

## КЛИНИЧКИ ИСТРАЖУВАЊА

## АНАЛИЗА НА МАЈЧИНСКИТЕ И АКУШЕРСКИТЕ ФАКТОРИ ЗА РИЗИК ЗА ПРЕМАТУРНА РЕТИНОПАТИЈА КАЈ ПРЕМАТУРУСИ ЧИЈА ТЕЖИНА Е НАД 1500Г И ГЕСТАЦИСКА ВОЗРАСТ НАД 30 НЕДЕЛИ

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## Извадок

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**Печатарски права:** © 2018 Игор Исјановски. Оваа статија е со отворен пристап дистрибуирана под условите на нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригиналниот(ите) автор(и) и изворот

**Конкурентски интереси:** Авторот изјавува дека нема конкурентски интереси.

Прематурната ретинопатија (РОП) е главна причина за слепило кај предвремено родените бебиња. Инциденцата на РОП се зголемува во земјите во развој и се должи на зголемување на преживување на предвремено родените деца. Прематурната ретинопатија (РОП) е сериозна компликација кај предвремено родени деца која може да доведе до слепило, освен ако се дијагностицира и се третира рано. Цел на оваа студија е да се проучат мајчините и акушерските фактори на ризик за РОП. Материјал и методи: Истражувањето претставува аналитичка „Case control“ студија во периодот 2015-2016г. Во студијата се вклучени 163 предвреме родени деца кои не ги исполнуваат критериумите на Американската академија за офталмологија (ААО), со родилна тежина се над 1500 г и гестациска старост над 30 недела. Мајките се поделени во две групи во однос на новородените со РОП и без. За оставување на целите се користеше дводелен анкетен прашалник, првиот дел од прашалникот се однесува на прашања за мајката. Резултати: ИВФ (ин витро фертилизација) ја зголемува веројатноста за РОП повеќе од два пати OR=2.1256 (1.1133-4.0585). Како независни фактори мултипната бременост ја зголемува веројатноста за РОП за два и пол пати. Прееклампсијата делува протективно, ја намалува веројатноста за настанување на РОП. Начинот на породување, возраста на мајката, број на бремености, број на раѓања, консумирање на алкохол, пушење, наркотици не претставуваат ризик фактори. Треба да се обрне големо внимание на дефинирањето на ризик факторите, нивната комплексност, развојот и прогресијата на прематурната ретинопатија и нејзината превенција кои се само еден дел од прашањата со кој се соочуваат офталмолозите и неонатолозите во текот на својата работа. Во студијата се потврдија истите ризик фактори кои се регистрираат на кај прематурусите според ААО (родилна тежина под 1500 г и под 30-та гестациска недела). Заклучок: протоколите за скрининг на РОП да се модифицираат, покрај инклузијата критериуми на ААО да се вклучат и прематуруси според препораката на неонатолозите за зголемен ризик за развој на прематурна ретинопатија, а се со родилна тежина над 1500 г и над 30-та гестациска недела.

## CLINICAL SCIENCE

## ANALYSIS OF MATERNAL AND OBSTETRIC RISK FACTORS FOR PREMATURE RETINOPATHY IN PREMATURES WHOSE WEIGHT WAS OVER 1500G AND GESTATIONAL AGE ABOVE 30 WEEK

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## Abstract

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**Key words:** risk factors, retinopathy, premature neonates

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Retinopathy of Prematurity (ROP) is a major cause of preventable blindness in preterm infants. The incidence of ROP is increasing in developing countries due to increased survival of preterm infants. Retinopathy of prematurity (ROP) is a serious complication of prematurity and can lead to blindness unless is recognized and treated early. The aim of our study was to study maternal and obstetric risk factors for ROP. Material and methods: The research was an analytical „Case control“ study in the period 2015-2016. The study included 163 premature babies that not meet the criteria of the American Academy of Ophthalmology (AAO), with BW more than 1500 g and gestational age more than 30 GW. Mothers were divided into two groups according to the newborns with ROP and without. In order to achieve the goals, a two-part survey questionnaire was used, the first part of the questionnaire refers to questions for the mother. Results: In Vitro Fertilization increases the chance of ROP two times OR=2.1256 (1.1133-4.0585). As independent factors, multiple pregnancies increase the chance of ROP for fourth times OR = 4.0721 (2.3899-9.2511). Preeclampsia acts protective, reduces the chance of occurrence of ROP OR = 0.2147 (0.0706-0.6526). The way of delivery, the number of pregnancies, number of births, alcohol consumption, smoking, narcotics, did not present as risk factors. Conclusions: We should pay attention to the definition of risk factors, their complexity, the development and progression of retinopathy prematurata and its prevention, because they are just one of the issues facing ophthalmologists and neonatologists throughout his work. The study confirmed the same risk factors that are registered on neonatal prematuruses according to AAO (birth weight below 1500 g and under the 30th gestation week). Conclusion: Based on the analysis of the study, a conclusion and recommendation protocols criteria to screen for ROP to modify, despite inclusion criteria of AAO to include premature neonates in screening for ROP according to the recommendation of neonatologists to increased risk of premature retinopathy, with birth weight over 1500 g and over 30 gestation weeks.

## Introduction

Premature retinopathy or Retinopathy of prematurity-ROP is a disease that occurs in premature babies and involves the blood vessels of the retina of the eye during development. This results in the development of vascular shunts, with neovascularization and in more severe forms, with traction ablation of retina. The development of retinal vascular shunts and neovascularization in ROP are believed to be related to local ischemia, which is a dominant feature of other proliferative retinopathies such as sickle-cell retinopathy and diabetic retinopathy. The only specificity of ROP refers to its occurrence only in premature infants with an immature and incomplete vascularized retina<sup>1-4</sup>.

In premature babies, normal development of retinal blood vessels can be interrupted, so that the peripherally placed parts during their development remain without vascularization. Ischemia that stimulates neovascular proliferation occurs in peripheral parts of the retina. The development of vitreoretinal proliferation and traction ablation of the retina on this surface causes permanent loss of eye function<sup>1-3,5</sup>.

There are numerous risk factors responsible for the development of premature retinopathy that obstruct the normal development of retinal vascularity, among which maternal and obstetric risk factors and many others that combine and complement each other.

This eye condition tends to occur only in premature babies. It usually affects both eyes and is the leading cause of vision loss in children. Out of the 28,000 U.S. babies born weighting less than 1500g as many as 16,000 will develop some form of ROP. Fortunately, most of these 90% have a mild case and won't need treatment. More severe forms of ROP can cause vision loss and even blindness if not treated<sup>1-3,6</sup>.

Other risk factors that could contribute to the ROP over the years, surprisingly, research has lead to findings that pre-eclampsia in the mother can lead to a more favorable outcome for newborns, the researchers explain it that stress causes

hypertension and intrauterine late maturation of eye<sup>1-3,8-10</sup>. The research of in vitro fertilization as a risk factor is contradictory. Friling et al found no significant differences in the incidence and severity of ROP between IVF and natural conception, such as Chinese and Korean studies<sup>12,13</sup>. Watts P. and Adams GGW register that IVF- children with ROP had lower gestational age and birth weight than those IVF babies who have not developed ROP. IVF according to them is a risk factor for the development of ROP. They in their research register that 41.6% of IVF babies progress to stage 3 ROP compared with only 9.3% of naturally conceived children<sup>14</sup>. Conceiving with IVF, unlike other techniques is a major risk factor for the development of ROP. The authors advise to increased vigilance in screening babies conceived by IVF method.<sup>1-3,15-16</sup>. McKibbin and Dabbs after treatment with IVF, 20% of babies were fulfilling screening criteria for ROP<sup>17</sup>.

Mother's smoking has been identified as an important risk factor for ROP18. In 2006, suggest that elevated mother's glucose can also play a role in the risk factor<sup>19-21</sup>.

The aim of the study was to identify and analyse maternal and obstetric risk factors for retinopathy of prematurity in prematures whose weight was over 1500g and gestational week above 30.

## Materials and methods

The research was an analytical „case control“ study (retrospective with prospective approach) in the period 2015-2016. The study included 163 premature babies that did not fulfill criteria according the American Academy of Ophthalmology (AAA) (birth weight  $\leq$  1500 g and gestational age  $\leq$  30 weeks). They were examined outside the AAO protocol, and in cooperation with neonatologists. They are involved because of a recommendation of neonatologists because of the possibility to develop ROP. They were prematures whose birth weight were above 1500gr and gestational age over 30 weeks. In order to achieve the objectives used two-part questionnaire designed specifically suited for this pur-

pose and clinical examination.

The group was divided into premature with ROP and without ROP.

The first part of the questionnaire refers to questions about the mother, and the second part is filled in by the doctor. First part: Method of fertilization / natural pathway and in vitro fertilization, type of pregnancy (one child, twins, triplets), number of pregnancies and births, multiple prenatal maternal factors - smoking, alcohol, drugs, diabetes, preeclampsia, the age of the mother, the method of deliver.

Inclusion criteria of prematuruses in screening for early detection of ROP: birth weight (BW) which was over 1500 gr. and Gestational age (GW) which was over 30 .Exclusive criteria: Infants with ocular congenital anomalies, such as cataracts, microphthalmia, anophthalmia, and coloboma in one or both eyes or systemic anomalies.

The Data were analyzed with Statistical Package for the Social Sciences (SPSS for windows, version 17.0). Descriptive statistics include mean and standard deviation for numerical variables, and percentage of different categories of categorical variables. Comparison of groups was done by chi-square ( $\chi^2$ ) test and t-test. Odd ratio was constructed of the risk factors that were significant. For CI (confidence interval  $\pm$  95% CI) is defined statistical significance level of error of less than 0,05 (p) The results are presented in tables and graphics.

## Results

The study included 163 premature babies, of which 63(38.7%) were with ROP and 100(61.3%) were without ROP.

In the group of preterm infants, IVF was registered in 63 mothers, and natural reproduction in 100 mothers. In the group of mothers with IVF, in preterm infants, ROP was found in 47.1%, %, and in 52.9% not. In the group of mothers with natural fertility, in preterm infants ROP was registered at 29.5% , and not at 70.7%.The percentage difference between preterm infants with ROP of was statistically significant for  $p < 0.05$  ( $p = 0.0212$ , Difference

test). A statistically significant association between the fertilization method and the registration of ROP for  $p < 0.05$  (Pearson Chi-square: 5.2965,  $p = .021368$ ) was recorded. According Odds ratio IVF increases the chance for ROP was two  $OR = 2.1256(1.1133-4.0585)$ .

According the delivery, in the group of mothers with caesarea section, in preterm infants, ROP was found in 40.6%, and in 59.4% not. In the group of mothers with vaginal delivery, in preterm infants ROP were registered at 35.4%, and not at 64.6%. There was no statistically significant association between the way of delivery and registration of ROP for  $p > 0.05$  (Pearson Chi-square: 0.4231,  $p = 0.515398$ ).

Multiple pregnancies in a greater percentage of 63.5% were registered in the ROP group, and in the group without ROP it was registered with 27.0%, the percentage difference was statistically significant for  $p < 0.05$  ( $p = 0.000$ ). There was statistically significant association between the multiple pregnancies and registration of ROP for  $p < 0.05$  (Pearson Chi-square: 21.2608,  $p = 0.00008$ ). According to the Odds-ratio, multiple pregnancies increase the chance for ROP four times  $OR = 4.0721(2.3899-9.2511)$

In both groups a statistically significant greater percentage mothers did not smoke (90.5%, 90.0%). There was no statistically significant association between the smoking and registration of ROP for  $p > 0.05$  (Pearson Chi-square: 0.0099,  $p = 0.920740$ ).

In the group with ROP, mothers do not consume alcohol 96.9% and consume 3.1%. In the group without ROP, mothers do not consume alcohol 98.4%, and consume 1.6% There was no statistically significant association between alcohol consumption and the manifestation of ROP for  $p > 0.05$  (Pearson Chi-square: .07567,  $p = .384372$ ).

In the group with ROP, mothers did not take narcotic substances 84.1% and took 15.9%. In the group without ROP mothers did not take narcotic substances 88.0% and took 12.0%. There was no statistically significant association between maternal use of narcotic substances and

the manifestation of ROP for  $p > 0.05$  (Pearson Chi-square: 0.4966,  $p = .481008$ ).

In the group with ROP, pre-eclampsia was not manifested in 93.6% and was manifested at 6.4%. In the group without ROP, pre-eclampsia was not manifested in 76.0% and was manifested at 24%. There was statistically significant association between the pre-eclampsia and

registration of ROP for  $p < 0.05$  (Pearson Chi-square: 8.4638,  $p = 0.003622$ ). According to the Odds-ratio, pre-eclampsia was not a risk factor, it acts protective (reduces the chance) for ROP, OR = 0.2147 (0.0706-0.6526)

One mother with diabetes was registered in the group with ROP (table 1).

**Table No 1**

	N=163	%
with ROP	63	38.7
without ROP	100	61.3
<b>way of fertilization</b>	<b>IVF(N/%)</b>	<b>natural fertilization(N/%)</b>
with ROP	40/47.1	23/29.5
without ROP	45/52.9	55/70.5
<b>way of delivery</b>	<b>Caesarean section(N/%)</b>	<b>Vaginal delivery (N/%)</b>
with ROP	41/40.6	22/35.5
without ROP	60/59.4	60/64.5
<b>pregnancy</b>	<b>single(N/%)</b>	<b>twin(N/%)</b>
with ROP	23/37.5	37/58.7
without ROP	73/73.0	29/29.0
<b>smoking</b>	<b>yes N/%</b>	<b>no N/%</b>
with ROP	6/9.5	57/90.5
without ROP	10/ 10.0	90/90.0
<b>alcohol</b>	<b>yes N/%</b>	<b>no N/%</b>
with ROP	1/ 1.6	62/98.4
without ROP	4/ 4.0	96/96.0
<b>narcotic substances</b>	<b>yes N/%</b>	<b>no N/%</b>
with ROP	10/ 15.9	53/84.1
without ROP	12/ 12.0	88/88.0
<b>pre-eclampsia</b>	<b>yes N/%</b>	<b>no N/%</b>
with ROP	4/ 6.3	59/92.1
without ROP	24/ 24.0	76/76.0
<b>diabetes mellitus</b>	<b>yes N/%</b>	<b>no N/%</b>
with ROP	1/ 1.6	62/98.4
without ROP		100/100.0

## Discussion

Retinopathy is the most important cause of blindness in children, which in many cases can be prevented. Although great progress has been made in the diagnosis and treatment of ROP, it is one of the major diseases causing blindness in

children ROP is a multifactorial disease, involves many risk factors. The definition of risk factors, their complexity, the development and progression of premature retinopathy and its prevention are just some of the issues facing ophthalmologists and neonatologists<sup>22</sup>.

Assessment of IVF in the occurrence of premature retinopathy is debatable, i.e. different authors have come up with different conclusions. Berg et al.<sup>25</sup> have come to the conclusion that IVF is closely related to the emergence of ROP in premature babies. In contrast, Friling et al.<sup>24</sup> did not find significant differences in the occurrence and severity of premature retinopathy between the natural conception and IVF. Watts and Adams<sup>25</sup> come to the conclusion in their study that IFV more often than other artificial insemination techniques were a major risk factor for developing a severe form of ROP. In our study we came to the conclusion that IVF increases the chance for ROP more than two and a half times.

ROP occurs in a greater percentage in multiple pregnancies in relation to single pregnancy in mothers, multiple pregnancy increases the chance of ROP for tri times. Blumenfeld et al.<sup>26</sup> in a large series reported that there was no difference in the incidence or severity of ROP between single or multiple pregnancies. The antenatal risk factors analysis in Kumar's study showed that multiple pregnancies were significant in the ROP group ( $p = 0.00$ )<sup>27</sup>.

In the study of Seiberth and Lindarkomp,<sup>28</sup> were registered insignificant relationship between the mode of delivery and the occurrence of ROP. But it is in disagreement with Shah et al.<sup>29</sup> who found that cesarean section was significantly associated with the occurrence of ROP. No significant relationship has been gained between the mode of delivery (caesarean section and spontaneously) and the occurrence of ROP in our study.

The study did not obtain a link between the number of births and the registration of premature retinopathy.

Babic GS<sup>30</sup>, concluded in her study that smoking before pregnancy, during pregnancy, how many cigarettes are smoked per day, the level of mother's education and the socioeconomic factors were risk factors for the occurrence of ROP.

However, smoking of the mother was not recommended due to the large number of systemic side effects that can cause the mother and the newborn. In our study

neither confirmed nor denied smoking that was a risk factor for the occurrence of ROP and was not denied and did not confirm that it acts protective for the occurrence of premature retinopathy. We obtained these results on the basis of the small number of mothers who smoke in the group.

There was no statistically significant link between alcohol consumption and ROP manifestation in the group. There was also no significant link between the consumption of narcotic substances and the manifestation of ROP in both groups. In contrast to our obtained results, Babić<sup>30</sup> came to the opposite conclusion that the consumption of alcohol and narcotic substances is a risk factor for the occurrence of ROP.

However, very few studies have been published on the relationship between preeclampsia and ROP, and they are contradictory<sup>22, 30-33</sup>. Filho et al. in their study concluded that preeclampsia reduces the risk of ROP by 60% and is a protective factor<sup>31</sup>. Seibrth came to the same conclusions in his research<sup>28</sup>. The findings of Filho and Seibrth were similar to ours. In our study, preeclampsia was not a risk factor, but rather acts as a protective factor, reduced the chance of ROP occurring. Studies in Turkey have found that preeclampsia was a risk factor precisely, and Gebesce et al.<sup>34</sup> study find that the odds ratio = OR for maternal preeclampsia with the univariate logistic regression was OR=3.2 (1.002-11.535), and was confirmed by the Özkan study and colleagues<sup>35</sup>.

Tunay et al. in their research found that diabetes in the mother was a risk factor for the occurrence of ROP 36 the mother's diabetes was registered as an independent risk factor for ROP -OR = 25,040 (12,728-49,264,311). In our research, 4 cases of mothers of diabetics were registered.

## Conclusions

- In vitro fertilization, multiple pregnancies were risk factors and increase the chance of premature retinopathy occurring.

- Preeclampsia was not a risk factor for ROP, but it has a protective effect
- In the study the next factors were not risk factors for the occurrence of premature retinopathy: the method of delivery (caesarean section and spontaneous), number of pregnancies, number of births, alcohol, smoking and narcotics.

The study confirmed the same risk factors that are registered on neonatal prematurus according to AAO (birth weight below 1500 g and under the 30th gestation week). Based on the analysis of the study, a conclusion and recommendation are that protocols criteria to screening for ROP have to modify, despite inclusion criteria of AAO to include prematurus in screening for ROP according to the recommendation of neonatologists which increased risk of premature retinopathy, with birth weight over 1500 g and over 30 gestation weeks

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