Original Article

Peripapillary Retinal Nerve Fiber Layer Thickness Changes in Preterm Children with or without Retinopathy of Prematurity History

Siamak Zarei-Ghanavati[1], Hadi Ostadimoghaddam[2], Marzieh Najjaran[3], Nasser Shoeibi[1], Mohammed Ziaei[4]

[1]Eye Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [2]Refractive Errors Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [3]Department of Optometry, School of Paramedical Sciences and Rehabilitation, Mashhad University of Medical Sciences, Mashhad, Iran, [4]Department of Ophthalmology, New Zealand National Eye Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Abstract

Purpose: To investigate peripapillary retinal nerve fiber layer (pRNFL) thickness changes in preterm children with or without retinopathy of prematurity (ROP) history compared to full-term children.

Methods: A retrospective comparative cohort study assessing pRNFL thickness was completed in children aged 4–8 years. Four groups of children were included (n = 30 each group): children with a history of ROP who were treated with intravitreal bevacizumab, children with ROP who received no treatment, and preterm children without ROP compared to age- and gender-matched full-term children.

Results: A total of 120 eyes from 120 children were enrolled in this study. Both treated and regressed ROP children showed a significantly thinner pRNFL in the nasal quadrant compared to full-term children (P = 0.017 and P = 0.008, respectively). The pRNFL in the superior quadrant of treated ROP children was thinner than the preterm and control groups (P = 0.015 and P = 0.023, respectively), whereas the inferior quadrant of treated ROP children was thinner than the preterm group alone (P = 0.008). The pRNFL thickness in the temporal quadrant was comparable between groups (P = 0.129). The average spatial distribution profile of pRNFL thickness in treated ROP children was significantly thinner than in the preterm group (P = 0.041).

Conclusion: pRNFL thickness is significantly altered in children with a prior history of treated ROP with thinning of the nasal and superior quadrants compared to full-term children.

Keywords: Intravitreal bevacizumab, Peripapillary retinal nerve fiber layer, Retinopathy of prematurity

Address for correspondence: Marzieh Najjaran, Department of Optometry, School of Paramedical Sciences and Rehabilitation, Mashhad University of Medical Sciences, Mashhad, Iran.
E-mail: mnajjaran@yahoo.com
Submitted: 08-Aug-2023; **Revised:** 15-Sep-2023; **Accepted:** 03-Nov-2023; **Published:** 10-Aug-2024

Introduction

Premature birth is accompanied by several ocular and neuronal development abnormalities, especially the sight-threatening sequelae of retinopathy of prematurity (ROP).[1,2] Laser photocoagulation and cryotherapy as conventional treatments and the increasingly popular intravitreal antivascular endothelial growth factor (anti-VEGF) injections that have been shown to provide favorable structural and visual outcomes,[3-5] are the two main treatment paradigms for ROP patients.

Several previous studies have reported alterations in peripapillary retinal nerve fiber layer (pRNFL) thickness in preterm children.[6-9] The severity of ROP,[6,7] abnormalities in macular development due to preterm birth[9] as well as the effects

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joco

DOI: 10.4103/joco.joco_159_23

How to cite this article: Zarei-Ghanavati S, Ostadimoghaddam H, Najjaran M, Shoeibi N, Ziaei M. Peripapillary retinal nerve fiber layer thickness changes in preterm children with or without retinopathy of prematurity history. J Curr Ophthalmol 2023;35:381-6.

of photocoagulation or cryotherapy[6,10] have been postulated to be the reason for this phenomenon.

However, longitudinal studies of pRNFL thickness in ROP children with prior anti-VEGF treatments are limited. Thinner pRNFL has been found in ROP children aged 4–6 years with a previous history of intravitreal ranibizumab treatment.[11] Furthermore, the studies are inconsistent when analyzing the association between visual function and pRNFL thickness in this patient population, with some studies showing no association[7] and others reporting an association between reduced visual acuity and thinning of the RNFL.[8,9]

This study sought to compare pRNFL thickness and its association with visual function in ROP children with a prior history of intravitreal bevacizumab (IVB) treatment and compare it to three groups, including regressed ROP children without any treatment, preterm children with no ROP, and full-term children.

Methods

This retrospective comparative cohort study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional review board of the Mashhad University of Medical Sciences with Medical Sciences Ethics Committee (code Number: IR.MUMS.REC.1399.613). Written informed consent was obtained from the parents or guardians of all children. The study included preterm children born from 2013 to 2017 who presented to the Khatam Eye Hospital, Mashhad, Iran, for a complete ophthalmic examination. Subjects were enrolled after simple randomization using computer software. Thirty preterm children with a history of ROP who received a single treatment of IVB 0.625 mg (0.025 mL) (Avastin; Genentech, South San Francisco, California, USA) aged 4–8 years at the time of data gathering were compared with three other age- and gender-matched groups included: regressed ROP children without treatment, preterm with no ROP occurrence, and full-term children (n = 30 each group). Full-term children (gestational age [GA] ≥37 weeks and birth weight [BW] ≥2500 g) who presented for routine eye examinations served as a control group.

Inclusion criteria were preterm with GA ≤32 weeks or BW <2000 g with adequate follow-up until complete retinal vascularization or regression was achieved with a normal fundus appearance and good cooperation for eye imaging. Exclusion criteria were a history of laser treatment, contact lens wear, and other ocular diseases, for example (cataract or glaucoma), ROP sequelae such as macular fold, dragging or retinal detachment, as well as cerebral or congenital defects.

Eligible participants were invited for further examination. Uncorrected visual acuity and best-corrected visual acuity (BCVA) were assessed using a Snellen chart and converted to logMAR. After measurement using an auto kerato-refractometer (Topcon KR-1; Topcon Corporation, Tokyo, Japan), followed by retinoscopy, subjective refraction was conducted by an experienced practitioner. Refraction data were recorded in spherical equivalent (SEQ). Cycloplegic refraction was completed 30 min after instilling three tropicamide 1% eye drops 5 min apart.

Following refraction, the same practitioner measured posterior segment parameters three times in the same dark room. Optical coherence tomography (OCT) imaging was obtained using the Optopol spectral domain OCT system (Revo NX, Optopol Technology, Zawiercie, Poland). This instrument has a superluminescent laser diode (830 nm) as a light source. It completes 110,000 scans/s with an axial resolution of 5 µm, transverse resolution of 12 µm, and a single scan depth of 2.4 mm. The pRNFL thickness parameters were calculated automatically with a 3D 6 mm × 6 mm scan pattern.

The RNFL profile represents the thickness of the area through which the measurement circle passes, and the RNFL grid represents the thickness of the area in the measurement circle, including four quadrants: superior, inferior, temporal, and nasal. NFL thickness map with rings around the disc, where RNFL thickness information is used for the average thickness profile of the nasal, superior, temporal, inferior, and nasal (NSTIN) region from a circular scan. Only high-quality images with QI ≥7 with no manual correction were included for further analyses [Figure 1].

Statistical analysis

Data were analyzed using commercial software (IBM SPSS 23.0; SPSS, Inc., Chicago, IL, USA). Quantitative data

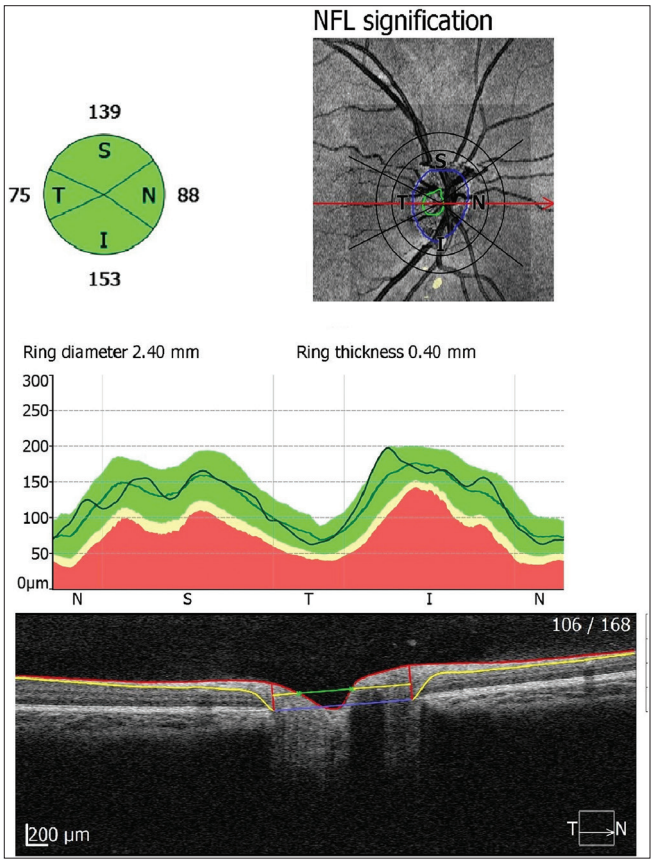

Figure 1: A representative retinal nerve fiber layer thickness output

were represented as mean, standard deviation, or median and interquartile for nonnormal variables. Analysis of variance (ANOVA) for normally distributed data and the Kruskal–Wallis test for nonnormally distributed data were used to compare group variables.

Pairwise *post hoc* comparisons of ANOVA and Kruskal–Wallis tests were evaluated using Tukey's (honestly significant difference) or Mann–Whitney *U*-test with Bonferroni adjustment, respectively. The Spearman correlation was used to analyze the correlation between pRNFL thickness and GA, BW, BCVA, and SEQ. Only right-eye data were included for analysis. $P < 0.05$ was considered statistically significant.

Results

A total of 120 children (n = 30 for each group) enrolled in the study. Demographic data are presented in Table 1. There was no significant difference in mean age, 6.63 ± 1.27 years ($P > 0.999$), nor sex between the two groups (50% male). It was found that 83.3% of the patients in the treated ROP group were in Stage 3 and 86.7% of the patients in the regressed ROP group were in Stage 2.

The mean distribution profile of the groups (NSTIN plot) was 113.26 ± 17.78, 122.53 ± 10.78, 126.73 ± 13.38, and 124.63 ± 12.89 µm, in treated, regressed ROP, preterm without ROP, and full-term children, respectively ($P = 0.031$). When completing between-group comparisons, *post hoc* analysis showed that ROP-treated children had a significantly thinner pRNFL thickness profile than preterm children ($P = 0.041$). With linear regression analysis and considering different parameters after adjusting for GA and BW, there was no significant difference in NSTIN thickness between groups ($P > 0.05$).

The pRNFL thickness of four quadrants as well as the average NSTIN plot of the studied groups is presented in Table 2. The mean pRNFL thickness in the superior, nasal, and inferior quadrants significantly differed between groups ($P = 0.007$, $P = 0.004$, and $P = 0.012$, respectively). The superior quadrant in treated ROP children was thinner than the preterm and control groups ($P = 0.015$ and $P = 0.023$, respectively). Both treated and regressed ROP groups had a thinner pRNFL in the nasal quadrant compared to full-term children ($P = 0.017$ and $P = 0.008$, respectively). The treated ROP group also showed a thinner pRNFL in the inferior quadrant compared to the preterm group ($P = 0.008$). However, the pRNFL thickness in the temporal quadrant was not significantly different between groups ($P = 0.129$).

The correlation analysis of each group was completed separately. There was a significant correlation between BCVA and temporal pRNFL thickness in treated patients ($r = 0.395$, $P = 0.031$). However, there were no significant correlations between other parameters such as GA, BW, and SEQ with pRNFL thickness in any quadrants (all $P > 0.05$).

Discussion

With increased survival rates of preterm infants due to improvements in perinatal care, a better understanding of ocular anatomical variations in this patient population is required. This study analyzed pRNFL thickness in preterm children aged 4–8 years who received IVB treatment, regressed ROP without treatment, preterm children without ROP, and full-term children. The results demonstrate that children with ROP have significant pRNFL thinning in the nasal quadrant compared to full-term children. Children with a history of ROP treatment also exhibit superior and inferior quadrants thinning

Table 1: Demographic data of the study population (n=30 each group)

Parameters	Treated ROP	Regressed ROP	Preterm without	Full-term	*P*
GA (weeks), *n* (%)	28 (1.5)	30 (3.5)	32 (3)	37	<0.001*
BW (g), *n* (%)	1045 (342.5)	1360 (363.75)	1625 (325)	3100 (650)	<0.001*
BCVA, logMAR	0.05±0.09	0.01±0.03	0.02±0.06	0.01±0.03	0.05
Amblyopia (*n*)	2/30	0/30	1/30	0/30	
Deviation (*n*)					
Exotropia	5/30	0/30	2/30	3/30	0.24†
Esotropia	1/30	0/30	1/30	0/30	
ROP zone, *n* (%)					
I	17 (56.7)	0	N/A	N/A	<0.001†,*
II	13 (43.3)	24 (80)	N/A	N/A	
III	0	6 (20)	N/A	N/A	
ROP stage, *n* (%)					
1	1 (3.3)	4 (13.3)	N/A	N/A	<0.001†,*
2	4 (13.3)	26 (86.7)	N/A	N/A	
3	25 (83.3)	0	N/A	N/A	
SEQ (D)	−0.29±2.55	0.56±0.60	0.76±1.10	0.24±1.64	0.3

*P<0.05 is statistically significant, †All P were obtained using Kruskal–Wallis except those indicated with which were obtained using the Chi-square test. Data are mean±SD or median (IQR). ROP: Retinopathy of prematurity, BCVA: Best-corrected visual acuity, SEQ: Spherical equivalent, D: Diopter, GA: Gestational age, BW: Birth weight, IQR: Interquartile range, N/A: Not assessable, SD: Standard deviation

Table 2: Nerve fiber layer thickness measurements (*n*=30 each group)

Parameters	Treated ROP	Regressed ROP	Preterm without ROP	Full-term	*P*
Superior (µm)	130 (30)	142.50 (23.75)	151 (40.75)	146 (19)	0.007†
					P=0.015[a,c]
					P=0.023[a,d]
Inferior (µm)	134.36±24.91	145.73±15.45	150.13±18.10	141.63±15.05	0.012‡
					P=0.008[a,c]
Temporal (µm)	70.50 (23.75)	74.50 (9.5)	77 (13.50)	81 (19.5)	0.129†
Nasal (µm)	82.70±18.93	81.66±12.02	89.50±11.99	95.13±19.35	0.004‡
					P=0.017[a,d]
					P=0.008[b,d]
NSTIN (µm)	118 (19.50)	121 (9.75)	125 (23.75)	126.50 (16.75)	0.031†
					P=0.041[a,c]

†All *P* were obtained using the ANOVA test except those indicated with which were obtained using Kruskal–Wallis test, ‡All Multiple comparisons were obtained using Mann–Whitney U-test with Bonferroni adjustment except those indicated with, which were obtained using Tukey's (HSD), [a]Treated ROP, [b]Regressed ROP, [c]Preterm without ROP, [d]Full-term. *P*<0.05 is statistically significant. Data are mean±SD or median (IQR). NSTIN: Nasal-superior-temporal-inferior-nasal areas thickness profile, ROP: Retinopathy of prematurity, SD: Standard deviation, IQR: Interquartile range, ANOVA: Analysis of variance, HSD: Honestly significant difference

of the pRNFL thickness compared to controls. However, pRNFL thickness in the temporal quadrant does not appear to be affected by ROP or its treatment. Moreover, there was a positive correlation in the temporal quadrant of pRNFL thickness with BCVA (in logMAR) in the treated ROP children.

PRNFL thinning has been shown to occur in children with a history of ROP in several previous studies,[6,10,12] as well as in adults with a history of preterm birth, irrespective of ROP occurrence.[13] Most studies report thinning of pRNFL thickness mainly in the superior, nasal, and inferior quadrants in treated ROP, which is consistent with the results of the present study.[1,6,10]

Acar *et al*. compared pRNFL thickness in 30 preterm, 33 regressed ROP, 28 laser-treated ROP, and 30 full-term children aged 4–8 years. They found a reduction in pRNFL thickness in the nasal, superior, and inferior quadrants in the laser-treated ROP children compared to other groups, but no difference in the temporal quadrant was found.[10]

In an OCT-A study by Lee *et al*., in 38 laser-treated, 40 regressed ROP, and 43 full-term children 4–12 years, a thinner superior and nasal and a thicker temporal pRNFL profile was reported in treated ROP children compared to controls. It has been suggested that abnormalities in the spatial distribution of the pRNFL thickness profile might be due to the abnormal inner retinal layers maturity and the thickening of the temporal sector might indicate the abnormal peripapillary neurovascular structural development in this patient population.[1,7,9]

Cheng *et al*. examined pRNFL thickness in 28 ROP children who received intravitreal ranibizumab, 26 children with regressed ROP, 46 preterm children with no ROP, and 104 full-term children aged 4–6 years. Their results suggested that treated ROP children had thinner nasal and superior pRNFL thickness as well as a reduction in average thickness profile compared to controls.[11] This is in keeping with the findings of this study.

The lack of a significant difference in the temporal quadrant of pRNFL thickness seen in this study is also compatible with other recent reports.[10,11] In a recent study by Cheng *et al*., children who received intravitreal ranibizumab showed no significant difference in the temporal quadrant of pRNFL thickness in preterm children with or without ROP.[11] However, this finding is controversial as other studies report an increase in temporal quadrant pRNFL thickness not only in treated ROP children[1,2,12] but also in adults with a history of ROP treatment.[13] The temporal pRNFL thickening has been postulated to be secondary to the migration of immature inner retinal layers to the temporal quadrant[7,9] to improve the macular area function in treated ROP children.[2] It is, however, noteworthy that previous studies had a limited number of anti-VEGF-treated children in their sample.[12]

Although the severity of ROP and a prior history of laser or cryotherapy treatment have been hypothesized to be associated with RNFL thinning,[6] temporal sector thickening showed a much more significant association with ROP occurrence in a multivariable analysis performed by Fieß *et al*. However, the sample size in the laser-treated group was small, with only four children included.[8] This suggests that anti-VEGF treatment in ROP children might have varying pRNFL thickness effects in different sectors. However, larger cohort studies are required to investigate this association.

No association was found between GA, BW, and pRNFL thickness in any quadrants in this study which is in keeping with the study by Cheng *et al*.[11] However, the results are inconsistent in this regard with several previous studies reporting an association between lower GA or BW with pRNFL thinning.[2,6-9] Fieß *et al*. found thinner pRNFL in 4–10-year-old children with a history of preterm birth. They demonstrated an association between lower GA and BW with thinner pRNFL irrespective of ROP occurrence. However, they did not evaluate the laser-treated children in a separate group.[8]

Although the underlying mechanism of thinning of the pRNFL in preterm children is not fully understood, lower GA and

BW,[2,7,8] ROP severity,[6] abnormalities in macular development in preterm children,[9] and neuronal and axonal damage in the inner retinal layers in laser or cryotherapy treated children[6,10] or neurodevelopment changes[14] may have an impact on pRNFL thickness. Furthermore, adverse ocular events such as poor structural outcomes and systemic effects such as severe neurodevelopmental delay, cerebral palsy, and hearing loss have been reported after intravitreal anti-VEGF treatment in some studies.[15,16]

The pRNFL thinning exhibited in ROP children, especially in the treated group, suggests that there is a benefit from long-term monitoring of this patient population to detect early signs of glaucomatous optic neuropathy. The association of pRNFL thickness with visual function has previously been reported with inconsistent findings.[1,7-9] The results of this study suggest that pRNFL thickness in the temporal quadrant correlates with BCVA in treated ROP children. However, the correlation was weak (r = 0.395). Brain structural and neurodevelopmental changes as well as abnormal macular development in premature eyes[8,14] may possibly be attributed to the pRNFL thickness and visual function alterations as premature infants are at a higher risk for adverse neurodevelopmental outcomes than term infants.[17]

Wang *et al*. showed a significant association between pRNFL in the temporal quadrant and visual acuity.[9] Cheng *et al*. found an association between reduced BCVA and pRNFL thinning in the superior quadrant of both regressed and intravitreal ranibizumab-treated ROP children.[11] Fieß *et al*. showed reduced visual function related to pRNFL thinning in all sectors in preterm children.[8] Lee *et al*. showed a negative association between pRNFL thickness and BCVA in the laser-treated ROP children.[1] Lee *et al*. compared pRNFL thickness between ROP-treated children (laser and/or IVB) and full-term children and found a positive correlation between SEQ and RNFL thickness in all patients.[12] However, both laser (90.2%) and IVB treatments (9.8%) were studied in one group, with no subgroup analysis of regressed ROP was performed. This study analyzed regressed ROP and IVB-treated children in separate groups and found no correlation between SEQ and pRNFL thickness. Differences in treatment options (laser vs. anti-VEGF), various subgroups, small sample sizes, different age range, and limited studies, including IVB-treated ROP children, make comparison of the aforementioned studies difficult.

The strength of this study was that the pRNFL thickness measurements were taken in a relatively large sample size of 4 age- and gender-matched groups of children, including those with IVB treatment as a separate group. This study has several limitations, including a single-center cross-sectional design which may have reduced the representativeness of our cohort, and the inclusion of children with reasonable cooperation, which may have introduced an element of bias.

In conclusion, this study demonstrates that the nasal quadrant of children with a history of ROP has a thinner pRNFL compared to their full-term counterparts. Furthermore, the superior and inferior quadrants of pRNFL in treated ROP children were thinner than controls. This should be considered in the long-term follow-ups of ROP children, especially those with previous treatment. Future cohort studies are required to investigate and confirm the association of pRNFL thickness with visual function in preterm children treated with different anti-VGEF agents.

Acknowledgment

This study was supported by the research deputy of Mashhad University of Medical Sciences, Mashhad, Iran.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Lee GI, Park KA, Oh SY, Kim SJ. Retinal and peripapillary vascular deformations in prematurely born children aged 4-12 years with a history of retinopathy of prematurity. Sci Rep 2023;13:3130.
2. Pueyo V, González I, Altemir I, Pérez T, Gómez G, Prieto E, *et al.* Microstructural changes in the retina related to prematurity. Am J Ophthalmol 2015;159:797-802.
3. Roohipoor R, Torabi H, Karkhaneh R, Riazi-Eafahani M. Comparison of intravitreal bevacizumab injection and laser photocoagulation for type 1 zone II retinopathy of prematurity. J Curr Ophthalmol 2019;31:61-5.
4. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003;121:1684-94.
5. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+retinopathy of prematurity. N Engl J Med 2011;364:603-15.
6. Åkerblom H, Holmström G, Eriksson U, Larsson E. Retinal nerve fibre layer thickness in school-aged prematurely-born children compared to children born at term. Br J Ophthalmol 2012;96:956-60.
7. Park KA, Oh SY. Retinal nerve fiber layer thickness in prematurity is correlated with stage of retinopathy of prematurity. Eye (Lond) 2015;29:1594-602.
8. Fieß A, Christian L, Janz J, Kölb-Keerl R, Knuf M, Kirchhof B, *et al.* Functional analysis and associated factors of the peripapillary retinal nerve fibre layer in former preterm and full-term infants. Br J Ophthalmol 2017;101:1405-11.
9. Wang J, Spencer R, Leffler JN, Birch EE. Characteristics of peripapillary retinal nerve fiber layer in preterm children. Am J Ophthalmol 2012;153:850-5.e1.
10. Acar DE, Acar U, Tunay ZO, Arman A, Goksuluk D. Retinal choroidal and retinal nerve fiber layer thickness in former preterm and full-term infants aged 4 to 8 years. Int Ophthalmol 2021;41:1071-9.
11. Cheng H, Cao D, Qian J, Gu W, Zheng Z, Ma M. Refractive status and retinal morphology in children with a history of intravitreal ranibizumab for retinopathy of prematurity. Eur J Pediatr 2023;182:3121-8.
12. Lee YS, Chang SH, Wu SC, See LC, Chang SH, Yang ML, *et al.* The inner retinal structures of the eyes of children with a history of retinopathy of prematurity. Eye (Lond) 2018;32:104-12.
13. Fieß A, Schäffler A, Mildenberger E, Urschitz MS, Wagner FM, Hoffmann EM, *et al.* Peripapillary retinal nerve fiber layer thickness in adults born extremely, very, and moderately preterm with and without retinopathy of prematurity: Results from the gutenberg prematurity eye study (GPES). Am J Ophthalmol 2022;244:88-97.
14. Rothman AL, Sevilla MB, Mangalesh S, Gustafson KE, Edwards L, Cotten CM, *et al.* Thinner retinal nerve fiber layer in very preterm versus

term infants and relationship to brain anatomy and neurodevelopment. Am J Ophthalmol 2015;160:1296-308.e2.
15. Duggan TJ, Cai CL, Aranda JV, Beharry KD. Acute and chronic effects of intravitreal bevacizumab on lung biomarkers of angiogenesis in the rat exposed to neonatal intermittent hypoxia. Exp Lung Res 2021;47:121-35.
16. Morin J, Luu TM, Superstein R, Ospina LH, Lefebvre F, Simard MN, *et al.* Neurodevelopmental outcomes following bevacizumab injections for retinopathy of prematurity. Pediatrics 2016;137:e20153218.
17. Hee Chung E, Chou J, Brown KA. Neurodevelopmental outcomes of preterm infants: A recent literature review. Transl Pediatr 2020;9:S3-8.