Delay in Retinal Photoreceptor Development in Very Preterm Compared to Term Infants

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PURPOSE. We compared photoreceptor development from spectral domain optical coherence tomography (SD-OCT) imaging in very preterm infants (VPT, <32 weeks gestational age) with those of term infants.

METHODS. The microanatomy of foveal SD-OCT images obtained at the bedside at 37 to 42 weeks term equivalent postmenstrual age (TEA) was reviewed with qualitative and quantitative analysis of retinal and especially photoreceptor layers in the macula. Measures of maturity included presence of the cone outer segment tips (COST) or the ellipsoid zone (EZ) at foveal center, distance from Bruch's membrane (BM) to the EZ at the foveal center, and radial distance from foveal center to first appearance of the EZ.

RESULTS. The incidence of the EZ developed at the foveal center was lower in VPT infants (9/64, 14%) versus term infants (22/47, 47%, $P < 0.001$) and lower in VPT infants with macular edema (3/46) versus VPT without edema (6/18, $P = 0.01$). Mean $\pm$ SD distance from the foveal center to the visible EZ was $783 \pm 440 \mu\text{m}$ in VPT, and $492 \pm 501 \mu\text{m}$ in term infants, $P = 0.002$. The height of the BM-to-EZ at the foveal center did not differ in VPT versus term infants. The COST band was not visible in any infant.

CONCLUSIONS. Photoreceptor inner and outer segment development in VPT infants appears delayed when compared to term infants, and the photoreceptor RPE junction remains immature in all infants at TEA. Delayed maturation of photoreceptors could contribute to differences in visual function in some VPT infants.

Keywords: photoreceptor, prematurity, foveal development, retinopathy of prematurity, optical coherence tomography, ellipsoid zone

Preterm infants who are born at less than 32 weeks' gestational age (very preterm, VPT) are at high risk for ocular and visual pathway abnormalities secondary to retinopathy of prematurity (ROP), myopia, amblyopia, strabismus, and optic nerve abnormalities, along with systemic factors, such as cerebral damage.^{1–6} In addition, these infants develop lower visual acuities when compared to term-aged infants.^{7–9} These visual acuity deficits sometimes are not corrected by careful refraction, nor are they attributed to clinical ROP, strabismus, amblyopia, or other structural abnormalities.

Recent optical coherence tomography (OCT) studies report that prematurity is associated with persistent changes in foveal structure.^{10–13} The majority of these studies used low-resolution time-domain OCT, and few used higher resolution spectral domain (SD)-OCT. One group used adaptive optics SD-OCT and assessed not only foveal structure, but also foveal and parafoveal retinal vasculature.¹⁴ Together, these OCT studies reported that macular structure slightly differs in children from 5 to 26 years of age who were born prematurely when compared to children who were born at term, regardless of ROP history. The predominant finding across these studies is an increase in central retinal thickness in children with a history of

preterm birth due to persistence of inner retinal layers and a flatter foveal pit.^{10,12,14,15} In addition, one group reported a significantly smaller foveal avascular zone diameter in preterm children and speculated that preterm birth results in abnormal foveal vascularization, and, therefore, failure of the inner retina neurons to migrate away from the foveal center.¹⁶ All of these studies evaluated children who were born prematurely, and most of these groups focused their studies on inner retinal layers, and minimal comments have been made about outer retinal layers, specifically photoreceptors. One of these groups reported a lack of photoreceptor layer abnormalities,¹⁴ and another reported presence of the external limiting membrane (ELM) across the foveal center, but the inner and outer segments were only visualized perifoveally and not in the foveal center.¹⁷ The latter group did not comment on the incidence of this finding in preterm infants, but speculated that their older, more term-aged counterparts developed the ELM earlier in the foveal center than the preterm infants.

In our former study, we presented human foveal development visualized by SD-OCT imaging, directly correlated these findings with human histologic specimens, and created a timeline for onset of retinal layers. One notable finding from

FIGURE 1. The SD-OCT foveal images of a VPT and term infant at 39 weeks PMA. Gray arrows indicate the EZ proximity to the foveal center in *left* image, and gray triangle indicates presence of the immature EZ at the foveal center in *right* image.

this foveal development study was the extreme immaturity of the foveal outer retina in the months before and shortly after term equivalent postmenstrual age (PMA, time of expected birth), especially in premature infants.^{18,19} These findings suggested that prematurity itself may alter the development of the photoreceptors. We hypothesized that the photoreceptor development of term equivalent VPT infants, as reflected in the microanatomy visible on SD-OCT imaging, is considerably different from that found in term infants. We proposed that photoreceptor development may be delayed in VPT compared to term infants.

METHODS

This prospective observational study was performed under an Institutional Review Board (IRB)-approved protocol in accord with the Declaration of Helsinki. The data were captured under two separate IRB-approved protocols, in which 87 VPT infants and 60 term infants were imaged by SD-OCT. Written informed consent was obtained from all participants' parents or guardians.

For premature infants in this study, SD-OCT imaging was performed at the time of standard dilated fundus examination for ROP in the Neonatal Intensive Care Unit.^{20,21} Criteria for ROP screening included infants born at or under 1500 g, or at or under 30 weeks PMA who were at least 30 weeks PMA, and had reached four weeks of life at the time of the first eye examination.²² For the term infants in this study, the dilated fundus examination and the SD-OCT imaging were part of a research protocol.²³ Basic demographics and health history were collected from the infants' medical records.

All SD-OCT imaging was performed with a portable, handheld unit (Bioptigen, Inc., Research Triangle Park, NC, USA) following a previously published, age-specific protocol described by Maldonado et al.,²¹ without the use of a lid speculum or sedation. Macular rectangular volume scans were obtained at 0° and 90°. Volumetric scans were obtained in each imaging session. All volumes were graded and the best foveal volumes for each eye were selected. After the SD-OCT images were converted into Digital Imaging and Communications in Medicine format, one of two trained SD-OCT readers (ALR or DT) qualitatively evaluated the best foveal volume for each infant for the presence of retinal layers, such as the ellipsoid zone (EZ), at the fovea and for the presence of macular pathology, such as cystoid macular edema (CME)²⁴ and subretinal fluid (SRF).²⁵ The reader selected one representative foveal B-scan to be used for quantitative analysis per subject (if good quality images of both eyes were available, a single image of right or left eye was selected randomly). Infants were included in the full-term infants arm of the study if they were born between 37 and 42 weeks PMA and in the VPT infants arm if they were born before 32 weeks PMA. In addition, VPT

or full-term infants were included in this study if they had at least one visit between 37 and 42 weeks PMA in which a high quality foveal frame was captured at sufficient image quality to identify the EZ if present. Only one visit during this time period was included. If analysis of the EZ proximity was not possible due to the presence of SRF, these infants were excluded from this study.

Each image was reviewed with OsiriXv4.1.2 software (Pixmeo, Bernex, Switzerland) for presence of the EZ at the foveal center and, if present, the distance from Bruch's membrane (BM) to the inner border of the EZ was measured manually and named BM-to-EZ height. If the EZ was not present at the foveal center, the location where the EZ first appeared as distinct from the RPE on either side of fovea was marked (Fig. 1) and the distance was measured manually from foveal center. Presence of cone outer segment tips (COST), CME, and SRF at the foveal center were qualitatively identified, if present. To determine the reproducibility of this grading and to perform an inter-reader agreement analysis, the two independent SD-OCT readers repeated the photoreceptor measurements for 20 ($n = 20$ eyes) randomly selected infants.

Statistical analysis was performed using JMP Pro software v10.0 (SAS Institute, Inc., Cary, NC, USA). Gestational age, age at imaging, and birth weight are reported as mean $\pm$ SD with P values comparing the two groups calculated using the Wilcoxon ranked-sum test. The sex, race, and ROP P values were calculated using a 2-tailed Fisher's exact test.

Normality of distributions were assessed by Shapiro-Wilk goodness of fit test to determine if analyses were performed with parametric or nonparametric tests. Incidence of the EZ at the fovea by demographic parameters as well as by presence of CME within the VPT group was calculated with a 2-tailed Fisher's exact test or Wilcoxon ranked-sum test. The height of the EZ separation from the RPE was analyzed between groups by a Wilcoxon ranked-sum test. Within group analysis was performed by linear regression for gestational age, birth weight, and age at imaging, and a Wilcoxon ranked-sum test for sex and race, as well as presence of CME and ROP parameters within the VPT group. The mean EZ distances from the foveal center in horizontal versus vertical scans were compared with a Wilcoxon ranked-sum test to determine if both scan orientations may be analyzed together. A 2-tailed t -test was used to analyze the mean EZ distance from the fovea in VPT versus term infants. Within each group, the mean EZ proximity to the fovea was assessed by sex with a 2-tailed t -test, race with a Kruskal-Wallis test, and gestational age, birth weight, and age at imaging with linear regression. Within the VPT infant group, the mean EZ distance was analyzed by presence of CME with a Wilcoxon ranked-sum test, maximum ROP stage, and plus disease status with Kruskal-Wallis tests and need for laser photocoagulation with a 2-tailed t -test.

TABLE. Infant Demographics

	Very Preterm N = 64 Eyes	Full-Term N = 47 Eyes	P Value*
	Mean ± SD	Mean ± SD	
Gestational age, wk	25.9 ± 2.0	39.3 ± 1.0	<0.001
Age at imaging, wk	39.5 ± 1.8	39.3 ± 1.0	0.47
Birth weight, g	823.0 ± 214.5	3327.4 ± 464.7	<0.001
Sex, n (%)			0.012
Male	41 (64.0)	18 (38.3)	
Race, n (%)			<0.001
Caucasian	24 (37.5)	15 (31.9)†	
African-American	35 (54.7)	12 (25.5)	
Hispanic	2 (3.1)	20 (42.6)	
Multiple	3 (4.7)	0 (0.0)	
Maximum ROP stage, n (%)			<0.001
No ROP	7 (10.9)	47 (100.0)	
1	7 (10.9)	0 (0.0)	
2	26 (40.6)	0 (0.0)	
3	22 (34.4)	0 (0.0)	
4A	1 (1.6)	0 (0.0)	
4B	1 (1.6)	0 (0.0)	
Plus disease, n (%)‡			-
No plus	25 (43.9)	-	
Preplus	14 (24.5)	-	
Plus	18 (31.6)	-	
Laser photocoagulation, n (%)‡			-
Yes	19 (33.3)		

* Wilcoxon rank-sum test for gestational age, age at birth, and birth weight; 2-tailed Fisher's exact test for sex, race, maximum ROP stage, plus disease, and laser photocoagulation.

† Includes one Asian subject.

‡ Includes the 57 VPT subjects diagnosed with ROP.

RESULTS

Study Subjects

From the total 101 VPT infants consented between January 2009 and October 2013, 65 VPT infants had high quality foveal images captured between 37 and 42 weeks PMA, at term-age equivalent PMA. Of these infants, 64 had identifiable retinal layers on OCT images and were enrolled in the study ($n = 64$ eyes). Of the 60 term infants consented for the study, 1 infant withdrew and 3 additional infants were imaged at 36 weeks PMA. Thus, 56 term infants had high quality foveal images obtained between 37 and 42 weeks PMA that were analyzed. Of these 56 term infants, 47 had identifiable retinal layers and were included in the present study ($n = 47$ eyes). Study infant demographics are described in the Table. Very preterm infants (mean gestational age, 26 weeks; range, 23–31) had lower gestational age than term infants (mean gestational age, 39 weeks; range, 37–42; $P < 0.001$). At the time of imaging, the mean PMA was 40 weeks in VPT and 39 weeks PMA in term infants ($P = 0.47$). Mean birth weight was 823 g in the VPT versus 3327 g in the term infant group ($P < 0.001$). There were 41 (64%) males in the VPT and 18 (38%) in the term infant groups. In terms of worse (highest) stage of ROP clinically noted, the VPT group included 7 infants with no ROP, 7 with stage 1 ROP, 26 with stage 2, 22 with stage 3, 1 with stage 4a, and 1 with stage 4b. Preplus disease was present in 14 while plus disease was present in 18 VPT infants. There also were

statistically significant differences in race between the two groups, as illustrated in the Table.

Photoreceptor Morphology

Analysis of photoreceptor layer, particularly the EZ presence at the foveal center and the EZ proximity (distance) to the foveal center from 37 to 42 weeks PMA, demonstrated delayed appearance of this zone in the foveal center in VPT infants (Fig. 1). Nine of 64 (14%) VPT versus 22 of 47 (47%) term infants had the EZ at the foveal center ($P < 0.001$). Within each group, the incidence of the EZ did not significantly differ by sex or race, nor by any measure of ROP severity in the VPT group. There was an association between greater incidence of EZ at the fovea as VPT ($P = 0.02$) and full term ($P = 0.02$) infants were imaged at increasing PMA. However, at most time points, a higher proportion of term infants had the EZ at the foveal center compared to VPT infants (Fig. 2). While there was no difference in birth weight when analyzing presence of EZ at the fovea in either group or for gestational age in the VPT infants, full term infants with EZ at the fovea had a greater gestational age (39.6 ± 0.9 weeks PMA) than those without EZ at the fovea (39.0 ± 1.1 weeks PMA, $P = 0.044$). The BM-to-EZ height did not differ by term status (median [range] for VPT and term infants of 39 [29–58] and 38 [26–67] μm , respectively) or, within each group, by, birth weight, age at imaging, sex, or race, or ROP severity (data not shown). There was a trend toward increasing the BM-to-EZ height with increasing gestational age for term infants ($R^2 = 0.15$, $P = 0.08$), but not VPT infants. Additionally, the COST band was not visible in any infant.

The majority of infant retinal SD-OCT imaging, 39 (71%) VPT and 19 (76%) term infant, was performed with vertically-oriented scans (superior to inferior across the macula). The mean EZ radial distance from the foveal center did not significantly differ by scan orientation when considering all infants ($P = 1.00$) or within the VPT ($P = 0.87$) and term ($P = 0.77$) groups, suggesting the centripetal migration of the EZ toward the foveal center is symmetric. Therefore, horizontal and vertical scans were analyzed together. The mean distance from the foveal center to the visible EZ was 783 (± 440) μm in VPT, and 492 (± 501) μm in term infants (Fig. 3, $P = 0.002$). There was no significant relationship within each group between the EZ proximity to the fovea and the sex, race, birth weight, or ROP severity (the latter for the VPT group only). Decreasing EZ distance to the fovea correlated with increasing gestational age ($P = 0.03$) and age at imaging ($P = 0.05$) for the term group, but not the VPT group.

The grading system demonstrated reliable reproducibility. The intragrader and intergrader assessments of EZ presence at the fovea had 95% exact agreement. Intragrader intraclass correlations (ICC, with 95% confidence intervals [CI]) for the EZ distance to fovea and the BM-to-EZ height were 0.94 (0.87–0.98) and 0.97 (0.92–0.99), respectively. The ICC (95% CI) for intergrader reproducibility of the EZ distance to fovea and the BM-to-EZ height were both 0.86 (0.68–0.94).

Retinal Pathology Associated With Photoreceptor Morphology

Cystoid macular edema was present in 46 of 64 VPT infants (72%) and 3 of 47 (6%) term infants ($P < 0.001$). The pattern of CME in VPT infants varied greatly, from single foveal cystoid structure to schisis-like edema continuous through the macula, producing a bulging foveal contour.²⁴ All term infants with CME had small cystoid structures that did not disrupt the foveal contour. Further subanalysis found a lower incidence of the EZ at the fovea in VPT infants with CME (3/46) versus those

FIGURE 2. Proportion of infants with the developed EZ at the foveal center. At increasing PMA, incidence of EZ at the fovea was higher in VPT and full term infants. However, at most time points, a higher proportion of term infants had the developed EZ at the foveal center compared to VPT infants.

without CME (6/18, $P = 0.01$). In addition, there was a greater median distance of the EZ from the fovea in VPT infants with CME (896 μm ; range, 0–2106 μm) than those without CME (637 μm ; range, 0–1218 μm , $P = 0.003$), but no correlation between CME and the BM-to-EZ height in the 7 VPT infants with the EZ present at the foveal center.

Three VPT infants and 8 term infants had SRF from 37 to 42 weeks PMA. All VPT infants who presented with SRF on SD-OCT also had either stage 4A or 4B ROP. A description of the SRF observed in 15% term infants at birth by SD-OCT has been reported previously by our group. The cause of SRF in these healthy, term infants is unknown and does not appear to be related to birthing trauma or inflammation and vascular disease,²³ while in VPT infants, it is associated with advanced ROP. The pattern of SRF in the VPT infants was submacular and also extended outside the foveal region, while in term infants the pattern of SRF was a small dome directly under the fovea. Analysis of the EZ proximity in these eyes with SRF was

challenging and possible in 2 VPT infants, while not possible in one VPT and 8 term infants; therefore, these infants were excluded. However, the EZ appeared to be present in the foveal center despite presence of SRF in one term infant.

DISCUSSION

Bach and Seefelder²⁵ provided the first description of human foveal development and immaturity of foveal photoreceptors, and subsequently similar findings were noted in monkeys²⁶ and humans.²⁷ Maldonado et al.²⁸ illustrated in vivo human foveal development through 3D mapping of SD-OCT volumes. They prospectively described persistence of the inner retinal layers at the fovea of immature neonates compared to adults and reported a centrifugal development of the inner layers and a concurrent centripetal development of the outer layers on SD-OCT. Hendrickson et al.¹⁹ confirmed these findings by histological studies on human foveal development, which showed progressive thickening of the foveal outer nuclear layer after birth as cone packing and elongation of inner and outer segments (IS and OS) occurred. Inner segment EZ is an array of longitudinally oriented mitochondria that appears as a hyperreflective band on OCT. Initially IS and OS are noted as hyperreflective RPE thickening approximately 33 to 36 weeks PMA in the periphery; subsequently, EZ is separated from similarly reflective RPE by the elongating hyporeflective OS approximately 37 to 39 weeks PMA in the periphery.¹⁸ In adults, EZ disruption correlates with poor visual acuity in various retinal diseases, such as diabetic macular edema and retinal vein occlusion.^{29,30} Clearly, photoreceptor development is important for visual function/acuity and delay in development may predict acuity.

Recently, we directly correlated SD-OCT images with histological specimens of the human fovea, showing a shallow foveal pit indenting inner retinal layers and short, undeveloped

FIGURE 3. Proximity (distance) of the EZ to foveal center in VPT and term infants assessed by a 2-tailed Fisher's exact test.

foveal photoreceptors in preterm infants at birth.^{18,19} This current study further evaluated foveal photoreceptor development in VPT infants compared to term infants. It demonstrated that the photoreceptors, specifically the EZ, can be identified on SD-OCT images of the fovea in VPT and term infants, and, for the first time to our knowledge, that the EZ proximity and the BM-to-EZ height at the foveal center can be quantified reproducibly. Moreover, comprehensive analysis and measurements of the EZ exposed the delayed development and maturation of this zone in VPT infants compared to term infants, both at term equivalent postmenstrual age (TEA).

We noted that the incidence of the developed EZ at the foveal center was lower in VPT infants when compared to term infants, and, thus, the average proximity of the developed EZ to the foveal center was significantly further in VPT infants than in term infants. When considering only infants without the EZ at the fovea, no significant difference between the VPT and term groups was noted with respect to sex, race, or severity of ROP. These findings suggest delayed development of the EZ in VPT infants. Further subgroup analysis of VPT infants with and without macular edema demonstrates more delayed EZ development in the edema subgroup. These findings suggested that macular edema may be part of a spectrum of delayed foveal, and more broadly systemic, development in TEA VPT. While the etiology of CME in the VPT population remains speculative, this anatomic abnormality may be a biomarker of neurologic health, as VPT infants with a history of CME have poorer neurodevelopmental outcomes as toddlers than VPT infants without a history of CME.³¹ Because the VPT infant subgroup without CME was so small in the current analysis, this premise should be tested in a larger study.

The COST band, recently defined as the cone OS ensheathed by apical processes of the RPE,³² was not identified in any infants. At term, peripheral photoreceptors lengthen with the elongation of IS and OS, and OS separates the IS band from the RPE. The IS and especially OS are very short in the foveal center and shorter centrally than peripherally for weeks after birth. The absence of the COST band at birth in our study is consistent with our previous finding of immature foveal OS.¹⁸

To date, the few studies that examined retinal and foveal development in individuals with a history of prematurity compared children at 6 to 26 years of age, and none looked at these differences during the critical time of foveal development in infancy.^{10,12,14,15,33} Others also have reported no association between visual acuity and foveal hypoplasia in ROP.^{10,34} In these studies visual acuity was abnormal in many children with regressed ROP, but there was no significant association between visual acuity and total retinal thickness or foveal depth by a simple linear regression model. While there appears to be no relationship between visual acuities and foveal thickness, delayed foveal development, specifically photoreceptor maturation at the time of critical visual system development, may contribute to the reduced visual acuity seen in children with a history of prematurity or regressed ROP.

Previous studies using multifocal electroretinography have reported that, even in mild ROP, there are pronounced functional deficits.³⁵ They reported abnormal cone function and defective central rod function in premature children. We believe that these functional deficits can be explained in part by delayed photoreceptor development. However, confirmation of this hypothesis would require further studies specifically evaluating photoreceptor development, and correlating with multifocal electroretinography and visual acuity.

To our knowledge, this is the first study to assess photoreceptor development as visualized by SD-OCT in VPT infants who have reached term-equivalent PMA (between 37 and 42 weeks PMA) and compare these findings to term infants

at birth (PubMed search terms: optical coherence tomography, photoreceptor development, prematurity). However, the results of this study must be considered in light of several limitations. Lateral SD-OCT measurements rely on an age-dependent optics model described by Maldonado et al.²¹ In addition, the limits of SD-OCT lateral resolution preclude measuring cell density. Thus, we cannot view packing or lateral migration of cells. Cystoid macular edema and SRF may have developed after or resolved before the one imaging session included in this study and, thus, their incidence may be underestimated; further characterization of these phenomena is required. This is a single center study and patterns could vary across populations and by race and ethnicity; the small sample size also precludes such subgroup analysis. Term infants that had SRF were excluded as detailed EZ analysis could not be performed, contributing to an even smaller sample size and potentially introducing sample bias. However, one can note that the EZ continues to develop in these eyes despite SRF presence. Despite exclusion of these subjects and overall small sample size, this study provides valuable information about foveal morphology.

In conclusion, our study demonstrated differences in foveal morphology on SD-OCT between VPT and term infants at TEA suggestive of photoreceptor immaturity in premature infants. This opens the exciting discussion of a possible retinal, specifically photoreceptor, origin to visual acuity impairment in children with a history of prematurity. Validation by larger-scale studies in this field would be necessary and extremely valuable. Specifically, longitudinal studies that directly compare anatomic information at birth and functional information, such as visual acuities from the same infants later during childhood, could yield normative data regarding natural phenotypic variants in retinal microanatomy that relate to subsequent visual outcomes.

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References

1. Tucker J, McGuire W. Epidemiology of preterm birth. *Br Med J*. 2004;329:675–678.
2. Iwata S, Nakamura T, Hizume E, et al. Qualitative brain MRI at term and cognitive outcomes at 9 years after very preterm birth. *Pediatrics*. 2012;129:e1138–e1147.
3. Allin MP, Kontis D, Walshe M, et al. White matter and cognition in adults who were born preterm. *PLoS One*. 2011;6:e24525.
4. Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. *Br J Ophthalmol*. 1983;67:302–305.
5. Gallo JE, Lennerstrand G. A population-based study of ocular abnormalities in premature children aged 5 to 10 years. *Am J Ophthalmol*. 1991;111:539–547.
6. Dowdswell HJ, Slater AM, Broomhall J, Tripp J. Visual deficits in children born at less than 32 weeks' gestation with and

- without major ocular pathology and cerebral damage. *Br J Ophthalmol*. 1995;79:447-452.
7. Good WV, Hardy RJ, Dobson V, et al. Final visual acuity results in the early treatment for retinopathy of prematurity study. *Arch Ophthalmol*. 2010;128:663-671.
 8. Wu WC, Lin RI, Shih CP, et al. Visual acuity, optical components, and macular abnormalities in patients with a history of retinopathy of prematurity. *Ophthalmology*. 2012;119:1907-1916.
 9. O'Connor AR, Stephenson TJ, Johnson A, et al. Visual function in low birthweight children. *Br J Ophthalmol*. 2004;88:1149-1153.
 10. Recchia FM, Recchia CC. Foveal dysplasia evident by optical coherence tomography in patients with a history of retinopathy of prematurity. *Retina*. 2007;27:1221-1226.
 11. Akerblom H, Holmstrom 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;96:956-960.
 12. Tariq YM, Pai A, Li H, et al. Association of birth parameters with OCT measured macular and retinal nerve fiber layer thickness. *Invest Ophthalmol Vis Sci*. 2011;52:1709-1715.
 13. Tariq YM, Burlutsky G, Mitchell P. Macular parameters and prematurity: a spectral domain coherence tomography study. *J AAPOS*. 2012;16:382-385.
 14. Hammer DX, Iftimia NV, Ferguson RD, et al. Foveal fine structure in retinopathy of prematurity: an adaptive optics Fourier domain optical coherence tomography study. *Invest Ophthalmol Vis Sci*. 2008;49:2061-2070.
 15. Park KA, Oh SY. Analysis of spectral-domain optical coherence tomography in preterm children: retinal layer thickness and choroidal thickness profiles. *Invest Ophthalmol Vis Sci*. 2012;53:7201-7207.
 16. Yanni SE, Wang J, Chan M, et al. Foveal avascular zone and foveal pit formation after preterm birth. *Br J Ophthalmol*. 2012;96:961-966.
 17. Vinekar A, Avadhani K, Sivakumar M, et al. Macular edema in premature infants. *Ophthalmology*. 2012;119:1288-1289, author reply 1289-1290.
 18. Vajzovic L, Hendrickson AE, O'Connell RV, et al. Maturation of the human fovea: correlation of spectral-domain optical coherence tomography findings with histology. *Am J Ophthalmol*. 2012;154:779-789.e2.
 19. Hendrickson A, Possin D, Vajzovic L, Toth CA. Histologic development of the human fovea from midgestation to maturity. *Am J Ophthalmol*. 2012;154:767-778.e2.
 20. Lee AC, Maldonado RS, Sarin N, et al. Macular features from spectral-domain optical coherence tomography as an adjunct to indirect ophthalmoscopy in retinopathy of prematurity. *Retina*. 2011;31:1470-1482.
 21. Maldonado RS, Izatt JA, Sarin N, et al. Optimizing hand-held spectral domain optical coherence tomography imaging for neonates, infants, and children. *Invest Ophthalmol Vis Sci*. 2010;51:2678-2685.
 22. Fierson WM. American Academy of Pediatrics Section on O, American Academy of O, American Association for Pediatric O, Strabismus, American Association of Certified O. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics*. 2013;131:189-195.
 23. Cabrera MT, Maldonado RS, Toth CA, et al. Subfoveal fluid in healthy full-term newborns observed by handheld spectral-domain optical coherence tomography. *Am J Ophthalmol*. 2012;153:167-175.e3.
 24. Maldonado RS, O'Connell R, Ascher SB, et al. Spectral-domain optical coherence tomographic assessment of severity of cystoid macular edema in retinopathy of prematurity. *Arch Ophthalmol*. 2012;130:569-578.
 25. Bach LSR. *Atlas zur Entwicklungsgeschichte des Menschlichen Auges*. Leipzig, Germany: W. Engelmann; 1914:1-148.
 26. Hendrickson A, Kupfer C. The histogenesis of the fovea in the macaque monkey. *Invest Ophthalmol Vis Sci*. 1976;15:746-756.
 27. Hendrickson AE, Yuodelis C. The morphological development of the human fovea. *Ophthalmology*. 1984;91:603-612.
 28. Maldonado RS, O'Connell RV, Sarin N, et al. Dynamics of human foveal development after premature birth. *Ophthalmology*. 2011;118:2315-2325.
 29. Maheshwary AS, Oster SE, Yuson RM, Cheng L, Mojana F, Freeman WR. The association between percent disruption of the photoreceptor inner segment-outer segment junction and visual acuity in diabetic macular edema. *Am J Ophthalmol*. 2010;150:63-67.e1.
 30. Ota M, Tsujikawa A, Kita M, et al. Integrity of foveal photoreceptor layer in central retinal vein occlusion. *Retina*. 2008;28:1502-1508.
 31. Rothman AL, Tran-Viet D, Gustafson KE, et al. Poorer neurodevelopmental outcomes associated with cystoid macular edema identified in preterm infants in the intensive care nursery [published online ahead of print, November 4, 2014]. *Ophthalmology*. doi:10.1016/j.ophtha.2014.09.011.
 32. Spaide RF, Curcio CA. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: literature review and model. *Retina*. 2011;31:1609-1619.
 33. Ecsedy M, Szamosi A, Karko C, et al. A comparison of macular structure imaged by optical coherence tomography in preterm and full-term children. *Invest Ophthalmol Vis Sci*. 2007;48:5207-5211.
 34. Wang J, Spencer R, Leffler JN, Birch EE. Critical period for foveal fine structure in children with regressed retinopathy of prematurity. *Retina*. 2012;32:330-339.
 35. Fulton AB, Hansen RM, Moskowitz A, Barnaby AM. Multifocal ERG in subjects with a history of retinopathy of prematurity. *Doc Ophthalmol*. 2005;111:7-13.