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Biphasic Change in Retinal Nerve Fibre Layer Thickness from 30 to 60 Weeks Postmenstrual Age in Preterm Infants

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Abstract

Background/Aims: The optic nerve development during the critical postnatal weeks of preterm infants is unclear. We aimed to investigate the change of retinal nerve fibre layer (RNFL) in preterm infants.

Methods: We used an investigational handheld optical coherence tomography (OCT) system to serially image awake preterm infants between 30 and 60 weeks postmenstrual age (PMA) at the bedside. We assessed RNFL thickness in the papillomacular bundle and nasal macular ganglion cell layer + inner plexiform layer (GCL+IPL) thickness. We applied a segmented mixed model to analyze the change in the thickness of RNFL and GCL+IPL as a function of PMA.

Results: From 631 OCT imaging sessions of 101 infants (201 eyes), RNFL thickness followed a biphasic model between 30 and 60 weeks, with an estimated transition at 37.8 weeks PMA (95% confidence interval (95%CI): 37.0 to 38.6). RNFL thickness increased at 1.8 μm/week (95%CI: 1.6 to 2.1) before 37.8 weeks and decreased at −0.3 μm/week (95%CI: −0.5 to −0.2) afterwards. GCL+IPL thickness followed a similar biphasic model, in which the thickness increased at 2.9

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μm/week (95%CI: 2.5 to 3.2) before 39.5 weeks PMA (95%CI: 38.8 to 40.1) and then decreased at −0.8 μm/week (95%CI: −0.9 to −0.6).

Conclusion: We demonstrate the feasibility of monitoring RNFL and GCL+IPL thickness from OCT during the postnatal weeks of preterm infants. Thicknesses follow a biphasic model with a transition age at 37.8 and 39.5 weeks PMA, respectively. These findings may shed light on optic nerve development in preterm infants and assist future study designs.

INTRODUCTION

Although the survival of preterm infants has increased worldwide,[1] the risk of major neurodevelopmental disabilities in the later life of very preterm infants remains approximately 50%.[2] Very preterm infants are also at risk of developing ophthalmic diseases, including retinopathy of prematurity (ROP), optic atrophy, myopia, strabismus, amblyopia, and visual field deficit.[3–5] In the retina, ganglion cells project axons through the innermost retina to form the optic nerve, marking the beginning of the anterior visual pathway.[6] The unmyelinated axons of retinal ganglion cells form most of the retinal nerve fibre layer (RNFL).[7]

Portable handheld optical coherence tomography (OCT) has enabled rapid, non-contact, and high-resolution imaging of the retinal layers and optic nerve in awake infants,[8] and their RNFL thickness has been correlated with brain MRI findings[9] as well as cognitive and motor functions in infants,[10] making the RNFL a potential biomarker for brain and cognitive integrity. But to date, there have been no *in vivo* descriptions of the development of the optic nerve or the visual pathway during the critical postnatal weeks of preterm infants since most previous studies that assessed RNFL thickness in infants included only 1 OCT imaging session per infant.[10–14] Understanding how RNFL thickness changes in preterm infants may shed light on optic nerve development, guide clinicians to address retinal or optic nerve pathology in infants, and assist the design of future studies.

The primary purpose of this study is to investigate the longitudinal change (i.e., the pattern and rate) of RNFL thickness from 30 to 60 weeks postmenstrual age (PMA) in preterm infants enrolled in the STudy of Eye imaging in Preterm infantS (BabySTEPS; ClinicalTrials.gov identifier: NCT02887157). As a seminal prospective study using RNFL thickness as a measure, we also tested the inter-grader reproducibility of RNFL thickness and the inter-eye relationship of RNFL thickness across different PMAs. We assessed the association of RNFL thickness with central foveal thickness, which has been associated with the severity of macular oedema.[15] A nonpositive association would suggest that RNFL thickness measurement is not influenced by macular oedema severity. Additionally, we analyzed ganglion cell layer + inner plexiform layer (GCL+IPL) thickness outside the foveal centre to test the hypothesis that the longitudinal change in RNFL thickness and GCL+IPL thickness follows the same pattern.

METHODS

Study Participants and Procedure

BabySTEPS is a prospective observational study to assess the visual and neurological development of preterm infants. This study involves human participants and was approved by the Duke University Health System Institutional Review Board (IRB #: Pro00069721) and adhered to the tenets of the Declaration of Helsinki. We described the BabySTEPS design, OCT image capture, image processing, and thickness measurements in our previous papers.[13 15] Briefly, we enrolled 118 infants eligible for retinopathy of prematurity (ROP) screening based on the American Association of Pediatrics guidelines[16] from August 2016 through November 2019. The parent or legal guardian provided informed consent to participate in the study. We excluded infants with ocular opacity that would preclude eye imaging or who had a health condition (e.g., anencephaly) other than prematurity that had a profound impact on brain development.

We obtained infant medical data from the medical record consistent with data collected for the Generic Database, a registry of clinical information of very low birth weight infants born alive in Eunice Kennedy Shriver NICHD Neonatal Research Network centres (ClinicalTrials.gov identifier: NCT00063063). Certified imagers used an investigational handheld high-speed, swept-source OCT system to image awake infants in the Duke intensive care nursery or Duke Regional Hospital nursery during each ROP clinical examination while infants' pupils dilated.[15] The imaging was performed without pharmacologic pupil dilation if there were no corresponding clinical ROP screening exams. Per imaging session, one imager held the non-contact OCT probe[17] to image the infant without eyelid speculums and a second imager operated the software (Figure 1). The near-infrared light from OCT was nearly invisible to infants. Imagers typically imaged infant's right eyes followed by the left eyes, although the imaging protocol did not require a fixed order of imaging infants' eyes. Across the study, 4 imagers performed the handheld OCT examinations. We used proprietary infant-specific software (DOCTRAP V66.2) to automatically segment the OCT images and review for corrections by a trained grader (K.P.W.).[13 15] Based on the corrected segmentation, we extracted the central foveal thickness,[15] nasal macular GCL+IPL thickness at 1000 μm nasal to the fovea,[15] and RNFL thickness in the papillomacular bundle (PMB)[13] for each imaging session. To assess inter-grader reproducibility of RNFL thickness, we randomly selected 10 OCT volumes (1 per infant) that were segmented by the primary grader (K.P.W.) for PMB RNFL at 31 ± 1, 33 ± 1, 36 ± 1, 39 ± 1, and 41 ± 1 weeks postmenstrual age (PMA) windows, for segmentation by a second grader (D.T.) masked to the original grading.

In the present study, we included all infant eyes with ≥ 1 eligible OCT imaging session. Eligible sessions occurred before or on 60 weeks 6 days PMA and did not meet any of the following exclusion criteria: PMB RNFL thickness could not be segmented; RNFL thickness was measured on < 90% of the PMB arc[13]; the imaging session occurred after treatment for ROP.

Statistical Analysis

We analyzed the data using MATLAB (The MathWorks, Inc, Natick, MA) and R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). We calculated the intraclass correlation coefficients (ICC) of RNFL thickness for assessing the inter-grader reproducibility. The 95% confidence interval (CI) of the ICC was calculated based on the percentile bootstrap method.

We calculated the Pearson correlation coefficients (r) of the inter-eye relationship of PMB RNFL thickness, the association between PMB RNFL thickness and central foveal thickness, and the association between PMB RNFL thickness and nasal macular GCL+IPL thickness at 31 ± 1, 33 ± 1, 36 ± 1, 39 ± 1, and 41 ± 1 weeks PMA. We did not include temporal macular GCL+IPL thickness in the analysis because the temporal macula may be affected by ROP in these preterm infants. For infants with multiple OCT imaging sessions during a 2-week window, we selected the session closest to the target PMA and randomly selected 1 session if an infant had imaging sessions at equal intervals from the target PMA. We compared the difference in RNFL thickness between the right and left eyes via a paired *t*-test.

We included eyes with ≥ 4 eligible OCT imaging sessions for assessing longitudinal change in PMB RNFL thickness. A segmented regression model is a widely employed statistical method to evaluate the existence and location of a transition point where the slope of a linear regression changes significantly.[18] We performed a segmented mixed model (in R 3.6.2; developed by Muggeo et al[18 19]) of PMB RNFL thickness as a function of PMA with the eye as the unit of analysis and data from both eyes were included for analysis. In this model, we accounted for the inter-eye correlation of an infant and longitudinal correlation among measures from the same eye by using eye-level random intercept, infant-level random intercept, transition point, and slope difference. We also performed a segmented regression model of nasal macular GCL+IPL thickness as a function of PMA.

RESULTS:

Study Cohort and Inter-Grader Reproducibility

Among 118 infants enrolled in the BabySTEPS, we successfully captured 1752 eye imaging sessions in which 1691 (96.52%) sessions had the PMB imaged successfully for RNFL (2.11% not imaged, 1.31% imaged but insufficient to determine optic nerve foveal axis, and 0.05% insufficient quality for grading the PMB RNFL). Of 1691 OCT images with successfully imaged PMB, we were able to measure the PMB RNFL thickness in 1522 (90.01%) sessions. 17 of 118 infants were excluded from the study because 11 infants were transferred out of nursery before any OCT imaging, 5 infants died before any OCT imaging, and 1 infant did not have any RNFL thickness measurement due to poor image quality. One eye of the remaining 101 infants was excluded because the RNFL thickness was not measurable on OCT due to poor image quality. In total, 201 eyes from 101 infants (51.5% female) had at least 1 eligible OCT imaging sessions (631 sessions in total) and were included in the present study. The mean ± standard deviation (SD) of gestational age

was 28.0 ± 2.7 weeks, and the birth weight was 979.5 ± 290.4 grams. Table 1 shows the characteristics of the study cohort.

We found excellent inter-grader reproducibilities of PMB RNFL thickness at 31, 33, 36, 39, and 41 weeks PMA (ICC = 0.88 to 0.97; Supplemental Table 1). The mean difference between the RNFL thickness measured by 2 graders ranged from −0.5 to 2.8 μm across different PMAs. Overall, the RNFL thickness across all PMAs measured by the 2 graders had a mean ± SD difference of 0.5 ± 3.8 μm (ICC = 0.92).

RNFL and GCL+IPL Thickness at Different PMA Windows

PMB RNFL thickness was highly correlated between right and left eyes in all PMA windows (r = 0.80 to 0.88; Table 2). RNFL thickness was higher (by 1.5 to 3.4 um) in the right eyes than in the left eyes across all PMAs, and the inter-eye difference was statistically significant at 36 and 41 weeks ($P < 0.001$ and = 0.02, respectively; Table 2).

Nasal macular GCL+IPL was correlated between right and left eyes in all age windows (r = 0.62 to 0.84) without any statistically significant inter-eye difference (Supplemental Table 2).

We found a weak, negative association between PMB RNFL thickness and central foveal thickness in both right and left eyes across all PMAs (r = −0.39 to −0.17; Supplemental Table 3). PMB RNFL thickness was positively associated with nasal macular GCL+IPL thickness in both right and left eyes across all PMAs (r = 0.45 to 0.63; Supplemental Table 4).

Longitudinal Change in RNFL and GCL+IPL Thickness

We included 145 eyes of 77 infants who had at least 4 eligible OCT imaging sessions in the longitudinal analysis, and their changes in RNFL thickness and nasal macular GCL+IPL thickness over time are shown in Supplemental Figure 1. In a representative infant (#91 in Supplemental Figure 1), RNFL thickness in the right and left eye increased from 57.0 to 70.5 μm (right) and from 50.6 to 62.7μm (left) between 31 and 39 weeks and then declined to 63.8 μm (right) and 52.3 μm (left) at 57 weeks (Figure 2). RNFL remained thicker in the right than in the left eye across the 3 PMAs.

The longitudinal change in PMB RNFL thickness followed a biphasic model with a transition PMA of 37.8 weeks (95% CI: 37.0 to 38.6) (Figure 3A). The estimated slope was 1.8 μm/week (95% CI: 1.6 to 2.1) before and −0.3 μm/week (95% CI: −0.5 to −0.2) after the transition PMA. The difference in slope between before and after the transition point was 2.2 μm/week (95% CI: 2.0 to 2.5; $P < 0.001$).

Similarly, the longitudinal change in nasal macular GCL+IPL followed the biphasic trend of the RNFL with a transition at 39.5 weeks PMA (95% CI: 38.8 to 40.1) (Figure 3B). The estimated slope was 2.9 μm/week (95% CI: 2.5 to 3.2) and −0.8 μm/week (95% CI: −0.9 to −0.6) before and after the transition age, respectively (difference in slope = 3.6 μm/week, 95% CI: 3.2 to 4.0; $P < 0.001$).

DISCUSSION

Using bedside swept-source OCT with custom-built, handheld ultra-compact imaging probes, we successfully assessed PMB RNFL thickness in 101 awake preterm infants between 30 and 60 weeks PMA and achieved excellent inter-grader reproducibility of RNFL thickness at each PMA window. The longitudinal change in RNFL thickness in preterm infants followed a biphasic model between 30 and 60 weeks PMA, with a transition at 37.8 weeks PMA. RNFL thickness increased at 1.8 μm/week before the transition and decreased at −0.3 μm/week afterwards. Nasal macular GCL+IPL thickness was moderately associated with PMB RNFL thickness from 31 to 41 weeks PMA (r = 0.45 to 0.63) and followed the same biphasic longitudinal change with a similar transition age at 39.5 weeks. The right and left eyes were highly correlated in both the RNFL and GCL+IPL thickness from 31 to 41 weeks PMA (r = 0.80–0.88 for RNFL and 0.62–0.84 for GCL+IPL). Interestingly, RNFL was thicker (by 1.5 to 3.4 um) in the right than in the left eyes across all PMA windows. We found a weak negative association between RNFL thickness and central foveal thickness (r = −0.39 to −0.17).

Our previous pilot study of 27 very preterm infants showed that PMB RNFL thickness increased by 15 μm from 33.8 to 38.3 weeks PMA,[10] consistent with our present finding (Figure 3A). However, our prior study did not assess RNFL thickness after 42 weeks PMA. Patel et al measured peripapillary temporal RNFL thickness in full-term infants and found that RNFL thickness decreased from birth (approximately 40 weeks PMA) to 18 months of age,[12] corresponding to our finding of RNFL thinning after 37.8 weeks PMA in preterm infants.

The observed biphasic change in RNFL thickness in preterm infants may be related to a change in the ganglion cell axon number, oedema, or both. During natural fetal development, each optic nerve contains about 2.85 million optic fibres at the end of the second trimester (14–27 weeks PMA).[20] About 1.85 million supernumerary fibres are eliminated during the third trimester (after 28 weeks PMA).[20 21] Therefore, we expected to find RNFL thinning between 30 and 40 weeks PMA in preterm infants. Interestingly, we observed a significant increase, instead of a decrease, in RNFL thickness from 30 to 37.8 weeks PMA in preterm infants, suggesting that a change from the intrauterine to extrauterine environment may alter optic nerve development. One hypothesis is that early visual stimulation in these premature infants may prevent normal third-trimester axon elimination and promote retinal ganglion cell growth.[21 22] This hypothesis is supported by a previous finding in cultured rat cells that retinal ganglion neurons that receive an electrical signal produce more neurotropic factors, which may promote the growth of nearby neurons.[23] If this hypothesis is correct, the number of retinal ganglion cells should also increase in the same time frame, which is consistent with our finding on the increase of nasal macular GCL+IPL thickness from 30 to 39.5 weeks PMA. However, this hypothesis cannot explain why RNFL and GCL+IPL thickness start to decline after term-equivalent age.

Macular oedema is another possible factor responsible for the biphasic change in RNFL thickness in preterm infants. Approximately 60% of preterm infants have macular oedema,[15 24] so it is possible that the onset and resolution of macular oedema could

affect these measures. If this is the case, PMB RNFL thickness should be positively associated with the central foveal thickness, a biomarker for macular oedema severity.[15] However, we found a weak, negative association between RNFL thickness and central foveal thickness, undermining this hypothesis. The underlying mechanism for the negative association between central foveal thickness and RNFL thickness is yet unclear.

Other factors that could play a role in the biphasic change in longitudinal thickness of the RNFL and the GCL+IPL include: RNFL oedema secondary to inflammation or high intracranial pressure; development or loss of astrocytes, microglia or Müller cell components;[25] myelinations of the optic nerve reaching the lamina cribrosa at term-age (it progresses from the brain toward the globe starting at 32 weeks PMA).[26] Since OCT cannot yet differentiate oedema from ganglion cell axons or other cells in the RNFL thickness measurement or myelin behind the lamina cribrosa, future studies are required to understand the underlying mechanism responsible for our observations.

Many previous studies in adults and school-aged children have reported that RNFL thickness, assessed by OCT, is statistically significantly higher in the right than in the left eyes.[27–35] We recently reported a similar inter-eye RNFL thickness difference at 36 weeks in preterm infants and discussed possible underlying mechanisms.[13] Here, we added that RNFL thickness in the right eyes was consistently higher than RNFL thickness in the left eyes across all PMA windows, although only borderline significant at 31, 33, and 39 weeks (P = 0.07, 0.06, and 0.07, respectively; Table 2). The lack of statistical significance in the 3 PMA windows may be due to lower statistical power caused by a relatively small number of infants with RNFL thickness measures at these PMA weeks.

Our results provide several insights for the design of future studies aiming to investigate the clinical value of RNFL thickness in preterm infants. First, the excellent inter-grader reproducibility of RNFL thickness suggests PMB RNFL thickness measured at a young PMA as a reproducible anatomic outcome measure in future studies. However, the reproducibility was slightly lower at 31 weeks (ICC = 0.88) than at older PMAs (ICC = 0.96 to 0.97), which should be considered in the future study design and statistical power calculation. Second, due to the high inter-eye correlation in RNFL thickness across all PMAs (r = 0.80 to 0.88), future studies may only need to image 1 eye per infant, which will reduce the number of imagings by half. However, since RNFL is thicker in the right than in the left eyes, future studies should choose the same eye laterality among the entire cohort. Besides, future studies should account for the dynamic change in PMB RNFL thickness during the postnatal weeks of preterm infants. One example is to evaluate RNFL thickness within a narrow age window to minimize the confounding effect of RNFL longitudinal change.

Our study has several limitations. First, since our study included imaging sessions from 30 to 60 weeks PMA, we do not yet know how RNFL thickness changes after 60 weeks PMA. We are pursuing these answers as we follow this cohort to early school age in the BabySTEPS2 (ClinicalTrials.gov identifier: NCT04995341). Second, we do not have RNFL thickness measurements after term age in several infants because we excluded imaging sessions after ROP treatment, or some infants were lost to follow-up. Third,

neurodevelopmental outcomes that are required to determine the predictive value of RNFL thickness for neurodevelopment are still being gathered (at age 2 years). Fourth, we only included nasal macular GCL+IPL thickness in the present study because ROP may affect the temporal macula, and OCT macular volumes did not consistently include both superior and inferior macular quadrants. The longitudinal change in GCL+IPL thickness in other macular quadrants may differ from the nasal macula. Finally, since the present study aims to investigate the pattern and rate of RNFL thickness change in preterm infants, we did not investigate the impact of maternal factors, birth factors, infant systemic diseases, and ROP treatments on the longitudinal change in RNFL thickness among preterm infants. These questions will be addressed in future studies.

CONCLUSIONS

PMB RNFL thickness can be measured with an excellent inter-grader reproducibility between 31 to 41 weeks PMA. The longitudinal change in RNFL thickness follows a biphasic model between 30 and 60 weeks PMA, with an estimated transition age of 37.8 weeks. Also, the longitudinal change in nasal macular GCL+IPL thickness follows a similar biphasic model with a transition at 39.5 weeks. To our knowledge, the study is the first to describe the change in RNFL and GCL+IPL thickness in preterm infants from 30 to 60 weeks PMA. These findings may shed light on the optic nerve development in preterm infants and may assist the design of future studies aiming to evaluate the clinical application of RNFL thickness in preterm infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages:

- What is already known on this topic
  - Retinal nerve fiber layer (RNFL) thickness assessed by the optical coherence tomography (OCT) is a noninvasive biomarker for optic nerve integrity and a potential biomarker for brain and cognitive integrity in infants but the longitudinal change of RNFL thickness and optic nerve development during the critical postnatal weeks of preterm infants are unclear.
- What this study adds
  - Handheld OCT systems can monitor RNFL and ganglion cell layer + inner plexiform layer (GCL+IPL) thickness during the postnatal weeks of preterm infants.
  - RNFL thickness in preterm infants increased at 1.8 μm/week from 30 to 37.8 weeks postmenstrual age (PMA) and then decreased at −0.3 μm/week from 37.8 weeks to 60 weeks PMA.
  - The longitudinal change in nasal macular GCL+IPL thickness follows a similar biphasic model with a transition at 39.5 weeks PMA.
- How this study might affect research, practice or policy
  - Our findings shed light on the optic nerve development in preterm infants and may assist the design of future studies aiming to evaluate the impact of diseases and interventions on the optic nerve (and visual pathway) in preterm infants.

SYNOPSIS

Our prospective study of 101 preterm infants found that the retinal nerve fibre layer thickness increased before (1.8 μm/week) and decreased after (−0.3 μm/week) 37.8 weeks postmenstrual age, shedding light on the optic nerve development.

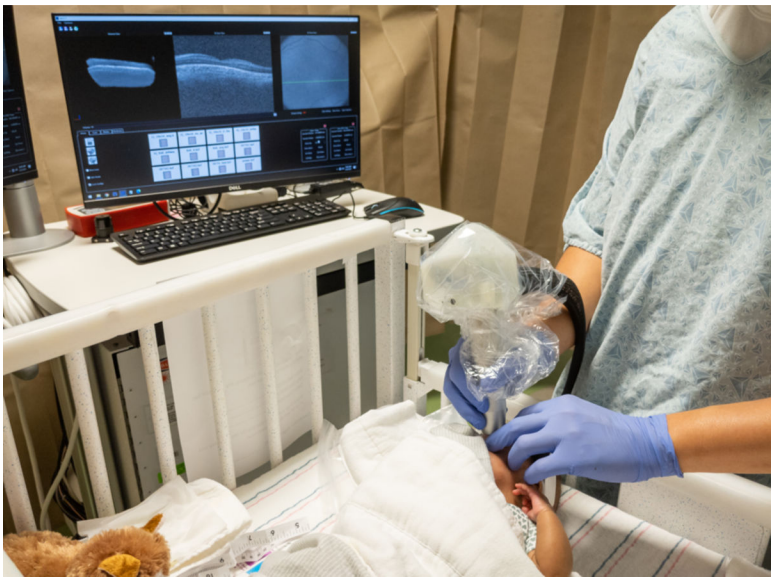

Figure 1.

Bedside handheld optical coherence tomography (OCT) imaging of a preterm infant. The viewing screen is across from the imager who is holding the eyelids open with the left hand and holding the handpiece (which is in a single-use disposable cover) with the right hand. Note the handpiece is held near the tip of the imaging barrel for accurate positioning, the OCT investigational device does not touch the infant and the black tether cord transmits the signal from the handpiece to the OCT system in the cart.

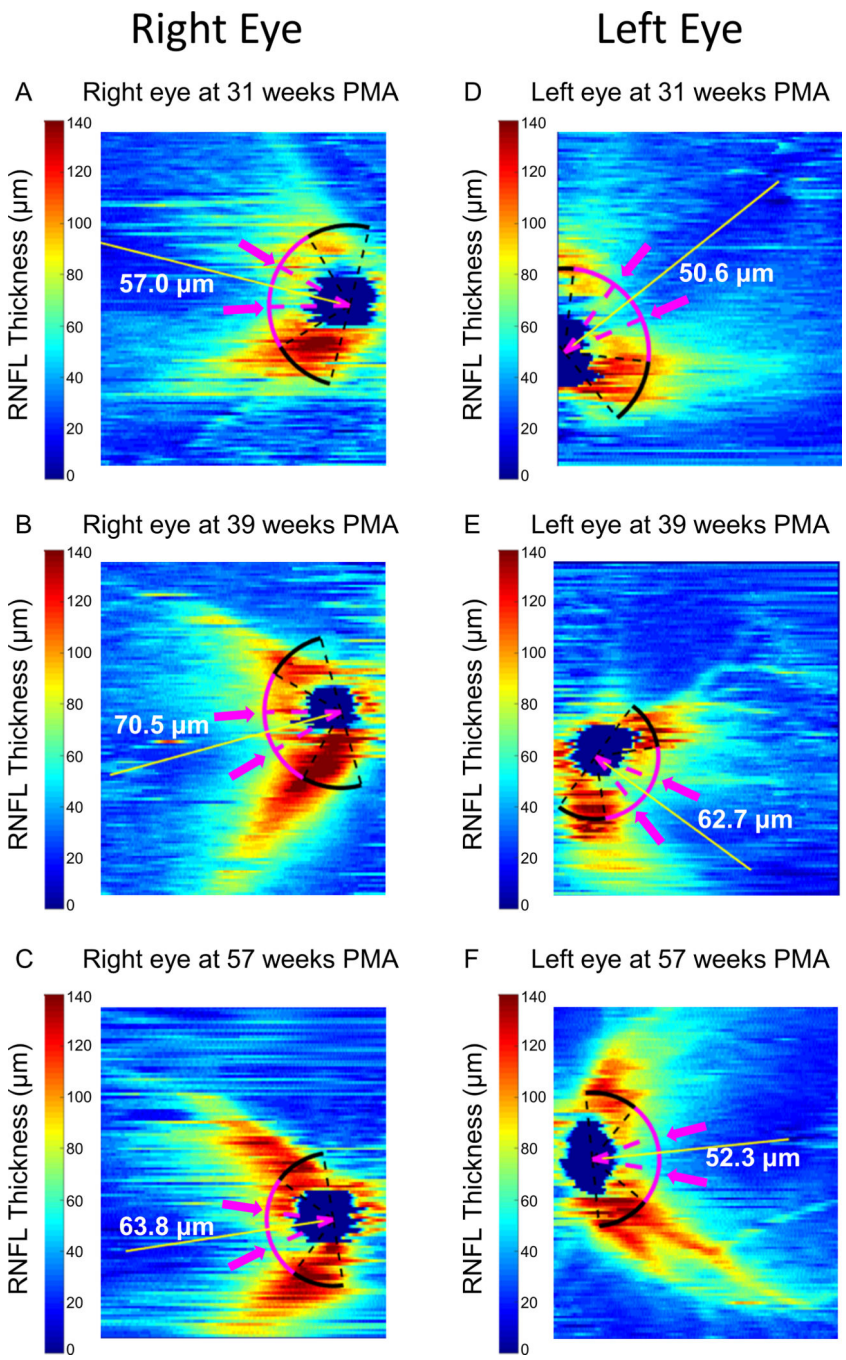

Figure 2.

Demonstration of the longitudinal change of retinal nerve fibre layer (RNFL) thickness in (A–C) the right eyes and (D–F) the left eyes. In each figure, the solid yellow line indicates the organising axis from the optic nerve centre to the fovea. The pink arc between two dashed pink lines and arrows represent the papillomacular bundle (arc from −15 to +15 degrees relative to the organising axis), where we measured the RNFL thickness in the study. In the right eye, RNFL thickness increased from 57.0 to 70.5 μm between 31 and 39 weeks and then declined to 63.8 μm at 57 weeks. Similarly, RNFL thickness increased from 50.6

to 62.7 μm between 31 and 39 weeks and then declined to 52.3 μm at 57 weeks. RNFL remained thicker in the right eye than in the left eye at all the three postmenstrual ages (PMA).

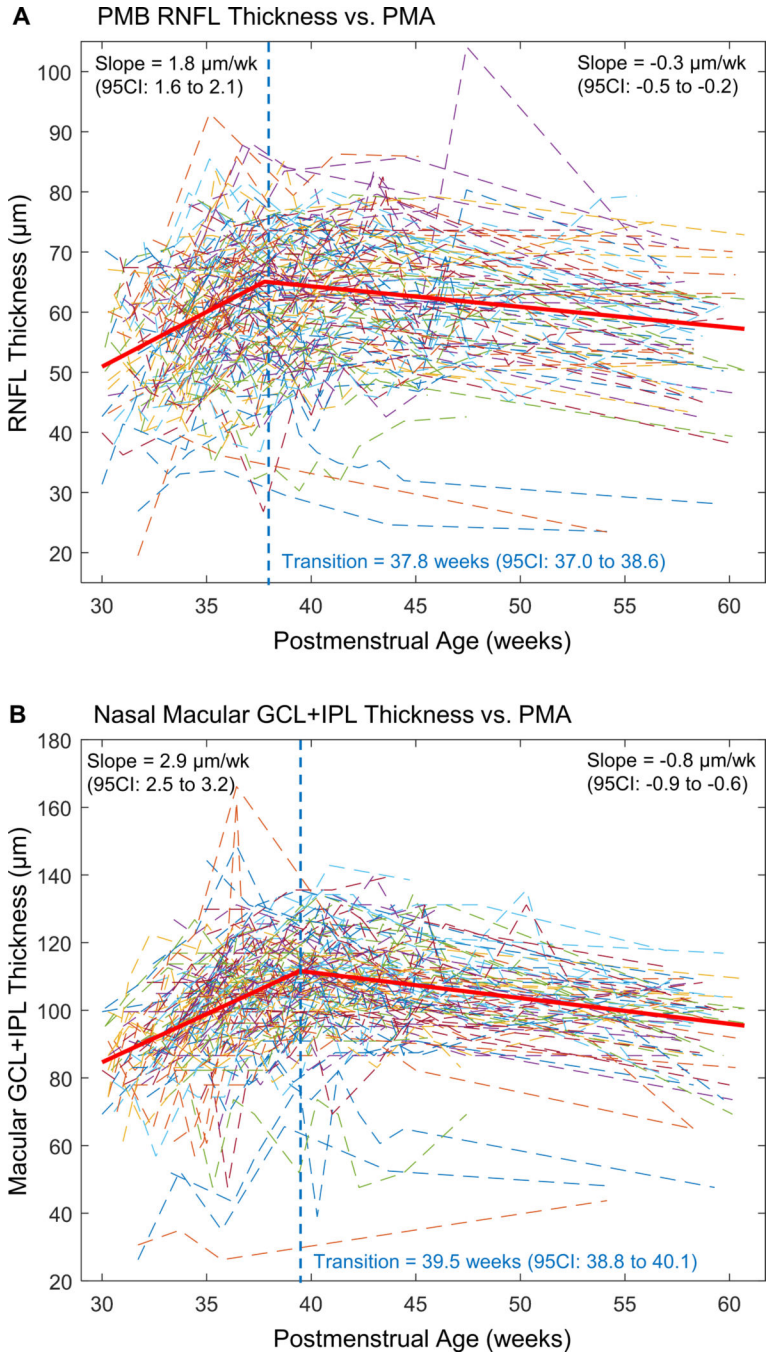

Figure 3.

Longitudinal change of (A) retinal nerve fibre layer (RNFL) thickness at papillomacular bundle (PMB) and (B) nasal macular ganglion cell layer+inner plexiform layer (GCL+IPL) thickness in 145 eyes of 77 infants. The raw data of individual eyes are shown in online supplemental figure 1. Each line represents the data of an eye. We estimated the segmented linear regression (red line) based on a segmented mixed regression model. (A) The longitudinal change of PMB RNFL thickness follows a biphasic trend with an estimated transition postmenstrual age (PMA) of 37.8 weeks (95% CI: 37.0 to 38.6). The estimated

slope is 1.8 μm/week (95%CI: 1.6 to 2.1) and −0.3 μm/week (95%CI: −0.5 to −0.2) before and after the transition age, respectively (difference in slope=2.2 μm/week, 95%CI: 2.0 to 2.5; p<0.001). (B) Interestingly, the longitudinal change of nasal macular GCL+IPL follows the same biphasic trend with an estimated transition PMA of 39.5 weeks (95%CI: 38.8 to 40.1). The estimated slope is 2.9 μm/week (95%CI: 2.5 to 3.2) and −0.8 μm/week (95%CI: −0.9 to −0.6) before and after the transition age, respectively (difference in slope=3.6 μm/week, 95%CI: 3.2 to 4.0; p<0.001).

Table 1.

Characteristics of the Study Cohort on Infant-Level

Number of infants (eyes)	101 (201)
Number of OCT imaging sessions[a]	631
Number of OCT imaging sessions per infant, median (Q1–Q3)	5 (4–8)
Gestational age, mean ± SD, wks	28.0 ± 2.7
Birth weight, mean ± SD, gm	979.5 ± 290.4
Sex, n (%)	
Female	52 (51.5)
Race, n (%)	
African-American	47 (46.5)
Asian	5 (5.0)
White	45 (44.6)
More than one	4 (4.0)
Ethnicity, n (%)	
Non-Hispanic	92 (91.1)
PMA at the first imaging session, median (Q1–Q3), wks	33.1 (31.7–34.4)
PMA at the last imaging session, median (Q1–Q3), wks[b]	47.1 (38.5–58.2)
Maximum ROP stage, n (%)[c]	
Stage 0	43 (42.6)
Stage 1	16 (15.8)
Stage 2	26 (25.7)
Stage 3	15 (14.9)
Stage 4	1 (1.0)
Maximum plus disease, n (%)[c]	
None	83 (82.2)
Pre-plus disease	7 (6.9)
Plus disease	11 (10.9)
Any treatment for ROP, n (%)[d]	
None	89 (88.1)
Laser photocoagulation	3 (3.0)
Bevacizumab and laser photocoagulation	9 (8.9)

OCT = optical coherence tomography; PMA = postmenstrual age; Q1 = first quartile; Q3 = third quartile; ROP = retinopathy of prematurity; SD = standard deviation.

[a] Among 631 OCT imaging sessions, 533 (84.5%) sessions have RNFL thickness measurements from both eyes of the same infants.

[b] The last imaging session before or on 60 weeks and 6 days PMA. Imaging sessions after the treatment for retinopathy of prematurity were excluded from the analysis, which contributed to the large interquartile range of PMA at the last imaging session.

[c] The highest stage across all visits in the worse eye for each infant.

[d] The ROP treatment that an infant received regardless of the eye laterality.

Table 2.

Inter-eye Relationship of Retinal Nerve Fiber Layer Thickness at the Papillomacular Bundle Among Infants with Data from Both Eyes

Postmenstrual age	Number of Infants	RNFL Thickness in Right Eyes (μm)	RNFL Thickness in Left Eyes (μm)	RNFL Thickness in Right – Left Eyes (μm)	*P* for inter-eye difference in RNFL Thickness	r for inter-eye correlation in RNFL Thickness
31 weeks	21	54.9 ± 11.0	52.6 ± 11.5	2.3 (−0.2, 4.8)	0.07	0.88
33 weeks	50	55.8 ± 11.4	54.0 ± 10.3	1.8 (−0.1, 3.7)	0.06	0.82
36 weeks[a]	76	63.1 ± 11.7	59.7 ± 10.6	3.4 (1.7, 5.0)	< 0.001	0.80
39 weeks	59	63.1 ± 10.5	61.6 ± 10.4	1.5 (−0.2, 3.2)	0.07	0.81
41 weeks	47	64.3 ± 10.9	62.2 ± 9.7	2.2 (0.4, 3.9)	0.02	0.83

r = Pearson's correlation coefficient; RNFL = retinal nerve fiber layer.

Values are mean ± standard deviation and mean (95% confidence interval).

[a]Data at 36 weeks PMA were reported in our previous paper: Shen LL, Mangalesh S, McGeehan B, et al. Birth Weight Is a Significant Predictor of Retinal Nerve Fiber Layer Thickness at 36 Weeks Postmenstrual Age in Preterm Infants. Am J Ophthalmol. 2020 Sep 4;222:41–53.