Original Article

J Babol Univ Med Sci
23; 2021. P: 323-330

The Relationship between Maternal and Neonatal Diseases and Retinopathy of Prematurity and Its Progression

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J Babol Univ Med Sci; 23; 2021; PP: 323-330

Received: Feb 1st 2021, Revised: Mar 1st 2021, Accepted: May 19th 2021.

ABSTRACT

BACKGROUND AND OBJECTIVE: Retinopathy of Prematurity (ROP) is a vasoproliferative retinal disease in preterm infants that can lead to disorders and blindness throughout life if not diagnosed and treated at an early age. Therefore, this study was performed to investigate the relationship between retinopathy of prematurity and various maternal and neonatal diseases.

METHODS: This case-control study was performed on 828 premature infants (303 infants with ROP and 525 infants without ROP as controls) born in Ayatollah Rouhani Hospital, Babol, Iran, in 2009-2019. All medical information about maternal and neonatal diseases was collected from patient files. Preliminary eye examinations and follow-up were performed based on the local ROP treatment and follow-up guide to diagnose the stage and zone of ROP. Then, neonates were compared based on retinopathy and lack of infection in both groups in terms of maternal and neonatal diseases including congenital heart defect, premature rupture of membranes, anemia, urinary tract infection, hypertension, sepsis, transient tachypnea of the newborn, respiratory distress syndrome, gestational diabetes and preeclampsia.

FINDINGS: Out of 828 evaluated neonates, 303 had ROP, including infants with preeclampsia (odds ratio of 2.54, $p<0.001$), infants with respiratory distress syndrome (odds ratio of 2.2, $p<0.001$) and infants with congenital heart defects (odds ratio of 1.53, $p=0.047$) had a higher chance of developing ROP. Moreover, 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.

CONCLUSION: The results of the study showed that maternal preeclampsia, respiratory distress syndrome and congenital heart defects are among the diseases affecting the incidence of ROP.

KEY WORDS: *Retinopathy of Prematurity (ROP), Premature Infant Diseases, Premature Birth.*

Please cite this article as follows:

Haghshenas Mojaveri M, Rasoulinejad SA. The Relationship between Maternal and Neonatal Diseases and Retinopathy of Prematurity and Its Progression. J Babol Univ Med Sci. 2021; 23: 323-30.

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Introduction

Retinopathy of Prematurity (ROP) is a vasoproliferative retinal disease in preterm infants that is the leading cause of lifelong visual impairment and blindness at an early age (1-3 years) and imposes a huge economic and psychological burden on health care systems (1-3). ROP is caused by the formation of abnormal new blood vessels in the growing retina (4-6). The severity of ROP consists of five stages that begin with the initial phase and lead to advanced ROP that is associated with bleeding, fibrovascular changes, vitreous detachment, and retinal detachment (7-10).

On the other hand, the three retinal zones involved in ROP include zone I (the zone defined by a circle focused on the optic nerve), zone II (centrifugally extended zone from the edge of zone I), and zone III (the remaining anterior myopic crescent from zone II). Each zone indicates the spread of ROP involvement in patients' retina. ROP is a multifactorial disease. Many studies have analyzed the relationship between the pathogenesis of ROP and risk factors such as low birth weight, preterm delivery, hypoxia and other factors (11-14). Several studies have shown that some underlying diseases in mothers and infants may play a role in the development and progression of ROP (15-19). To prevent the progression of ROP and to provide timely treatment programs in affected infants, it is essential to identify high-risk infants by considering risk factors for the development and progression of ROP (20).

In this study, to evaluate the effect of some maternal and neonatal diseases such as premature rupture of the membranes, urinary tract infection, hypertension, gestational diabetes, maternal preeclampsia, sepsis, transient tachypnea of the newborn, respiratory distress syndrome and neonatal anemia, and congenital heart defects as potential risk factors for ROP, examinations were performed to identify risk factors for ROP progression.

Methods

This case-control study was performed on 828 premature infants in the ophthalmology center of Ayatollah Rouhani Hospital in Babol from 2009 to 2019 after approval by the ethics committee of Babol University of Medical Sciences with the code IR.MUBABOL.REC.1399.373. Preliminary examinations were performed one hour after administration of 2.5% phenylephrine and 0.5% tropicamide. Fundoscopic examinations were performed using binocular indirect ophthalmoscope (Keeler, Vintage plus), 28-d lens, scleral depressor and pediatric speculum. The ROP stage was assessed according to The International Classification of Retinopathy of Prematurity (ICROP). The first examination and then follow-up examinations and ROP treatment were performed according to the local treatment guideline (Table 1) (21).

Table 1. Guide to the preliminary indirect ophthalmoscopic examination and follow-up examination in premature infants for ROP in Babol University of Medical Sciences, Iran

Which infants?
All infants at gestational age less than 34 weeks and weighing less than 1500 g at birth admitted to the neonatal unit or NICU for treatment.
When?
At the end of 31 weeks of age based on the last menstrual period * or 4 weeks after birth.
Before discharge from the hospital.
Follow up?
Pre-threshold and threshold of ROP: Refer for treatment.
ROP stage 2, zone 2: Repeat the eye examination after 1 week.
Other ROP stages: Repeat the examination after 2 weeks.

***The age based on the last menstrual period (in weeks) is equal to the gestational age at birth plus the chronological age of the infant (22).**

In addition, examinations were regularly continued and, if necessary, treatment protocols, including injection of antibodies against vascular endothelial growth factor, were performed and their results were recorded. All medical records were collected and then, their information was retrospectively evaluated.

Neonates were divided into two groups of without ROP symptoms (as control group) and infants with different stages of ROP (as case group). In this study, the relationship between ROP and six categories of maternal disorders, including premature rupture of the membranes, preeclampsia, hypertension, gestational diabetes, urinary tract infection, oligohydramnios, and five categories of neonatal diseases including respiratory distress syndrome, sepsis, transient tachypnea of the newborn, anemia, and congenital heart defects was evaluated.

Gestational age less than 34 weeks and gestational weight less than 1500 g (simultaneously) were determined as inclusion criteria and infants with

gestational age more than 34 weeks or gestational weight more than 1500 g were excluded from the study.

Statistical analysis: Statistical analysis was performed using SPSS software version 21. Qualitative variables were described as percentages. To identify risk factors for ROP progression, each disease was first analyzed by univariate logistic regression analysis. Then, multivariate logistic regression analysis was performed. The odds ratio and 95% confidence interval of each disease were evaluated in logistic regression models. In some cases, due to the lack of data, the model was calculated using Bayesian logistic regression and was marked with "*" in the tables and $p<0.05$ was considered significant.

Results

A total of 828 premature infants were analyzed in this study, of which 525 infants without ROP were considered as control group (gestational age of 33.13±2.32 weeks) and 303 infants with ROP as case group (gestational age 30.28±2.33 weeks). 124 of them underwent treatment. In the case group, 135 of them were girls, and 163 were boys (5 missing data) and in the control group, 283 of them were girls and 242 were boys. Of the patients with ROP, 106 patients were in stage 1, 115 in stage 2, and 76 in stage 3 of ROP (4 missing data). In addition, 62 infants had ROP in zone I, 156 had ROP in zone II, and 77 had ROP in zone III (8 missing data). In the second examination, ROP was improved in 158 patients.

Relationship between maternal diseases and ROP incidence: in the control group, the number of infants with maternal preeclampsia was 233 (44.38%) and in the case group was 203 (67%) ($p<0.001$). Univariate analysis showed that infants with maternal preeclampsia were 2.544 times more likely to develop ROP ($p<0.001$, 95% confidence interval [3.425, 1.898]). Furthermore, based on multivariate analysis results that normalized the effects of other diseases, infants with maternal preeclampsia were 1.963 times more likely to develop ROP ($p<0.001$, 95% confidence interval [3.425, 1.898]). Among mothers of controls (infants without ROP), the incidence of premature rupture of the membranes, hypertension, urinary tract infection, gestational diabetes and oligohydramnios were 95 (18.1%), 41 (7.81%), 16 (3.05%), 35 (6.67%), and 25% (4.76%), respectively. Although the incidence of maternal diseases was higher in the control group than the case group, but according to the analysis of the results, there was no significant relationship between the incidence of ROP and some maternal diseases including premature rupture of the membranes, hypertension, urinary tract infection, gestational diabetes and oligohydramnios in preterm infants (Table 2). In addition, univariate (U) and multivariate (M) analysis indicate the relationship between maternal preeclampsia ($pU<0.001$, $pM<0.001$) and the incidence of ROP.

Table 2. Univariate and multivariate analysis to investigate the relationship between ROP in preterm infants and maternal diseases

Maternal diseases	Control group N(%)	Case group N(%)	p-value	Univariate analysis Odds ratio (CI-95%)	p-value	Multivariate analysis Odds ratio (CI-95%)	p-value
Preeclampsia	233(44.38)	203(67)	0.290	2.544(1.898-3.425)	<0.001	1.963(1.415-2.729)	<0.001
Premature rupture of membranes	95(18.1)	69(22.77)	0.130	1.335(0.94-1.889)	0.105	1.028(0.694-1.519)	0.888
Hypertension	41(7.81)	28(9.24)	0.522	1.202(0.721-1.978)	0.473	0.994(0.568-1.723)	0.984
Urinary tract infection	16(3.05)	15(4.95)	0.181	1.657(0.8-3.416)	0.169	1.38(0.639-2.99)	0.409
Gestational Diabetes	35(6.67)	25(8.25)	0.382	1.259(0.731-2.138)	0.398	1.018(0.56-1.825)	0.952
Oligohydramnios	25(4.76)	9(2.98)	0.290	0.614(0.268-1.288)	0.218	0.576(0.242-1.267)	0.187

Relationship between maternal diseases and stability or worsening of ROP in the second examination: In this study, there was no significant association between stability or worsening of ROP and maternal diseases including preeclampsia, premature rupture of the membranes, hypertension, urinary tract infection, gestational diabetes and oligohydramnios. Moreover, univariate and multivariate analysis of reduced or stable zone of ROP in the presence of maternal diseases showed that there was no significant relationship between stability or worsening of ROP in the affected zone and maternal diseases including preeclampsia, premature rupture of the membranes, hypertension, urinary tract infections, gestational diabetes and oligohydramnios (Table 3).

Relationship between neonatal diseases and incidence of ROP: The number of infants with respiratory distress syndrome in the case group (174 patients, 57.43%) was significantly higher than the control group (208 patients, 38.86) (p<0.001). Furthermore, infants with respiratory distress syndrome were 2.122 times more likely to develop ROP (p<0.001, 95% confidence level [1.594-2.833]). However, with the normalization of other diseases in multivariate analysis, patients with respiratory distress syndrome were 1.508 times more likely to develop ROP (p=0.010, 95% confidence interval [2.102-2.063]). In addition, infants with congenital heart defects and ROP (46 patients, 15.8%) were significantly more than infants with congenital heart defects and without ROP (55 patients, 10.48%) (p=0.042). According to the results of univariate analysis, the probability of ROP in infants with congenital heart defects was 1.53 times or 53% higher than in normal infants (p=0.047, 95% confidence interval [1.002-3.326]). However, in multivariate analysis with normalization of other diseases, there was no relationship between the odds ratio of congenital heart defect and ROP (p=0.997). Unlike respiratory distress syndrome and congenital heart defect, the number of infants with transient tachypnea of the newborn and anemia in the case group (10 (3.3%) and 19 (6.29%), respectively) was significantly lower than the control group (85 patients (16.19%) with p<0.001 and 80 patients (15.24%) with p=0.01, respectively). Univariate analysis showed that the odds ratio of transient tachypnea of the newborn is 0.177 (p<0.001, 95% confidence interval [0.33-0.885]), which means that infants with transient tachypnea of the newborn have 82.3% odds of developing ROP. In addition, in multivariate analysis with normalization of other diseases, infants with transient tachypnea of the newborn were 0.263 times less likely to develop ROP (p<0.001, 95% confidence interval [0.124-0.505]). Similarly, infants with anemia were 0.373 times or 62.7% less likely to develop ROP (p<0.001, 95% confidence interval [0.216-0.616]). In multivariate analysis with normalization of other diseases, patients with anemia were 0.386 times or 61.4% less likely to develop ROP (p=0.001, 95% confidence interval [0.219-0.651]). Sepsis was not significantly associated with ROP (Table 4).

Table 3. Univariate and multivariate analysis to evaluate the stability or worsening (lack of recovery) of ROP in premature infants with maternal diseases

Maternal diseases	Increase or stabilization of the ROP stage				Decrease or stabilization of the ROP zone			
	Univariate analysis		Multivariate analysis*		Univariate analysis		Multivariate analysis*	
	Odds ratio (CI-95%)	p-value	Odds ratio (CI-95%)	p-value	Odds ratio (CI-95%)	p-value	Odds ratio (CI-95%)	p-value
Preeclampsia	1.158 (0.281-4.311)	0.828	1.909 (0.424-8.342)	0.383	0.355 (0.096-1.058)	0.083	0.613 (0.179-2.109)	0.434
Premature rupture of membranes	0.7 (0.179-3.438)	0.6243	0.855 (0.183-3.915)	0.8513	0.887 (0.303-2.982)	0.8347	1.284 (0.358-4.669)	0.714
Hypertension	0.853 (0.135-16.623)	0.8858	0.848 (0.11-6.587)	0.8834	0.467 (0.116-2.329)	0.3027	0.515 (0.108-2.412)	0.388
Urinary tract infection	2.774 (0.126-63.928)*	0.5193	4.147 (0.198-96.946)	0.3665	4.614 (0.236-88.562)*	0.305	6.94 (0.345-142.975)	0.210
Gestational Diabetes	0.75 (0.117-14.711)	0.7967	0.766 (0.095-5.939)	0.7934	1.565 (0.256-30.147)	0.6837	1.652 (0.233-11.445)	0.604
Oligohydramnios	0.267 (0.03-5.709)	0.274	0.344 (0.031-3.748)	0.3876	0.2 (0.023-1.754)	0.1192	0.185 (0.022-1.589)	0.123

*The model was calculated using Bayesian logistic regression.

Relationship between neonatal disease and stability or worsening of ROP in the second examination: According to univariate and multivariate analysis of reduced or stable zone of ROP in the presence of neonatal disease, only in infants with congenital heart defects, the likelihood of stability and progress of the ROP zone decreased by 69.4% (nonsignificant). In addition, in multivariate analysis with normalization of other diseases, infants with congenital heart defects were 0.291 times or 70.9% less likely to move towards advanced ROP (nonsignificant). However, univariate and multivariate analysis of the increase or stability of ROP in the presence of neonatal disease showed that there was no significant association between stability or worsening of ROP and neonatal diseases, including respiratory distress syndrome, sepsis, transient tachypnea of the newborn, anemia or congenital heart defect. Moreover, except for congenital heart defects, there was no significant relationship between the stability and progression of ROP in terms of the affected zone and neonatal diseases such as sepsis, transient tachypnea of the newborn and anemia (Table 5).

Table 4. Univariate and multivariate analysis to investigate the relationship between ROP in preterm infants with neonatal diseases

Neonatal diseases	Control group N(%)	Case group N(%)	p-value	Univariate analysis			Multivariate analysis		
				Odds ratio (CI-95%)	%	p-value	Odds ratio (CI-95%)	%	p-value
Respiratory distress syndrome	204(38.86)	174(57.43)	<0.001	2.122 (1.594-2.833)	112.2	<0.001	1.508 (1.102-2.063)	50.8	0.010
Sepsis	23(4.38)	9(2.97)	0.359	0.668 (0.29-1.416)	33.2	0.313	0.628 (0.252-1.423)	37.2	0.286
Transient tachypnea of the newborn	85(16.19)	10(3.3)	<0.001	0.177 (0.085-0.33)	82.3	<0.001	0.263 (0.124-0.505)	73.7	<0.001
Anemia	80(15.24)	19(6.29)	0.001	0.373 (0.216-0.616)	62.7	<0.001	0.386 (0.219-0.65)	61.4	0.001
Congenital heart defect	55(10.48)	46(15.18)	0.042	1.53 (1.002-2.326)	53	0.047	0.999 (0.628-1.583)	0.1	0.997

Table 5. Univariate and multivariate analysis to evaluate the stability or worsening (lack of improvement) of ROP in premature infants with neonatal diseases

Neonatal diseases	Increase or stabilization of the ROP stage				Decrease or stabilization of the ROP zone			
	Univariate analysis		Multivariate analysis*		Univariate analysis		Multivariate analysis*	
	Odds ratio (CI-95%)	p-value	Odds ratio (CI-95%)	p-value	Odds ratio (CI-95%)	p-value	Odds ratio (CI-95%)	p-value
Respiratory distress syndrome	0.946 (0.23-3.511)*	0.9342	1.097 (0.303-3.986	0.8763	1.216 (0.449-3.226)	0.6938	1.475 (0.522-4.327)	0.468
Sepsis	2.794 (0.135-63.141)*	0.5193	2.495 (0.112-54.558)	0.5568	0.409 (0.074-3.109)	0.3227	0.526 (0.084-3.177)	0.488
Transient tachypnea of the newborn	2.502 (0.112-56.507)	0.5689	1.984 (0.066-58.419)	0.6929	0.864(0.119-17.4)	0.8982	0.926 (0.109-7.695)	0.955
Anemia	0.202 (0.036-1.562)	0.0810	0.2033 (0.028-1.482)	0.1124	0.258 (0.052-1.403)	0.0934	0.228 (0.039-1.343)	0.097
Congenital heart defect	0.456 (0.114-2.275)	0.2881	0.33 (0.07-1.513)	0.1528	0.306 (0.103-0.94)	0.0331	0.291 (0.09-0.95)	0.039

*The model was calculated using Bayesian logistic regression.

Discussion

Our results showed that there is a significant relationship between ROP and neonatal diseases such as respiratory distress syndrome, congenital heart defect, transient tachypnea of the newborn, anemia and maternal preeclampsia. Our study showed that infants born to mothers with preeclampsia, infants with respiratory distress syndrome, and infants with congenital heart defects were more likely to develop

ROP. In contrast, infants with neonatal anemia or transient tachypnea of the newborn were less likely to develop ROP. Our findings also show that the odds of stability and worsening of ROP are lower in infants with congenital heart defects. Similar to our results, Akkoyun et al. found that respiratory distress syndrome is a significant risk factor for ROP progression (23). In addition, Chang et al. reported that respiratory distress syndrome is associated with the development of ROP (24). These findings are very convincing due to the lack of primary oxygen and secondary hyperoxia with retinal oxygenation, which can lead to the formation of new blood vessels and lead to ROP. Contrary to our results, Al-Qahtani et al. found that septicemia was significantly associated with ROP progression (25).

Moreover, Abdel et al. showed that sepsis was significantly associated with ROP. However, they found little association between the occurrence of ROP and respiratory distress syndrome, patent ductus arteriosus, intraventricular hemorrhage, and hypotension (26). In a cohort study by Shulman et al., preeclampsia was associated with 2.46 times increased risk of ROP. Preeclampsia was also inversely associated with ROP progression ($p = 0.009$) and appears to be a protective factor for ROP (27).

This study has limitations such as retrospective nature, low number of premature infants, failure to investigate other underlying diseases such as iron deficiency or folate deficiency anemia, hydrocephalus, viral infections, genetic disorders, coagulation diseases and others, lack of evaluating the severity of maternal and neonatal diseases and short-term follow-up. In future studies, it is suggested that other risk factors and their combinations such as various infectious diseases, deficiencies of supplements and vitamins, different types of anemia, abnormalities in vascular membranes, adhesion molecules, leukocytes, blood coagulation, mutations or genetic polymorphisms and other underlying diseases be used to predict ROP.

In this study, our results showed that preeclampsia, respiratory distress syndrome, congenital heart defect, transient tachypnea of the newborn, and anemia are neonatal diseases that contribute to ROP. Preeclampsia, respiratory distress syndrome, and congenital heart defects increase the odds of developing ROP, but transient tachypnea of the newborn and anemia play a reducing or even protective role against ROP; contrary to expectations, congenital heart defects play an important role in preventing the progression of ROP. These findings may provide valuable information for diagnosing high-risk preterm infants and determining the risk of ROP progression, leading to timely treatment and prevention of ROP progression in affected infants.

Conflict of interest: The authors did not declare any conflict of interest.

Ethical considerations: The authors state that in this study, all relevant ethical principles have been observed, including the confidentiality of the questionnaires, the informed consent of the participants in the research, and the freedom to withdraw from the research.

Acknowledgment

We would like to thank the neonatal unit of Ayatollah Rouhani Hospital in Babol.

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