Scripta Scientifica Medica, 2022;54(4):36-42
DOI: 10.14748/ssm.v54i4.9033

ISSN 0582-3250 (Print)
ISSN 1314-6408 (Online)

ORIGINAL ARTICLES

INCIDENCE OF RETINOPATHY OF PREMATURITY IN VARNA REGION, BULGARIA, AND EVALUATION OF PERINATAL RISK FACTORS

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ABSTRACT

INTRODUCTION: Retinopathy of prematurity (ROP) is a vasoproliferative disorder that is still a leading cause of preventable childhood blindness around the world.

AIM: The aim of this article is to determine the incidence and evaluate the perinatal risk factors associated with the development of retinopathy of prematurity and its progression.

MATERIALS AND METHODS: Eighty-five children, in the period June 2019–January 2021, were prospectively analyzed. All children have fulfilled the screening ROP criteria in the Republic of Bulgaria: gestational age (GA) ≤32 gestational weeks (g.w.) and birth weight (BW) ≤1501 g. Children with higher GA and/or higher BW were included if additional risk factors were detected, or based on the neonatologist's assessment.

RESULTS AND DISCUSSION: Of the screened children, 21 (24.7%) showed no signs of ROP, and 64 (75.3%) developed any stage of ROP. The mean BW for the cohort was 1064.8 g (±227.2), and the mean GA was 28.1±2.2 g.w. After univariate analysis, the following risk factors were found to be significant for ROP development: low birth weight, invasive mechanical ventilation, anemia of prematurity, ≥2 hemotransfusions, and hyaline membrane disease. The above-mentioned factors were also found to be statistically significant for ROP progression, including GA. After multivariate logistic regression analysis, BW was the only independent risk factor both for ROP development and progression (OR: 3.352 (95% CI 2.803–3.902), p<0.001).

CONCLUSION: The incidence of ROP in the Varna region of Bulgaria is relatively high. Low BW, anemia of prematurity, and invasive mechanical ventilation are significant and independent risk factors for ROP development.

Keywords: *retinopathy of prematurity, incidence, risk factors, screening*

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Received: October 17, 2022
Accepted: December 2, 2022

INTRODUCTION

Retinopathy of prematurity (ROP) is a vasoproliferative disorder characterized by the abnormal development of retinal blood vessels in prematurely born infants (1). The pathogenesis of this condition is complex, but the main mechanism is associated with interruption of normal maternal-fetal interactions, vasoconstriction of immature retinal vessels, retinal ischemia, and subsequent neovascular-

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ization (2). Clinical presentation varies from spontaneous regression to bilateral retinal detachment and irreversible vision loss in the most severe cases (1).

The progress of neonatal care in the last decades has led to a better survival rate among premature children, which increases the number of babies at risk of developing ROP (3). This is called the Third Epidemic of ROP, emerging in the 1990s and affecting mostly middle-income countries in Latin America, Eastern Europe, and Southeast Asia (4).

Today, it is accepted that ROP is a multifactorial disease, and the main risk factors are premature birth, especially before 32 gestational weeks (g.w.), and low birth weight at birth (< 1500 g) (5,6). Screening programs for ROP in most countries are based on these two criteria.

There are several more factors that have been reported in the literature to have a correlation with this disorder: invasive mechanical ventilation (1,7,8) persistent ductus arteriosus (9), neonatal sepsis (8,9), anemia (7), intraventricular hemorrhage (IVH) (8,9), multiple blood transfusions (9), and thrombocytopenia (7).

In our available literature, we did not find a study published in the last 10 years that evaluated the problems of ROP associated with disease incidence and the supposed risk factors in Northeastern Bulgaria. The purpose of this study is to fill this vacancy.

AIM

The aim of this article is to determine the incidence and evaluate the perinatal risk factors associated with the development and progression of retinopathy of prematurity.

MATERIALS AND METHODS

The current study includes premature children, followed prospectively in the period June 2019–January 2020, treated in the Neonatal Intensive Care Unit in the Prof. Dr. Dimitar Stamatov Specialized Hospital of Obstetrics and Gynecology for Active Treatment, Varna.

All included children have met the criteria of the National Strategy for ROP Screening and Treatment, accepted in Bulgaria in 2009 and revised in 2014 (10). According to it, all children with BW ≤1500 g and GA ≤32 g.w., as well as babies with a higher birth weight and a bigger GA with associated risk factors and comorbidities, are considered at the discretion of the treating neonatologist. All children were enrolled after receiving informed consent from their parents. Children with severe congenital ocular and non-ocular malformations were excluded from the study, as were children who did not show up for required follow-up examinations.

Enrolled children were divided into two main groups:

Group I: patients without ROP (N = 21)

Group II: patients with ROP (N = 64)

Group II was divided into two subgroups:

Group IIA: patients with ROP who regressed spontaneously and for whom treatment was not necessary. In this group were children diagnosed with stage 1 or 2 ROP, without plus disease. These cases were denoted as mild ROP (N=42).

Group IIB: patients with ROP in whom the disease has progressed to the point of needing treatment. In this group are patients diagnosed with type 1 pre-treshold ROP according to the ETROP criteria (11), threshold ROP according to the criteria of the CRYO-ROP study (12) retinal fold involving the macula, or retrolental tissue. At this writing, 172 infants had been examined three months after randomization. An unfavorable outcome was significantly less frequent in the eyes undergoing cryotherapy (21.8%, as well as aggressive ROP. These cases were denoted as severe ROP (N=22).

For data input, a special form was used in which information from medical records and parents was collected.

Birth weight was determined in the first minutes of life of the patients and GA was established by the treating obstetrician, according to information for the last menstrual cycle or ultrasound check-ups in the first trimester of pregnancy.

The ROP screening program started between 4 and 6 weeks after delivery, or when the postconceptual age of 32 weeks was reached.

The following mydriatic regimen was used: triple application of a "cocktail" consisting of 0.5% tropicamide and 2.5% phenylephrine in the conjunctival sac. If adequate mydriasis was impossible to achieve, the latter was written down on the screening form and in the medical record.

All examinations were performed by an experienced ophthalmologist with binocular indirect ophthalmoscopy and a 20D lens. A sclerodepressor was used to achieve a full view of the peripheral retina. The eye was kept open with a pediatric eye speculum and topical anesthetic, proxymetacaine hydrochloride 0.5% (Alcaine®, Alcon), was applied before examination. In some cases, the findings were photodocumented with RetCam (RetCam II, Clarity Medical Systems, Pleasanton, CA).

Objective findings were interpreted according to the International Classification of ROP (ICROP) (13). Zone of vascularization, stage of disease, and condition of blood vessels (presence or absence of plus disease) were described.

After the initial findings, the frequency of follow-up visits was determined, or a decision for treatment was taken according to the recommendations of the ETROP Study (11).

Children without ROP were examined again after 10 days, and those with signs of ROP, according to eye status, were examined every 7 days or more frequently.

Statistical Analysis

Initial data were input via Microsoft Office Excel. Specialized software was used for statistical analysis—Statistical Package for Social Sciences (SPSS) for Windows, version 26.0 (SPSS Inc., Chicago, Illinois, USA).

We investigated ten potential risk factors (BW, GA, sex, multiple gestation, anemia, hemotransfusions (≥2), persistent ductus arteriosus, hyaline membrane disease, invasive mechanical ventilation, and neonatal pneumonia) and aimed to find interactions between variables and determine those that play a role in ROP development and progression.

Results were described as numbers (n), frequencies (%), mean values with standard deviations (SD) and medians. The initial analysis was performed with univariate analysis with suitable statistical tests—Student's t-test for evaluation of continuous variables and $\chi 2$-test/Fisher's exact test for evaluation of categorical variables. For the determination of independent ROP risk factors, multivariate logistic regression was used. Those factors that have been proven statistically significant from the univariate analysis were included in the multivariate analysis.

For all variables, p-values, odds ratios, and 95% confidence intervals were calculated. For a significant result and rejection of the null hypothesis, a p-value ≤0.05 was accepted.

The current study adheres to the tenets of the Declaration of Helsinki and has been approved by the Research Ethics Committee at the Medical University of Varna (№ 94/25.06.2020).

RESULTS

A total of 85 children were included in the study; 50 (58.8%) were male and 35 (41.2%) were female. In 64 (75.3%) children, ROP signs were observed and in 22 (25.89%), severe ROP that needed treatment.

The cohort's mean BW was 1064.8 g (±227.2 g), with values ranging from 670 g to 1630 g. The mean GA was 28.1 g.w. (±2.2), with values ranging from 24 to 34 g.w. Most of the children enrolled in the study developed stage 1 ROP—23 children (27.0%), stage 2—18 children (21.2%), stage 3—in 21 children (24.7%), stage 4a—in 2 children (2.4%). Stage 4b and stage 5 were not described. Three children (3.5%) were diagnosed with aggressive ROP.

From the enrolled children, 29 (34.1%) were born from multiple pregnancies; from them, 25 (29.4%) were twins, and 4 (4.7%) were triplets.

In cases where treatment was necessary, intravitreal anti-VEGF injections or laser therapy were performed. In one case, cryotherapy was applied. Treated children were followed up in the next 48 hours as well as on the 7th day after treatment. In cases with anti-VEGF injections, the follow-ups continued until the postmenstrual age of 65 weeks was reached. There were no cases of ROP reactivation after treatment.

The distribution of children according to their BW and ROP development is presented in Table 1.

In the following statistical analysis, we have discovered a statistically significant difference between group I (without ROP) and group II (with ROP), as well as between group IIA (mild ROP) and group IIB (severe ROP) according to the BW factor. Birth weight proves to be a significant risk factor for ROP development and progression.

In Table 2, we have presented the children's distribution according to their GA and ROP development:

Table 1. Children's distribution according to their birth weight and ROP development.

Birth weight	Without ROP (N,%)	ROP (N,%)				Total: (N,%)
		St. 1	St.2	St.3	St. 4a	
< 999 g	0 (0%)	8 (9.4%)	7 (8.2%)	13 (15.3%)	1 (1.2%)	29 (34.1%)
1000-1250 g	14 (16.5%)	10 (11.8%)	7 (8.2%)	6 (7.1%)	1 (1.2%)	38 (44.7%)
1251-1500 g	6 (7.1%)	5 (5.9%)	4 (4.7%)	2 (2.4%)	0 (0.0%)	17 (20.0%)
> 1501 g	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
Total:	21 (24.7%)	23 (27.0%)	18 (21.2%)	21 (24.7%)	2 (2.4%)	85 (100%)

Table 2. Children's distribution according to their GA and ROP development.

GA	Without ROP (N,%)	ROP (N,%)				Total:
		St. 1	St. 2	St. 3	St. 4a	
< 28 wks	8 (9.4%)	12 (14.1%)	7 (8.2%)	12 (14.1%)	1 (1.2%)	40 (47.1%)
29-30 wks	11 (12.9%)	10 (11.8%)	11 (11.8%)	9 (10.6%)	1 (1.2%)	42 (49.4%)
> 31 wks	2 (2.4%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.5%)
Total:	21 (24.7%)	23 (27.0)	18 (21.2%)	21 (24.7%)	2 (2.4%)	85 (100%)

In the subsequent analysis, we did not discover a statistically significant difference between groups I or II regarding the GA, but we have found one when comparing groups IIA and IIB.

Among other investigated risk factors, we found a statistical significance for the following factors: invasive mechanical ventilation, anemia of prematurity, hyaline membrane disease, ≥ 2 hemotransfusions. We have not found a significant association between ROP and the following risk factors: gender, multiple pregnancies, persistent ductus arteriosus, and neonatal pneumonia.

Results from the univariate analysis are presented in Table 3:

After initial analysis, all risk factors that had been proven to be significant from the univariate analysis were submitted to multivariate stepwise regression analysis. Results are presented in Table 4. Analysis showed that independent risk factors for ROP development were low BW, anemia of prematurity, and invasive mechanical ventilation.

We performed logistic regression analysis on statistically significant factors regarding ROP progression and found out that only BW was an indepen-

Table 3. Univariate analysis of potential risk factors for ROP

Risk Factor	Group I vs Group II		Group IIA vs IIB	
	χ2/t-value	p-Value	χ2/t-value	P-value
Birth weight	-2.969	0.006	3.842	<0.001
Gestational age	-1.680	0.103	3.076	0.003
Sex	0.109	0.741	1.478	0.224
Multiple gestation	0.948	0.330	0.005	0.943
Anemia of prematurity	8.264	0.004	4.841	0.028
≥ 2 hemotranfusions	8.163	0.004	0.794	0.408
Invasive mechanical ventilation	20.244	0.001	4.440	0.035
Hyaline-membrane disease	5.144	0.023	11.128	0.001
Neonatal pneumonia	0.445	0.505	0.717	0.397
Persistent ductus arteriosus	0.008	0.930	0.059	0.808

Table 4. Multivariate logistic regression for independent risk factors for ROP development.

Risk factor	OD (95% CI)	P-value
Invasive mechanical ventilation	2.345 (1.753-2.938)	0.002
Anemia	3.000 (2.365-3.444)	0.003
Birth weight	3.828 (3.268-4.389)	0.029
≥ hemotranfusions	0.085 (0.017-0.417)	0.057
Hyaline-membrane disease	0.794 (0.207-2.396)	0.124

dent risk factor for both ROP development and progression—OR: 3.352 (95% CI 2.803–3.902), p<0.001.

DISCUSSION

Retinopathy of prematurity continues to be an important cause of preventable blindness worldwide, especially in middle-income countries. Globally, at least 50 000 children are blind from ROP (4).

We studied the distribution of ROP among premature children who were subjected to ROP screening in a neonatal intensive care unit (NICU) in Varna, Bulgaria, as well as the role of several potential risk factors for ROP development and progression. In our study, we discovered a high rate of ROP (75.3%) and severe ROP requiring treatment (25.9%). Data about the incidence of ROP and ROP requiring treatment vary significantly between different studies. Differences in screening criteria, the size of the examined cohorts, and the level of neonatal care are the probable explanations for this heterogeneity.

We compared our results to a similar study conducted in the same NICU more than 15 years ago (8). In this study, 686 neonates were screened, and the total number of ROP cases was 143 (20.85%). The established incidence was significantly lower than ours. One possible explanation could be that the mean BW and GA in that previous study were significantly higher compared to ours: 1319.5 g (±323) and 30 (±2) g.w., respectively. Improvements in the neonatal care in the last years have led to increased survival rate of high-risk neonates, thus increasing the risk of developing ROP (3). Our results confirm that global trend.

An incidence similar to ours has been described by authors in another country with a developing economy—Mexico. The reported rate of ROP in the cohort of 261 patients was 82.76%. Severe ROP with a need for treatment was found in 32.87% of the patients (14).

Studies from several middle-income countries reported lower ROP incidence: 55.7% (15), 66.4% (1), and 34.1% (6). When comparing the rate of severe ROP, these studies showed results close to ours—29.1% (15), 23.5% (1), and 26.3% (6).

We compared our data with that of two high-income European countries famous for their well-developed ROP screening programs: Sweden and Germany.

In Sweden, there is a national web-based ROP registry that was started in 2006: SWEDROP. Swedish data covered a 10-year period and included 7249 children, of whom 31.9% (2310 of 7249) were diagnosed with ROP, and treatment was needed in 6.1% of the cases (440 of 7249) (16).

In Germany, there is also a ROP registry in which only children who need treatment are included. An incidence of 3.2% of ROP requiring treatment has been described (17).

High-income countries with well-established ROP screening programs declare a much lower incidence of both ROP and ROP requiring treatment compared to our study.

We investigated 10 potential risk factors, which were subjected to univariate analysis, and the following risk factors were confirmed as statistically significant: low BW, anemia, hemotransfusion, hyaline membrane disease, and invasive mechanical ventilation.

The above-mentioned variables have been submitted to multifactorial analysis with stepwise logistic regression, and as significant and independent risk factors for ROP development, were confirmed: low BW, invasive mechanical ventilation, and anemia of prematurity.

Our results confirmed the role of low BW as an independent and significant factor in the progression and severity of ROP. In the univariate analysis, GA dropped as a significant factor for ROP development. This could be explained by the relatively small number of children enrolled as well as the fact that all infants in the study had lower GA in comparison to the normal population. Other authors achieved similar results (1,15).

Tzvetkova et al. reported that factors increasing the risk for ROP were short gestation, low BW, sepsis, IVH, oxygen therapy, and mechanical ventilation, which corresponds to our results (8).

Borteca et al. reported that BW is one of the most closely associated factors with ROP. The authors have found a significant association between BW and both stage 2 and stage 3 ROP, as well as a near-significant association with stage 1 ROP (1).

Akkoyun et al. found that BW was an independent significant risk factor for the development of stage 1 and 2 ROP, as well as an independent significant risk factor for progression to stage 3 (15).

The mean BW of babies in our study was 1064±227 g, which is lower compared to authors in other middle-income countries. Borteca et al. reported a mean BW of 1234±373 g (1), and Akkoyun et al. reported 1365±421 g (15). There is known heterogeneity according to BW of babies developing ROP in middle-income countries, where bigger and more mature babies develop ROP compared to high-income countries.

The role of oxygen in the pathogenesis of ROP was proven almost 70 years ago (18). The choice of oxygen therapy, its duration, and oxygen concentration are still debatable. Several authors confirm the role of prolonged mechanical ventilation as a significant risk factor for ROP development (1,7,8). We discovered that mechanical ventilation was an independent and significant risk factor for ROP development but not for the progression of the disease.

Borteca et al. have reported that mechanical ventilation was a significant ROP predictor, but was only significantly correlated with stages 2 and 3 ROP in their multivariate model (1).

Slidsborg et al. found that mechanical ventilation was a statistically independent risk factor for treatment-demanding ROP (7).

Often, premature children develop anemia, especially infants born before 28 g.w. (19). This is due to immaturity of the hemopoietic system, insufficient erythropoietin production, ineffective compensatory mechanisms, consummative coagulopathy, and iatrogenic blood loss due to the need for frequent blood samples (20). Our results proved that anemia of prematurity is an independent and significant factor for ROP development but not for the progression of the disease. Other authors share similar results (20), while others deny this connection (9).

Lundgren et al. investigated 227 children born before 28 weeks of gestation and found that the duration of anemia during the first week of life was an independent risk factor for ROP warranting treatment, and preventing early anemia may decrease this risk (21).

Tandon et al. found that anemia in their cohort of infants was significantly associated with ROP incidence but not an independent risk factor (20).

A major portion of premature children undergo hemotransfusions because of anemia at some point during their hospitalization. In our multiple regression model, hemotransfusion has dropped out as a significant risk factor. Other authors share similar results (22). Hadi et al. found that the need for red blood cell or plasma transfusion is one of the risk factors for the development of threshold ROP (9). The potential pathogenetic mechanism that could explain their role is associated with the deposition of iron ions, which catalyzes the production of free radicals, increasing the oxidative stress on the retina (23).

CONCLUSION

The incidence of ROP in the Varna region is relatively high. Low BW, anemia of prematurity, and invasive mechanical ventilation are independent and significant risk factors for ROP development.

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