tvst

Article

Evaluation of Ocular Biometric and Optical Coherence Tomography Parameters in Preterm Children Without Retinopathy of Prematurity

Andrea Lillianne Barr Kumarakulasinghe[1], Norshamsiah Md Din[1], Umi Kalthum Mohd Noh[1,2], Syed Zulkifli Syed Zakaria[3], Tin Aung[4,5], and Safinaz Mohd Khialdin[1]

[1] Department of Ophthalmology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latiff, Bandar Tun Razak, Cheras, Kuala Lumpur, Malaysia
[2] Department of Ophthalmology, Sunway Medical Centre Jalan Lagoon Selatan, Bandar Sunway, Petaling Jaya, Selangor, Malaysia
[3] Department of Paediatrics, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latiff, Bandar TunRazak, Cheras, Kuala Lumpur, Malaysia
[4] Singapore Eye Research Institute, Singapore National Eye Center, 11 Third Hospital Avenue, Singapore
[5] Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Correspondence: Safinaz Mohd Khialdin, Department of Ophthalmology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latiff, Bandar TunRazak, 56000 Cheras, Kuala Lumpur, Malaysia. e-mail: drsafinaz_1978@yahoo.com.my

Received: August 5, 2021
Accepted: January 13, 2022
Published: March 8, 2022

Keywords: premature; preterm; ocular biometry; retinopathy of prematurity; ocular growth

Citation: Kumarakulasinghe ALB, Md Din N, Mohd Noh UK, Syed Zakaria SZ, Aung T, Mohd Khialdin S. Evaluation of ocular biometric and optical coherence tomography parameters in preterm children without retinopathy of prematurity. Transl Vis Sci Technol. 2022;11(3):8, https://doi.org/10.1167/tvst.11.3.8

Purpose: To evaluate and compare biometric and optical coherence tomography parameters of ocular structures in preterm children without retinopathy of prematurity with term children.

Methods: A cross-sectional, comparative study was carried out from 2018 to 2019. In this study, 124 eyes of 62 preterm children were compared with 132 eyes of 66 term children aged between 7 and 9 years. Preterm children were born at 28 to 32 weeks with a birth weight of less than 2 kg with no ocular abnormalities, and term children were delivered at 37 or greater weeks and had a birth weight of 2 kg or more. All children had standardized eye examinations, and ocular measurements using the anterior and posterior segment optical coherence tomography and laser interferometry.

Results: Significant differences were found between the term and preterm children for horizontal corneal diameter: median, 12.2 mm (interquartile range [IQR], 0.4) versus median, 12.1 mm (IQR, 0.6; $P < 0.005$); axial length median, 23.03 mm (IQR, 1.10 mm) versus median, 22.88 mm (IQR, 1.35 mm; $P = 0.017$); global retinal nerve fiber layer thickness: mean $\pm$ standard deviation, 106.54 $\pm$ 10.23 µm versus mean $\pm$ standard deviation, 103.65 $\pm$ 10.178 µm ($P = 0.024$); temporal retinal nerve fiber layer thickness: median, 76 µm (IQR, 16 µm) vs median, 74 µm (IQR, 14 µm; $P = 0.012$); and the angle opening distance at 750 µm nasal: mean $\pm$ standard deviation, 0.815 $\pm$ 0.23 mm vs mean $\pm$ standard deviation, 0.749 $\pm$ 0.21 mm ($P = 0.016$). No significant differences were found for other anterior segment and angle parameters.

Conclusions: Preterm children with no retinopathy of prematurity have smaller eyes and thinner retinal nerve fiber layers than their term counterparts. The long-term effects of interrupted ocular growth in preterm children should be further studied into adulthood.

Translational Relevance: Preterm children maybe more predisposed to certain eye conditions because they have smaller eyes, and thus should be further monitored clinically.

Introduction

Preterm births are a leading cause of mortality and morbidity among children.[1] An estimated 15 million infants are born preterm every year.[1] In Malaysia, the preterm birth rate is 12.3% of 576,400 births in 2010, ranking us 41st worldwide.[2]

Prematurity can cause debilitating ocular diseases such as retinopathy of prematurity (ROP), glaucoma, and refractive errors.[3] However, the need for proper ocular follow-up in preterm children has neither been established nor recognized.[3] Preterm children with no ocular complications are not routinely followed beyond 1 year of age if their eyes seem to have no abnormalities. Because proper guidelines have not been established, the long-term sequelae of prematurity to ocular health may be left undetected.

It is known that the premature eye has relative anterior microphthalmos as a consequence of arrested development of the anterior segment.[3] Studies show that preterm infants have flatter anterior chambers, thicker lenses, and smaller corneal diameters as compared with their term counterparts.[4,5] The lens in premature infants were also found to be more spherical, because the lens loses its spherical shape during gestation.[5] A study on children aged 12 years showed that there was an inverse correlation between low birth weight and cup disc ratios (CDR) compared with the normal population.[6] Children with a lower birth weight had larger CDRs, suggesting that growth restriction inadvertently affects optic nerve head development.[6] Additionally, the mean intraocular pressure (IOP) in premature infants was found to be higher than term infants, thought to be due to an increase in central corneal thickness (CCT).[7]

Although uncommon, angle closure glaucoma is the main type of glaucoma associated with prematurity.[3] The incidence of glaucoma and other ocular diseases in premature children with no ROP is, however, not well-established. Greater lens thickness and shallow anterior chambers result in narrowed angles and predisposition to angle closure glaucoma.[8] The more anteriorly positioned lens can also cause decreased anterior chamber depth (ACD).[8] However, there are other factors that may contribute to the development of glaucoma in these premature eyes. Hansson and Jerndal[9] found a continuous monolayer of endothelial cells, forming a membrane lining the iridocorneal angles, up to about 8 months of age in premature infants, in their study done on enucleated eyes of infants of varying ages with no ROP. This membrane normally splits along the border between neighboring cells before term. It is assumed that arrested development can cause this lining to persist, leading to aqueous outflow resistance and consequently, congenital glaucoma.[9] If this is the postulation, all preterm children, and not only preterm infants with ROP, would be at risk of glaucoma.

Preterm infants are also known to have more refractive errors,[3,10] such as myopia, hyperopia, and astigmatism, occurring four times more often in preterm than in term children.[3] Although they are shown to have smaller eyes with shorter axial lengths (AXLs), they commonly develop myopia,[10] attributed to decreased corneal curvature, a thicker lens, and a shallower ACD.[3,5,10]

This study aims to determine the differences in ocular biometrics of the anterior and posterior segments as assessed with the optical coherence tomography (OCT) between preterm children without ROP and term children aged between 7 and 9 years.

Methods

This cross-sectional observational study included children aged between 7 and 9 years and born preterm but without ROP or any other ocular abnormalities, and compared with their age-matched term counterparts. The preterm children were identified from the Vermont Oxford Network Database in Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia. The term children were selected by convenience sampling from a nearby primary school or siblings of the preterm children who fulfilled the inclusion and exclusion criteria. All research procedures adhere to the tenets of the Declaration of Helsinki and were approved by the ethics committee of this institution. The parents of the children were fully informed and written consent was obtained before any ocular measurements were taken.

Inclusion criteria of the term children were children aged between 7 and 9 years, delivered at 37 or more weeks and had birth weight of 2 kg or greater. The inclusion criteria of the preterm children were 7 to 9 years of age, very preterm, delivered between 28 and 32 weeks of gestation,[1] and had birth weight of less than 2 kg. We chose a narrow age range to eliminate age-related variations in the study variables, such as the angle and retinal nerve fiber layer (RNFL) parameters in a growing child. Exclusion criteria were any ocular abnormalities except for refractive errors, ROP in the preterm group, any past ocular procedures, and patients with systemic diseases that could affect the outcome of the tests, like Down syndrome or pulmonary hypertension.

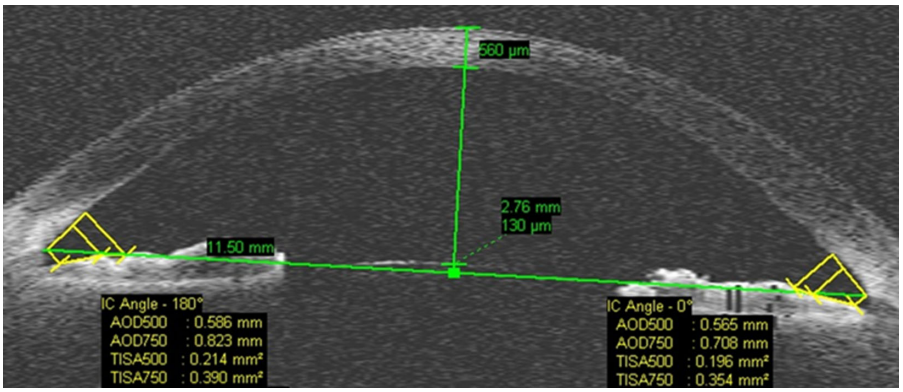

Figure 1. Measurement of the CCT, anterior lens vault (LV), and nasal and temporal angles. The caliper is placed on both nasal and temporal scleral spurs and anterior LV is measured as the part of the lens above the connecting line. Automated angle assessment done using calipers placed on the scleral spur. SS, scleral spur. (A, B) Scleral spur iris end point. (C) AOD500 corneal end point. (D) AOD500 iris end point. (E) AOD750 corneal end point. (F) AOD750 iris end point.

Both eyes from all the children were analyzed. All children had anterior segment imaging using the anterior segment OCT (ZEISS Visante OCT Model 1000, software version 3.0.0.8139; Carl Zeiss Meditec, Dublin, CA), ocular biometry using the IOL Master (software version 5.4.3 Carl Zeiss Meditec, Dublin, CA), IOP measurement using the Reichert Tono-Pen XL Applanation Tonometer (Reichert, Depew, NY), measurement of the RNFL thickness using the Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), and fundus examination to determine the CDR. The Visante anterior segment OCT was used to measure the CCT, the iridocorneal angle, and the anterior lens vault. Images were taken with the subjects looking at the internal fixation light, under room light conditions with undilated pupils. The CCT was measured manually using a caliper placed from the corneal epithelium to the endothelium.

For each eye, the angles were measured by first identifying the scleral spur on the nasal and temporal sides. The Visante angle assessment software (version 3.0.0.8139; Carl Zeiss Meditec, 2010) was then used to assess the nasal and temporal angles by manually placing the tool on the identified scleral spur and the parameters were then automatically measured. Specific parameters measured were the angle opening distance (AOD) at 500 µm (AOD500) and 750 µm (AOD750) from the scleral spur, and the trabecular iris space area (TISA) at 500 μm^2 (TISA500) and 750 μm^2 (TISA750) from the scleral spur (Figs. 1 and 2). The anterior lens vault was measured as the space between the anterior pole of the lens and a horizontal line joining the two scleral spurs. Two raters (AB and NMD) measured the angle parameters and intraclass correlation coefficient was calculated to assess the agreement between the two raters on CCT, lens vault, and all angle parameters (AOD500, AOD750, TISA500, and TISA750).

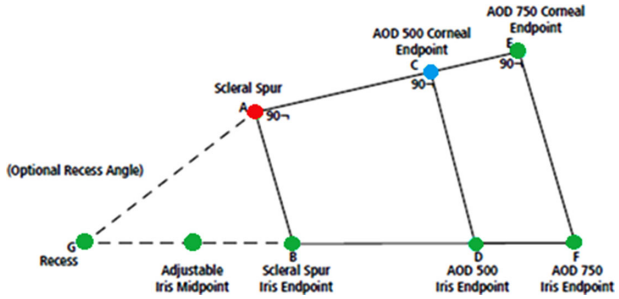

Figure 2. Definitions of the Iridocorneal angle measurements. Reprinted with permission from Visante OCT Model 1000 System Software Version 3.0 User Manual.[11] AOD500, distance between C and D; AOD750, distance between E and F; TISA500, area of the polygon formed by A, C, D, and B; TISA750, area of the polygon formed by A, E, F, and B.

Laser interferometry (IOL Master) was then used to obtain the biometry measurements including AXL, ACD, and horizontal corneal diameter. The images were also taken with the subjects fixating on the internal fixation light, under room light conditions with undilated pupils. A total of five readings were taken for AXL in both eyes, five readings for ACD, and three readings for horizontal corneal diameter. The average for each of these values were used.

A drop of 1% proparacaine was used as local anesthesia. The IOP was measured with a Tonopen three times and the average was taken for analysis. Measurements with a standard deviation of 5% or less were taken. The eyes were then dilated with cyclopentolate 0.5%. After 20 minutes, the peripapillary RNFL thickness was measured with the Spectralis OCT. The software provides the average thickness for the global as well as superior, inferior, nasal, and

temporal quadrants. Finally, subjects were examined at the slit lamp for clinical assessment of the vertical CDR.

Demographic and clinical data were then collected and analyzed using the SPSS version 21.0 (SPSS, Inc, Armonk, NY). The normality of the data was tested using the Kolmogorov–Smirnov test. A comparison of the measurements between the two groups was done using the χ^2 test for categorical data, and continuous data were tested using the unpaired *t*-test or the Mann–Whitney *U* test, depending on normality of distribution. Generalized estimating equation were used to evaluate factors affecting the RNFL thickness to account for intereye correlation from the same subject. A *P* of value of less than 0.025 was considered significant to account for the two eyes from each subject.

Results

A total of 132 eyes of 66 term children and 124 eyes of 62 preterm children were included. More than one-half of the preterm children were male (Table 1). There was no difference in median age between the term and preterm children (median, 8.0 years; interquartile range, [IQR], 2; $P = 0.923$).

The term children had a higher median gestational age (median, 38.0 weeks; IQR, 2 weeks) than the preterm (median, 30.0 weeks; IQR, 3 weeks; $P < 0.001$) and a higher median birth weight (median, 2985 g; IQR, 520 g vs 1435 g; IQR, 530 g; $P < 0.001$).

The inter-rater agreement between the primary investigator and a glaucoma consultant for assessment of the angle and CCT parameters by Visante OCT was good, with an intraclass correlation coefficient value ranging between 0.709 and 0.955 (mean, 0.874).

The horizontal corneal diameter was significantly smaller in the preterm (median, 12.1 mm; IQR, 0.6 mm), compared with the term group (median, 12.2 mm; IQR 0.4 mm; $P < 0.005$). The AXL was also shorter in the preterm (median, 22.875 mm; IQR, 1.35 mm) than the term group (median, 23.025 mm; IQR, 1.10 mm; $P = .017$). There was no significant difference in mean CCT, lens vault, or mean ACD. We also found no significant difference in the mean IOP and CDR (Table 2). Although the RNFL was thinner in all quadrants of the preterm children, significant differences were only found in the temporal (median, 73 µm; IQR,13 µm vs median, 76 µm; IQR, 16 µm; $P = 0.012$) and global RNFL thickness (mean, 103.65 ± 10.18 µm vs mean, 106.54 ± 10.232 µm; $P = 0.024$) in the preterm and term groups respectively. We found that AOD 750 in the nasal area was significantly more narrowed in the preterm compared with the term group (Table 2). There was no significant difference in the other parameters.

Pearson's correlation analysis was performed for all the significant parameters against birth weight and gestational age (Table 3). All parameters showed significant weak positive correlation except for the temporal quadrant which did not show significant correlation with gestational age.

Univariate linear regression analysis was modelled to identify factors affecting the global RNFL thickness. We found gestational age, prematurity, birth weight, lens vault, corneal diameter, cup to disc ratio, AXL, and AOD750t to be significantly affecting the global RNFL thickness (Table 4).

We then included all the significant parameters into the generalized estimating equation, nesting both eyes from the same patient, to account for possible intereye correlation from the same individual. We found only corneal diameter and AXL to be significant factors

Table 1. Demographic Data of the Study Population

Variable	Term ($n = 66$)	Preterm ($n = 62$)	*P* Value
Gender, *n* (%)			
Male	27 (40.9)	37 (59.7)	0.003[a]
Female	39 (59.1)	25 (40.3)	
Race, *n* (%)			
Malay	61 (92.4)	43 (69.4)	0.000[b]
Chinese	1 (1.5)	19 (30.6%)	
Indian	4 (6.1)	0 (0%)	
Age, median (IQR), years	8.0 (2)	8.0 (2)	0.923[c]
Gestational age, median (IQR), weeks	38.0 (2)	30.0 (3)	0.000[c]
Birth weight, median (IQR), g	2985 (520)	1435 (530)	0.000[c]

[a] χ^2 test.
[b] Fishers exact test.
[c] Mann–Whitney *U* test unless stated otherwise.

Table 2. Biometric Measurements of the Studied Eyes

Measurement	Term ($n = 132$)	Preterm ($n = 124$)	*P* Value	Mean Difference (95% CI)
CCT, median (IQR), µm	570 (50)	565 (50)	0.96[a]	
Anterior lens vault, mean (SD), µm	−86.74 (± 177.87)	−109.68 (± 181.54)	0.31[b]	22.935 (−21.313, 67.183)
ACD, mean (SD), mm	3.42 (± 0.24)	3.37 (± 0.27)	0.13[b]	0.049 (−0.014,0.112)
Horizontal corneal diameter, median (IQR), mm	12.2 (0.4)	12.1 (0.6)	**0.000**[a]	
AXL, median (IQR), mm	23.025 (1.1)	22.875 (1.35)	**0.017**[a]	
IOP, median (IQR), mmHg	17.0 (3)	16.0 (3)	0.359[a]	
CDR, median (IQR)	0.3 (0.1)	0.3 (0.2)	0.808[a]	
RNFL inferior, mean (SD), µm	134.99 (± 19.795)	131.25 (± 16.262)	0.101[b]	3.742 (−0.733,8.217)
RNFL superior, median (IQR), µm	140.0 (20)	139.0 (21)	0.338[a]	
RNFL nasal, mean (SD), µm	75.74 (±14.576)	73.40 (±15.127)	0.209[b]	2.339 (−1.317,5.995)
RNFL temporal, median (IQR), µm	76 (16)	73 (13)	**0.012**[a]	
RNFL global, mean (SD), µm	106.54 (± 10.232)	103.65 (± 10.178)	**0.024**[b]	2.893 (0.379,5.406)
AOD 500 temp, median (IQR), mm	0.589 (0.249)	0.600 (0.240)	0.624[a]	
AOD 750 temp median (IQR), mm	0.822 (0.338)	0.874 (0.309)	0.269[a]	
TISA 500 temp median (IQR), mm	0.192 (0.092)	0.198 (0.084)	0.721[a]	
TISA 750 temp median (IQR), mm	0.363 (0.168)	0.382 (0.160)	0.563[a]	
AOD 500 nasal median (IQR), mm	0.570 (0.261)	0.523 (0.193)	0.083[a]	
AOD 750 nasal, mean (SD), mm	0.815 (± 0.226)	0.749 (± 0.205)	**0.016**[b]	0.065 (0.012,0.118)
TISA 500 nasal median (IQR), mm^2	0.187 (0.081)	0.174 (0.075)	0.200[a]	
TISA 750 nasal median (IQR), mm^2	0.356 (0.141)	0.334 (0.118)	0.116[a]	

For the biometric measurements in the studied eyes, there was significant difference seen in the horizontal corneal diameter, axial length, temporal and global RNFL and the AOD 750 nasal. CI, confidence interval.

[a]Mann–Whitney *U* test.

[b]Unpaired *t*-test,

affecting the global RNFL thickness after adjusting for all the other significant factors from the univariate linear regression (Table 5).

Discussion

Children born premature are said to be premature for life.[5] The premature eye has relative anterior microphthalmos as a consequence of arrested development of the anterior segment.[3] These changes are irrespective of the occurrence of ROP.[5] The eyes of a fetus undergo the most active development from 6 months to term in utero.[5,12] Growth spurts occur at 16 to 20 weeks, 28 to 32 weeks, and 37 weeks, increasing the eye size significantly.[5] These spurts could be hindered in preterm infants. The eye continues to grow after birth until about 3 years of age, where little increase is seen thereafter until 13 years of age.[12,13] The lens, however, continues to grow throughout life.

Table 3. Correlation Between Birth Weight and Gestational Age With the Ocular Parameters

Variable	Birth Weight (r, *P* Value)	Gestational Age (r, *P* Value)
Corneal diameter	0.353, $P =$ **0.000**	0.255, $P =$ **0.000**
AXL	0.160, $P =$ **0.011**	0.127, $P =$ **0.043**
RNFL temporal	0.154, $P =$ **0.014**	0.120, $P = 0.054$
RNFL global	0.147, $P =$ **0.018**	0.174, $P =$ **0.005**
AOD 750 nasal	0.127, $P =$ **0.042**	0.125, $P =$ **0.045**

All ocular parameters showed positive correlation with birth weight and gestational age except for the temporal quadrant which did not show correlation with gestational age.

Table 4. Univariate Linear Regression Analysis to Identify Factors Affecting the Global RNFL Thickness

Independent Variables	Regression Coefficient	95% Confidence Interval	*P* Value
Age, years	−0.43	−1.99 to 1.13	0.59
Gender	1.01	−1.53 to 3,54	0.78
Gestational age, weeks	0.41	0.12 to 0.71	0.005
Prematurity	−2.89	−5.5 to −0.38	0.024
Birth weight, grams	0.002	0.0003 to 0.003	0.018
CCT, um	0.007	−0.03 to 0.044	0.722
Lens vault	0.01	0.003 to 0.017	0.005
ACD, mm	−0.25	−5.21 to 4.71	0.922
Corneal diameter, mm	3.17	0.23 to 6.1	0.034
IOP, mm Hg	0.23	−0.28 to 0.74	0.374
CDR	−18.8	−30.6 to −7.00	0.002
AOD500t	−5.12	−11.04 to 0.79	0.09
AOD750t	−5.05	−9.81 to −0.28	0.038
AOD500n	−3.64	−10.71 to 3.42	0.31
AOD750n	−5.58	−11.37 to 0.22	0.059
TISA500t	−9.86	−27.58 to 7.85	0.27
TISA750t	−7.51	−17.29 to 2.26	0.131
TISA500n	−6.42	−27.8 to 14.95	0.55
TISA750n	−6.7	−18.66 to 5.28	0.27
AXL, mm	−1.81	−3.05 to −0.57	0.004

Table 5. Generalized Estimating Equations to Evaluate Factors Affecting the Global RNFL Thickness by Significant Factors From Univariate Linear Regression Analysis

Variables	Regression Coefficient	95% Confidence Interval	*P* Value
Gestational age	0.85	−0.37 to 2.07	0.171
Prematurity	4.29	−6.54 to 15.12	0.44
Birth weight	−0.00006	−0.0046 to 0.0045	0.98
Lens vault	−0.0008	−0.0082 to 0.0065	0.82
Corneal diameter, mm	4.13	0.91 to 7.35	**0.012**
Cup to disc ratio	−12.02	−24.1 to 0.05	0.051
AXL, mm	−2.61	−4.3 to −0.93	**0.002**
AOD750t	−1.3	−5.47 to 2.92	0.552

Both eyes from each patient were nested in this model. After performing the generalized estimating equation analysis, only the corneal diameter and AXL were the significant factors affecting the global RNFL thickness.

In our study, we found a statistically significant difference in a few ocular parameters between the term and preterm children. The horizontal corneal diameter and AXL were shorter, the temporal and global RNFL thinner, and the nasal AOD 750 was narrower in the preterm children. Kirwan et al.[4] also found smaller corneal diameters in preterm infants at 31 weeks of gestation, but they also found thicker CCT in these infants compared with their term counterparts. The CCT, however, showed a decrease toward term that was progressive and statistically significant, whereas the corneal diameter was progressively longer toward term, showing an inverse correlation between these two parameters.[4] In our study, the CCT showed no significant difference between the term and preterm group. The corneal diameter however, was significantly smaller in the preterm group even at 7 to 9 years of age. This finding may be attributed to the fact that the rapid phase of corneal growth occurs during the first few months of life and subsequently slows down.[14] This rapid growth, however, is a deceleration compared with intrauterine cornea growth,[14] indicating that corneal

growth happens mostly in utero. Corneal growth was found to be most rapid during fetal life and ceases around a year after birth.[12] The corneal diameter was found to significantly increase during the last weeks of gestation.[15] Therefore, premature children would likely have arrested development at this stage, which may persist. In addition, Tucker et al.[15] also found postconceptional age to be a more significant predictor than birth weight on corneal diameter. We found corneal diameter correlated better with birth weight ($r = .353$; $P = 0.000$), than with gestational age ($r = .255$; $P = 0.000$).

We found a significantly shorter AXL in the preterm group compared with the term group. Tucker et al.[15] show a parallel linear relationship of postconceptional age with both birth weight and AXL. They found an AXL increased from 12.6 mm at 25 weeks to 16.2 mm at 37 weeks. A previous study showed that the diameter and circumference of the eyeball has an almost linear, parallel increase from 12 to 30 weeks of gestation.[13] This rate of growth however, reduced after 31 weeks.[13] The sagittal diameter (AXL) was found to be shortest during fetal life, but became equal to or longer than other meridians after birth.[17] The AXL was approximately 16 to 17 mm at birth, but increased to about 23 mm by 3 years of age, showing little increase thereafter.[13] As with the horizontal corneal diameter, the AXL in preterm children also seems to have a disruption in development, because the development is seen to occur mostly during 12 to 30 weeks of gestation.[13] We found a weak but significant correlation between AXL and birth weight, but not with gestational age.

RNFL loss generally occurs before perimetry visual field changes,[16] and the OCT may quantify this loss, assisting in the early diagnosis of optic nerve diseases before visual field loss. The normal RNFL thickness generally follows the ISNT rule, being thickest in the inferior and superior quadrant and thinnest in the temporal quadrant.[16] A violation of this rule may indicate glaucoma. The inferior rim is usually the first to be affected and is most strongly associated with glaucoma.[16] Although we found a generalized decrease in the mean RNFL in all quadrants of preterm eyes, the temporal and global RNFL were significantly thinner than in term children. The nasal and temporal quadrants have a generally low area under the receiver operating characteristic curves, especially in early glaucoma; thus, the thinning of these areas may give rise to the possibility of a nonglaucomatous optic neuropathy.[16]

We also found that the RNFL thickness in both groups of eyes did not follow the ISNT rule, with the superior quadrant being the thickest followed by the inferior, temporal, and nasal quadrants. This finding agrees with reports by Leung et al.[17] among normal children at a mean age of 9.75 years.

Several studies have found that global RNFL thickness in preterm eyes were thinner than term eyes.[18–20] These studies, however, included both preterm children with and without ROP. Åkerblom et al.[19] studied preterm and term children at a mean age of 8.6 and 10.1 years, respectively. They found that the global, superior, and nasal RNFLs were decreased in those with severe and treated ROP, but not in preterm children with mild or no ROP.[19] The thinner RNFL in those with severe and treated ROP was attributed to axonal death, owing to ablation of peripheral retina and also owing to the retinopathy itself, causing destruction to the ganglion cells.[19] They also concluded that premature children with a lower birth weight have a thinner RNFL owing to a negative effect on neural development. It was also noted that RNFL thickness had no association with visual acuity.[19] Another study on preterm children at a mean age of 10.6 years, also suggested that the thinner RNFL in premature children was associated with subclinical optic nerve hypoplasia.[18] The retinal ganglion cells start to form the RNFL and optic nerve only in the 8th week of gestation.[19] Keeping this factor in view, because the temporal area is the thinnest in the normal population, this thinning could, thus, be more pronounced in the preterm group owing to a disruption in normal neurodevelopment. A study on premature infants at 37 to 42 weeks, with and without ROP found that the papillomacular bundle and temporal RNFL were significantly thinner in those with ROP.[20] They also attributed these findings to arrested neurodevelopment and brain structure. This finding is in line with our findings, which shows persistent thinning at the temporal side in older preterm children.

A normative study of RNFL thickness among Hong Kong children showed a negative correlation of AXL and mean RNFL, where a 1 mm increase in AXL resulted in a reduction of RNFL by 2.7 to 2.9 um,[17] agreeing with our finding which showed reduction in global RNFL thickness by 2.61 um with every 1 mm increase in AXL. Although we found a significant weak positive correlation between global RNFL and both birth weight and gestational age, these two parameters were no longer significant when modelled using generalized estimating equation. Instead, the corneal diameter and AXL were found to be significant factors after adjusting for the angle and other clinical parameters. Åkerblom et al found increased RNFL thickness with larger birth weight but had no correlation with gestational age.[19]

Although all other AOD500 and AOD750 were not significantly different between the two groups, the nasal AOD750 was smaller in preterm compared with the term eyes, indicating a narrower angle opening at this quadrant. We could not find similar reports in the literature on angle assessment in both normal and preterm children. In adults, however, Maruyama et al.[21] found that the mean nasal AOD750 was 0.58 ± 0.24 mm. The superior angle is usually the narrowest whereas the inferior angle is the widest. The lateral angles are of intermediate width.[22] We postulate that although the angles in the preterm eyes are nonoccludable, the nasal angles seem to be narrower than term children. This condition may increase their susceptibility to angle-related problems in future, because angles narrow over time and the increase in lens thickness in later ages may aggravate the condition.

We only studied the temporal and nasal angles in these children, because the reproducibility of superior and inferior angles has been reported to be poor,[23] more so in children. This is due to the lid covering the superior angle and poorer image quality at the inferior angle causing variability in placement of the scleral spur.[23] The scleral spur was manually identified, but we tried to overcome this bias by calculating intraclass correlation coefficient to assess the interobserver agreement. Furthermore, the majority of our participants were Malay, and ethnicity may contribute to physiological differences in the eye.[24] With all these limitations, we propose future studies to evaluate the association between preterm birth and eye dimensions, especially angle-related problems at later ages, taking into consideration the ethnicity distributions.

Conclusions

Preterm children with no ROP have smaller eyes, more narrow angles, and thinner RNFL than their term counterparts. The effect from interrupted growth and development of ocular structures may not be evident so soon in life, but may cause effects later in life, which should be further studied into adulthood.

Acknowledgments

The authors thank the assistant science officers for their help in obtaining the ocular measurements.

Funded by the UKM Fundamental Grant (FF-2017-473).

Disclosure: **A.L.B. Kumarakulasinghe,** None; **N. Md Din,** None; **U.K. Mohd Noh,** None; **S.Z. Syed Zakaria,** None; **T. Aung,** None; **S.M. Khialdin,** None

References

1. World Health Organization. Preterm birth. 2018 Available at: www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed June 9, 2019.
2. Blencowe H, Cousens S, Chou D, Oestergaard M, Say L, Moller A-B, et al. Born too soon: the global epidemiology of 15 million preterm births. *Reprod Health*. 2013;10(Suppl 1):S2.
3. Mundey K, Chaudhry M, Sethi S. Long term ophthalmic sequelae of prematurity. *J Clin Ophthalmol Res*. 2015;3(1):3–7.
4. Kirwan C, O'Keefe M, Fitzsimon S. Central corneal thickness and corneal diameter in premature infants. *Acta Ophthalmol Scand*. 2005;83(6):751–753.
5. O'Connor AR, Wilson CM, Fielder AR. Ophthalmological problems associated with preterm birth. *Eye*. 2007;21(10):1254–1260.
6. Samarawickrama C, Huynh C, Liew G, Burlustky G, Mitchell P (2009) Birth weight and optic nerve head parameters. *Ophthalmology*. 116:1112–1118.
7. Uva MG, Reibaldi M, Longo A, Avitabile T, Gagliano C, Scollo D, et al. Intraocular pressure and central corneal thickness in premature and full-term newborns. *J Am Assoc Pediatr Ophthalmol Strabismus*. 2011;15(4):367–369.
8. Nongpiur ME, He M, Amerasinghe N, Friedman DS, Tay W-T, Baskaran M, et al. Lens vault, thickness, and position in Chinese subjects with angle closure. *Ophthalmology*. 2011;118(3):474–479.
9. Hansson H-A, Jerndal T. Scanning electron microscopic studies on the development of the iridocorneal angle in human eyes. *Invest Ophthalmol*. 1971;10(4):252–265.
10. Saunders KJ, McCulloch DL, Shepherd AJ, et al. Emmetropisation following preterm birth. *Br J Ophthalmol*. 2002;86:1035–1040.
11. *Visante OCT model 1000 system software version 3.0 user manual*. 1st ed. Dublin, CA, USA: Carl Zeiss Meditec; 2012:344.
12. Augusteyn RC, Nankivil D, Mohamed A, Maceo B, Pierre F, Parel JM. Human ocular biometry. *Exp Eye Res*. 2012;102:70–75.
13. Harayama K, Amemiya T, Nishimura H. Development of the eyeball during fetal life. *J Pediatr Ophthalmol Strabismus*. 1981;18(4):37–40.

14. Ronneburger A, Basarab J, Howland HC. Growth of the cornea from infancy to adolescence. *Ophthalmic Physiol Opt*. 2006;26(1):80–87.
15. Tucker SM, Enzenauer RW, Levin AV, Morin JD, Hellmann J. Corneal diameter, axial length, and intraocular pressure in premature infants. *Ophthalmology*. 1992;99(8):1296–300.
16. Vazquez LE, Huang LY. RNFL analysis in the diagnosis of glaucoma – measuring peripapillary retinal nerve fiber layer thickness with spectral-domain optical coherence tomography provides an objective and reliable estimate of glaucomatous optic nerve damage. *Glaucoma Today*. 2016;47–48.
17. Leung MMP, Huang RYC, Lam AKC. Retinal nerve fiber layer thickness in normal Hong Kong Chinese children measured with optical coherence tomography. *J Glaucoma*. 2010;19(2):95.
18. Wang J, Spencer R, Leffler JN, Birch EE. Characteristics of peripapillary retinal nerve fiber layer in preterm children. *Am J Ophthalmol*. 2012;153(5):850–855.
19. 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(7):956–960.
20. 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(6):1296–1308.e2.
21. Maruyama Y, Mori K, Ikeda Y, Ueno M, Kinoshita S. Morphological analysis of age related iridocorneal angle changes in normal and glaucomatous cases using anterior segment optical coherence tomography. *Clin Ophthalmol Auckl NZ*. 2014;8:113–118.
22. Campa C, Pierro L, Bettin P, Bandello F. Anterior chamber angle assessment techniques, glaucoma - basic and clinical concepts. *Intech*. 2011;89:590.
23. Kim DY, Sung KR, Kang SY, Cho JW, Lee KS, Park SB, et al. Characteristics and reproducibility of anterior chamber angle assessment by anterior-segment optical coherence tomography. *Acta Ophthalmol (Copenh)*. 2011;89(5):435–41.
24. Leung CK, Palmiero P-M, Weinreb RN, Li H, Sbeity Z, Dorairaj S, et al. Comparisons of anterior segment biometry between Chinese and Caucasians using anterior segment optical coherence tomography. *Br J Ophthalmol*. 2010;94(9):1184.