Objective: To investigate whether the severity of cystoid macular edema (CME) in neonates who were 31 to 36 weeks' postmenstrual age, as viewed by spectral-domain optical coherence tomography (SD-OCT) imaging, predicts the severity of retinopathy of prematurity (ROP) or is related to systemic health.

Design: Of 62 prematurely born neonates in a prospective institutional review board–approved study, 42 met the following inclusion criteria: at least 1 SD-OCT imaging session prior to 37 weeks' postmenstrual age and prior to ROP laser treatment, if a laser treatment was performed, and an ophthalmic ROP examination at or after 41 weeks' postmenstrual age, evidence of complete retinal vascularization in zone III, or documentation through telephone report of such information after transfer of care. Measures of CME severity, including central foveal thickness, retinal layer thicknesses, and foveal-to-parafoveal thickness ratio in 1 eye per subject, were compared with ROP outcomes: laser treatment, maximum plus disease, and maximum ROP stage. Systemic health factors were also correlated.

Results: Cystoid macular edema was present in 50% of neonates. Multiple elongated cystoid structures within the inner nuclear layer were most common. The presence of CME was not associated with ROP outcomes. The central foveal thickness, the thickness of the inner retinal layers, and the foveal-to-parafoveal thickness ratio were higher in eyes that required laser treatment or that developed plus disease or ROP stage 3. Cystoid macular edema was not clearly associated with systemic factors.

Conclusions: Cystoid macular edema is common in premature infants screened for ROP before 37 weeks' postmenstrual age, with the most common SD-OCT phenotype of a bulging fovea from multiple elongated cystoid spaces. Detection of CME is not associated with ROP severity; however, tomographic thickness measurements could potentially predict a higher risk of requiring laser treatment or developing plus disease or ROP stage 3. Systemic health factors are probably not related to the development of CME.

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that in the study eye. Continuous variables were compared using the Wilcoxon rank sum test for equal medians in 2 groups, and the Kruskal-Wallis test was used for multiple group comparisons. Categorical variables were analyzed using the Fisher exact test. The relationship between CME and systemic health factors was analyzed using a multivariate logistic regression. A Bonferroni correction factor was used to adjust for multiple comparisons across systemic health factors. A P value of less than .05 was otherwise considered statistically significant.

RESULTS

The median birth weight was 760 g, and the median gestational age was 26 weeks (Table 1). Of the 42 neonates, 12 (29%) required laser treatment by 41 weeks' PMA. Two subjects required laser treatment in only 1 eye. Subjects receiving ROP laser treatment had a lower birth weight and an earlier gestational age compared with subjects who did not receive laser treatment ($P= .046$ and $P = .005$, respectively). The Apgar scores and the frequency of systemic health factors were similar in the laser and nonlaser groups (Table 1). Eleven subjects had a final outcome of plus disease, and 6 developed pre-plus disease. The maximum ROP stage for the study eyes was as follows: stage 0 (19%), stage 1 (7%), stage 2 (43%), and stage 3 (31%).

Cystoid macular edema was not detected by clinical examination in any of the eyes of these subjects. Half of all subjects ($n=21$) had CME detected on SD-OCT images during at least 1 visit and in at least 1 eye (Table 1).
group). Cystoid macular edema was bilateral in all 19 subjects who underwent bilateral SD-OCT imaging. Cystoid macular edema was documented in 1 eye of 2 subjects (both at 35 weeks’ PMA) who did not undergo an adequate SD-OCT imaging session for the fellow eye. The prevalence of CME ranged from 13% of eyes at 31 weeks’ PMA to 60% of eyes at 34 weeks’ PMA to 65% of eyes at 36 weeks’ PMA, although with very small numbers of eyes per weekly interval (Figure 2).

Cystoid structures, on SD-OCT imaging, in the setting of ROP were identified as hyporeflective round or elongated structures separated in most instances by a vertical hyperreflective band (Figure 3). These structures were either single or multiple and were always located exclusively at the level of the INL. In a review of study eyes, a single central cystoid structure was infrequent (5% of eyes), whereas multiple cystoid structures were found in 95% of eyes. The shape of the cystoid structures was elongated in 81% of eyes and extended across the macula (involving the foveal and parafoveal area) in 76% of eyes. Cystoid macular edema also had an effect on the foveal contour, creating a bulging fovea in 62% of eyes and also

Table 2. CME Morphologic Characteristics in the Study Eyes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Progression to Laser Treatment in Study Eyes With CME</th>
<th>Vascular Outcome in Study Eyes With CME</th>
<th>Maximum ROP Stage in Study Eyes With CME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eyes With CME</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Eyes, Total No. (%)</td>
<td>21 (100)</td>
<td>14 (67)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Quantity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>1 (5)</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Multiple</td>
<td>20 (95)</td>
<td>13 (93)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly round</td>
<td>4 (19)</td>
<td>1 (7)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Predominantly elongated</td>
<td>17 (81)</td>
<td>13 (93)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Lateral location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foveal only</td>
<td>1 (5)</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Parafoveal only</td>
<td>4 (19)</td>
<td>3 (21)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Continuous</td>
<td>16 (76)</td>
<td>10 (72)</td>
<td>6 (86)</td>
</tr>
<tr>
<td>Axial location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INL only</td>
<td>21 (100)</td>
<td>14 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>INL and PRL</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Foveal contour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep</td>
<td>4 (19)</td>
<td>3 (21)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Shallow</td>
<td>4 (19)</td>
<td>4 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bulging</td>
<td>13 (62)</td>
<td>7 (50)</td>
<td>6 (86)</td>
</tr>
</tbody>
</table>

Abbreviations: CME, cystoid macular edema; INL, inner nuclear layer; PRL, photoreceptor layer; ROP, retinopathy of prematurity.
producing an elevated PRL at the foveal center in 28% of eyes (Table 2 and Figure 3).

Cystoid macular edema was present in 57% of male neonates and 42% of female neonates ($P = .16$). Those in the CME group had similar birth weights compared with the non-CME group ($P = .65$) but earlier gestational ages ($P = .04$). Race was evenly distributed among these groups ($P = .90$). The subjects with CME and the subjects without CME had similar Apgar scores and similar clinical records for the following systemic factors: surgery for patent ductus arteriosus, culture-proven sepsis, surgery for necrotizing enterocolitis, and the presence of intraventricular hemorrhage or periventricular leukomalacia. Cystoid macular edema was detected in subjects with maximum ROP stages 0, 1, 2, and 3. The presence of CME, per se, was not associated with an increased likelihood of laser treatment in the study eye (odds ratio, 1.6 [95% CI, 0.4-6.2]), of plus disease (odds ratio, 1.3 [95% CI, 0.3-5.0]), or of maximum ROP stage in the study eye (Table 1). The morphological characteristics of CME, except foveal contour, did not differ between those who received laser treatment and those who did not, between those with plus disease and those without, or between ROP stage subgroups (Table 2). There appeared to be a trend toward more severe CME with a bulging fovea in eyes that underwent laser treatment, that had plus disease, or that had a higher stage of ROP (Table 2).

The severity of CME as measured by the thickness of retinal layers at the fovea or by the ratio of foveal-to-parafoveal thickness (ie, the FP thickness ratio), which provided a quantitative measure of foveal contour, appeared to be symmetric and to be associated with measures of severity of ROP (Figure 4). The mean (SD) absolute difference between repeated measures of the CFT and the FP ratio for the same eye and visit were 7 (6) µm and 0.045 (0.045), respectively. The CFT was notably similar between the 2 eyes for each subject,
across the range of CME severity, with a mean (SD) absolute difference of 10.0 (8.8) µm between the 2 eyes (Figure 5). The presence of CME was associated with a significantly greater IRL thickness, INL thickness, PRL thickness, CFT, and FP thickness ratios (Table 3). The median CFT, the median IRL thickness, and the median FP thickness ratio were significantly higher in the laser group than in the nonlaser group (Table 4). The median CFT, IRL thickness, and FP thickness ratio were also significantly higher in the plus disease group than in the other groups (Table 4). The median CFT, IRL thickness, and FP thickness ratio were significantly higher in eyes with maximum ROP stage 3 than in the other eyes (Table 4).

We performed a broad search among systemic factors hypothesized to be related to CME. For the large number of factors, this exploratory study was not powered to identify weak associations (Table 5). The presence or absence of CME did not vary with any of the prematurity or systemic health factors assessed in Table 5. After applying a Bonferroni correction, we found that only 1 systemic variable appeared associated with a CME measure; bronchopulmonary dysplasia was associated with PRL thickness in eyes with CME (P = .001) (Table 5).

Of the 21 subjects with CME, 7 had previous SD-OCT examinations free of CME. Cystoid macular edema did not resolve in any subject prior to 36 weeks’ PMA. Although our study was not designed for long-term follow-up, we observed the resolution of CME in 9 of 17 neo-

Figure 5. Correlation of control foveal thickness between study and fellow eyes. The central foveal thickness (CFT) was highly correlated in both eyes of the same subject, with a correlation coefficient of 0.989 and a mean (SD) absolute difference of 10.0 (8.8) µm.

Table 3. Quantitative Assessment of CME Severity

<table>
<thead>
<tr>
<th>Retinal Measurementa</th>
<th>Median (Range)</th>
<th>Presence of CME in Study Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Eyes (n = 42)</td>
<td>No (n = 21)</td>
</tr>
<tr>
<td>CFT, µm</td>
<td>166 (91-449)</td>
<td>132 (91-231)</td>
</tr>
<tr>
<td>IRL thickness, µm</td>
<td>117 (58-384)</td>
<td>94 (62-186)</td>
</tr>
<tr>
<td>INL thickness, µm</td>
<td>68 (32-316)</td>
<td>57 (39-101)</td>
</tr>
<tr>
<td>PRL thickness, µm</td>
<td>33 (13-65)</td>
<td>29 (13-65)</td>
</tr>
<tr>
<td>FP thickness ratio</td>
<td>0.75 (0.40-1.51)</td>
<td>0.55 (0.40-0.96)</td>
</tr>
</tbody>
</table>

Abbreviations: CFT, central foveal thickness; CME, cystoid macular edema; FP, foveal-to-parafoveal; INL, inner nuclear layer; IRL, inner retinal layer; PRL, photoreceptor layer.

aContinuous CME outcome variables.
bDetermined by use of the Wilcoxon rank sum test.

Table 4. Association of Quantitative Markers of CME Severity to ROP Outcome

<table>
<thead>
<tr>
<th>Retinal Measurement</th>
<th>Median (Range)</th>
<th>Progression to Laser Treatment in Study Eye</th>
<th>Vascular Outcome in Study Eye</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 30)</td>
<td>Yes (n = 12)</td>
<td>P Valuea</td>
<td>No Plus (n = 25)</td>
</tr>
<tr>
<td>CFT, µm</td>
<td>145 (91-370)</td>
<td>236 (98-449)</td>
<td>.03</td>
<td>140 (91-370)</td>
</tr>
<tr>
<td>IRL thickness, µm</td>
<td>108 (58-328)</td>
<td>194 (68-384)</td>
<td>.02</td>
<td>106 (65-328)</td>
</tr>
<tr>
<td>INL thickness, µm</td>
<td>65 (32-263)</td>
<td>102 (46-316)</td>
<td>.11</td>
<td>65 (39-263)</td>
</tr>
<tr>
<td>PRL thickness, µm</td>
<td>33 (13-65)</td>
<td>42 (22-59)</td>
<td>.20</td>
<td>29 (13-65)</td>
</tr>
<tr>
<td>FP ratio</td>
<td>0.65 (0.40-1.51)</td>
<td>1.09 (0.48-1.46)</td>
<td>.02</td>
<td>0.64 (0.40-1.36)</td>
</tr>
</tbody>
</table>

(continued)
nates who were examined after 37 weeks' PMA. The earliest age of resolution of CME was at 36 weeks' PMA, and the oldest age at which CME persisted was 43 weeks' PMA (Table 6).

**Comment**

In premature neonates screened for ROP in a tertiary neonatal intensive care unit, CME was common, did not differ by race, and, when present, was almost always bilateral. Increased severity of CME, identified by greater CFT, IRL thickness, and FP thickness ratio, was associated with subsequent laser treatment, with plus disease, and with higher ROP stage. Although follow-up imaging visits were limited, CME resolved in 9 of 17 subjects imaged after 36 weeks' PMA, and CME resolved as early as 36 weeks' PMA in 1 subject and was still present in numerous subjects after 40 weeks' PMA (Table 6). It is unclear whether CME in premature neonates is pathologic, and the high frequency of this finding might suggest a transient stage of foveal development.

The CME in these neonates, imaged between 31 and 36 weeks' PMA and before any progression to severe ROP, was not visible during indirect ophthalmoscopy. It is also notable that CME has not been noted by ROP experts in studies that use color fundus photography to assess the premature infant macula.29 Furthermore, Lee et al17 and Vinekar et al26 both found CME on SD-OCT images of neonates undergoing routine ROP screening (Lee et al17 from 31 through 42 weeks and Vinekar et al26 from 35 to 52 weeks) but not with indirect ophthalmoscopy (In Lee et al,17 one case of CME was observed with ophthalmoscopy).

Lee et al17 found CME in 61% of eyes from neonates with a median birth weight of 810 g and median gestational age of 26 weeks' PMA, whereas Vinekar et al26 re-

### Table 5. Relationship Between Neonatal Systemic Health Factors and CME

<table>
<thead>
<tr>
<th>Factor</th>
<th>Presence of CME in Study Eye</th>
<th>P Value for Retinal Measurement in Study Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prematurity factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.68 (0.47-0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Birth weight</td>
<td>1.00</td>
<td>.72</td>
</tr>
<tr>
<td><strong>Demographic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs female</td>
<td>1.79 (0.52-6.11)</td>
<td>.35</td>
</tr>
<tr>
<td>White vs African American</td>
<td>1.12 (0.32-3.39)</td>
<td>.83</td>
</tr>
<tr>
<td><strong>Systemic factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar score of 1</td>
<td>0.90 (0.69-1.17)</td>
<td>.43</td>
</tr>
<tr>
<td>Apgar score of 5</td>
<td>0.84 (0.58-1.23)</td>
<td>.38</td>
</tr>
<tr>
<td>Surgery for PDA</td>
<td>3.60 (0.67-21.60)</td>
<td>.13</td>
</tr>
<tr>
<td>Culture-proven sepsis</td>
<td>1.33 (0.17-10.25)</td>
<td>.91</td>
</tr>
<tr>
<td>Surgery for NEC</td>
<td>0.63 (0.09-4.23)</td>
<td>.64</td>
</tr>
<tr>
<td>Presence of IVH</td>
<td>1.82 (0.52-6.33)</td>
<td>.35</td>
</tr>
<tr>
<td>Presence of PVL</td>
<td>4.71 (0.48-46.22)</td>
<td>.18</td>
</tr>
<tr>
<td>Presence of BPD</td>
<td>1.97 (0.52-7.49)</td>
<td>.32</td>
</tr>
<tr>
<td>Presence of hydrocephalus</td>
<td>1.58 (0.24-10.60)</td>
<td>.64</td>
</tr>
</tbody>
</table>

Abbreviations: BPD, bronchopulmonary dysplasia; CFT, central foveal thickness; CME, cystoid macular edema; FP, foveal-to-parafoveal; IRL, inner nuclear layer; INL, inner retinal layers; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus; PRL, photoreceptor layer; PVL, periventricular leukomalacia.

*P < .003 is considered statistically significant.

**Table 4. Association of Quantitative Markers of CME Severity to ROP Outcome (continued)**

<table>
<thead>
<tr>
<th>Retinal Measurement</th>
<th>Median (Range)</th>
<th>Maximum ROP Stage in Study Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFT, µm</td>
<td>121 (103-202)</td>
<td>160 (117-227) 202 (173-257)</td>
</tr>
<tr>
<td>IRL thickness, µm</td>
<td>80 (68-160)</td>
<td>111 (78-175) 106 (58-328)</td>
</tr>
<tr>
<td>INL thickness, µm</td>
<td>63 (39-117)</td>
<td>62 (62-127) 65 (32-263)</td>
</tr>
<tr>
<td>PRL thickness, µm</td>
<td>29 (23-36)</td>
<td>33 (26-49) 31 (13-65)</td>
</tr>
<tr>
<td>FP ratio</td>
<td>0.50 (0.40-1.01)</td>
<td>0.66 (0.54-0.97) 0.86 (0.42-1.36)</td>
</tr>
</tbody>
</table>

Abbreviations: CFT, central foveal thickness; CME, cystoid macular edema; FP, foveal-to-parafoveal; INL, inner nuclear layer; IRL, inner retinal layers; PRL, photoreceptor layer; ROP, retinopathy of prematurity.

*a Determined by use of the Wilcoxon rank sum test.
We hypothesize that CME is a manifestation of increased activity and insulin-like growth factor 1 levels coincides with the timing of ROP phase II, when VEGF and that cellular metabolic stress from the rapid development of the foveal cones during this time frame may also further contribute to the CME. Cystoid macular edema in premature neonates may also reflect the contribution of increased intracapillary hydrostatic pressure as a result vascular congestion from plus disease. Hence, it would be interesting to view SD-OCT images of the infant macula before and after anti-VEGF therapy for ROP. We would predict resolution of VEGF-driven edema after such treatment.

In contrast to the cases of CME found in adults, in which round and elongated cystoid structures coexist and reside in multiple retinal layers, the cases of CME found in infants had cystoid structures confined exclusively to the INL with multiple elongated cystoid structures across the central macula (Figure 3). In adults with CME, there is evidence for both extracellular fluid accumulation and intracellular swelling of Muller cells, whereas, in infants with CME, the underlying pathophysiology may predominantly be the swelling of Muller cells or perhaps the accumulation of extracellular fluid bridged by the Muller cells.

The effect of CME on foveal development, active at this period of time, is of interest. Older children and adults with a history of ROP show persisting IRLs at the foveal center on OCT scans. This may be related to prematurity, or, noting the relationship between increased IRL thickness and CME (Table 3), we feel that it might be due to a different study design and study population, it also suggests that CME may relate to the severity of ROP or the developmental stage of the retina.

In adults, CME is a pathologic entity associated with a common mechanism of alteration of the blood-retinal barrier in diseases such as diabetic retinopathy and vascular occlusions. The pigment epithelium-derived factor level and the VEGF level have also been reported to play a role in the pathogenesis of adult CME. In our study, the severity of CME was associated with the severity of ROP and was prominent between 31 and 36 weeks' PMA in extremely low-birth-weight infants. This coincides with the timing of ROP phase II, when VEGF activity increases and insulinxlike growth factor 1 levels decrease. We hypothesize that CME is a manifestation of the retinal effects of these neurohumoral factors and that cellular metabolic stress from the rapid development of the foveal cones during this time frame may also further contribute to the CME. Cystoid macular edema in premature neonates may also reflect the contribution of increased intracapillary hydrostatic pressure as a result vascular congestion from plus disease. Hence, it would be interesting to view SD-OCT images of the infant macula before and after anti-VEGF therapy for ROP. We would predict resolution of VEGF-driven edema after such treatment.

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Table 6. Characteristics of the 21 Subjects With CME at Any Visit Divided by Final Outcome of Laser Treatment

<table>
<thead>
<tr>
<th>Subject</th>
<th>Laser Treatment in Study Eye</th>
<th>Retinal Measurementa</th>
<th>Age at First Detection of CME, wk</th>
<th>Vascular Outcome in Study Eye</th>
<th>Duration of Plus or Pre-plus, wk</th>
<th>Maximum ROP Stage in Study Eye</th>
<th>ROP Stage When CME First Detected</th>
<th>Systemic Factors</th>
<th>Age of CME Resolution</th>
<th>Age of Persistent CME</th>
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<tr>
<td>1</td>
<td>No</td>
<td>113 0.48</td>
<td>36</td>
<td>Pre-plus</td>
<td>33-36</td>
<td>2</td>
<td>2</td>
<td>BPD, sepsis</td>
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</tr>
<tr>
<td>2</td>
<td>No</td>
<td>138 0.57</td>
<td>32</td>
<td>No plus</td>
<td>2</td>
<td>1</td>
<td>PDA, sepsis</td>
<td>U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>150 1.01</td>
<td>34</td>
<td>No plus</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>39 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>163 0.63</td>
<td>36</td>
<td>No plus</td>
<td>0</td>
<td>0</td>
<td>N</td>
<td>40 wk</td>
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<td></td>
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<tr>
<td>5</td>
<td>No</td>
<td>166 0.82</td>
<td>36</td>
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<td>2</td>
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<td>BPD, IVH, PVL</td>
<td>3 mo</td>
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<tr>
<td>6</td>
<td>No</td>
<td>173 0.75</td>
<td>32</td>
<td>No plus</td>
<td>2</td>
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<td>N</td>
<td>38 wk</td>
<td></td>
<td></td>
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<tr>
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<td>179 0.78</td>
<td>36</td>
<td>Pre-plus</td>
<td>37-42</td>
<td>3</td>
<td>2</td>
<td>BPD, surgery for NEC</td>
<td>41 wk</td>
<td></td>
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<tr>
<td>8</td>
<td>No</td>
<td>192 1.08</td>
<td>33</td>
<td>No plus</td>
<td>2</td>
<td>2</td>
<td>BPD, PDA</td>
<td>N</td>
<td>42 wk</td>
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<tr>
<td>9</td>
<td>No</td>
<td>202 0.95</td>
<td>35</td>
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<td>0</td>
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<td>10</td>
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<td>227 0.97</td>
<td>31</td>
<td>No plus</td>
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<td>11</td>
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<td>280 1.51</td>
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<td>Pre-plus</td>
<td>33-38</td>
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<tr>
<td>12</td>
<td>No</td>
<td>329 1.13</td>
<td>33</td>
<td>No plus</td>
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<td>1</td>
<td>BPD, IVH, PDA</td>
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<tr>
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<td>34</td>
<td>No plus</td>
<td>2</td>
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<td>N</td>
<td>38 wk</td>
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<td></td>
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<tr>
<td>14</td>
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<td>370 1.36</td>
<td>34</td>
<td>No plus</td>
<td>2</td>
<td>2</td>
<td>U</td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>Yes</td>
<td>127 0.58</td>
<td>35</td>
<td>Plus</td>
<td>35-37</td>
<td>3</td>
<td>3</td>
<td>IVH</td>
<td>38 wk</td>
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<tr>
<td>16</td>
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<td>240 1.25</td>
<td>33</td>
<td>Plus</td>
<td>36-39</td>
<td>3</td>
<td>1</td>
<td>IVH</td>
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<td>BPD, PVL</td>
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<tr>
<td>18</td>
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<td>309 1.23</td>
<td>33</td>
<td>Plus</td>
<td>33-36</td>
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<td>BPD, IVH, PDA, PVL, sepsis</td>
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<td>19</td>
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<td>329 1.28</td>
<td>34</td>
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<td>34-35</td>
<td>3</td>
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<td>345 1.28</td>
<td>36</td>
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<td>35-38</td>
<td>3</td>
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<td>IVH</td>
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<tr>
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<td>Plus</td>
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<td>3</td>
<td>2</td>
<td>IVH, PDA</td>
<td>N</td>
<td>43 wk</td>
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</tbody>
</table>

Abbreviations: BPD, bronchopulmonary dysplasia; CFT, central foveal thickness; CME, cystoid macular edema; FP, foveal-to-parafoveal; INL, inner nuclear layer; IRL, inner retinal layer; IVH, intraventricular hemorrhage; N, CME was not resolved by the week stated in the last column; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PRL, photoreceptor layer; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; U, unable to determine age of CME resolution because no follow-up imaging was obtained.

aContinuous CME outcome variables.
36 weeks' PMA, during normal foveal development, the PRL should be thinnest at the foveal center, representing the cone monolayer, but in our study, 28% of subjects with CME presented with an elevated, "spiky" PRL at the foveal center, which could represent some type of photoreceptor swelling or traction. Because the integrity of the PRL is associated with good visual outcomes in adults with CME, the bulging PRL (Figure 3) is a concern for possible chronic photoreceptor alteration, despite a return to normal morphology on later SD-OCT imaging. Future studies are needed to evaluate visual function in children with and without a history of CME after premature birth.

Greater CME severity was associated with laser treatment, plus disease, and maximum ROP stage (Table 4), and, to our knowledge, this has not been shown in previous studies. The association between CFT and ROP stage has been shown in studies involving adults with a history of ROP and premature infants at a slightly older age. It is striking to note that this association is established prior to laser treatment and before 37 weeks' PMA and thus would not likely be secondary to treatment. Early SD-OCT imaging may be an important tool that could contribute to an ROP evaluation and may provide an early indicator of the mature foveal morphology. Although we did not find an association between the presence of CME and laser treatment or between the presence of CME and the presence of plus disease (Table 1), because of the low frequency of laser treatments in the available study population, our study was not well suited for assessing a relationship between presence of CME and outcome of laser treatment. Our findings may also be affected by the different CME phenotypes found in our study; for instance, a single central cystoid structure might not represent the same event as prominent CME with a bulging fovea (Figure 3).

The limitations of this study in a neonatal intensive care unit setting included difficulty in contacting parents to obtain consent and the fact that SD-OCT imaging was only permitted in parallel with an ROP examination and the early transfer of subjects to other institutions. Thus, subjects could not be imaged at regular intervals and could have undetected CME or CME that was not monitored to resolution. We did not obtain blood samples and could not obtain ocular fluid samples to test for systemic or ocular factors that might explain the processes behind the edema. Furthermore, we did not pursue fluorescein angiography in this vulnerable population, although it could have added to our understanding of the vascular status and source of fluid in the macula.

To our knowledge, this study is the first attempt to investigate the association between transient CME in infants and ROP severity, with the aim of motivating further research in the area. We have explored CME findings at an age of prematurity when intensive metabolic, humoral, and vascular changes occur, with the intent to test the predictive value of SD-OCT imaging at this stage of ocular development. A multicenter study of SD-OCT imaging outside a single nursery is necessary to test our findings. For these subjects, subsequent visual testing studies should be done later in life to understand the effect of macular edema on vision at this important stage of visual development.

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Author Contributions: Dr Toth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


