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SOME OF THE RISK FACTORS FOR RETINOPATHY OF PREMATURITY

Gordana Stanković – Babić[1,2], Ana Oros[3], Milena Vujanović[4], Sonja Cekić[2], Marina Jonović[5]

Retinopathy of prematurity (ROP) remains the main cause of visual impairment in preterm infants.

The study was aimed to assess the impact of some of the risk factors (gestational age, body weight of children at birth, associated diseases in children, maternal age at delivery, maternal smoking during pregnancy, multiple pregnancies) on the occurrence of ROP in the sample of premature infants.

We statistically processed the results (Student's t test and the χ^2 test) of 93 preterm infants of both sexes: 39 boys and 54 girls, examined by indirect ophthalmoscope (Haine 500, Germany) in mydriasis. The examination included all premature neonates with birth weight ≤ 2000g and/or gestational age ≤37 weeks, as well as neonates >37 weeks which have associated risk factors (oxygen, ventilation, sepsis, etc).

Among 93 premature infants, with normal findings on the retina there were 72 children (77.42%), while in 21 (22.58%) children we found ROP. Ophthalmological findings: the first stage of ROP was found in 15.05%, the second stage of ROP in 2.15% and third stage of ROP in 5.38% of the examined children. There were no patients with an aggressive form of ROP. Children with ROP were statistically of lower gestational age - 32.10 ±2.70 compared to children without ROP - 35.37 ±1.72 ($p<0.001$). Children with ROP had at birth significant lower body weight of 1741g ±579.19 than children without ROP - 2168.75 ±528.58 ($p<0.01$). Mothers of the children with ROP were, at the time of giving birth, over 29 ±6.09 years old compared to mothers of children without ROP who were 26.42 ±5.75 years old ($p=0.0773$). The presence of other diseases was significantly more prevalent in children with ROP 52.38% vs. 2.78% ($p<0.001$). The number of mothers of children with ROP who smoked during their pregnacy was considerable - 57.14 % vs. 37.50% (percent of non-smoking mothers), though the difference was not statistically significant.

Knowing the risk factors and their mechanisms of action requires a comprehensive approach to the complex problem of preventing prematurity, ROP, and appropriate ROP treatment. *Acta Medica Medianae 2014;53(3):5-10.*

Key words: *retinopathy of prematurity, risk factors, premature infants*

University of Niš, Faculty of Medicine, Ophthalmology Department, Niš, Serbia[1]
Clinic for Eye Diseases, Clinical Centre Niš, Serbia[2]
University of Novi Sad, Faculty of Medicine, Clinic for Eye Diseases, Clinical Centre Novi Sad, Serbia[3]
Clinic for Eye Diseases, Clinical Centre Niš, Serbia[4]
Gynecological and Obstetrics Clinic, Clinical Centre Niš, Serbia[5]

Contact: Gordana Stanković-Babić
Clinic for Eye Diseases, Clinical Centre Niš
Bulevar Zorana Djindjića 48, 18000 Niš, Serbia
E-mail: gordanasb@open.telekom.rs

Introduction

Retinopathy of prematurity (ROP) remains the main cause of visual impairment in former preterm infants (1). Previously known as retrolental fibroplasia (2), it is characterized by abnormal vascular development of retina in premature infants (3).

The development of the human retinal vasculature begins to form arround the 16th week of gestation and completes at term (i.e., the 40th week of gestation) (4). The unique feature of ROP relates to its occurrence only in premature infants with immature and incompletely vascularised retina (4,5). ROP is a biphasic disease. The first phase begins with delayed retinal vascular growth after birth and partial regression of existing vessels, followed by a second phase of hypoxia-induced pathological vessel growth. Two major risk factors of ROP are the use of oxygen and a decreased gestation period. Excessive oxygen contributes to ROP through regulation of vascular endothelial growth factor (VEGF). Suppression of VEGF by oxygen in phase I of ROP inhibits normal vessel growth, whereas elevated levels of VEGF induced by hypoxia in phase II of ROP precipitate pathological vessel proliferation. Insulin-like growth factor 1 (IGF-1) is a critical non-oxygen-regulated factor in ROP. IGF-1 acts indirectly as a permissive factor allowing maximal VEGF stimulation of vessel growth. Lack of IGF-1 in preterm infants prevents normal retinal vascular growth in phase I of ROP despite the presence of VEGF. As infants mature,

the rising levels of IGF-1 in phase II of ROP allows VEGF to stimulate the pathological neovascularization. These findings suggest that restoration of IGF-1 to normal levels might be useful in preventing ROP in preterm infants (6). Understanding both mechanisms of normal retinal vascular development and the pathophysiological processes, ROP is the key to developing new therapeutic approaches to prevent its complications of the(7).

The International Classification of Retinopathy of Prematurity (ICROP) uses a number of parameters to describe the disease. The disease may affect several zones (1,2, and 3), and its severity is also determined by the presence of "plus disease (stages 1-5). Especially aggressive form of ROP is AP ROP (8). Stage 5 is the severest form of ROP, the final stage of the disease and the main cause of visual impairment and blindness. This stage is a total retinal detachment in the shape of a funnel - stage 5A is an open funnel and stage 5B is a closed funnel. However, even the milder forms of ROP (stage 1,2) leave ocular sequel in the form of ametropias, refractive errors (especially myopia), strabismus, glaucoma, cataracts (9).

Treatment for ROP might include: a) cryotherapy (freezing) to prevent the spread of abnormal blood vessels; it was the original mode of treatment since 1970s.; b) Laser surgery (eg, xenon, argon and diode) has shown to be as effective as cryotherapy for ROP; c) Scleral buckling surgery and/or vitrectomy was performed for stages 4 and 5, but with the poor anatomical and visual prognosis (5,10,11). A promising future strategy to counter ROP is to use anti-VEGF therapy (VEGF-specific neutralizing antibody, bevacizumab). Timing (stage/zone of ROP), dose (0.4–12.5 mg intravitreal), and frequency of administration of bevacizumab, as well as treatment with photocoagulation, varied among reports (12).

In the future, evaluation of candidate genetic polymorphism influencing the outcome of ROP may provide new information about the pathogenesis of the disease. Screening of genetic polymorphisms may also help to identify and treat those infants who are at high risk in a timelier manner (13).

The dominant risk factors for ROP are low gestational age (especially <32 weeks of gestation), low birth weight (<1500g, especially <1250g), sepsis and oxygen therapy (10,14- 21). Neonatal sepsis, oxygen exposure and low gestational age may have synergistic effects, while oxygen exposure and sepsis may have antagonistic effects of developing ROP (20). Also, high blood concentrations of oxygen and carbon dioxide (18,22) and low blood pH are associated with increased risk of severe ROP (18). Other risk factors for ROP are concurrent illness (19), heart disease, infection, apnea, respiratory distress, bradycardia, white race, intraventricular hemorrhage, prolonged parenteral nutrition, lung maturation, steroid treatment, blood transfusions (10,19) and maternal factors such as preeclampsia, heavy smoker, older maternal age, multiple births, in vitro fertilization (19) etc.

Aims

The study was aimed to assess the impact of some of the risk factors (gestational age, body weight of children at birth, associated diseases in children, maternal age at delivery, maternal smoking during pregnancy, multiple pregnancies) on the occurrence of ROP in the sample of premature infants.

Material and methods

We statistically processed the results (Student's t test and the χ^2 test) of 93 preterm infants of both sexes examined by indirect ophthalmoscope (Haine 500, Germany) in mydriasis. All premature neonates were included by examination, with birth weight ≤2000g and/or gestational age ≤37 weeks as well as neonates >37 weeks which have associated risk factors (oxygen, ventilation, sepsis, etc). Screening for ROP included children from the central, southern and eastern Serbia.

Results

We examined 93 premature infants, among whom there were 39 boys and 54 girls. Normal findings were found in 72 children (77.42%), whereas 21 (22.58%) subjects had ROP (Table 1). Ophthalmological findings: I ROP stage in 15.05%, II stage of ROP in 2.15% and III stage of ROP in 5.38% of the examined children. Laser was applied in 6 (28.57%) children with ROP. There were no patients with an aggressive form of ROP (Table 2).

Table 1. Stages of ROP in examined children

ROP stage	N	%
0	72	77,42%
1	14	15,05%
2	2	2,15%
3	5	5,38%
Total	93	100,00%

The results of considered effects of risk factors are: children with ROP were statistically significantly of lower gestational age of 32.10 ± 2.70 compared to children without ROP 35.37 ± 1.72 ($p<0.001$). Children with ROP had at birth significantly lower body weight of $1741g \pm 579.19$ than children without ROP - 2168.75 ± 528.58 ($p<0.01$). Mothers of the children with ROP were, at the time of the birth of their children, over 29 ± 6.09 years old compared to mothers of the children without ROP who were 26.42 ± 5.75 years old ($p=0.0773$) (Table3). The presence of other diseases was significantly more prevalent in children with ROP 52.38% vs. 2.78% ($p<0.001$)(Table 4).

The number of mothers of children with ROP who smoked during their pregnacy was considerable - 57.14% vs. 37.50% (percent of non-

smoking mothers), though the difference was not statistically significant (Table 5).

ROP is frequently found in male children, without statistically significant difference (P=0.1758) (Table 6), or in multiple pregnancies (p=0.6745), twins, triplets (p=0.7443) (Table 7).

Table 2. Localization of ROP

Zones	ROP		Non ROP		Total	
0	1	4,76%	0	0,00%	1	1,08%
1	6	28,57%	17	23,61%	23	24,73%
2	12	57,14%	39	54,17%	51	54,84%
3	2	9,52%	16	22,22%	18	19,35%
Total	21	100,00%	72	100,00%	93	100,00%

χ^2=4,74, df=3, p=0,1916
χ^2=0,96, df=1, p=0,3453

Table 3. Gestational age, birth weight of children and the average age of mothers in relation to the presence of ROP

	ROP			Non ROP			t-test	p
	N	X	SD	N	X	SD		
Gestational age	21	32,10	2,70	72	35,37	1,72	5,24	p<0,001
Birth weight	21	1741,67	579,19	72	2168,75	528,58	3,19	p<0,010
Age of mothers	21	29,00	6,09	72	26,42	5,75	1,79	p=0,0773

Table 4. Presence of other diseases in the examined children

Other diseases	ROP		Non ROP		Total	
With	11	52,38%	2	2,78%	13	13,98%
Without	10	47,62%	70	97,22%	80	86,02%
Total	21	100,00%	72	100,00%	93	100,00%

χ^2=29,27, df=1, p<0,001

Table 5. Maternal smoking during pregnancy and the presence of ROP in their children

Maternal smoking during pregnancy	ROP		Non ROP		Total	
Yes	12	57,14%	27	37,50%	39	41,94%
No	9	42,86%	45	62,50%	54	58,06%
Total	21	100,00%	72	100,00%	93	100,00%

χ^2=1,83, df=1, p=0,1758

Table 6. Gender distribution of children

Gender	ROP		Non ROP		Total	
Male	12	57,14%	27	37,50%	39	41,94%
Female	9	42,86%	45	62,50%	54	58,06%
Total	21	100,00%	72	100,00%	93	100,00%

χ^2=1,83, df=1, p=0,1758

Table 7. Children born as twins, triplets or singleton babies

Children	ROP		Non ROP		Total	
Singletons	16	76,19%	50	69,44%	66	70,97%
Twins	5	23,81%	21	29,17%	26	27,96%
Triplets	0	0,00%	1	1,39%	1	1,08%
Total	21	100,00%	72	100,00%	93	100,00%

χ^2=0,79, df=2, p=0,6745
χ^2=0,36, df=2, p=0,7443

Discussion

The introduction of intensive care units into neonatal nurseries has caused a significant increase in the survival rate of infants of very low birth weight (500-1500g) with significant ROP increase (23). More than 50% of premature children with weight less than 1250 g at birth is registered in ROP, 10% of newborns develop III stage of ROP. The incidence of ROP is more common in infants of white against the black race, in boys than girls (13). Early treatment has shown an improvement in baby's chances for normal vision. Laser treatment should start within 72 hours of the eye exam. Some babies with "plus disease" , especially aggressive form of ROP (AP ROP) need immediate treatment (11,5).

Retinopathy of prematurity (ROP) has being increasingly recognized as an important cause of childhood blindness in industrialized and developing countries (24). Effective strategy for decreasing ROP-related blindness is performing the retinal examinations in neonatal intensive care units. All interested parties must cooperate in developing and implementing complete screening protocols. Hospital officials, nursery personnel, neonatologists and ophthalmologists, all have responsibility in ensuring adequate screening. Great migrations of population as well as big differences in characteristics of premature infants, together with underlying multifactor diseases, besides retinopathy of prematurity, send a warning signal to be very cautious (26). Future safe and nondestructive therapeutic strategies combined with preventive approaches need to be made in keeping with the unique developmental requirements of the premature infant (25).

The level of blindness in one country depends on the level of development of neonatal care and the opportunities to implement screening (26). According to the National group for ROP of Serbia, the screening criteria are 2000g and 37 weeks of gestation, however, the screening is to be adapted to each region. The region of Vojvodina requires the screening criteria to be lowered to 1750gr and 33 gestational weeks, as demonstrated by the tests performed at the same institution in the period from 1995 to 2001(5). A two-year prospective study (2007-2008) in Vojvodina was to examine the possibilities of changing the screening criteria. Although this study has given ground to shift the limits of screening, they adhered to broad screening criteria as recommended by the American Academy of Sciences (2000g / 37weeks of gestation) (26).

Risk factors for the occurrence of ROP in our sample of premature infants (≤2000g and/or g≤37 weeks) are lower gestational age ($p < 0.001$), lower body weight of children at birth ($p<0.01$), associated diseases in children ($p<0.001$). Risk factors of the mothers were maternal age ($p=0.0773$) at delivery and maternal smoking during pregnancy, with no statistically significant differences. Even though the sample of preterm children was small, the influence of risk factors for the occurrence of ROP was considerable. These parameters - gestational age, body weight of children at birth, associated diseases in children, maternal age at birth, maternal smoking during pregnancy are risk factors for the occurrence of ROP, which is in accordance with results of other authors (1,3,5, 10,13-21).

The most important risk factor for the development of retinopathy of prematurity is premature birth (21). However, low birth weight, as a consequence of premature childbirth or the effects of intrauterine growth restriction are the most significant factors of perinatal and neonatal mortality in both cases. Maternal risk factors include the level of maternal education, maternal habit - smoking before pregnancy, during pregnancy, number of cigarettes smoked per day, socioeconomic factors, demographic and social factors as well as risk factors in the prior pregnancy, current pregnancy and delivery. Demographic and social factors are maternal age <16 or >40 years, drugs addiction, alcohol, cigarettes, socioeconomic factors, marital status-singleness,emotional or physical stress. Past medical history is also important such as genetic disorders, DM, HTA, asymptomatic bacteriuria, rheumatic diseases (SLE), prolonged use of drugs. Risk factors in prior pregnancy are intrauterine fetal death, neonatal death prematurity, intra uterine growth restriction,congenital malformations, inborn errors of metabolism and sensitization by blood group. Risk factors in the current pregnancy are placental abruption, placenta previa, sexually transmitted diseases (HSV, chlamydia, syphilis, HIV), acute medical or surgical disease, pre-eclampsia, pluripare, treatment of infertility - invitro fertilization, etc. Risk factors in delivery are preterm delivery (<37th week) fetal distress, pelvic presentation, cesarean section, forceps delivery, Apgarscore <4 in the 1^{st} minute (27).

Knowing the risk factors and mechanisms of action requires a comprehensive approach to the complex problem of preventing prematurity, ROP, and appropriate ROP treatment. The neonatologist refers a patient to the ophthalmologists if there is a risk factor for ROP. Further check-ups are scheduled by ophthalmologist according to clinical findings (retinal vascular-maturity, level and zone of ROP). The team of doctors who participate in care of premature infants should have an ophthalmologist as well.

Approximately 20% of all premature babies can develop some form of strabismus or refractive error over time. This is why babies under the age of 32 weeks or less than 1500 g receive a follow-up care every 6 months (28). During the first months of life, preterm infants showed to have more myopia, astigmatism and anisometropia than full-term infants (8,26,29-

34). Recommendations for follow-up examinations must include all aspects of visual function, i.e., visual acuity, contrast sensitivity, visual fields, refraction, strabismus, and perceptual problems (30). Children born prematurely are reported to have an increased incidence of visual impairment, because of retinopathy of prematurity, but also because of perinatal lesions in the brain (35). Therefore, it is necessary to continue with monitoring of these children by ophthalmologists, pediatricians, neurologists, if necessary neurosurgeons, physiatrists, etc. due to the complexity of the problem.

Ophthalmological examinations and timely treatment of preterm infants significantly reduce blindness and visual impairment. Neonatologists and ophthalmologists jointly prepare the program for the prevention of blindness.

Conclusion

Risk factors for the occurrence of ROP in our sample of premature infants were gestational age, body weight of children at birth, associated diseases in children, maternal age at delivery, maternal smoking during pregnancy. Ophthalmological findings of the 93 preterm babies were as follows: 22.58% had ROP, the first stage of ROP was reported in 15.05%, II stage of ROP in 2.15% and III stage of ROP in 5.38% of the examined children, without an aggressive form of ROP.

Ophthalmological examinations and timely treatment of preterm infants significantly reduce blindness and visual impairment. Neonatologists and ophthalmologists jointly build the program for the prevention of blindness.

Althought the sample of preterm children was small, the influence of risk factors for their occurrence was condiderable. These parameters – gestational age, body weight of children at birth, associated diseases in children, maternal age at birth, maternal smoking during pregnancy are the risk factors for the occurrence of ROP.

The paper highlights the importance of timely screening for ROP in the prevention of blindness. Effective strategy for decreasing ROP-related blindness is in performing retinal examinations in neonatal intensive care units.

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NEKI OD FAKTORA RIZIKA ZA PREMATURNU RETINOPATIJU

Gordana Stanković-Babić, Ana Oros, Milena Vujanović, Sonja Cekić, Marina Jonović

Prematurna retinopatija (ROP) ostaje glavni razlog narušenog vida kod prevremeno rođene dece.

Cilj studije bio je da se proceni značaj nekih faktora rizika (gestacijska starost, telena masa na rođenju, udružene bolesti kod dece, godine majke na porođaju, pušenje tokom trudnoće, višestruka trudnoća) na pojavu ROP-a u uzorku prevremeno rođene dece.

Statistički su obrađeni podaci (Student's t test i χ^2 test) 93 prevremeno rođene dece oba pola, 39 dečaka i 54 devojčica, pregledane indireknim oftalmoskopom (Haine 500, Germany) u midrijazi. Sva prevremeno rođena deca uključena u ispitivanje bila su telesne mase na rođenju ≤2000g i/ili gestacijske starosti ≤37 nedelja, kao i neonatusi >37 nedelje koji su imali udružene faktore rizika (kiseonik, ventilacija, sepsa i sl.).

Među 93 prematurusa, sa normalnim nalazom na retini bila su 72 deteta (77.42%), dok je 21 (22.58%) ispitanik imao ROP. Oftalmološki nalaz: 1. stadijum ROP-a 15.05%, 2. stadijum 2.15% i 3. stadijum kod 5.38% ispitivane dece. Nije bilo bolesnika sa agresivnom formom ROP-a. Deca kod koje je utvrđen ROP bila su statistički niže gestacijske starosti, 32.10 ± 2.70, u poređenju sa decom bez ROP-a, 35.37 ± 1.72 ($p < 0.001$). Deca sa ROP-om su na rođenju imala manju telesnu masu od 1741 g ± 579.19, nego deca bez ROP-a, 2168.75 ± 528.58 ($p<0.01$). Starost majki dece sa ROP-om bila je 29 ± 6.09 godina, u poređenju sa majkama dece bez ROP-a, 26.42 ± 5.75 ($p=0.0773$). Signifikantno je veće prisustvo drugih bolesti bilo kod dece sa ROP-om, 52.38%, u odnosu na 2.78% ($p<0.001$). Broj majki dece sa ROP-om koje su pušile tokom trudnoće bio je veliki u odnosu na one koje nisu, 57,14% prema 37,50%, mada razlika nije bila statistički značajna.

Poznavanje faktora rizika i mehanizama delovanja obavezuje nas na sve-obuhvatni pristup kompleksnom problemu sprečavanja pematuriteta, ROP-a, kao i odgovarajući tretman ROP-a. *Acta Medica Medianae 2014;53(3):5-10.*

Ključne reči: *prematurna retinopatija, faktori rizika, prematurusi*

