Correlation between maternal anemia during pregnancy and severity of retinopathy of prematurity

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ABSTRACT

Objectives: To explore the association between maternal anemia in pregnancy and the incidence and severity of retinopathy of prematurity (ROP).

Method: The retrospective analytical study was conducted between February 2021 and August 2022 at two hospitals at King Hussein Medical City within the Jordanian Royal Medical Services (JRMS) (The King Hussein Hospital and Queen Rania Hospital for Children). It included 82 premature newborns screened for ROP that were born to mothers with a documented Packed Cell Volume (PCV) test in the last three months of pregnancy. Premature babies were followed up to document the presence, severity, and need for treatment for ROP.

Results: Out of 82, 35 mothers were found anemic (PCV ≤ 33), and 47 had normal PCV. Seventeen premature newborns with any ROP stage were born to mothers with anemia and 21 were born to mothers with normal PCV. Nineteen needed treatments with laser photocoagulation and/or Anti-VEGF intravitreal injection; ten of those were born to mothers with low PCV. Plus, disease was found in 10 premature newborns; 5 were ≥ 31 weeks' gestational age, and 5 were < 31 weeks' gestational age. The need for any treatment for ROP was significantly associated with the child's gestational age, with the risk being more premature.

Conclusion: Mother's age and the PCV during the late pregnancy do not affect the incidence or severity of ROP. No significant association was evident between the risk of Plus disease and the gestational age of newborns. The need for treatment showed a significant association with the newborn's gestational age.

Keywords: Anemia, retinopathy of prematurity, pregnancy, PLUS disease.

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Introduction

Prematurity is one of the major causes of death in children under five years, with 1 million deaths due to preterm birth. There are various significant disabilities noted once they survive the preterm period (1). Retinopathy of prematurity (ROP) is one of the most common causes of visual impairment or blindness in premature infants caused by an abnormal growth of retinal vessels. With the increase in health care advancement and technology, extremely preterm (born before 28 weeks of gestational age (GA)) and very preterm babies (born between 28 and 32 weeks of GA) have better survival, increasing the burden of ROP. The prevalence in middle east varies between 17–38% (2,3).

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ROP is the most widely recognized cause of visual impairment after preterm birth and is defined as a vision-threatening disease associated with abnormal retinal vascular development at the boundary of vascularized and avascular peripheral retina (4). Retinal blood vessels gradually grow and develop to surround the retina from the optic disk beginning at 16 weeks of gestational age, reaching the nasal retina at 32 weeks and the temporal retina at 36 to 40 weeks, and prematurity affects the growth of these vessels, which becomes very weak and leads to visual impairment in severe cases (5). ROP is largely preventable if diagnosed and treated at early stages. Many perinatal and postnatal factors, such as prematurity, low birth weight hypoxia, prolonged oxygen supplementation, respiratory distress syndrome, twin pregnancy, anemia, blood transfusions, sepsis and intraventricular hemorrhage, being recognized as contributory factors in developing ROP (6). Shifting research focus to non-oxygen related risk factors should be emphasized.

ROP occurs during the development and maturation of blood vessels. Considering the sequel of complications associated with ROP and preventing the condition may help to reduce poor outcomes in this disease. It is associated with serious complications such as refractive errors, glaucoma, strabismus, and cataracts.

Iron is an essential nutrient that has a key role in the growth and development of a child. Most of the required iron for the infant in the first six months of life is transferred during the third trimester of pregnancy. Hence prematurity may affect the normal iron metabolism of the infant. They need additional iron for coping with catch-up growth, early onset erythropoiesis, iatrogenic blood loss, limited dietary sources of iron, and low endowment of iron stores at birth (7-9). Recent reviews by WHO showed that early supplementation of low-dose vitamin A and iron among preterm infants doesn't reduce the burden of ROP at six months of infant age (10, 11). Research on ROP has been mostly restricted to interventions once the child is born. Preterm infants better takes these supplements before being born. Therefore, this study explores the association between anemia caused by different reasons (measured as PCV) among pregnant women in the last trimester and the development of ROP among premature infants.

Methods

This retrospective study was conducted between February 2022 and August 2022 at two centers within the Jordanian Royal Medical Services (The King Hussein Hospital and Queen Rania Hospital for Children), tertiary referral centers for premature newborns with ROP suspicion from multiple hospitals in Jordan. Eighty-two premature newborns with a requested eye check (newborns with less than 34 weeks gestation or less than 1500 grams birth weight) to rule out ROP that were born to mothers with a requested PCV test in the last three months of pregnancy were included in this study. The PCV test of the mother before delivery was recorded, and the premature newborns were followed up with frequent eye checks to document the presence and the severity of ROP and any need for treatment. Parental consent forms were obtained, and approval from the local Ethics Committee was provided.

Maternal anemia is defined by PCV $\leq$ 33% in the third trimester (12). The PCV tests for the mothers were collected from Electronic Medical Records (EMR) if the mother was followed up within the JRMS hospitals or from their medical files if they were being followed up outside the JRMS hospitals and the first presentation was for ROP screening after delivery. We use PCV as an indicator for anemia because it is the cheapest and most available test in all peripheral hospitals and primary health care centres.

Screening for ROP as per the protocol followed in our hospital was for newborns with less than 34 weeks gestation or less than 1500 grams birth weight.

Infant's eye examinations were performed for the first time as inpatient or outpatient at 31 corrected age if the neonatal gestational age (GA) is $\leq$ 27 weeks or after four weeks if the neonatal GA is > 27 weeks.

For pupillary dilation, we used eye drops with 1% cyclopentolate and 2.5% phenylephrine in combination, one drop for each eye, repeating 2 to 3 times every 15 minutes. We used the Retcam 3 device and the binocular indirect ophthalmoscopy with a 20-diopter and 30-diopter lenses to screen and follow up neonates. Anaesthetic eye drops were used before conducting the examination to decrease the pain during the examination.

With the Retcam 3 device (at Queen Rania Hospital for Children), we gently place a sterile speculum to open the eye and place a coupling gel over the cornea. The lens of the Retcam touches the cornea to obtain

live images from the fundus in the following sequences: posterior pole, temporal, inferotemporal, inferior, inferonasal, nasal, superionasal, superior, and superiotemporal.
In cases where Retcam 3 device is unavailable (at King Hussein Hospital), the examination is done using a binocular indirect ophthalmoscopy with a 20-diopter and 30-diopter lenses (Volk, Germany), a sterile lid speculum and scleral depressor to check the peripheral retina in the same sequence as the Retcam 3 device. Premature newborns after the first screening test were followed with a time interval related to the presence and the severity of the ROP stage. Laser photocoagulation or Anti-VEGF intravitreal injection was given if needed according to the ROP treatment guidelines.

Statistical analysis

The recorded data were compiled and entered into an excel spreadsheet computer program (Microsoft Excel 2010), and then exported to the data editor page of IBM SPSS version 22.0 (SPSS Inc., Chicago, Illinois, USA). categorical data were expressed in frequency and percentages, while the scale data expressed in mean and standard deviation, moreover the Chi-square test was used for bivariate associations and binary logistic regression for multivariable prediction , alpha level set at <0.05 to consider statistically significant and the study power set at 0.80%.

ROP staging

The International Classification of Retinopathy of Prematurity (ICROP) was published in 2 parts, the first in 1984 and later expanded in 1987. An international group of pediatric ophthalmologists and retinal specialists has developed a consensus document that revises some aspects of ICROP (13). For details of ROP staging, see table below.

Results

Table I shows the results obtained from the baseline analysis of the study sample. The table shows that the proportion of mothers in less than 30 years and more than 30 age groups are almost equal. (57.3%) of mothers had normal PCV (>33). Around 54% of newborns were at the ROP stage of 0, followed by 24.4% at the ROP stage of 2. No treatment was required in (76.8%) of newborns. The gestational age of (65.9%) of newborns was more than 31 weeks. Around 12% showed signs of Plus disease.
There was no significant association of the ROP stage with the mother's age (p = 0.064) and PCV (p = 0.162), respectively. **Table II.**

The need for treatment in the newborn was not significantly associated with the mother's PCV (p = 0.317). However, the need for treatment is significantly affected by the newborn's gestational age (p = 0.000). A greater proportion of subjects with a gestational age of < 31 weeks required treatment than those with a gestational age of more than 31 weeks **Table III.**
No significant association was evident between the risk of Plus disease and the newborn's gestational age (p = 0.259). **Table IV.**

ROP staging

Stage 1	A demarcation line identified as relatively flat and white, which lies within the retina's plane, distinguishes the avascular retina anteriorly from the vascularized retina posteriorly.
Stage 2	Ridge is the specific finding which arises in the demarcation line. White or pink-colored appearance above the plane of the retina and vessels that leave it posterior to the ridge to enter are characteristics of Stage 2. Popcorn-shaped areas of neovascular tissue produce several small heaps on the retina surface, which are detected behind the ridge.
Stage 3	Extraretinal fibrovascular proliferation or neovascular tissue leads into the vitreous from the ridge. The increased proliferation results in a ragged appearance in which these neovascularization zones persist through the vitreous. Stage 3 lesions are classified according to severity types, i.e., mild, moderate, and severe.
Stage 4	Partial retinal detachment consists of extrafoveal (stage 4A) and foveal (stage 4B) types. The duration of fibrovascular traction and degree of contraction may cause various grades of retinal separation. During the ophthalmologic examination, partial retinal detachments start at the fibrovascular areas and lead to the vascularized retina.
Stage 5	Tractional total retinal detachment.

Table I: Descriptive statistics

Independent variables	Number	Percentage
Mother's age (years)		
< 30	40	48.8
≥ 30	42	51.2
Mother's PCV		
< 33	35	42.7
≥ 33	47	57.3
ROP stage		
0	44	53.7
1	13	15.9
2	20	24.4
3	5	6.1
Treatment need		
Yes	19	23.2
No	63	76.8
Gestational age of newborn (weeks)		
< 31	28	34.1
≥ 31	54	65.9
Plus disease found in newborn		
Yes	10	12.2
No	72	87.8
Total	82	100

Table II: Association of ROP stage with mother's PCV and mother's age

Stage of ROP	Mother's age (years)		Chi square value	p-value	Mother's PCV		Chi square	p-value
	< 30	≥ 30			< 33	≥ 33		
0	19 (47.5)	25 (59.5)	7.266	0.064	18 (51.4)	26 (55.3)	5.131	0.162
1	8 (20)	5 (11.9)			9 (25.7)	4 (8.5)		
2	8 (20)	12 (28.6)			6 (17.1)	14 (29.8)		
3	5 (12.5)	0			2 (5.7)	3 (6.4)		

The test applied was the Chi-square test.

Table III: Association of the need for treatment with mother's PCV and Gestational age of newborn (weeks)

Need of treatment	Gestational age of newborn (weeks)		Chi square value	p-value	Mother's PCV		Chi square value	p-value
	< 31	≥ 31			< 33	≥ 33		
Yes	13 (46.4)	6 (11.1)	8.593	0.000*	10 (28.6)	9 (19.1)	1.001	0.317
No	15 (53.6)	48 (88.9)			25 (71.4)	38 (80.9)		

The test applied was the Chi-square test, *indicates a statistically significant difference.

Table IV: Association of risk of Plus disease with Gestational age of newborn (weeks)

Risk of Plus disease	Gestational age of newborn (weeks)		Chi square value	p-value
	< 31	≥ 31		
Yes	5 (17.9)	5 (9.3)	2.903	0.259
No	23 (82.1)	49 (90.7)		

The test applied was the Chi-square test

To iterate the aforementioned results the binary logistic regression was used to predict the ROP (absence vs present) as a function of mother's age, mother's PCV and gestational age . The omnibus tests of model coefficients show a significant result X^2=18.18,p<0.001 with 26.6% of variance is explained , Moreover the results in table (5) revealed that the baby gestational age was inversely associated with presence of ROP. The odds of having ROP was 0.611times less likely for additional one week of gestation p=<0.001 in other word more gestation age the percentage of ROP will decrease by 39.0%. Neither while maternal age nor PCV have a significant impact on ROP

Table V

Predictors	B	Wald	Sig	Odds ratio	CI 95.0%	
					lower	upper
GA	-0.493	10.528	<0.001	0.611	0.453	0.823
Mother age	-0.075	2.271	0.132	0.928	0.841	1.023
PCV	-0.059	1.320	0.251	0.943	0.852	1.043

Discussion

In our hospital-based study, we observed no increased incidence or severity of ROP in premature infants born to mothers with low PCV in comparison to premature infants born to mothers with normal PCV levels. This finding contradicts a study in Turkey that found babies born to mothers with iron deficiency anemia with markedly decreased hemoglobin, hematocrit, mean corpuscular volume, serum iron, and ferritin levels were more likely to develop retinopathy of prematurity (14). In this study that was conducted at the Gaziantep University Hospital Ophthalmology Clinic in Turkey between 2010 and 2013, they measure anemia related to iron deficiency, and the other factors causing anemia in mothers other than iron (i.e., vitamin B12 and folic acid deficiencies) were excluded. However, in our study we measure anemia as a PCV value regardless of the cause.

Reviewed medical literature indicates that the risks of prematurity and very low birth weight are increased when the woman is an adolescent or is more than 35 years old (15), and these two factors are significant risk factors increasing the incidence of ROP. Another retrospective study was conducted at Chang Gung Memorial Hospital from 2002 to 2004 showed that low birth weight and increased maternal age are significant risk factors associated with the development of ROP (16). In our study population, maternal age was not found to be associated with the increased incidence or severity of ROP in premature infants. There are 20 patients aged 35 and above and none below 20, and running regression analysis on this subset shows no significant association of ROP with maternal age ($p = 0.229$).

Many analytic studies of risk factors that influenced the development of active ROP revealed that statistically significant effect was observed in case of gestational age, birth weight, Apgar score in the first and fifth minute, as well as longer duration of oxygen therapy (17). Other studies suggest that, on one hand, gestational age is the first risk factor to determine ROP development risk; on the other hand, the duration of supplemental oxygen therapy is the first predictor of ROP worsening (18). Our study revealed that the need for any treatment for ROP was significantly associated with the child's gestational age, with the risk being more premature. However, no significant association was evident between the risk of Plus disease and the gestational age of newborns.

Considering the multi-factor causation in the development of ROP, future well-designed randomized clinical trials should be designed to understand the actual impact of antenatal maternal anemia on the development of ROP. The major limitations of this study are the small sample, single centre and the retrospective study design. In addition, other associated factors that may have a potential role in the pathogenesis of ROP were not considered. A large sample, multicentre and prospective study design is required to explore the impact of maternal anemia in the development of ROP.

Conclusion

The analysis of maternal anemia in pregnancy as a risk factor for ROP in this study revealed no increased incidence or severity of ROP in premature infants born to mothers with low PCV. Maternal age also was not found to be associated with the increased incidence or severity of ROP. However, gestational age and being more premature remains one of the significant risk factors for active ROP development and the need of treatment, which correlates with our findings in this study.

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