of mothers with pre-eclampsia/GHTN/eclampsia were higher in the group with adequate and delayed maturation. 21.1% of the ROP babies had intrauterine growth restriction, while 44.1% of babies with delayed maturation and 38.5% babies with adequate maturation had IUGR. 15.8% of the ROP babies had their births complicated with placenta previa. 5.1% of the babies with adequate maturation had placenta previa. 27.8% of ROP babies had premature rupture of membranes, when compared to 16.7% of babies with delayed maturation and 15.4% of them with adequate maturation.

The fetal factors observed were oxygen supplementation, hypoxia, respiratory distress syndrome, transient tachypnea of newborn, apnea of prematurity, antenatal steroids, surfactants, meconium aspiration syndrome, bronchopulmonary dysplasia, anemia of prematurity, blood transfusion, intraventricular haemorrhage, neonatal jaundice, fetal tachycardia, fetal bradycardia, congenital heart disease, congestive cardiac failure, PDA, neonatal hypoglycemia, adequate postnatal weight gain, breastfed within 1 hour, neonatal sepsis, necrotizing enterocolitis, meconium liquor, fetal distress and neonatal depression.

All the ROP babies were hypoxic. 70.6% of the babies depended on CPAP during hypoxia. 47.1% of the ROP babies required both CPAP and intubation for survival, when compared to 11.8% babies with delayed retinal maturation and 15.4% of babies with adequate maturation. Hypoxia was associated with delay in retinal maturation. The data was statistically significant(P value=0.05). The distribution based on the proportion of cases with presence of hypoxia requiring oxygen support is given in figure-3

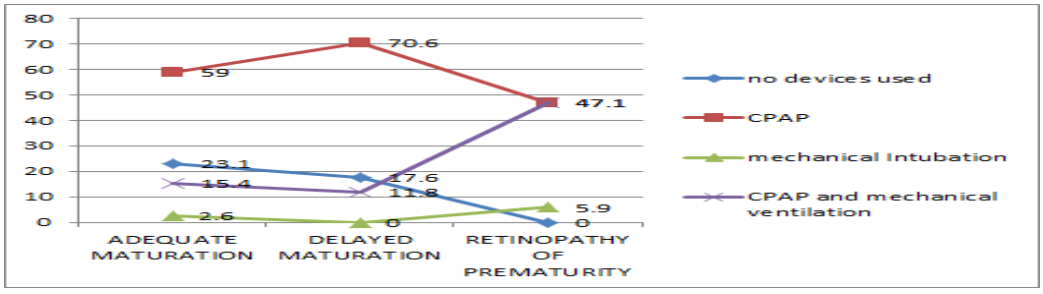

Fig. 3: The distribution based on the proportion of cases with presence of hypoxia requiring oxygen support

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The distribution of cases based on the proportion of respiratory factors among the categories of retinal maturation is given in table 2.

	ADEQUATE MATURATION	DELAYED MATURATION	RETINOPATHY OF PREMATURITY	P VALUE
OXYGEN THERAPY	N=5	N=3	N=5	0.343
	%=13.2	%=16.7	%=29.4	
RDS	N=30	N=15	N=17	0.128
	%=78.9	%=83.3	%=100	
TRANSIENT TACHYPNEA OF NEWBORN	N=1	N=1	N=0	0.606
	%=2.7	%=5.6	%=0	
APNEA OF PREMATURITY	N=9	N=3	N=7	0.228
	%=23.7	%=16.7	%=41.2	
ANTENATAL STEROIDS	N=27	N=16	N=10	0.09
	%=77.1	%=94.1	%=62.5	
SURFACTANTS	N=9	N=2	N=10	0.003
	%=25	%=11.1	%=62.5	
MECONIUM ASPIRATION SYNDROME	N=1	N=0	N=0	0.627
	%=2.6	%=0	%=0	
BRONCHOPULMONARY DYSPLASIA	N=2	N=2	N=4	0.178
	%=5.1	%=11.1	%=21.1	

Table-2:The distribution of cases based on the proportion of respiratory factors among the categories of retinal maturation

29.4% of the ROP babies required oxygen therapy in the neonatal period, while 16.7% of babies with delayed maturation and 13.2% of babies with adequate maturation, also required the same. Among 76 infants studied,62 infants developed respiratory distress. Respiratory distress was commonly associated with preterm births. All ROP babies developed RDS, compared to 83.3% of babies with delayed retinal maturation and 78.9% of babies with adequate maturation. 41.2% of the ROP babies had apnea of prematurity, in comparison to 16.7% of babies with delayed maturation and 23.7% of babies with adequate maturation.

94.1% of the babies with delayed retinal maturation administered antenatal steroids. 62.5% of the babies with ROP and 77.1% of babies with adequate maturation have also been administered steroids antenatally. 62.5% of ROP babies required surfactant administration. Only 11.2% of the babies with delayed maturation and 25% of the babies with adequate maturation required surfactants. This was statistically significant. 21.1% of the ROP babies had bronchopulmonary dysplasia. 11.1% of babies with delayed maturation and 5.1% of babies with adequate maturation also had bronchopulmonary dysplasia.

The distribution based on the proportion of hemodynamic factors among the categories of retinal maturation is given in figure 4

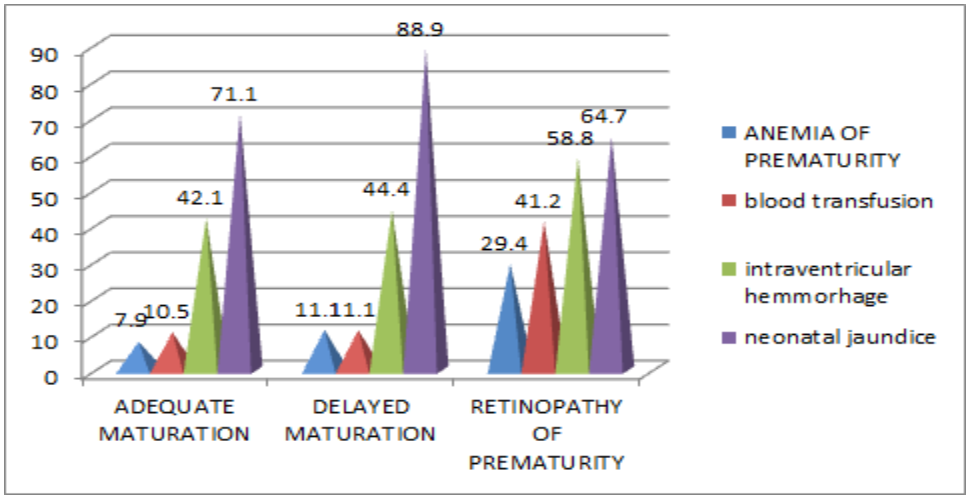

Figure 4:The distribution based on the proportion of hemodynamic factors among the categories of retinal maturation

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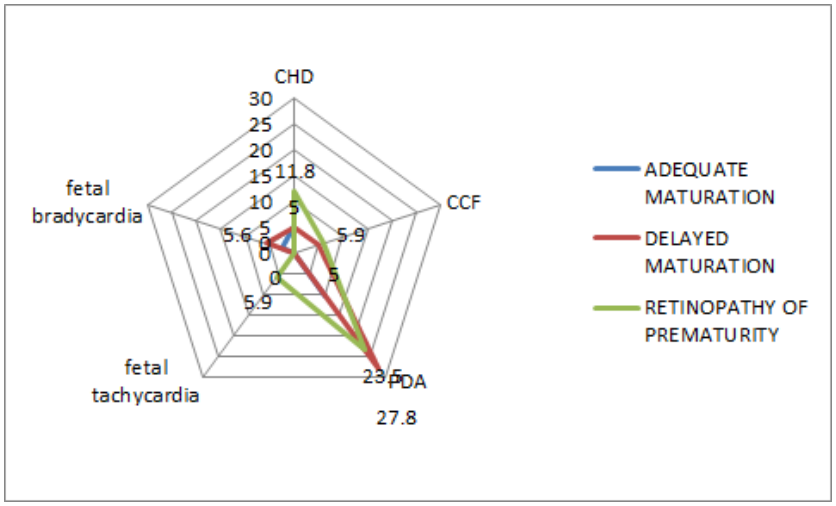
29.4% of the ROP babies had anaemia of prematurity. 11.1% of the babies with delayed retinal maturation and 7.9% of them with adequate maturation also had anaemia of prematurity (p 0.094). 41.2% of the ROP babies required blood transfusion. The babies who required blood transfusion among those with delayed maturation and adequate maturation were 11.1% and 10.5% respectively. The data is statistically significant (p 0.016). 88.9% of the babies with delayed retinal maturation developed neonatal jaundice in the postnatal period. The proportion of ROP babies and babies with adequate maturation are 64.7% and 71.1% respectively (p 0.22). The proportion of babies with intraventricular hemorrhage was more among ROP cases (p 0.506).

The distribution based on the proportion of cardiac factors among the categories of retinal maturation is given in figure 5



27.8% of the babies with delayed maturation had PDA. Their proportion were 23.5% and 10.5% respectively among the ROP babies and babies with adequate maturation (p 0.225). The proportion of babies with CHD (p 0.65) and fetal tachycardia (p 0.18) was more among ROP cases followed by the group with delayed retinal maturation . Fetal bradycardia was seen among those with delayed maturation as compared to ROP cases (p 0.602). All these factors were less among those with adequate maturation. CCF was not observed among kids with adequate retinal maturation (p 0.327).

The distribution based on the proportion of nutritional factors among the categories of retinal maturation is given in Table 3

	ADEQUATE MATURATION	DELAYED MATURATION	RETINOPATHY OF PREMATURITY	P VALUE
NEONATAL HYPOGLYCEMIA	N=6	N=3	N=1	0.603
	%=15.8	%=16.7	%=6.3	
ADEQUATE POSTNATAL WEIGHT GAIN	N=35	N=17	N=13	0.113
	%=97.2	%=94.4	%=81.3	
BREASTFED WITHIN 1 HOUR	N=13	N=10	N=2	0.027
	%=44.8	%=62.5	%=14.3	

Table 3: The distribution based on the proportion of nutritional factors among the categories of retinal maturation

81.3% of the ROP babies had adequate postnatal weight gain, compared to 94.4% of the babies with delayed retinal maturation and 97.2% of the babies with adequate maturation. Hence, adequate postnatal weight gain might be contributing to the maturation of retina also . Only 14.3% of the ROP babies were breastfed within 1 hour of their birth. 62.5% of the babies with delayed maturation and 44.8% of the babies with adequate maturation were breastfed within 1 hour. Therefore, breastfeeding immediately after birth promotes retinal maturation (p 0.027).

The distribution based on the proportion of miscellaneous factors among the categories of retinal maturation is given in figure 6

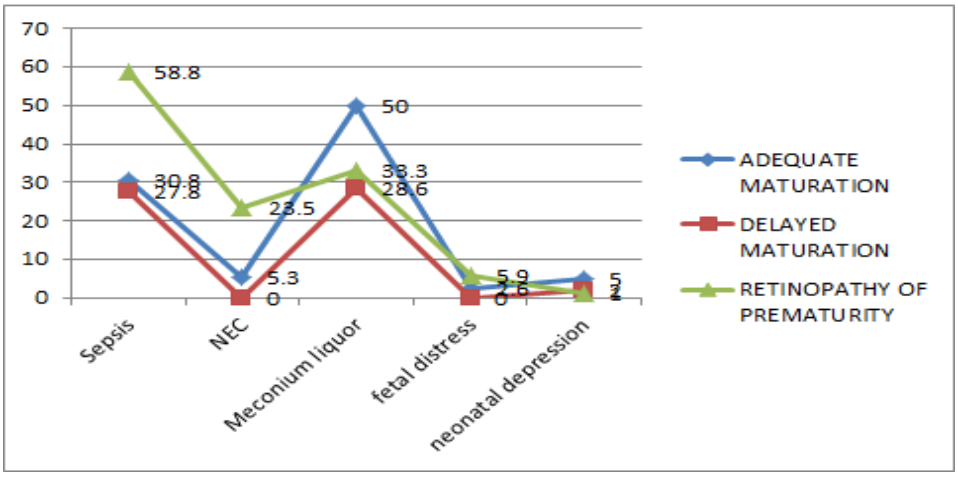


Fig 6: The distribution based on the proportion of miscellaneous factors among the categories of retinal maturation

58.8% of the ROP babies developed sepsis in the neonatal period. Only 27.8% of the babies with delayed maturation and 30.8% of the babies with adequate maturation developed sepsis (p 0.091). The proportion of NEC among ROP babies was higher than that of others. 23.5% Vs 5.3% ; p 0.026). The proportion of meconium stained liquor was higher among those with adequate retinal growth (p 0.312).

IV. DISCUSSION

Preterm babies are at risk of developing retinopathy of prematurity , a potential blinding disease. Even for those who have not developed ROP, retinal maturation may be delayed. The delay may be responsible for further sequelae like refractive errors, retinal and vitreous degenerative changes , amblyopia and squint. Thorough screening of at risk babies is essential in not only detecting ROP patients but identifying kids with delayed retinal maturation. By ensuring regular followup of this group, early detection of the visual consequences can be assured.

Various factors , both maternal and fetal, have been associated with ROP. However, studies considering delayed maturation apart from ROP, are scanty. This study attempts to find out the proportion of the various maternal and fetal risk factors in the study group and the relation of each factor with the maturation of retina, adequate, delayed or ROP.

Among demographic factors, delayed retinal maturation was statistically associated with a lower gestational age at birth. The studies Wongnophirun A et al, Ying GS et al,Yau GS et al,Azami M et al, Akkawi MT et al,and Alajbegovic et al states statistical association between delayed retinal maturation and both lower gestational age and low birth weight[1,2,3,4,5,6].Solans Pérez de Larraya AM et al stated only gestational age as a factor delaying retinal maturation[7].

Male gender was associated with a higher incidence in the delay of retinal maturation. Gender predilection was not observed by Hakeem AH et al[8]. Braimah et al reported that females were more prone for delayed maturation[9].

Birth order was not associated with retinal maturity. This is in concordance with Blumenfeld LC et al[10]. Akkawi MT et al states that type of multiple gestation affects delay in retinal maturation[5]. There was no association between retinal maturation and maternal parity.

Maternal age was not related to retinal maturation in this study. However, WU WC et al states higher maternal age as a factor delaying retinal maturation[11]. But according to Uchida A et al the severity of ROP (requiring laser treatment), is lower in babies born to mothers less than 33 years old[12].

No association between type of delivery and retinal maturation. Braimah et al noticed a decreased incidence of ROP in babies born via caesarean delivery[9].Yau GS et al notices increased risk in babies born via vaginal delivery[3].

Maternal factors observed were not associated with retinal maturation. Maternal anaemia has no statistical association with retinal maturation. Dai al et al points to maternal iron deficiency anaemia as a risk factor for delayed retinal maturation[13].

This study couldn't draw any association between retinal maturation and gestational diabetes mellitus. In the study Kindinger LM et al, they state that optimizing maternal health pre-conception by controlling obesity and thereby associated gestational diabetes can possibly reduce the incidence of preterm birth and associated complications like retinopathy of prematurity[14].

This study didn't show any association between retinal maturation and gestational hypertension/preeclampsia/eclampsia. Huang et al had findings agreeing to this[15]. Yau GS et al and Azaami M et al found a decreased prevalence of delayed retinal maturation among babies born to mothers with preeclampsia[3,4].

This study didn't find any association between retinal maturation and intrauterine growth restriction. Chu A et al and Siswanto JE et al found IUGR as a factor causing delayed retinal maturation[1617].

Previous abortion, premature rupture of membranes ,placenta previa, abruptio placenta and maternal hypothyroidism were not related to retinal maturation, according to this study. Fowler JR et al says chorioamnionitis as a factor causing delayed retinal maturation[18]. PROM is a main cause for chorioamnionitis. Mitra S et al stated that when gestational age was unadjusted, chorioamnionitis was a risk factor[19]. Chen Y et al found placental abruption as a risk factor in delaying maturation[20].

Babies who had adequate retinal maturation needed less device support for hypoxia. CPAP was the commonly used assistive method of ventilation. If babies with delayed maturation are considered, it is evident that those with ROP required both CPAP and mechanical ventilation as compared to others . The proportion of babies with mechanical intubation among the group with ROP was higher.

When respiratory factors were evaluated, there was a rising trend in the proportion of babies requiring oxygen support, respiratory distress, apnea of prematurity, use of surfactants and bronchopulmonary dysplasia. The use of antenatal steroids was found to be protective. Meconium aspiration was not observed among babies with delayed maturation.

Presence of hemodynamic factors like anemia of prematurity, need for transfusion and intraventricular bleeds were more common among those with delayed maturation and ROP. The proportion of kids with neonatal jaundice was more among those with delayed maturation but did not increase with ROP. Cardiac factors like CHD, PDA and fetal tachycardia were more frequent among those with delayed maturation.

The proportion of babies with neonatal hypoglycemia was similar in either group. Adequate weight gain and breastfeeding soon after birth were more observed among those with adequate retinal maturation. Presence of sepsis and NEC was associated with delay in maturation.

Use of surfactants, breastfeeding soon after birth showed statistically significant relation with retinal maturation. Breastfeeding soon after birth appeared to be protective. Though statistically not significant, our observations appear to be clinically relevant. Small data subgroups might have affected the statistical power. This work can be considered as a pilot in this regard and can be followed by further studies with larger sample size in each subgroup.

V. CONCLUSION

Gestational age at birth, birth weight and male gender was associated with delay in retinal maturation. Maternal factors did not affect the outcome. Hypoxia and need for assistive devices, nutritional factors, hemodynamic factors, use of surfactants , sepsis and NEC were associated with poor retinal maturation. CHD and PDA were frequent among those with delayed maturation. Use of antenatal steroids, adequate gain in weight and breastfeeding soon after birth were protective. Identification of at-risk factors (fetal and demographic) and their prognostication is essential in predicting delayed retinal maturation in preterm babies.

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