ORIGINAL ARTICLE

ASSOCIATION OF BREASTFEEDING WITH THE RISK OF RETINOPATHY OF PREMATURITY

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Background: Premature neonates are at risk of various health complications. The objective of this study was to find out the association of breastfeeding in development of retinopathy of prematurity (ROP). **Methodology:** This descriptive cross-sectional study was conducted at Paediatric Unit of Institute of Mother and Child Health (IMCH), Nawabshah. The study participants were divided into two groups based on their feeding type as breastfed group (exclusively breastfed infants) and formula fed group (>60% per day formula milk feed). Ophthalmoscopy was done with a binocular indirect ophthalmoscope for evidence of retinopathy. Data was analysed on SPSS-20. **Results:** The baseline characteristics among both groups were same with almost no significant association except the stage of ROP and weight at discharge. The frequency of developing ROP was more among infants who were on formula feed (38.3%) as compared to infants on breastfeed (31.2%) but the results were non-significant. Most of the infants developed stage 2 or stage 3 ROP among formula feed group (23.3%) in comparison to breastfeed infants (8.8%). The severity of ROP reported strong significant association among the groups (p<0.05). The multivariate logistic regression analysis reported that the type of feeding was a strong predictor of severity of ROP (stage 2 or 3). **Conclusion:** Development of ROP is more frequent among formula fed infants as compared to infants on breastfeed, but no significant association was found. However, the severity of ROP had significant association with type of feeding.

Keywords: Breastfeed, Formula feed, Prematurity, Retinopathy of prematurity

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INTRODUCTION

Prematurity refers to the birth of an infant before completing 37 weeks of gestation.[1] The rate of preterm births varies across countries, with estimates ranging from 5% in European nations to 18% in Malawi. In Pakistan, the preterm birth rate is reported as 18.89%.[2] Premature neonates are at risk of various health complications, including respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular haemorrhage, hyperbilirubinemia, patent ductus arteriosus, and retinopathy of prematurity (ROP).[3]

ROP is a vascular disorder that affects the immature retina of preterm infants. While it is both preventable and treatable, several factors contribute to its development, such as low birth weight, oxygen therapy, and inadequate nutritional support.[4,5] Infants diagnosed with ROP may experience vision-related issues, including refractive errors, blindness, strabismus, visual field defects, and impaired colour vision.[6] The frequency of ROP varies depending on healthcare resources, with rates between 5% to 8% in developed nations and up to 30% in developing countries.[7] Research conducted in Pakistan has reported an ROP incidence of 10.5% among premature infants[8], with urban Punjab showing a higher incidence of 24.6%[9]. Although the exact causes of ROP are not fully known, prematurity, low birth weight, and retinal immaturity are recognized as primary risk factors. Additional contributing factors include oxygen supplementation, congenital heart disease, metabolic imbalances, anaemia, infections, and blood transfusions.[10,11]

Breast milk is believed to offer protective benefits against ROP because of its antioxidant and immune-boosting properties.[12] It contains essential nutrients, including vitamins C and E and beta-carotene, which provide stronger antioxidant effects compared to formula milk.[13] Breast milk has immunomodulatory components such as immunoglobulin A in secretions, lactoferrin, cytokines, lysozymes, and various cellular elements that support the infant's immune system.[14] These protective factors may reduce the risk of conditions like necrotizing enterocolitis (NEC) and sepsis, which in turn lowers the likelihood of ROP development.[15]

In Pakistan, the absence of large-scale studies, make it difficult to determine the exact incidence of the condition. Potential protective factors, such as breast milk, remain underexplored. The current study aimed to find out the association of breastfeeding in development of retinopathy of prematurity.

MATERIAL AND METHODS

A descriptive cross-sectional study was conducted at the paediatric unit of Institute of Mother and Child Health (IMCH), Nawabshah from Jul 2024 to Jan 2025. The study got ethical approval from the Institutional Review Board. Informed consent was taken from the parents.

The neonates having birth weight of less than 2.5 Kg and gestational age of less than 37 weeks were included. Infants either having any congenital malformation or congenital cataract or parents refused to give assent were excluded. Sample size was calculated to be 140 using the OpenEpi calculator.

Feeding type of the neonates, including formula feed or breastfeed, was noted while the initial retinal examination for ROP was done after completing neonatal period. Date of last menstrual period and antenatal ultrasound reports were used to calculate the gestational age. The study participants were divided into two groups based on their feeding type as breastfeed group including exclusively breastfeed infants and formula feed group including more than 60% per day feed was on formula milk. Indirect ophthalmoscopy was done by a binocular indirect ophthalmoscope. Demographic data and the examination findings were recorded on preformed proforma. Severity of ROP was classified into five stages including demarcation line, visible ridge, blood vessel in the ridge. Sub-total retinal detachment and total retinal detachment in stage I to stage V respectively.

Statistical Package for Social Science (SPSS) version 20 was used to analyze the data. Mean±SD were calculated for numerical variables. Categorical variables were presented as frequency and percentage. Chi-square test was used to see association of categorical variables with occurrence of ROP while after adjusting the confounding factors, multivariate logistic regression analysis was performed and odd ratios were calculated for associated factors, keeping 95% confidence interval, and $p \leq 0.05$ considered statistically significant.

RESULTS

Current study included a total of 140 premature infants, out of which 80 infants were exclusively on breastfeed while 60 infants were on formula feed. The baseline characteristics among both groups were same with almost no significant association except the stage of ROP and weight at discharge. Majority of the study participants were female, belonging to lower socioeconomic status, among both groups, with no significant association. The gestational age of most infants was 32 to 34 weeks (66.2% and 70% respectively) and the mode of delivery was spontaneous vaginal delivery (SVD) (67.5% and 61.7% respectively) with birth weight 1.5 to 2 Kg (43.8% and 40% respectively) but all these having no significant association among the groups.

The frequency of developing ROP was more among infants who were on formula feed (38.3%) as compared to infants on breastfeed (31.2%) but the differences were non-significant. Most of the infants developed stage 2 or stage 3 ROP among formula feed group (23.3%) in comparison to breastfeed infants (8.8%), none of the case with stage 4 or stage 5 was diagnosed. The severity of ROP reported strong significant association among the groups ($p<0.05$). Breastfed infants were having more weight at discharge than formula fed infants and strong significant association was noted ($p<0.05$). The detailed characteristics of study participants among both groups are presented in Table-1.

Table-1: Characteristics of study participants (n=140)

Variables	Breastfeed n=80 [n (%)]	Formula milk n=60 [n (%)]	*p*
Gender			
Male	37 (46.2)	26 (43.3)	0.82
Female	43 (53.8)	34 (56.7)	
Socioeconomic status			
Lower	37 (46.2)	24 (40.0)	0.54
Middle	29 (36.3)	20 (33.3)	
Upper	14 (17.5)	16 (26.7)	
Gestational age			
≤32 weeks	27 (33.8)	18 (30.0)	0.27
32–34 weeks	53 (66.2)	42 (70.0)	
Mode of delivery			
SVD	54 (67.5)	37 (61.7)	0.69
C-Section	26 (32.5)	23 (38.3)	
Birth weight			
≤1.5 Kg	29 (36.2)	20 (33.3)	0.43
1.5–2 Kg	35 (43.8)	24 (40.0)	
≥2 Kg	16 (20)	16 (26.7)	
ROP	25 (31.2)	23 (38.3)	0.35
Severity of ROP (Stage 2 or 3)	7 (8.8)	14 (23.3)	0.003*
Weight at discharge (Kg)	2.57±1.5	2.19±1.3	0.01*

Gestational age and the birth weight were the two most important confounding factors in developing stage 2 or 3 ROP. The multivariate logistic regression analysis was performed, and the results reported that the type of feeding was a strong predictor of severity of ROP (stage 2 or 3), after adjusting the two important confounding factors. The odd ratios calculated for associated factors, keeping 95% confidence interval, are presented in Table-2.

Table-2: Multivariate regression analysis of associated factors in Stage 2 or 3 ROP

Parameters	OR	95% CI	*p*
Gestational age	0.91	0.857–0.952	0.003*
Birth weight	0.95	0.91–0.99	0.000*
Breastfeeding	0.23	0.074–0.48	0.005*

DISCUSSION

ROP is a multifactorial disease and the presence of prooxidant metabolite is one of the main contributing factor as it stimulates the retinal endothelial growth factor leading to excessive growth of retinal vasculature that is why studies stated that early neonatal nutrition can balance the oxidative stress, in turn decreasing the risk of development of ROP.[11] Human milk contains multiple antioxidants including inositol, vitamin E, catalase, glutathione peroxidase, taurine and carotenoids which counter the free radicals in preventing oxidative

stress. Notably the antioxidant carotenoid is only present in human milk but not in formula feed, it down regulates the endothelial growth factor which is an important predictor in the pathogenesis of ROP.[16] ROP is a complex disease influenced by multiple factors, with prematurity, low birth weight, and oxygen therapy being key contributors to its development. Our study found female predominance but no significant association with ROP. Similar findings were observed by other studies[8,17] reporting equal incidence of ROP among both genders.

Gestational age and the birth weight were the two most important factors, significantly associated with the occurrence of ROP in the current study. Worldwide studies reported strong significant association of ROP with the prematurity and the weight at the time of delivery.[17,18] On the other hand, a study conducted in China reported contradictory findings as there was no significant association of birth weight between ROP and non-ROP groups.[19]

Current study reported that the frequency of developing ROP was more among infants who were on formula feed as compared to infants on breastfeed but the result was non-significant. Research by Manzoni *et al*[20] and Ginovart *et al*[21] found that the frequency of ROP is lowest among those infants who were exclusively on breastfeed. Study by Metzger *et al*[22] reported that the preterm infants born between 24 and 28 weeks and were on breastfeeding, had lower rate of development of ROP. However, the study did not observe significant differences among those born before 32 weeks of gestational period.[22] On the other hand, Keraan *et al*[23] conducted a study and noted that a higher incidence of ROP among breastfeeding infants, though the authors did not provide a clear explanation for this outcome.

More infants developed stage 2 or stage 3 ROP among formula fed group (23.3%) in comparison to breastfed infants (8.8%), while the severity of ROP reported strong significant association among the groups. Current results align with a meta-analysis conducted by Zhou *et al*[24] which suggests that breastfeeding significantly reduces the risk of ROP at any stage, including severe cases. Porcelli *et al*[25] noted that those neonates who have higher intake of breastfeed during initial two weeks of life, are less likely to develop ROP, but there is no significant association of breastfeed and ROP on 4th week of life.

CONCLUSION

Development of ROP is more frequent among formula fed infants as compared to infants on breastfeed, but no significant association was found. The severity of ROP had strongly significant association with the type of feeding as stage 2 or stage 3 ROP cases were more among formula fed group in comparison to breastfed infants.

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