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The Relationship between Maternal Anemia and Retinopathy of Prematurity in Newborns

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ABSTRACT

Background: Retinopathy of Prematurity (ROP) is a leading cause of blindness in developed and developing countries. Maternal anemia can endanger the health of the fetus. Studies suggest a link between maternal anemia and an increased risk of ROP in newborns. Therefore, this study aimed to determine the relationship between maternal anemia and ROP in newborns.

Methods: This cross-sectional study was conducted on premature infants. Group 1 consisted of all infants diagnosed with ROP (n = 51). The control group included premature infants without ROP. Demographic characteristics and laboratory results were compared between the groups. Data were analyzed using IBM SPSS version 19.

Results: The results showed that 34 infants (75.6%) had ROP in both eyes, and the remainder in one eye. Regarding ROP stage, most infants (71.7%) were in stage 2 and zone 3. Hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were significantly lower in the ROP group than in the control group. Furthermore, the comparison of the two groups in terms of anemia (hemoglobin < 11 g/dL) indicated a significantly higher prevalence of maternal anemia in infants with ROP (23 [45.1%]) than in the control group (8 [15.4%]) (P = 0.001).

Conclusion: Our results suggest that maternal anemia and hemoglobin level are risk factors for the development of ROP in preterm infants. Given that the diagnosis and treatment of anemia in pregnant women is cost-effective and straightforward, it is crucial to prioritize diagnosis and treatment in mothers at high risk of preterm delivery to potentially reduce the incidence of ROP.

Keywords: Anemia, Neonate, Prematurity, Retinopathy

Introduction

Retinopathy of prematurity (ROP) is a leading cause of blindness in developed and developing countries (1). This disease has an inverse relationship with birth weight and gestational age (2-3). Multiple factors contribute to its development, leading to impaired growth and development of retinal blood vessels and the formation of misplaced vessels (4-5).

ROP in premature neonates is classified into 5 stages based on disease severity. Higher stages can cause retinal scarring and complications such as retinal detachment, vitreous hemorrhage, eye deviation, and amblyopia. Additionally, many affected individuals experience myopia (3).

Considering the quantitative and qualitative expansion of neonatal services and the significant increase in survival rates among premature infants, and recognizing that blindness is a major complication with profound impacts on an individual's life, the prevention and treatment of ROP are of paramount importance.

Maternal anemia can endanger the health of the fetus. Anemic mothers often experience fatigue, sleep disorders (6), infection, preeclampsia, and

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bleeding (7-9), while the fetus may suffer from premature delivery, low birth weight, and growth restriction (10-12). Although evidence suggests a potential link between maternal anemia and an increased risk of ROP in newborns (13), further research is needed. Therefore, we aimed to determine the relationship between maternal anemia and ROP in newborns.

Methods

This cross-sectional study was conducted on all premature neonates with retinopathy referred to Alzahra Hospital, Rasht, Iran, from January 2016 to January 2020. Subjects were included using convenience sampling. In Group 1, we enrolled all children diagnosed with retinopathy, excluding those with conditions such as heart disorder, congenital anomalies, recurrent bradycardia, ventricular-atrial block, hypotension, or cerebral hemorrhage, within the specified four-year period. After the final confirmation of retinopathy, the mothers' blood test results during pregnancy were examined. In the control group, premature infants of the same age and sex as those in the first group were examined for ROP. Data were collected using a form including sex, characteristics of ROP (affected side, stage, zone), and treatment method. A retina subspecialist performed weekly eye examinations in the NICU department. Examinations continued at regular intervals until retinal vessel completion, even after discharge.

Regarding the affected eye(s), three conditions were considered: right, left, and both eyes. ROP stage was classified from one to four. Stage 1 ROP is characterized by a line on the retina separating the normal retina from the premature retina. Stage 2 ROP is defined by a ridge with height and thickness on the retina. Stage 3 ROP involves the growth of fragile, new, abnormal blood vessels on the retina.

For Type 1 ROP, zone classification was as follows: zone 1 (any stage with plus disease), zone 1 (stage 3 without plus disease), zone 2 (stages 2 to 3 with plus disease). For Type 2 ROP, zone 1 was defined as stages 2 to 3 without plus disease, and zone 2 was defined as stage 3 without plus disease. The treatment method was categorized into four options: laser, injection, follow-up, and infant death.

Mothers of the newborns were referred to a single, specific laboratory for testing. Blood hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and white blood cell count (WBC) were measured using a SYSMEX-KX21N device (Japan). The presence or absence of maternal anemia was evaluated and compared between the two groups. Maternal anemia was defined as a hemoglobin level less than 11 g/dL in the first trimester, less than 10.5 g/dL in the second trimester, and less than 11 g/dL in the third trimester.

Data were collected and analyzed using descriptive statistics (number, percent, mean, standard deviation) and analytical statistics (t-test and chi-square) in IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp.). A significance level of $p < 0.05$ was considered statistically significant.

Ethical Approval

The study was approved by the Ethics Committee of Research at Guilan University of Medical Sciences (IR.GUMS.REC.1394.493).

Results

The results of this study, which included 99 infants (51 in the affected group and 48 in the non-ROP group), showed that 30 (51.7%) infants in the affected group and 28 (48.3%) in the non-ROP group were male. There was no significant difference in sex between the two groups ($p = 0.611$).

The results of retinopathy of prematurity showed that 34 babies (75.6%) had ROP in both eyes and the rest in one eye. In terms of retinopathy STAGE, most of the babies (71.7%) were in stage 2 and ZONE 3. Regarding the treatment, most of the 35 patients (70%) underwent laser treatment.

Table 1. The characteristics of ROP in neonates

		Number	Percent
ROP	left eye	6	13.3
	right eye	5	11.1
	both eyes	34	75.6
	Total	45	100.0
Stage	1.00	3	6.5
	2.00	33	71.7
	3.00	10	21.7
	Total	46	100.0
Zone	1.00	2	4.3
	2.00	9	19.1
	3.00	36	76.6
	Total	47	100.0
Treatment	Laser	35	70.0
	Injection	7	14.0
	Follow-up	6	12.0
	Death	2	4.0

Table 2. Comparison of mean laboratory results in two groups

	group	N	Mean	Std. Deviation	P-value
Hb	With ROP	51	11.0725	1.02354	.000
	Without ROP	52	12.3558	1.50404	
Hct	With ROP	51	32.9451	2.94885	.000
	Without ROP	52	36.0096	3.56190	
Mcv	With ROP	51	86.0980	12.69746	.914
	Without ROP	52	85.8173	13.64518	
McH	With ROP	51	29.3490	2.45221	.043
	Without ROP	52	30.3617	2.55185	
MCHC	With ROP	51	33.5233	1.46022	.015
	Without ROP	52	34.2056	1.32119	
RDW	With ROP	45	14.1067	1.13626	.971
	Without ROP	52	14.0981	1.15970	
WBC	With ROP	27	13.2537	3.26735	.125
	Without ROP	4	10.5500	2.47723	

Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width, WBC: white blood cell

A comparison of the two groups in terms of hemoglobin, hematocrit, MCH, and MCHC showed that the mean values of these variables in the patients with ROP were significantly lower than those in the control group. However, other variables, including WBC, RDW, and MCV, did not show significant differences between the two groups. Furthermore, the comparison of the two groups in terms of anemia (hemoglobin < 11 g/dL) showed that maternal anemia was significantly more prevalent in the infants with ROP (23 [45.1%]) than in the control group (8 [15.4%]) (P = 0.001).

Discussion

Several factors contribute to the development of ROP. Although some studies have reported that multiple pregnancies, apnea, race, intraventricular hemorrhage, light exposure, anemia, sepsis, prolonged mechanical ventilation, and multiple transfusions are risk factors for ROP, the precise role of these factors in the development of this disease remains undefined. Conversely, low birth weight and gestational age, as well as high postnatal oxygenation, have consistently been shown to increase the risk of ROP (14).

Our results demonstrated that the levels of hemoglobin, hematocrit, MCH, and MCHC in the retinopathy group were significantly lower than those in the control group. Moreover, a higher percentage of infants with ROP had mothers with anemia in the first trimester of pregnancy.

To date, studies have investigated the effect of maternal characteristics on the occurrence of ROP. A Turkish study indicated that maternal iron deficiency anemia was associated with the development of ROP (13). While the aforementioned study focused on iron deficiency anemia in mothers, our study only assessed anemia based on complete blood count (CBC) levels. Additionally, previous studies on maternal and neonatal parameters indicated that ROP was significantly related to maternal blood leukocyte count (15-16).

In addition to the articles mentioned above, some studies have considered the relationship between infant anemia and the occurrence of ROP. While Banerjee et al. reported a significant relationship between infant anemia and ROP (17), others did not find anemia to be an independent risk factor (18-19). Furthermore, a recent study examining the relationship between maternal and infant diseases and ROP and its progression found that, out of 828 neonates, 303 had ROP. Their results indicated that ROP occurred more frequently in infants with preeclampsia (odds ratio of 2.54, p < 0.001), respiratory distress syndrome (odds ratio of 2.2, p < 0.001), and congenital heart defects (odds ratio of 1.53, p = 0.047). Conversely, infants with transient tachypnea of the newborn (odds ratio of 0.7, p < 0.001) and infants with anemia (odds ratio of 0.373, p < 0.001) had a lower chance of developing ROP. They concluded that maternal preeclampsia, respiratory distress syndrome, and congenital heart defects are among the diseases affecting the incidence of ROP (20).

In conducting this study, several measures

were taken to mitigate potential sources of bias. First, we employed a cross-sectional design, focusing on a clearly defined cohort of premature infants diagnosed with retinopathy of prematurity (ROP) compared to a control group without ROP. This design allowed for a direct comparison while controlling for some confounding variables, such as gestational age and birth weight. To ensure a representative sample, we utilized convenience sampling of infants referred to Alzahra Hospital, which is a referral center for neonatal care in the region. Inclusion criteria were strictly defined to exclude infants with known confounding conditions (e.g., congenital anomalies or significant comorbidities), which helps reduce selection bias. Although this study showed significant results regarding maternal anemia and ROP, which can be very useful, there are limitations to the present study. We did not assess the risk factors related to maternal and neonatal complications that may have a potential role in the development of ROP. Therefore, prospective studies with detailed analyses of maternal and infant characteristics and attention to other underlying diseases and anemia characteristics, as well as controlling factors in the second and third trimesters, are needed.

The implications of our findings suggest that screening for anemia in pregnant women, particularly those at risk for preterm delivery, should be a priority. Early identification and management of anemia could be a cost-effective strategy to reduce the incidence of ROP in premature infants. This underscores the importance of comprehensive prenatal care, focusing not only on maternal health but also on neonatal outcomes, thereby potentially preventing significant long-term visual impairments in affected infants.

Conclusion

In this study, we found that there was a significant difference in the laboratory factors of hemoglobin, hematocrit, MCH, and MCHC, with these values being significantly lower in the group with ROP. Our results indicate that maternal anemia and hemoglobin level are risk factors for the development of ROP in preterm infants. Given that the diagnosis and treatment of anemia in pregnant women are practically cost-effective and straightforward, prioritizing diagnosis and treatment in mothers who are at high risk of preterm delivery is crucial and may reduce the incidence of ROP.

Acknowledgments

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Conflicts of interest

None.

References

1. Livshitz I. Preventative strategies in the management of ROP: A review of literature. Open J Pediatr. 2015;5(02):121.
2. Filippi L, Cavallaro G, Fiorini P, Daniotti M, Benedetti V, Cristofori G, et al. Study protocol: safety and efficacy of propranolol in newborns with Retinopathy of Prematurity (PROP-ROP): ISRCTN18523491. BMC Pediatr. 2010;10:83.
3. Chen J, Smith LE. Retinopathy of prematurity. Angiogenesis. 2007;10(2):133-140.
4. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, et al. International classification of retinopathy of prematurity, Third Edition. Ophthalmology. 2021;128(10):e51-e68.
5. Early Treatment for Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121(12): 1684-1694.
6. Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. J Womens Health Gend Based Med. 2001;10(4):335-341.
7. Murray-Kolb LE. Iron and brain functions. Curr Opin Clin Nutr Metab Care. 2013;16(6):703-707.
8. Beard J. Iron deficiency alters brain development and functioning. J Nutr. 2003;133(5 Suppl 1):1468S-72S.
9. Milman N. Postpartum anemia II: prevention and treatment. Ann Hematol. 2012;91(2):143-154.
10. Bhutta ZA, Darmstadt GL, Hasan BS, Haws RA. Community-based interventions for improving perinatal and neonatal health outcomes in developing countries: a review of the evidence. Pediatrics. 2005;115(2 Suppl):519-617.
11. Gambling L, Danzeisen R, Fosset C, Andersen HS, Dunford S, Srai SKS, et al. Iron and copper interactions in development and the effect on pregnancy outcome, metal-binding proteins and trace element metabolism. J Nutr. 2003;133(5): 1554S-1556S.
12. Scholl TO, Johnson WG. Folic acid: influence on the outcome of pregnancy. Am J Clin Nutr. 2000; 71(5):1295S-1303S.
13. Dai AI, Demiryürek S, Aksoy SN, Perk P, Saygili O, Güngör K. Maternal iron deficiency anemia as a risk factor for the development of retinopathy of prematurity. Pediatr Neurol. 2015;53(2):146-150.
14. Rivera JC, Sapieha P, Joyal JS, Duhamel F, Shao Z, Sitaras N, et al. Understanding retinopathy of prematurity: update on pathogenesis. Neonatology. 2011;100(4):343-353.

15. Woo SJ, Park KH, Jung HJ, Kim Sn, Choe G, Ahn J, et al. Effects of maternal and placental inflammation on retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol. 2012;250(6):915-923.
16. Woo SJ, Park KH, Lee SY, Ahn SJ, Ahn J, Park KH, et al. The relationship between cord blood cytokine levels and perinatal factors and retinopathy of prematurity: a gestational age-matched case-control study. Invest Ophthalmol Vis Sci. 2013;54(5):3434-3439.
17. Banerjee J, Asamoah FK, Singhvi D, Kwan AW, Morris JK, Aladangady N. Haemoglobin level at birth is associated with short term outcomes and mortality in preterm infants. BMC Med. 2015;13:16.
18. Englert JA, Saunders RA, Purohit D, Hulsey TC, Ebeling M. The effect of anemia on retinopathy of prematurity in extremely low birth weight infants. J Perinatol. 2001;21(1):21-26.
19. Yau GS, Lee JW, Tam VT, Liu CC, Yip S, Cheng E, et al. Incidence and risk factors of retinopathy of prematurity from 2 neonatal intensive care units in a Hong Kong Chinese population. Asia Pac J Ophthalmol (Phila). 2016 May;5(3):185-191.
20. Haghshenas Mojaveri M, Rasoulinejad S. The Relationship between Maternal and Neonatal Diseases and Retinopathy of Prematurity and Its Progression. J Babol Univ Med Sci. 2021;23(1):323-330.