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ORIGINAL PAPER

The state of refraction in prematurely born children with retinopathy depending on treatment methods used (diode laser and anti-VEGF) and selected demographic characteristics – observations

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ABSTRACT

Introduction: The authors present the prevalence of refractive errors in premature infants, demonstrating the relationship between refractive development and selected demographic characteristics and the forms of treatment used: diode laser, anti-vascular endothelial growth factor (anti-VEGF) and combination therapy.
Material and methods: The study included 56 healthy children without retinopathy of prematurity (ROP) and 63 children with ROP. Ophthalmologic evaluation and diagnosis were performed according to the International Classification of Retinopathy of Prematurity assessed in Ret-Cam 3. Treatment of ROP was carried out according to the guidelines of the Polish Ophthalmological Society using a diode laser (IRIDEX IQ 810) and an anti-VEGF intravitreal preparation (ranibizumab, Lucentis) at a reduced dose of 0.18 mg. Refractive measurements were taken at 7 months of age using a handheld computerized autorefractometer (Retinomax) after 1% tropicamide cycloplegia.
Results: A statistically significantly higher prevalence of high myopia (p = 0.019) and low astigmatism ($p < 0.001$) was observed in the eyes of premature infants with ROP and moderate hyperopia in the group without ROP ($p = 0.031$) regardless of the treatment used [mean +1.33 spherical diopters (Dsfr.); SD ±3.09 for eyes with ROP vs. mean +2.42 Dsfr.; SD ±2.11 for eyes without ROP]. Birth weight ($p = 0.01$) and gestational age ($p = 0.048$) correlated with changes in spherical refraction in children with ROP. There were statistically significant differences in high myopia ($p = 0.041$), low myopia (p = 0.010) and low hyperopia ($p = 0.014$) in the group of premature infants treated for ROP depending on the form of therapy.
Conclusions: There were statistically significant differences in high myopia ($p = 0.041$), low myopia ($p = 0.010$) and low hyperopia ($p = 0.014$) in the groups of premature infants with ROP and high myopia ($p = 0.019$) and low astigmatism ($p < 0.001$) in the groups treated with monotherapy or combined therapy. Birth weight ($p = 0.01$) and gestational age ($p = 0.048$) had a significant effect on refractive development in eyes with ROP.

KEY WORDS:
laser photocoagulation, anti-VEGF, retinopathy of prematurity, refractive errors.

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INTRODUCTION

According to the literature, newborns born at term show physiological hyperopia on post-cycloplegic refraction examination [1, 2], which decreases with the development and axial growth of the eyeball [3]. A meta-analysis comparing axial length (AL) measurements for a total of 6575 eyes from 27 papers published over the last 50 years confirms the aforementioned fact, indicating that the mean AL of the eyeball from the 12th to the 38th week of gestation increases by 5.1–16.2 mm, while from the 38th week of gestation to the child's 3rd year of life, this parameter changes by a value in the range 16.2–21.8 mm, according to data obtained in a group of 2272 eyes of preterm infants and 4303 eyes of term children [4]. The cited authors conclude that the increase in the AL of the eyeball is not linear, and according to the drawn curve, the rate of increase in the AL of the eyeball begins to decrease at around 30 weeks of gestation and becomes more pronounced after birth in the group of term babies [4]. On the other hand, in a preterm infant born before the 38th week of gestation, a premature change in environmental conditions contributes to a slower rate of growth of the AL of the eyeball, and a shorter eyeball shows higher hyperopia compared to the lower physiological hyperopia of children born at term [5].

Prematurity is a significant risk factor for the development of retinopathy of prematurity (ROP). A study by Munro *et al*. showed that eyes with features of ROP are characterized by both delayed and abnormal axial growth of the eyeballs compared to the eyeballs in a group of term newborns. In eyes with ROP, the anterior chamber depth, posterior segment depth and AL of the eyeball were smaller, while lens thickness was greater compared to term-born babies [6]. The presented change in anatomical conditions and curvature of optical elements of the preterm eyeball with features of ROP predisposes to myopia [6, 7].

The employed therapy profile is of key importance in regard to the occurrence of refractive defects in a group of premature infants with ROP. According to the literature, myopia and astigmatism are more common in preterm infants with ROP treated with laser-diode therapy compared to preterm infants with ROP not treated with laser-diode therapy [8]. Conversely, myopia is rarely observed among those treated with anti-vascular endothelial growth factor (anti-VEGF) agents [9].

The purpose of this study was to present the prevalence of refractive status as well as the relationship between refraction, selected demographic characteristics and the method of therapy applied in a group of premature children with ROP.

MATERIAL AND METHODS

The study group consisted of 152 prematurely born children evaluated during screening for the development of ROP and treated at the Department of Ophthalmology of the Pomeranian Medical University in Szczecin 2019–2021. The retrospective study was conducted based on the information from the patients' medical records. Thirty-three children were excluded from the follow-up for the following reasons: lack of continuity of ophthalmologic examinations (n = 10 children), lack of a proper age parameter value, which was one of the assumptions for performing ophthalmologic analyses (n = 10) at the time of the study, improperly managed medical records (n = 13). Finally, 119 children participated in the study – 56 children without features of ROP, including 24 boys (42.86%) and 32 girls (57.14%), and 63 children with features of ROP, including 33 boys (52.38%) and 30 girls (47.62%).

A detailed ophthalmologic evaluation and fundus examination were performed with the Ret-CAM 3 device, which allowed us to determine the stage of ROP3 and aggressive ROP type (A-ROP) lesions with symptoms plus retinal activity for each of the 126 eyes in the group of 63 premature infants with ROP according to the International Classification of ROP Lesions [10] (Table 1).

In the study group, treatment in the group of children with advanced ROP was carried out in accordance with the guidelines of the Polish Ophthalmological Society using a diode laser (IRIDEX IQ 810) and an anti-VEGF injectable (ranibizumab, Lucentis) in monotherapy or combined therapy [11]. Ranibizumab was administered at a dose of 0.18 mg/0.18 ml in a group of premature infants with a birth weight < 1500 g, in an aggressive form of A-ROP (features of zone I disease; ROP 3 and plus disease; features of rubeosis iridis with features of anterior and posterior ocular hypoxia in the course of ROP) or in the absence of favorable results after diode laser treatment [12]. Eyes with features of ROP were sorted based on the treatment methods used (Table 2).

Routine refractive examination was performed at an average of 7 months of the children's chronological age. Refraction measurements were taken with a hand-held autorefractometer (Retinomax) assessing the refraction of the eye from a distance of about 5–10 cm (at close range) after cycloplegia (1% tropicamide solution administered 3 times at 15-minute intervals), and the eye

TABLE 1. Stage of clinical progression of retinopathy of prematurity lesions among premature infants studied

ROP stage	1	2	3	4	5	A-ROP
Eyes, *n* (%)	2 (1.59%)	22 (17.64%)	68 (53.97%)	0 (0%)	2 (1.59%)	32 (25.4%)

A-ROP – aggressive form of retinopathy of prematurity, n – number of eyes with clinically confirmed ROP stage, ROP stage – degree of retinopathy of prematurity, % – percentage of eyes with ROP

TABLE 2. Analyzed demographic characteristics of the studied groups of premature infants with and without retinopathy of prematurity

Analyzed characteristics	Infants with ROP	Infants without ROP	*p*-value
Number of newborns	63	56	
Sex			0.299
Male	30 (47.62%)	32 (57.14%)	
Female	33 (52.38%)	24 (42.86%)	
Mean gestational age (weeks)	26.738 (±1.46)	30.1607 (±2.1)	< 0.001
Mean birth weight [g]	915.4 (±317.81)	1416.7 (±284.8)	< 0.001
Pregnancy			0.421
Single	48 (76.19%)	39 (69.64%)	
Multiple	15 (23.81%)	17 (30.36%)	
Birth			0.115
Vaginal	51 (80.95%) C	51 (91.07%) C	
Cesarean	12 (19.05%) V	5 (8.93%) V	
Mean Apgar score	5.54 (±1.62)	7.06 (±1.55)	< 0.001

ROP – retinopathy of prematurity

examination was performed 1 hour after administration. Depending on the measurement values obtained, the refractive status of each eye was defined as normal vision [refractive range of –0.5 to 0.5 spherical diopters (Dsfr.)], myopia (< –0.5 Dsfr.), hyperopia (> +0.5 Dsfr.) and astigmatism [> 0.75 cylindrical diopters (Dcyl.)] [13].

According to the recommendations of the American Academy of Ophthalmology, refractive defects were defined as high myopia (≥ –6 Dsfr.), moderate myopia (–3 to –6 Dsfr.), low myopia (–0.5 to –3 Dsfr.), low (+0.5 to +3 Dsfr.), moderate (+3 to +6 Dsfr.) and high (≥ +6 Dsfr.) hyperopia, and low (0.75 to 3 Dsfr.) and high (> 3 Dcyl.) astigmatism [14].

STATISTICAL ANALYSIS

The Statistica system (version 13.3; TIBCO Software Inc., USA) was used to perform all data analyses. The χ^2 test and Yates's χ^2 test were used to test for group difference in categorical data, while the Mann-Whitney *U* test and Mood's median test were used for continuous data. Normality analyses were performed by means of the Shapiro-Wilk test or the Lilliefors test. Levene's test was used to test the homogeneity of group variances.

Association between groups was determined by Spearman's rank correlation coefficient rho. Continuous data are presented as mean ±SD (standard deviation) (with a 95% confidence interval – CI) and categorical data are expressed as numbers (with percentages). *P*-values below 0.05 were considered statistically significant.

RESULTS

The birth age of the preterm children studied varied between 26 and 32 weeks (mean: 26.74 weeks, ±1.46), compared to the control group: 22–31.5 weeks (mean 30.16 weeks, ±2.1). Medical indications for early termination of pregnancy in the group of preterm infants included multiple pregnancy, preterm labor in progress, premature rupture of fetal membranes, placental dysfunction, pre-eclampsia and intrauterine infection, among others. Most of the newborns (n = 102, 85.7%) were delivered by cesarean section. Birth weight in the group of babies with ROP was between 740 and 1950 g (mean: 915.4 g, ±317.81), while in the group of premature babies without ROP it ranged between 400 and 1900 g (mean: 1416.7 g, ±284.8). There was a mean Apgar score of 5.54 (±1.62) for preterm infants diagnosed with ROP and a mean Apgar score of 7.06 (±1.55) for preterm infants without features of retinopathy. Mechanical ventilation was used for respiratory distress and respiratory failure in a group of 50 premature infants with ROP (79.37%) and in a group of 29 premature infants without ROP (51.79%). Ventilation was carried out in modes: SNIPPV, SIMV, HFO, HFNC. Among 68 subjects (57.14%), systemic steroid therapy was administered, mainly due to bronchopulmonary dysplasia, the frequency of which, in the group of preterm infants with ROP, was almost 4 times higher than in the group of preterm infants without features of retinopathy.

Refraction was measured in 119 newborns, constituting one group of 56 healthy preterm infants and one group of 63 preterm infants with ROP. The study noted a fairly wide range of values obtained, ranging from –1.75 to +6.25 Dsfr. (mean +1.33 Dsfr., ±3.09) for eyes with ROP features and from –5.0 to +7.25 Dsfr. (mean + 2.42 Dsfr., ±2.11) for eyes of premature infants without ROP features.

High myopia ($p = 0.019$) and low astigmatism ($p < 0.001$) were significantly more common in the group of prema-

TABLE 3. Refractive defects of eyes with retinopathy of prematurity and eyes without retinopathy of prematurity

Refractive error	Eyes with ROP	Eyes without ROP	*p*-value
High myopia, *n* (%)	12 (9.52)	6 (5.36)	0.019
Moderate myopia, *n* (%)	4 (3.17)	2 (1.79)	0.495
Low myopia, *n* (%)	6 (4.76)	0 (0)	0.225
Low hyperopia, *n* (%)	62 (49.2)	49 9 (43.75)	0.399
Moderate hyperopia, *n* (%)	30 (23.8)	42 (37.5)	0.031
High hyperopia, *n* (%)	5 (3.97)	6 (5.36)	0.421
Low astigmatism, *n* (%)	110 (87.3)	48 (42.86)	< 0.001
High astigmatism, *n* (%)	7 (5.56)	2 (1.76)	0.269

ROP – retinopathy of prematurity

TABLE 4. Ocular refractive status in groups of children treated with different therapeutic regimens – premature infants with and without retinopathy of prematurity features (ranibizumab, diode laser retinal panphotocoagulation, ranibizumab and diode laser panphotocoagulation)

Group	Eyes with ROP without treatment	Eyes with ROP treated with ranibizumab	Eyes with ROP treated with panphotocoagulation with laser-diode laser	Eyes with ROP treated with ranibizumab and panphotocoagulation with laser-diode laser	Eyes without ROP
Myopia, *N* (%)	0 (0)	2 (25)	2 (3.7)	18 (39.13)	8 (7.14)
Low, *n*	0	0	2	10	6
Moderate, *n*	0	1	0	3	2
High, *n*	0	1	0	5	0
Emmetropia, *n* (%)	1 (5.56%)	0 (0%)	3 (5.56%)	3 (6.52%)	7 (6.25%)
Hyperopia, *N* (%)	17 (94.44)	6 (75)	49 (90.74)	25 (54.35)	97 (86.6)
Low, *n*	13	2	32	15	49
Moderate, *n*	4	4	14	8	42
High, *n*	0	0	3	2	6
Astigmatism, *N* (%)	16 (88.89)	8 (100)	49 (90.74)	44 (95.65)	80 (71.43)
Low, *n*	15	8	47	40	78
High, *n*	1	0	2	4	2

ROP – retinopathy of prematurity

ture infants with ROP compared to the group of children without ROP. Moderate hyperopia ($p = 0.031$) was significantly more common in the group of premature infants without ROP compared to the group of children with ROP. The prevalence of refractive defects is shown in Table 3.

Children with ROP were divided into 4 study groups according to the treatment method used (Table 4). In severe ROP, combination therapy was required, employing laser photocoagulation with intravitreal injections, which was performed in 23 children (group 4, $n = 46$, 43%). In this group, myopia was confirmed in 39.13% of children ($n = 18$); hyperopia in 54.34% of newborns ($n = 25$) and astigmatism in 95.98% of premature babies ($n = 44$).

Subsequently, we analyzed the gestational age and birth weight of the children studied to assess the relationship with eye refraction. In the group of children with ROP, we found a significant correlation between gestational age and birth weight and refraction expressed in Dsfr. ($p = 0.01$ and $p = 0.048$, respectively) compared to preterm children without ROP ($p = 0.21$ and $p = 0.845$, respectively). We observed no significant association between the values of both gestational age and birth weight in relation to astigmatism in either the study group ($p = 0.311$ and $p = 0.326$) or the control group ($p = 0.579$ and $p = 0.481$). Additionally, no such association was found between refraction and the Apgar scale in premature infants with ROP (association of Apgar score/Dsfr. $p = 0.522$ and Apgar score/Dcyl. $p = 0.383$) or healthy children (association of Apgar score/ Dsfr. $p = 0.262$ and Apgar score/Dcyl. $p = 0.502$).

The analysis showed a statistically significant difference in the incidence of high myopia between the groups of premature infants with ROP who received different therapies ($p = 0.041$). High myopia was most common in the ROP group treated with anti-VEGF agents, fol-

lowed by the group undergoing combination therapy. In the group of premature infants treated by laser, high myopia was not recorded.

There was also a significant difference in the incidence of low myopia between the groups of premature infants treated with each method ($p = 0.010$). Low myopia was most common in the group undergoing combination therapy, followed by the group treated by laser. In the group of premature infants treated with anti-VEGF, low myopia was not recorded.

The incidence of low hyperopia showed a difference between the groups of premature infants treated with the aforementioned therapies ($p = 0.014$). Low hyperopia was most common in the group treated by laser, followed by the combined therapy group. The smallest percentage of patients with low hyperopia was observed in the group treated with anti-VEGF preparations.

There were no statistically significant differences in the incidence of moderate myopia ($p = 0.089$), moderate hyperopia ($p = 0.124$), high hyperopia ($p = 0.778$), low astigmatism ($p = 0.497$) and high astigmatism ($p = 0.430$) between the groups of premature infants treated with each method.

The number of coagulations performed with the diode laser in the retina did not correlate with changes in spherical ($p = 0.403$) and cylindrical ($p = 0.809$) refraction.

DISCUSSION

The main clinical risk factors for the development of ROP, i.e. low birth weight and low gestational age, have a direct impact on the incidence of refractive defects among the group of prematurely born children [3, 15, 16]. Similarly to the aforementioned authors, in regard to their study on the group of children with ROP, we also found a significant correlation between gestational age and birth weight in relation to refraction expressed in Dsfr. ($p = 0.01$ and $p = 0.048$, respectively) compared to preterm children without ROP ($p = 0.21$ and $p = 0.845$, respectively). We observed no significant association between gestational age and birth weight in relation to astigmatism in either the study group ($p = 0.311$ and $p = 0.326$) or the control group ($p = 0.579$ and $p = 0.481$). Additionally, no significant correlation between refraction and the Apgar scale was found either in premature infants with ROP (association of Apgar score/Dsfr. $p = 0.522$ and Apgar score/Dcyl. $p = 0.383$) or in healthy children (association of Apgar score/Dsfr. $p = 0.262$ and Apgar score/Dcyl. $p = 0.502$). This observation differs from the results of the authors Uprety *et al.*, who noted a correlation between myopia and low fetal age (Hbd) in premature infants without ROP features, and a lack thereof between Hbd week and astigmatism as well as a negative correlation of Hbd with birth weight [17]. In our study in the group of preterm infants without ROP, we found no correlation between gestational age and refraction expressed in Dsfr. and no association between gestational age and birth weight in preterm infants without ROP. We published similar findings in an earlier article indicating that there was no correlation between gestational age and birth weight in relation to myopia in children without ROP, and a significant association between hyperopia and birth weight in this group of children [18].

In contrast to the results of Uprety *et al.* we did not detect an association between astigmatism and birth weight [17]. It is possible that this is due to differences in the criterion of birth weight for inclusion in the study and the small number of children evaluated, with our group also having analyzed children with extremely low birth weight ($n = 12$ eyes, 6 newborns and $n = 2$ eyes, 1 newborn). This cannot be said about the study of Uprety *et al.*, where none of the 36 newborns included in the study showed such low birth weight [17]. According to Zhu *et al.*, low gestational age and low birth weight correlated with astigmatism in a group of children with ROP (42.85%) [15], which the results of our study did not confirm. However, astigmatism was more than twice as common in the group with ROP (92.86% ($n = 117$), including: low astigmatism 87.3% ($n = 110$) and high astigmatism 5.56% ($n = 7$). Unlike the aforementioned authors, Mao *et al.* did not observe an effect of gestational age and birth weight on the overall refractive status of the eyes of both premature infants with ROP as well as without ROP [19].

Prematurity is a significant risk factor for the development of ROP. Detection of clinically active ROP requires implementation of treatment within 72 hours, and the gold standard for effective therapy is retinal panphotocoagulation with a diode laser or the intravitreal injection of an anti-VEGF preparation in monotherapy or combined therapy, which is crucial for future vision quality. In their study, Sathar *et al.* evaluated the ocular refractive status of 798 premature infants ($n = 1596$), of whom 25% ($n = 398$) developed ROP [20]. Similarly to our results, the authors observed myopia in 19.85% ($n = 79$) of the group of children with ROP. The results of the studies differed in the prevalence of astigmatism and hyperopia. In the study by Sathar *et al.*, astigmatism developed in 60.55% ($n = 241$) of eyes with ROP and 54.05% ($n = 647$) of eyes without ROP. In our study, those proportions assumed the values of 76.98% ($n = 97$) and 71.43% ($n = 80$) respectively, with low astigmatism found among 87.3% ($n = 110$) and high astigmatism among 5.56% ($n = 7$). Low astigmatism was significantly more common in the group with ROP ($p < 0.001$). In the population studied by Sathar *et al.*, hyperopia occurred in 8.54% ($n = 34$) of eyes of patients with ROP and 5.16% ($n = 62$) of healthy eyes without ROP [20]. In the results reported in our article, the figures were 76.98% and 86.6%, respectively, with low hyperopia at 49.2% ($n = 62$), moderate hyperopia at 23.8% ($n = 30$) and high hyperopia at 3.97% ($n = 5$). Our study indicates a significantly higher prevalence of moderate hyperopia in the group without

ROP ($p = 0.031$), which is physiological refraction in this group of children. It is possible that refractive status was also related to the age at which the eye examination was performed, i.e. 7 months of life for children with ROP and 8 months of life for children without ROP in the authors' study. This is in contrast to the results of Sathar *et al*., who performed refractive assessment in premature infants at their chronological age of 15 months. Also, the observations of Semeraro *et al*. noted a reduction in hyperopia and astigmatism in infants 6–12 months of age [3]. Differences in the prevalence and value of refractive defects may also have been related to the period of the child's life when the measurements were made, as well as to the different cycloplegic drugs used in the studies. The use of other optometric tools to assess refractive status may also have played a role in the differing readings of refractive status.

According to the literature, there exists a significant association between refraction and ROP therapy. A study by Tiryaki *et al*. compared the influence of several ROP treatments (anti-VEGF therapy, laser panphotocoagulation therapy, and combination therapy) on refractive status. They noted significant differences in the association between various forms of treatment and spherical power and no relationship with cylindrical refractive status or incidence of myopia [21]. Other authors have emphasized the extent of the area of the sclerosed retina and a longer period of ROP regression as risk factors for myopia in patients undergoing laser therapy [22, 23]. Long-term observations by Anilkumar *et al*. indicate that myopia correlates with an increase in the AL of the eyeball [24]. According to publications by other authors, an important risk factor for myopia among preterm children is the severity of ROP-type lesions, including A-ROP [25, 26]. In the population we studied with A-ROP, no predominance of myopia over other refractive defects was observed. Inoue *et al*. suggested that the number of laser coagulations performed may positively correlate with the degree of myopia in children undergoing laser therapy [27]. In our study, the number of retinal laser coagulations did not correlate with changes in spherical ($p = 0.403$) and cylindrical ($p = 0.809$) refraction. In the study of the aforementioned authors, the procedure was performed using laser energy power of 150–300 mV for 0.3 seconds, while our operator used a higher laser power, in the range 250–590 mV for 0.3–0.6 seconds, which may indicate other unevaluated risk factors affecting the development of myopia in this group of premature infants. We find confirmation of our theory in other publications [28, 29]. In our study population, there was no correlation between the product of power and time and the development of spherical refractive defects of myopia or hyperopia ($p = 0.094$); nor was there any correlation between the aforementioned parameters and astigmatism expressed in Dcyl. ($p = 0.23$). The results of the meta-analyses available in the publications indicate that laser therapy leads to a higher risk of myopia compared to anti-VEGF injectable therapy, which was not confirmed in our study [9]. Geloneck *et al*. explain this difference as the effect of therapy on the development of the anterior segment of the eye, focusing on the development of this segment after injection or lack thereof after laser therapy [30]. In our study, we noted a statistically significant difference in the occurrence of high myopia between the groups of patients treated with the aforementioned methods. In our study, high myopia was most common in the group treated with anti-VEGF injections. In the group of patients treated by laser, high myopia was not recorded. Low myopia was more common in the group treated by laser. Moreover, low myopia was not recorded in the group of premature babies treated with anti-VEGF preparations. There was also no statistically significant difference in the incidence of moderate myopia between the groups of premature infants treated with the above-mentioned methods and those used in our study.

Currently, ranibizumab (Lucentis) is the only available on-label formulation for the treatment of severe forms of ROP, including A-ROP. However, the vast majority of publications analyzing refractive status focus on bevacizumab [9]. The authors of this paper used ranibizumab (Lucentis) in the treatment of severe forms of ROP and A-ROP, which was administered intravitreally at a dose of 0.18 mg/0.18 ml. The dose reduction allowed the regression of ROP, the achievement of physiological retinal vascularization in a short period of time and normal ocular development with a reduction in myopic refraction in the analyzed eyes. Furthermore, low doses of the drug probably reduced systemic exposure to the drug, which seems to be beneficial given the unknown long-term effects of anti-VEGF therapy [31].

In severe forms of ROP, combination therapy is sometimes required, combining laser photocoagulation with intravitreal injections [22]. The incidence of high and low myopia in the group where combined therapy (diode laser and anti-VEGF) was used is higher compared to the group treated with diode laser panphotocoagulation monotherapy. A possible reason for this may be the severity of active retinal vascular lesions of ROP ($n = 22$) in up to 68.37% of patients diagnosed with A-ROP and a greater extent of retinal laser ablation. Ittarat noted that the use of an anti-VEGF preparation prior to laser therapy for eyes with A-ROP allows faster regression and the use of fewer laser foci compared to laser monotherapy, limiting the development of myopia [32]. Laveti *et al*. also observed that administering anti-VEGF injections before laser panphotocoagulation yields better results than performing the therapy in reverse order [22].

It should be noted that in the literature there are few data on the association between the occurrence of myopia and the use of intravitreal ranibizumab, and most of the papers refer to bevacizumab and diode-laser. The results of the studies by Kimyon *et al*. [33] and

Chen *et al.* [34, 35] indicate a higher incidence of myopia in premature infants treated with bevacizumab (IVB) compared to ranibizumab (corrected 1 year of age 14.6% IVB vs. 0.0% IVR, as well as at 3 years of age (16.7% vs. 0.0%). In contrast, another study found no difference regarding myopia between IVB and IVR at a corrected age of 3 years [36]. Compared to laser, a higher incidence of high myopia was observed in infants for ROP in zone I, in the laser group compared to IVR and IVB groups [36]. The age of the ophthalmological examinations performed, the type of drugs used to paralyze accommodation and the type of device used for measurements seem to be important. Retinomax is a manual auto-refractor that examines refraction from a distance of about 5 cm in front of the eye, which causes myopization of the results due to reflex pupillary constriction and convergence. The younger the age of the subjects, the greater are the tension of accommodation and the lowering of the refractive measurement results. Tropicamide, due to the greater aspect of respiratory and neurological safety in premature infants compared to cyclopentolate, is a drug that affects accommodation less and that also lowers the refractive index, as we have already highlighted earlier [13].

So our observations, although slightly different from others in the literature, may suggest that low hyperopia in laser-treated children is probably an early stage leading to myopia later in life. The Retinomax method, which uses close examination distance, may affect the results of lower hyperopia in the group of examined children. Familial factors of myopia are important for the future refraction of children.

A limitation of our study is the lack of measurements of the refractive status of the eyes in the group of preterm infants before treatment and between laser-diode and anti-VEGF combination therapy procedures. In the future, we will try to answer the question of whether the use of anti-VEGF in combination therapies with laser therapy can affect the refractive status of this group of premature infants. Additionally, familial and genetic factors were not taken into account when interviewing all parents of treated children.

CONCLUSIONS

The presence of a statistically significant difference in the incidence of high myopia, moderate hyperopia and low astigmatism between the group of premature infants with and without ROP was confirmed. Birth weight and gestational age had a significant effect on the recorded refractive changes in the study group of children with ROP. Apgar scale score had no significant effect on refractive status in the group of premature children with and without ROP. The presence of statistically significant differences in the incidence of high myopia, low myopia and low hyperopia between groups of premature infants undergoing different therapies for ROP was confirmed. In our study, the number of laser coagulations in the retina did not correlate with changes in spherical and cylindrical refraction; however, it was found that the age of the ophthalmological examination, the type of drug used to assess refraction and the measuring device at close range could have influenced the obtained refraction results in groups of premature children.

DISCLOSURE

The authors declare no conflict of interest.

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