UOT: 617.735-053.32

Kazımova L.Ə., Rüstəmxanlı A.M.

VAXTINDAN ƏVVƏL DOĞULMUŞLARIN AQRESSİV RETİNOPATİYASINDA TƏKRARLANAN İNTRAVİTREAL ANTİ-VEGF TERAPİYASININ UZUNMÜDDƏTLİ NƏTİCƏLƏRİ (KLİNİK HAL)

Saf Hospital, Bakı, Azərbaycan

Korrespondensiya üçün:
Kazımova Leyda Əhməd qızı, SAF Hospital, cərrah-oftalmoloq.
E-mail: dr.oftkaf@mail.ru
https://orcid.org/0009-0004-4682-2410

İstinad üçün:
Kazımova L.Ə., Rüstəmxanlı A.M. Vaxtından əvvəl doğulmuşların aqressiv retinopatiyasında təkrarlanan intravitreal anti-VEGF terapiyasının uzunmüddətli nəticələri (klinik hal). Azərbaycan Oftalmologiya Jurnalı, 2026, 18; 2 (57): 00-00. (İngilis dilində).

Müəlliflərin iştirakı:
Tədqiqatın anlayışı və dizaynı: Kazımova L.Ə.
Materialın toplanması və işlənməsi: Kazımova L.Ə., Rüstəmxanlı A.M.
Statistik məlumatların işlənməsi: Kazımova L.Ə., Rüstəmxanlı A.M.
Mətnin yazılması: Kazımova L.Ə.
Redaktə: Kazımova L.Ə.

Müəlliflər münaqişələrin (maliyyə, şəxsi, peşəkar və digər maraqları) olmamasını təsdiqləyirlər.

Daxil olmuşdur 30.03.2026
Çapa qəbul olunmuşdur 22.06.2026

https://

XÜLASƏ

Vaxtından əvvəl doğulmuşların aqressiv retinopatiyası (AP-ROP) sürətlə proqressivləşən forması olub, zamanında müalicə edilmədikdə əlverişsiz anatomik və görmə nəticələrinin inkişafı ilə bağlı yüksək risk daşıyır.

Damar endotel böyümə faktoru əleyhinə (anti-VEGF) müalicəsi AP-ROP-un müalicəsində mühüm terapevtik üsullardan birinə çevrilmişdir. 30 gün fasilə ilə tətbiq edilmiş iki intravitreal anti-VEGF inyeksiyası ilə müalicə olunmuş AP-ROP olan bir uşaqda uzunmüddətli struktur və funksional nəticələri təqdim edirik. Müalicə nəticəsində "plus" xəstəliyi və neovaskulyar aktivliyin sürətli geriləməsi müşahidə olunmuş, ardınca isə tor qişanın damarlarının tədricən fizioloji vaskulyarizasiyası baş vermişdir. Altı yaşına qədər aparılan uzunmüddətli müşahidə xəstəliyin tam reqressiyasını göstərmiş, maksimal korreksiya olunmuş görmə itiliyi (MKGİ) 1,0 (logMAR 20/20) olmuşdur.

Optik koherens tomoqrafiyası (OKT) zamanı, xarici hüdudi membran (XHM) və ellipsoid zonası (EZ) daxil olmaqla, xarici tor qişa təbəqələrinin zədələnməsi və daxili retinal arxitekturunda yalnız kiçik dəyişikliklər müşahidə edildi. Bu klinik hal aqressiv ROP zamanı vaxtında aparılmış anti-VEGF müalicəsi nəticəsində uzunmüddətli əlverişli anatomik və funksional nəticələrin əldə olunma potensialını göstərir.

Açar sözlər: *vaxtından əvvəl doğulmuşların aqressiv retinopatiyası, optik koherens tomoqrafiyası, xarici hüdudi membran, tor qişanın inkişafı*

UOT: 617.735-053.32

Kazimova L.A. Rustamkhanli A.M.

LONG-TERM RESULTS OF REPEATED INTRAVITREAL ANTI-VEGF TREATMENT FOR AGGRESSIVE RETINOPATHY OF PREMATURITY (CLINICAL CASE)

Saf Hospital, Baku, Azerbaijan

For correspondence:
Kazimova Leyda Ahmad,
Surgeon Ophthalmologist,
SAF Hospital.
E-mail: dr.oftkaf@mail.ru
https://orcid.org/
0009-0004-4682-2410

For citation:
Kazimova L.A,
Rustamkhanli A.M.
Long-term results of repeated intravitreal anti-VEGF treatment for aggressive retinopathy of prematurity (clinical case).
Azerbaijan Journal of Ophthalmology,
2026, 18; 2 (57): 00-00.

Authors participation:
Concept and design of investigation:
Kazimova L.A,
Material collection and processing:
Kazimova L.A, Rustamkhanli A.M.
Statistical data processing:
Kazimova L.A, Rustamkhanli A.M.
Spelling text:
Kazimova L.A
Editing:
Kazimova L.A.

The authors confirm that there are no conflicts (financial, personal, professional and other interests).

Received 30.03.2026
Accepted 22.06.2026

https://

SUMMARY

Aggressive posterior retinopathy of prematurity (AP-ROP) represents a rapidly progressive form of retinopathy of prematurity (ROP) associated with a high risk of unfavorable structural and visual outcomes if not treated promptly.

Anti-vascular endothelial growth factor (anti-VEGF) therapy has become an important therapeutic option for posterior and aggressive forms of ROP. We report the long-term structural and functional outcome in a child with aggressive ROP treated with two intravitreal anti-VEGF injections administered with a 30-day interval. The treatment resulted in rapid regression of plus disease and neovascular activity, followed by gradual physiological retinal vascularization. Long-term follow-up until the age of 6 years revealed complete regression of the disease, with best-corrected visual acuity (BCVA) 1.0 (logMAR 20/20).

Optical coherence tomography (OCT) demonstrated preserved retinal stratification with intact outer retinal layers, including the external limiting membrane (ELM) and ellipsoid zone (EZ), with only subtle variations in inner retinal architecture. This case highlights the potential for favorable long-term anatomical and functional outcomes following timely anti-VEGF therapy in aggressive ROP.

Key words: *aggressive retinopathy of prematurity, optical coherence tomography, external limiting membrane, retinal development*

Retinopathy of prematurity remains one of the major causes of childhood blindness worldwide despite advances in neonatal care and screening programs. Improved survival of extremely premature infants has increased the population at risk of developing severe forms of ROP [1].

Aggressive retinopathy of prematurity represents a rapidly progressive variant characterized by posterior pole involvement, prominent plus diseases, and flat neovascularization without a clearly defined ridge [2].

Historically, peripheral retinal ablation using laser photocoagulation has been considered the standard treatment for severe ROP following the Early Treatment for Retinopathy of Prematurity (ETROP) study [3]. However, laser therapy causes destruction of peripheral avascular retina and may influence visual field and refractive development.

Intravitreal anti-VEGF therapy has emerged as an alternative strategy because it suppresses pathological angiogenesis while allowing continued physiological vascularization of the retina [4].

Optical coherence tomography has enabled detailed assessment of retinal microstructure in children born prematurely. Previous studies have demonstrated delayed foveal maturation, persistence of inner retinal layers, and increased central retinal thickness in these patients [5].

The integrity of outer retinal layers such as the ELM and EZ correlates strongly with photoreceptor function and visual acuity [6].

Case Presentation

A male infant was born by cesarean section at 26 weeks of gestation with a birth weight of 650g. The baby's twin did not survive. A premature infant was born at the Educational Surgical Clinic of Azerbaijan Medical University (AMU). The baby suffered from neonatal sepsis and apnea that required a stay at the neonatal intensive care unit (NICU) for 81 days. Supplemental oxygen was administered to the baby for 26 days. Blood transfusions were performed twice. The initial fundus examination was performed at 30 weeks due to the infant's general condition. The fundus examination was assessed as follows: fundus zone 1, pale optic disc, abnormal-sized vessels, and zones 2 and 3 avascular. The ophthalmologist noted a poorly dilating pupil, a small zone of vascularization, and dilated, tortuous vessels at the posterior pole, suggestive of zone 1 AP-ROP. (**Figure 1 - 3**). The second examination was conducted at 32 weeks. Following a platelet transfusion, the fundus condition worsened, with opacification of the vitreous body and slowed vascular growth, but no pathological vessels were observed. The next screening was conducted at 34 weeks. A neonate received intravitreal bevacizumab in both eyes at 34 weeks PMA for AP-ROP (zone 1 atypical stage 3 with plus disease). Weak mydriasis due to neovascularization of the iris. Zone 1: dilated and tortuous vessels characteristic of plus disease. The process was reactivated until the formation tunica vasculosa lentis in both eyes (**Figure 4**). Recurrence was noted at 38 weeks PMA in both eyes; a second injection of bevacizumab was administered.

The procedure was performed under sterile conditions after instilling 0.5% proparacaine as a topical anesthetic and 5% povidone-iodine (Betadine; Alcon) for antisepsis. To achieve the 0.03-mg dose, the hospital pharmacy diluted the standard 25 mg/ml bevacizumab to 1.0 mg/ml in sterile saline, and 0.03 ml of this solution was injected 1.0 mm posterior to the limbus using a 1.0-ml syringe with a 30-gauge needle. Fundus examination revealed aggressive retinopathy of prematurity with posterior pole involvement, marked vascular dilation and tortuosity consistent with plus diseases, and flat neovascularization without a well-defined ridge.

Considering the severity and rapid progression of the disease, Intravitreal anti-

VEGF therapy was performed. The first intravitreal injection was administered under sterile operating conditions using pediatric ophthalmic surgical protocols. Early follow-up demonstrated rapid regression of plus and neovascular activity.

Due to signs of persistent vascular activity during follow-up, a second intravitreal injection was administered 30 days after the first treatment.

Subsequent examinations demonstrated progressive regression of pathological vascular changes with gradual extension of physiological retinal vascularization toward the peripheral retina. No fibrovascular traction or retinal detachment developed during follow-up.

At the age of six years, the child underwent a comprehensive ophthalmological evaluation. Best -corrected visual acuity was 1.0, indicating normal central visual function for age. Fixation was stable, and binocular visual development was appropriate.

Fundus examination revealed a stable posterior pole with no evidence of active neovascularization or residual proliferative changes.

Optic Coherence Tomography Findings: Spectral-domain OCT imaging demonstrated well-defined retinal stratification. ELM was continuous, and EZ was preserved across the macular region, indicating intact photoreceptor architecture. The outer nuclear layer and photoreceptor layers appeared normally organized. Mild variations in the inner retinal layers and subtle irregularities in the foveal contour were observed (**Figure 5 - 6**). These findings are consistent with previously described alterations in retinal development associated with prematurity; nevertheless, the preservation of outer retinal layers correlated with the excellent visual acuity observed in this patient.

Ethics Statement

The study adhered to the principles of the Declaration of Helsinki. Written informed consent for publication of anonymized clinical information was obtained from the patient's legal guardians.

Discussion

Aggressive retinopathy of prematurity represents one of the most severe and rapidly progressive forms of ROP. It is associated with a high risk of unfavorable anatomical outcomes if treatment is delayed. The disease is characterized by pronounced vascular dilation and tortuosity, posterior pole involvement, and poorly demarcated neovascularization, reflecting an intense angiogenic response driven largely by VEGF signaling pathways [7].

The introduction of intravitreal anti-VEGF agents has significantly changed the therapeutic approach to severe ROP, particularly in cases involving posterior retinal zones. VEGF inhibition leads to rapid regression of pathological neovascularization and associated diseases, while potentially allowing physiological retinal vascularization to continue. The landmark BEAT-ROP trial demonstrated that intravitreal bevacizumab was particularly effective in zone 1 stage 3+ ROP and aggressive posterior disease, with significantly lower recurrence rates than conventional laser photocoagulation [8]. Subsequent clinical studies have confirmed the effectiveness of anti-VEGF therapy in aggressive ROP, although long-term structural retinal development after treatment remains an area of ongoing investigation [9].

One of the key advantages of anti-VEGF therapy compared with laser photocoagulation is the preservation of peripheral retinal tissue. Laser treatment results in permanent ablation of avascular retina, which may influence ocular growth, refractive outcomes, and peripheral visual fields. In contrast, pharmacologic inhibition of VEGF allows gradual continuation of physiological vascularization toward the peripheral retina, which may contribute to more normal retinal development [10].

Advances in OCT have enabled detailed

evaluation of retinal microstructure in premature infants and children with regressed ROP.

Several OCT studies have demonstrated that premature birth itself alters normal foveal development.

During normal retinal maturation, centrifugal migration of inner retinal layers and continued elongation of photoreceptor outer segments lead to the formation of the mature foveal depression. Premature birth interrupts this developmental process, frequently resulting in persistence of inner retinal layers within the foveal region and increased central macular thickness [11].

Importantly, however, structural variations in inner retinal architecture do not necessarily correlate with poor visual function. Increasing evidence suggests that the integrity of outer retinal layers plays a more critical role in determining visual outcomes. In particular, ELM and EZ represent key structural markers of photoreceptor health and function [12].

In the present case, long-term OCT evaluation performed at the age of six years demonstrated preserved retinal stratification, with an intact ELM and a clearly identifiable EZ. The outer nuclear layer and photoreceptor layers appeared well organized, indicating normal photoreceptor development. These findings correlate with the patient's excellent BCVA of 20/20. Although mild morphological variations in the configuration of the inner retinal layers were observed, these findings are consistent with previously reported structural features in children born prematurely. Dubis et al. demonstrated that incomplete migration of inner retinal layers and altered foveal contour may persist into childhood even in the absence of significant visual impairment. Similarly, Vajzovic et al. reported that children with a history of prematurity may exhibit increased central retinal thickness and persistence of inner retinal layers despite good visual acuity [13].

Another important consideration in patients treated with anti-VEGF therapy is the potential for late recurrence or persistent peripheral avascular retina.

Several studies have reported that careful long-term monitoring is required following anti-VEGF treatment, as delayed disease reactivation may occur months or even years after the initial therapy [14]. In the present case, regular follow-up examinations demonstrated stable disease regression without signs of late recurrence.

The excellent anatomical and functional outcome observed in this case may be attributed to several factors, including early diagnosis, timely initiation of therapy, and careful longitudinal monitoring. The administration of a second intravitreal injection at 30 days likely contributed to the stabilization of retinal vascular activity and the prevention of disease reactivation.

Overall, this case provides additional evidence supporting the potential for favorable long-term outcomes following anti-VEGF therapy in aggressive ROP.

The preservation of outer retinal microstructure, particularly the integrity of ELM and EZ, suggests that timely suppression of pathological angiogenesis may allow relatively normal maturation of photoreceptor layers. Correlation between visual acuity and ELM integrity.

A particularly noteworthy finding in this case is the maintenance of excellent BCVA (20/20) at 6 years of age, which closely correlates with the preserved microstructural integrity of the outer retina observed on OCT. Spectral-domain OCT demonstrated a continuous ELM and a clearly defined EZ, both indicative of intact photoreceptor architecture. The ELM is formed by adherents junctions between Müller glial cells at the photoreceptor inner segments and serves as a critical structural scaffold that maintains photoreceptor alignment, supports metabolic exchange, and stabilizes the outer nuclear layer [15].

Preservation of the ELM has been shown in multiple retinal disorders to correlate

with intact photoreceptor cell bodies and preserved outer segment organization, which are essential determinants of visual function/ In contrast, disruption or discontinuity of the ELM on OCT often predicts impaired visual acuity due to photoreceptor loss or misalignment [16].

In this patient, despite mild irregularities of the inner retinal layers reflecting developmental alterations associated with prematurity, the outer retinal architecture, including the ELM and EZ, remained intact. This structural preservation likely explains the full visual recovery, highlighting that functional visual outcomes in ROP are predominantly determined by the integrity of the outer retinal layers rather than by minor inner retinal deviations.

The observations support the concept that the ELM can serve as a reliable OCT biomarker of long-term visual potential in children treated for aggressive retinopathy of prematurity, providing both prognostic information and a mechanistic link between anatomical preservation and functional vision.

Further studies involving larger cohorts and long-term OCT monitoring are required to understand better the structural evolution of the retina after anti-VEGF treatment and to clarify the relationship between retinal microstructure and visual function in children with a history of aggressive ROP.

Conclusion

Repeated intravitreal anti-VEGF therapy administered with a 30-day interval resulted in complete regression of aggressive retinopathy of prematurity and excellent long-term visual outcome.

OCT imaging demonstrated preserved retinal microstructure, including intact outer retinal layers and ELM. Long-term OCT monitoring may provide valuable insights into retinal development after treatment for severe ROP.

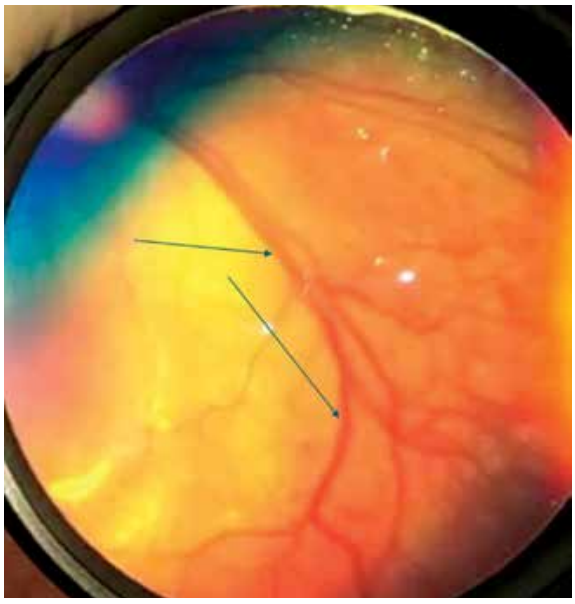

Figure 1. *Fundus photo: blue-arteriolar tortuosity, black-venular dilation.*

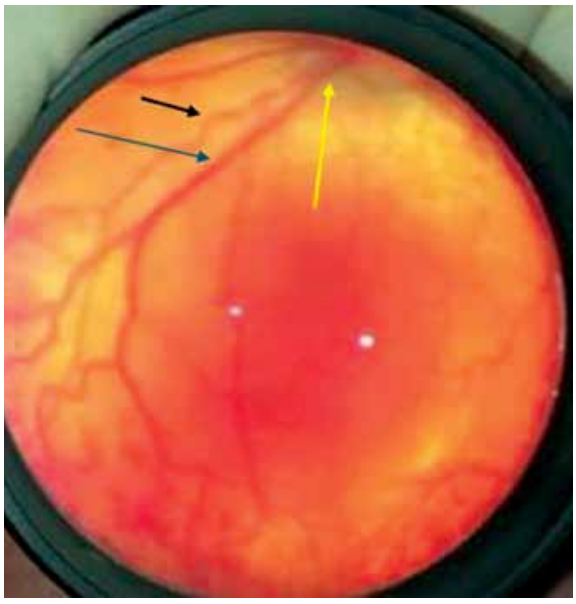

Figure 2. *Fundus photo: blue-arteriolar tortuosity, black-venular dilation, yellow-prominence of plus disease.*

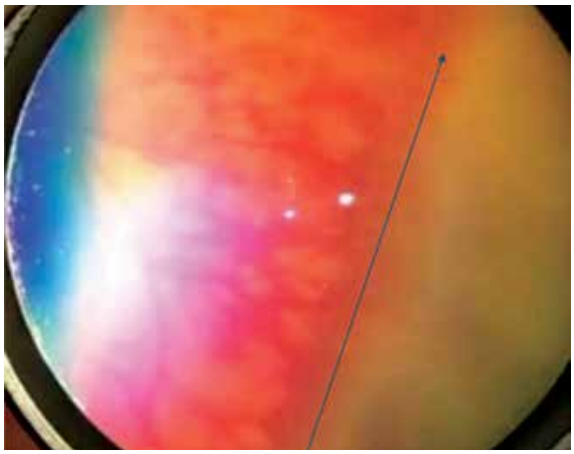

Figure 3. *Fundus photo: A clear demarcation zone separating the proliferative zone from the avascular zone. Blue-posterior disease. Stage 3 in Zone 1.*

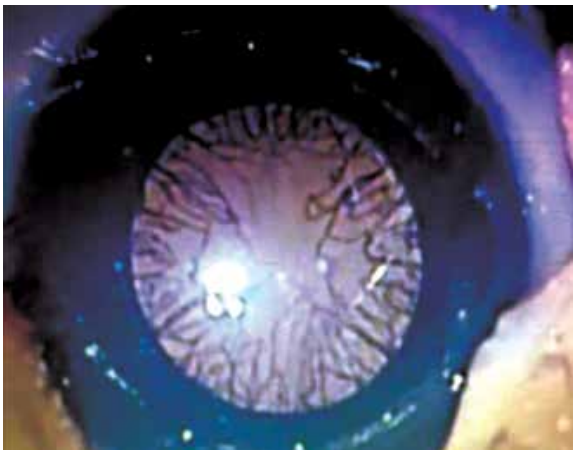

Figure 4. *Microskopic photo: Active reactivation was observed after one month of treatment. OU- Almost complete tunica vasculosa lentis.*

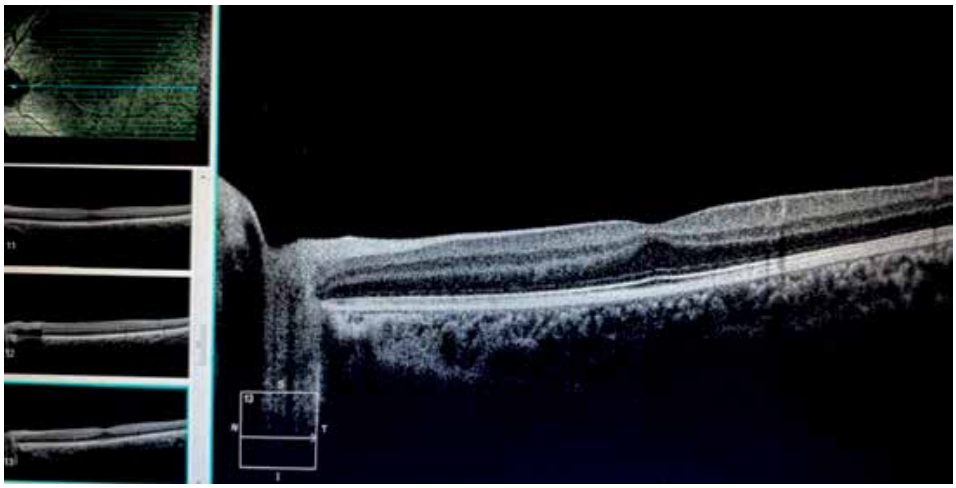

Figure 5. *OCT raster /OS – foveal depression is not formed; the indentation is minimal (orange). In the center of the fovea, it does not begin from the inner plexiform layer. Thickening of the inner retinal layers is observed, while ELM (yellow), EZ (blue), and RPE (green) are within normal limits.*

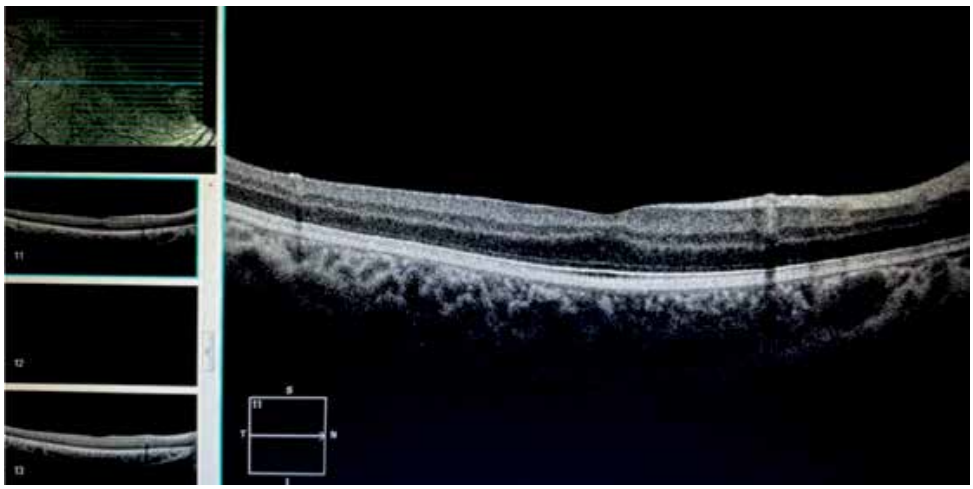

Figure 6. *OCT raster /OD – foveal depression is not formed; the indentation is minimal (orange). In the center of the fovea, it does not begin from the inner plexiform layer. Thickening of the inner retinal layers is observed, while ELM (yellow), EZ (blue), and RPE (green) are within normal limits.*

ƏDƏBİYYAT

REFERENCE

1. Rosenblatt, T.R. Key factors in a rigorous longitudinal image-based assessment of retinopathy of prematurity / T.R.Rosenblatt, M.H.Ji, D.Vail [et al.] // Sci. Rep., – 2021. Mar; 11. 1, – p. 5369. https://doi.org/10.1038/s41598-021-84723-7
2. Bellsmith, K. Aggressive Posterior Retinopathy of Prematurity / K.Bellsmith, J.Brown, S.Kim // Ophthalmology, – 2020. 127, – p. 1105-1112. https://doi.org/10.1016/j.ophtha.2020.01.052
3. Davitt, B.V. Incidence of cataract development by 6 months' corrected age in the Early Treatment for Retinopathy of Prematurity study / B.V.Davitt, S.P.Christiansen, R.J.Hardy [et al.] // J. AAPOS, – 2013. 17, – p. 49-53. https://doi.org/10.1016/j.jaapos.2012.10.011
4. Hejkal, T. Low-Dose Bevacizumab 0.03 mg for Treatment of Type 1 Retinopathy of Prematurity / T.Hejkal, S.Sinha, P.Rishi // Ophthalmol. Retina, – 2025. 9, – p. 807-811. https://doi.org/10.1016/j.oret.2025.02.009
5. Chiang, M.F. International Classification of Retinopathy of Prematurity, Third Edition (ICROP3) / M.F.Chiang, G.E.Quinn, A.R.Fielder [et al.] // Ophthalmology, – 2021. 128, 10, – p. 51-68. https://doi.org/10.1016/j.ophtha.2021.05.031
6. Hartnett, M.E. Pathophysiology and mechanisms of severe retinopathy of prematurity / M.E.Hartnett // Ophthalmology, – 2015. 122, 1, – p. 200-210. https://doi.org/10.1016/j.ophtha.2014.07.050
7. Tawfik, G.M. Comparison of intravitreal injection of ranibizumab versus bevacizumab for treatment of type 1 and aggressive retinopathy of prematurity in rural Egypt. A randomized clinical trial / G.M.Tawfik, E.A.Shahein, S.A.Dabour [et al.] // BMJ Open Ophthalmol., – 2022. Dec; 7. 1, – p. 001173. https://doi.org/10.1136/bmjophth-2022-001173
8. Kong, Q. Refractive outcomes after intravitreal injection of antivascular endothelial growth factor versus laser photocoagulation for retinopathy of prematurity: a meta-analysis / Q.Kong, W.K.Ming, X.S.Mi // BMJ Open, – 2021. 11, 2, – p. 042384. https://doi.org/10.1136/bmjopen-2020-042384
9. Eldaly, Z. Morphological Characteristics of Normal Foveal Avascular Zone by Optical Coherence Tomography Angiography / Z.Eldaly, W.Soliman, M.Sharaf [et al.] // J. Ophthalmol., – 2020. Aug; – p. 8281459. https://doi.org/10.1155/2020/8281459
10. Vajzovic, L. Maturation of the human fovea correlation of spectral-domain optical coherence tomography findings with histology / L.Vajzovic, A.E.Hendrickson, R.V.O Connell [et al.] // Ophthalmology, – 2012. 119, 12, – p. 2648-2655. https://doi.org/10.1016/j.ophtha.2012.07.018
11. Vinekar, A. Macular structure in premature infants using handheld spectral-domain optical coherence tomography / A.Vinekar, S.Mangalesh, C.Jayadev [et al.] // Am. J. Ophthalmol., – 2015. 159, 3, – p. 588-597. https://doi.org/10.1016/j.ajo.2014.12.007
12. Cuenca, N. Interpretation of OCT and OCTA images from a histological approach: clinical and experimental implications / N.Cuenca, I.Ortuno-Lizaran, X.Sanchez-Saez [et al.] // Prog. Retin. Eye Res., – 2020. 77, – p. 100828. https://doi.org/10.1016/j.preteyeres.2019.100828
13. Lujan, B.J. Directional optical coherence tomography provides accurate outer nuclear layer and henle fiber layer measurements / B.J.Lujan, A.Roorda, J.A.Croskrey [et al.] // Retina, – 2015. 35, 8, – p. 1511-1520. https://doi.org/10.1097/AE.0000000000000508
14. Ahn, S.J. Retinal Thickness Analysis Using Optical Coherence Tomography: Diagnostic and Monitoring Applications in Retinal Diseases / S.J.Ahn // Diagnostics, – 2025. Mar; 15. 7, – p. 833. https://doi.org/10.3390/diagnostics15070833
15. Fragiotta, S. Significance of Hyperreflective Foci as an Optical Coherence Tomography Biomarker in Retinal Diseases: Characterization and Clinical Implications / S.Fragiotta, S.Abdolrahimzadeh, R.Dolz-Marco [et al.] // J. Ophthalmol., – 2021. – p. 1-10. https://doi.org/10.1155/2021/6096017
16. Miki, A. The OCT findings of macula and associated factors in patients with a history of retinopathy of prematurity / A.Miki, S.Honda, Y.Matsumoto [et al.] // Invest. Ophthalmol. Vis. Sci., – 2015. 56, 7, – p. 950.