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Characterization of Foveal Development in Treatment-Naïve Extremely Preterm Infants

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Objective: To characterize and quantify foveal development in treatment-naïve extremely preterm infants using optical coherence tomography.

Methods: In this cross-sectional study, eyes treated for retinopathy of prematurity before imaging were excluded. Inner retinal thickness and outer retina thickness at foveal center and foveal rim were assessed. Extremely preterm (EPT, <28 weeks gestational age) eyes were compared with infants more than 28 weeks of gestation using a multivariable dimension reduction analysis (principal component analysis) and a bilinear factor mode analysis (partial least square discriminant analysis) to determine group intervariability. Further analyses were performed to investigate the effects of gestation on foveal development.

Results: Twenty-six infants born at gestational ages ranging from 22 to 39 weeks were imaged between 32 and 80 weeks postmenstrual age. A principal component analysis and partial least squares discriminant analysis revealed that the foveal inner retina thickness was the main difference between EPT infants and non-EPT infants. This difference was reflected by comparing their inner retinal thickness over time (32–80 weeks postmenstrual age), which revealed a sustained thicker foveal inner retina for EPT infants when compared with non-EPT infants. The foveal pit seemed to be shallower in EPT infants when compared with non-EPT infants.

Conclusions: Twenty-eight weeks of gestation seems to be a critical timepoint for foveal development; EPT infants had altered foveal inner retinal development throughout early postnatal development, which led to a thicker foveal inner retina and a shallower foveal pit soon after birth.

Translational Relevance: Measuring untreated foveal parameters informs about the effects of prematurity on the fovea and provides a baseline when comparing with post-treatment foveal development.

Introduction

Globally, the survival of premature infants has improved owing to advances in neonatal care. However, premature infants remain at high risk for death and disability.[1–3] Similarly, immaturity of retinal neural and vascular development at preterm birth leads to a higher incidence of retinopathy of prematurity (ROP).[4]

Our knowledge of foveal development is initially derived from a small number of histological studies in postmortem human tissues.[5–8] From these studies, we have learned that the foveal pit becomes discernable at around 25 fetal weeks (equivalent to 27 weeks gestational age [GA]), owing to centrifugal displacement of

the inner retinal layers.[5] Cone packing and elongation of the inner and outer segments cause the fovea to thicken soon after birth.[5,8] Therefore, the normal foveal development might be interfered when infants are born extremely preterm (EPT) (<28 weeks GA).

It has been documented that prematurity and ROP both alter foveal development, which has been associated with abnormalities that include an inability to displace inner retinal layers away from the fovea, causing thickening of the fovea that persisting into childhood and adulthood.[9–16] Advancements in optical coherence tomography (OCT) acquisition has allowed for the visualization of the fovea in supine infants, thus providing an opportunity to refine our understanding of foveal development. Therefore, the purpose of this study was to investigate OCT features that occur in foveal development during the postnatal period. It has been documented that ROP treatment affects foveal development,[17] which poses the question regarding foveal development in the absence of treatment. Our study explores the pathological progression that prematurity has on the developing retina, without the interference of ROP treatment. We hypothesized that infants born before 28 weeks of gestation (EPT infants), regardless of ROP, would demonstrate an attenuation of normal inner retinal thinning.

Methods

Subjects

An observational, cross-sectional study was performed at the Mattel Children's Hospital, University of California Los Angeles with institutional review board approval and parental consent. The study adhered to the guidelines of Health Insurance Portability and Accountability Act and the tenets of the Declaration of Helsinki. Infants were eligible for the study if undergoing ROP screening (i.e., <30 weeks of gestation, birth weight of <1500 g, or if deemed as having clinical instability per the clinical care team per 2013 American Association for Pediatric Ophthalmology and Strabismus/American Academy of Ophthalmology guidelines)[18] or if undergoing a sedated procedure in the neonatal intensive care unit. Exclusion criteria included genetic abnormalities or congenital infections known to affect eye structure or development. Infants who received ROP treatment before imaging were also excluded. EPT was defined as infants born at less than 28 weeks of gestation.[1] Non-EPT infants consisted of those born at a gestational age of 28 to 39 weeks.

Clinical Characteristics of Subjects

Demographic and clinical data were collected for each subject, including sex, GA, birth weight, and postmenstrual age (PMA) at the time of imaging. Indirect ophthalmoscopy for ROP screening was performed in those infants eligible for ROP screening. Stage of ROP was documented according to the International Classification of ROP.[18]

OCT Imaging

Before imaging and eye examinations, infant feeds were held for 4 hours to prevent reflux from gastroparesis. Eyes were dilated with cyclopentolate hydrochloride 0.2% phenylephrine hydrochloride 1% ophthalmic solution 1 hour before examination. Infants were imaged in a supine position. To maintain a clear cornea, ocular lubrication was applied throughout the imaging procedure. In addition, vital signs (heart rate and oxygen saturations) were monitored continuously using pulse oximetry. The Spectralis Flex Module (Heidelberg Engineering GmbH, Heidelberg, Germany) was used to obtain the OCT images, using an acquisition protocol consisting of seven horizontal B-scans spaced 60 to 120 microns apart through the central macula, with the foveal center defined as the shallowest point.[19]

Image Analysis

Images were reviewed by a masked certified OCT grader (Y.H,) from the Doheny Image Reading Center. Only one visit of each subject with the best image quality was included. As described previously, a single B-scan through the foveal center, as defined by the deepest foveal pit, was selected for analysis. When a foveal pit was absent, the foveal center was defined as the apex of the central bulge of the outer nuclear layer.[17,20] Total foveal thickness was measured from the internal limiting membrane to the inner border of the retinal pigment epithelium and Bruch's membrane complex at the foveal center (fovea), as well as the nasal and temporal foveal rim, which was defined as the thickest point in the parafoveal region (approximately 1000 µm from the foveal center).[20] The inner retinal thickness (IRT) was measured from the internal limiting membrane to the outer border of the inner nuclear layer at these same three locations (fovea, nasal, and temporal foveal rim). The outer retinal thickness (ORT) was measured from the inner border of the outer plexiform layer to the inner border of the retinal pigment epithelium–Bruch's membrane complex at the same three locations.[17,21] The foveal rim IRT and ORT

was defined as the average of the nasal and temporal foveal rim IRT and ORT, respectively. In addition, foveal rim thickness/foveal thickness (R/F) ratio was used as a parameter to describe foveal pit depth.[20] An R/F ratio closer to 1 suggests a shallower foveal pit. OCT images were also qualitatively assessed for other retinal features, including macular edema and the presence of an ellipsoid zone (EZ) in the fovea and peripheral area. Scan quality for all images was required to be greater than 15 dB to be considered as acceptable.

Statistical Analyses

Retinal parameters, including foveal IRT, foveal ORT, foveal rim ORT, foveal rim IRT, and R/F ratio, were transformed using a generalized logarithm transformation (glog)[22] and scaled using a mean-centered scale divided by the standard deviation of each feature[23] comparing EPT infants with non-EPT infants. To measure variability within samples a multivariable dimension-reduction analysis was implemented. Principal component analysis plots were plotted using the first and second principal component (PC), with the 95% confidence region displayed in the plot. Loading plots were generated using the first and second PC (orange = EPT group, blue = non-EPT group). A categorical bilinear factor model analysis was implemented to determine categorical distributions between the two groups. Similarly, the partial least squares discriminant analysis (PLS-DA) was plotted using the first and second component, displaying the 95% confidence region of the two groups, and loading plots used the first and second component (orange = EPT group, blue = non-EPT group). Variable importance in projection (VIP), an importance measure in the PLS-DA, was performed to predict which retinal parameters contributed to the separation of the two groups. After this data-driven analysis, the Student *t* test was performed to validate the VIP. Regression analysis was performed to evaluate the effect of GA and PMA on retinal parameters. Three phases were investigated: phase 1, preterm PMA period (32–36 weeks PMA); phase 2, term equivalent PMA period (time of expected birth, 37–42 weeks PMA); and phase 3, post-term PMA period (>43 weeks PMA). The Mann–Whitney *U* test was also performed to compare the difference between two groups at each phase. For the nonlinear parameters, scatter plots were drawn to visualize the change in various retinal parameters by PMA. Macular anatomic features can temporarily be distorted by macular edema[24]; therefore, images that exhibited severe macular edema that distort the foveal pit contour were excluded from the quantitative analysis for foveal or foveal rim thickness. Fisher's exact test was performed to compare categorical variables between the two groups. A *P* value of less than 0.05 was considered significant. Descriptive statistics are reported as mean ± standard deviation in Table.

Table. Subjects' Characteristics and Demographics

Characteristics	Total Infants	Extremely Premature Infants (EPT)	Nonextremely Premature Infants (Non-EPT)	*P* Value
No. of subjects	26	14	12	
No. of eyes	43	22	21	
Female subjects	11 (42%)	5 (36%)	6 (50%)	0.692
GA, wk				
Mean ± SD	28.73 ± 4.93	24.91 ± 1.38	33.19 ± 3.55	<0.0001
Range	22.14–39	22.14–27.57	28.86–39	
Birth weight, g				
Mean ± SD	1217 ± 901.1	667.6 ± 180.6	1858 ± 987.4	0.0002
Range	360–3501	360–1045	615–3501	
PMA on the day of imaging, wk				
Mean ± SD	43.99 ± 11.59	45.51 ± 12.08	42.39 ± 11.11	0.388
Range	32.43–79.86	32.43–79.86	32.43–71.57	
ROP stage by eye				
0	17	3	14	0.0005
1	8	5	3	
2	14	10	4	
3	4	4	0	

Results

Infant Characteristics

A total of 26 infants (43 eyes) with good image quality were included, with 14 infants (22 eyes) in the EPT group and 12 infants (21 eyes) in the non-EPT group. Demographic and ROP status of the subjects are shown in Table. As expected, GA and birth weight were significantly lower in the EPT group versus the non-EPT group. Nineteen eyes (86%) and 7 eyes (33%) were diagnosed as having ROP (stage 1–3) in the EPT group and the non-EPT group, respectively. Macular edema was found between 32 and 43 weeks PMA in both groups (either at the initial visit or at a follow-up visit). All macular edema only appeared in the inner nuclear layer.

Foveal Inner Retina Contributes to Separation of EPT and non-EPT Groups

Principal component analysis and PLS-DA demonstrated overlap in the 95% confidence region between EPT infants and non-EPT infants, which indicates that there are similarities between these groups (Figs. 1A,

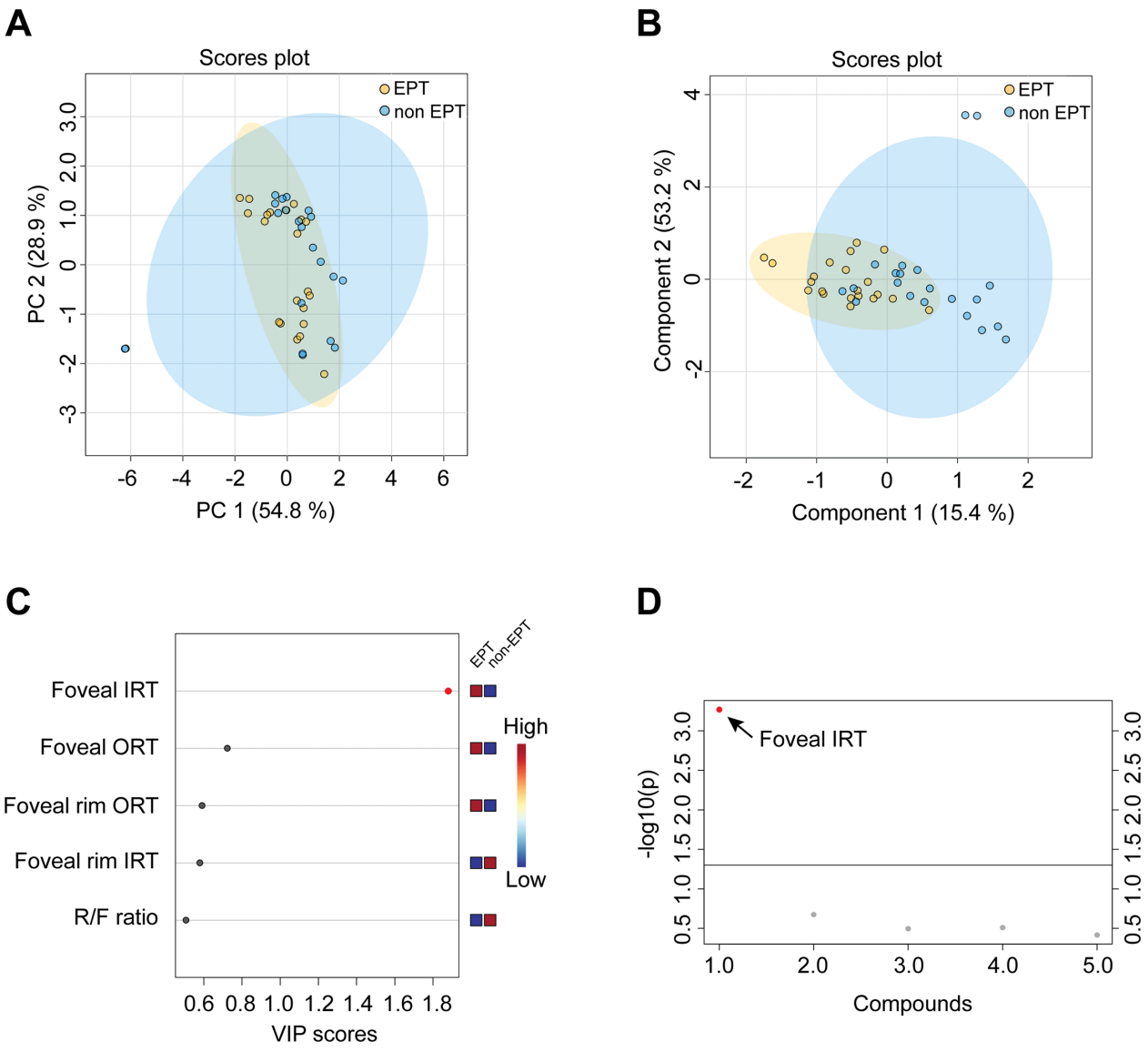

Figure 1. Comparison of extremely premature infants (EPT) and non-EPT infants by principal component analysis (PCA) and PLS-DA. PCA score plot (A) and PLS-DA score plot (B) shows some overlap between the two groups, but evaluation of VIP scores demonstrated that foveal inner retina thickness (IRT) is the top component with highest VIP scores that contribute toward the separation of the two groups (B). A further Student *t* test also shows foveal IRT is significantly different between the two groups (C). VIP scores for all measured components are pictured, with the colored boxes on the right indicating the relative value of the corresponding parameter in each group (B).

B). Despite this similarity, VIP score analysis demonstrated that IRT is a feature that contributes to separation of the two groups, which was further validated by the Student *t* test (Figs. 1C, D). Foveal IRT was significantly different between the EPT and non-EPT infants, suggesting that the developmental movement of foveal inner retina might be impaired in prematurity.

Correlation of Foveal and Foveal Rim Parameters with PMA

A regression model analysis demonstrated that foveal IRT negatively correlated with PMA for EPT infants and non-EPT infants from phase 1 (32–36 weeks PMA) to phase 3 (>43 weeks PMA) (Fig. 2A; slope $P = 0.617$; intercepts $P < 0.0001$). EPT infants consistently exhibited a thicker foveal IRT at every phase point when compared with non-EPT infants (Fig. 2A). This persistent thickness in the EPT group was statistically significant for all three phases. Contrasting the pattern observed for foveal IRT, foveal ORT demonstrated a positive correlation with PMA for both groups (Fig. 2B; slope $P = 0.901$; intercepts $P = 0.587$). This pattern persisted at every phase point but was not statistically significant. The total foveal thickness had a trajectory that had an initial decrease (from phase 1 to phase 2) followed by an increase (phase 2 to phase 3), which is consistent with previous reports (Fig. 2C). Similar to the foveal IRT, the total foveal thickness was statistically thicker for the EPT group at phases 1 and 2, when compared with the non-EPT group. Phase 3 did not show any statistical significance. Retinal foveal pit depth was represented by the R/F ratio. The trajectory of the R/F ratio had an initial increase from phase 1 to phase 2, followed by a decrease from phase 2 to phase 3 (Fig. 2D). The R/F ratio was statistically higher for phase 1 and phase 2, but did not demonstrate significance at phase 3. Similarly, the trajectory of foveal rim IRT had the same patter as the R/F ratio. The foveal rim IRT became thicker from phase 1 to phase 2 in both groups, followed by a decrease from phase 2 to phase 3 (Supplemental Fig. S1A). The foveal rim ORT showed a positive

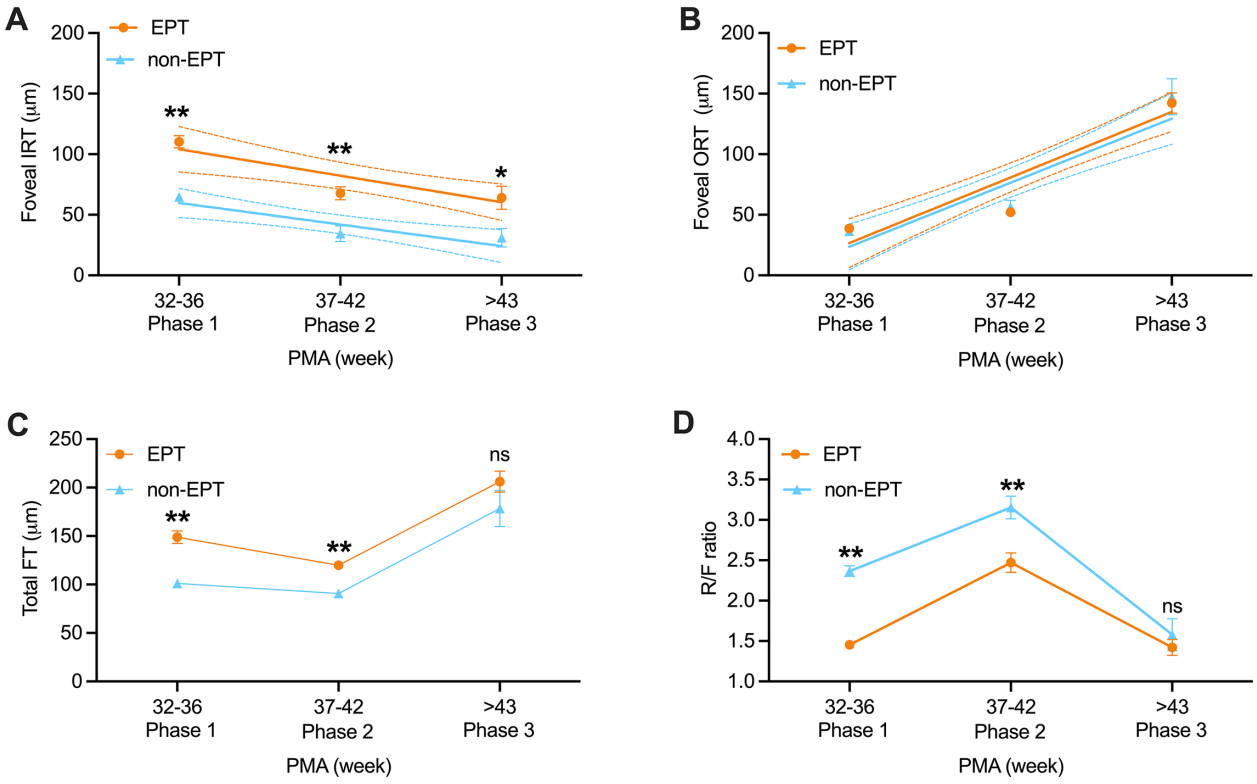

Figure 2. Foveal parameters of EPT (*orange*) compared with non-EPT infants (*blue*) by PMA. (A) Mean foveal IRT became thinner with increasing PMA in both groups. The foveal IRT presented thicker in the EPT group compared with the non-EPT group thorough the observation period. (B) The mean foveal ORT became thicker with increasing PMA in both groups. (C, D) The trajectory of total foveal thickness (FT) and foveal R/F ratio, respectively. The dotted lines represent the 95% confidence interval of the solid line. In A–C, $n = 6$ eyes in phase 1, 5 eyes in phase 2, and 10 eyes in phase 3 in the EPT group; $n = 7$ eyes in phase 1, 9 eyes in phase 2, and 5 eyes in phase 3 in the non-EPT group. In D, $n = 6$ eyes in phase 1, 5 eyes in phase 2, and 10 eyes in phase 3 in the EPT group; $n = 5$ eyes in phase 1, 9 eyes in phase 2, and 5 eyes in phase 3 in the non-EPT group. Mann-Whitney test, $^*P < 0.05$, $^{**}P < 0.01$, ns, not significant.

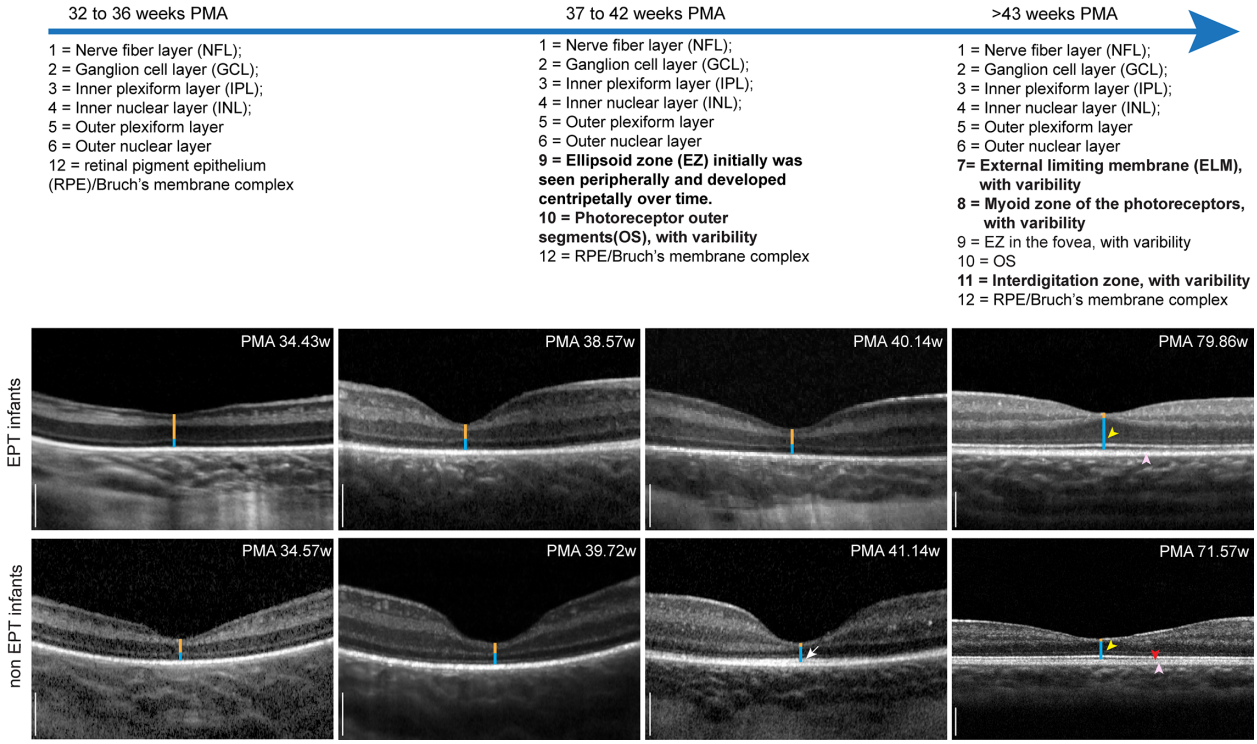

Figure 3. Development of foveal layers by three PMA periods. The new retinal layers that form during each period are bolded. The *white arrow* indicates the presence of the EZ at the foveal center. The *yellow arrowhead* indicates the presence of the ELM at the foveal center. The *red arrowhead* indicates the interdigitation zone, and the *pink arrowhead* indicates the retinal pigment epithelium–Brunch's membrane complex. Orange lines indicate inner retinal layers, and blue lines indicate outer retinal layers. Vertical scale bar = 200 µm.

correlation with PMA at every phase point (Supplemental Fig. S1B). Supplemental Figure S2 shows foveal retinal thickness changes over time in five premature subjects.

Development of Foveal Layers

Figure 3 shows the presence of 7 to 12 retinal layers in the three PMA phases evaluated in our cohort. The only feature noted to be different between EPT and non-EPT infants was the EZ at the foveal center. The EZ was seen in the peripheral macula as early as 34 to 35 weeks PMA in both groups. However, in the non-EPT infants, the EZ could be identified at the foveal center as early as 41 weeks PMA, but no EZ was detectable at the fovea in the EPT infants until at least 44 weeks PMA.

Discussion

Different efforts have been made to understand the developing retina during prematurity, which have begun to elucidate the complexity of this process. However, the majority of these studies either include premature infants that have been treated for ROP (which has been demonstrated to affect retinal development) or do not separate cohorts based on the severity of prematurity. This presents a gap in the literature that has not explored the effects of prematurity on retinal development in the absence of treatment.

Our study seeks to bridge this gap by investigating retinal development in a treatment-naïve cohort that is separated by the severity of prematurity (EPT infants vs non-EPT infants). In both groups, the foveal inner and outer retinal layers developed independently of each other. We used objective, data-driven analyses (principal component analysis and PLS-DA) to screen for OCT retinal parameters in both groups (Fig. 1). Based on the VIP scores from the PLS-DA, we found that foveal IRT was the main component that distinguishes EPT infants from non-EPT infants. Namely, the displacement of foveal inner retina layers was significantly affected by the severity of prematurity.

Prior OCT studies in children and young adults with a history of prematurity or ROP treatment demonstrated abnormal anatomical foveal structures, including the persistent presence of the inner retina at the fovea center, and a shallower foveal pit,[9–16,25]

suggesting that prematurity or the combination of prematurity and ROP treatment interferes with normal foveal pit maturation. Our study revealed that the foveal inner retina was thicker in EPT infants throughout the observation period (phases 1–3) when compared with non-EPT infants and negatively correlated with PMA (Fig. 2A). This finding has been corroborated by a previous independent study.[20] In this study, prematurity was associated with thickening at the foveal center, which includes both the inner and the outer central fovea thicknesses.[20] Our study demonstrates that, from these two parameters, IRT is the main contributor for aberrant retinal foveal development (Fig. 1). Furthermore, this study included imaging of infants after both laser and anti-vascular endothelial growth factor (VEGF) treatment,[17] which might affect the natural development of the premature retina, highlighting the importance of studying premature retinal development in the absence of treatment.

In contrast with foveal inner retinal thinning, which occurs at approximately 27 weeks of gestation, the foveal outer retinal development mainly occurs after birth and continues throughout childhood.[5,6] This process involves foveal cone packing and elongation, which is seen as a thickening of the outer retina on OCT.[21,26] Previous studies demonstrated that bevacizumab (anti-VEGF) treatment is associated with a more rapid foveal outer retinal thickening[17] and that the foveal outer retina thickens faster when infants are born at earlier GAs.[20] However, the latter study included both laser– and anti-VEGF–treated infants; mentioned elsewhere in this article, this factor can potentially interfere with their findings. Contrasting those results, the foveal outer retina in our treatment-naïve cohorts did not show any significant difference in thickness or growth rate between EPT infants and non-EPT infants. In addition, the EZ was observed as a hyper-reflective band, which has been attributed to mitochondria-rich photoreceptors and are a marker for photoreceptor development. Our results showed that the EZ can be visualized in the peripheral region as early as 34 to 35 weeks PMA in both groups, but reached the fovea center relatively earlier in non-EPT infants at 41 weeks PMA (compared with 44 weeks in EPT infants). This finding suggests that photoreceptor development in EPT infants may be delayed when compared with non-EPT infants, a finding that is similar to a previous report.[27] Altogether, considering that the time course of EZ present in foveal center seem to vary across infants and that the effect of treatment (laser or anti-VEGF) on the foveal retinal development has not been well-documented,[17,21] we are cautious to draw a conclusion on what the influence of severity of prematurity itself has on the growth rate of outer retinal thickening. This conclusion would require further longitudinal studies with large sample size to confirm.

Foveal pit deepening is due to both centrifugal migration of inner retinal layers and centripetal migration of outer retina layers, which can be measured as the R/F ratio.[20] A prior study has shown that the foveal pit reaches its maximum depth around 43 weeks PMA as the inner retina has been mostly displaced but foveal cone packing has not yet begun.[26] Similarly, we demonstrated that the foveal pit deepens with increasing PMA until phase 2 (37–42 weeks PMA), and then decreases in both groups. Furthermore, it was not surprising to see that EPT infants seem to have a shallower foveal pit compared with non-EPF infants; this factor has already been observed in previous studies.[20,28] What is more interesting is that our findings point toward foveal inner retina as the most critical component that drives variations in the developing retina during prematurity.

It is important to acknowledge the limitations in our study. One limitation of this study is its small sample size and lack of longitudinal data. We addressed these limitations by using a data-driven analysis to eliminate bias and increase the objectivity of our findings. Another limitation is that we did not have individual's axial length to correct the lateral scale. We minimized this factor by choosing the highest point within the parafoveal region. To make our data comparable with previous studies, we adopted the same retina-layer segmentation methods as described in prior publications.[17,21] The strength of this study is that both groups were treatment naïve, allowing us to remove laser and anti-VEGF treatment as confounders.

In conclusion, we assessed the retinal thickness at both the fovea and foveal rim using a data-driven analysis. EPT infants demonstrated different foveal development patterns compared with non-EPT infants, which allowed us to monitor the natural progression of retinal development in the absence of any treatment. These differences are mainly driven by persistence of the inner retina in EPT infants which affects foveal pit depth.

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