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Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity Study: Findings at 4 to 6 years of age

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Abstract

Purpose—To report the prevalence of myopia and high myopia in children <6 years of age born preterm with birth weights <1251 g who developed high-risk prethreshold retinopathy of prematurity (ROP) and who participated in the Early Treatment for ROP (ETROP) trial.

Methods—Surviving children from the cohort of 401 participants who had developed high-risk prethreshold ROP in one or both eyes underwent cycloplegic retinoscopy at 6 and 9 months corrected age and yearly between 2 and 6 years postnatal age. Eyes were randomized to receive treatment at high-risk prethreshold ROP or conventional management, with treatment only if threshold ROP developed. Myopia (spherical equivalent ≥0.25 D) or high myopia (≥5.00 D) in eyes at 4, 5, and 6 year examinations was reported.

Results—At ages 4, 5, and 6 years, there was no difference in the percentage of eyes with myopia (range, 64.8%–69.9%) and eyes with high myopia (range, 35.3%–39.4%) between earlier treated (ET) and conventionally managed eyes (CM).

Conclusions—Approximately two-thirds of eyes with high-risk prethreshold ROP during the neonatal period are likely to be myopic into the preschool and early school years. In addition, the

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increase in the proportion of eyes with high myopia that had been observed in both ET and CM eyes between ages 6 months and 3 years does not continue between ages 3 and 6 years.

Results from the Early Treatment for ROP (ETROP) study indicate that the structural and functional outcomes of eyes with ROP can be improved if retinal ablation is performed at a severity of retinopathy less than classic threshold, that is, at prethreshold severity determined to be high risk for progressing to poor structural outcome.[1–3] Examination of refractive error at 6 and 9 months' corrected age and at 2 and 3 years' postnatal age showed no difference in terms of spherical equivalents for the prevalence of myopia (≥0.25 D) or high myopia (≥5.00 D) in eyes treated at an earlier stage of ROP (ET) compared to eyes that were managed conventionally with treatment if ROP progressed to threshold (CM).[4,5] However, prevalence of myopia was high, increasing from approximately 58% to 68% between 6 and 9 months and changed little between 9 months and 3 years of age. Prevalence of high myopia was approximately 19% at 6 months' corrected age and increased by 4% to 8% at study examinations to 3 years of age. Zone of acute-phase ROP or presence or absence of plus disease had little effect on the prevalence of both myopia and high myopia. In contrast, eyes with straightened temporal vessels or macular heterotopia had a higher percentage of eyes with myopia and high myopia than did eyes without these findings. The purpose of the present study is to report refractive error between ages 4 and 6 years in children who participated in the ETROP study. A primary goal is to determine whether prevalence of high myopia continues to increase after 3 years of age.

Subjects and Methods

A total of 401 infants with birth weights <1251 g were enrolled in the ETROP randomized trial between October 1, 2000, and September 30, 2002, at 26 participating centers in the United States.[2] Study protocols were approved by the review boards of all participating institutions and complied with all guidelines of the US Health Insurance Portability and Accountability Act. Informed consent was obtained from parents or guardians of all participants prior to enrollment in the randomized trial and at entry into the long-term follow-up portion of the study.

During the neonatal period, all infants in this cohort had developed prethreshold ROP in one or both eyes that, based on the Risk Management for ROP program,[1] put the eyes at high risk (≥15%) of a poor structural outcome at 3 months after term. Prethreshold ROP was defined as ROP of less severity and extent than threshold ROP (defined as stage 3 ROP with plus disease, located in zone 1 or zone 2, and involving 5 continuous or 8 cumulative clock hours) but with at least one of the following: any stage ROP in zone 1; zone 2, stage 2 with plus disease; or zone 2, stage 3 without plus disease or with plus disease, but with less than the number of sectors required for threshold ROP. In the 317 infants who developed high-risk prethreshold ROP in both eyes, one eye was randomly assigned to treatment within 48 hours, and the fellow eye was observed until threshold ROP developed and was treated or until regression began. Of the 84 eyes of 84 infants with unilateral high-risk prethreshold ROP, 44 infants were randomized to early treatment in the high-risk prethreshold ROP eye, and 40 were randomized to conventional management.

Standardized follow-up eye examinations, including cycloplegic retinoscopy, were conducted by a study-certified ophthalmologist when infants reached 6 and 9 months' corrected age and at 2, 3, 4, 5, and 6 years postnatal age. Cyclopentolate hydrochloride, 1%, was used as the cycloplegic agent unless medically contraindicated, in which case either 0.5% cyclopentolate or 1% tropicamide was used.

Data Analysis

Myopia was defined as spherical equivalent of ≥0.25 D of myopia, and high myopia was defined as a spherical equivalent of ≥5.00 D of myopia, in keeping with refractive error categories from previous studies.[4–7] Refractive error data were unavailable in some eyes with retinal detachment, media opacity, pupillary miosis, or other conditions that made refracting difficult. Further, eyes that had undergone vitrectomy, scleral buckling procedures, iridectomy, glaucoma procedures, or cataract surgery were excluded.

A Theil regression was used to assess the changing rate per month (slope) of the percentage of myopia for the ET and CM groups along the follow-up for myopia and high myopia. The method does not assume the percentage of myopia follows a normal distribution.[8] The trend was estimated by the median of the pairwise slopes comparing ET and CM eyes. The Sen-Adichie statistic was used to test for the equality of the slopes between the early treatment and the conventional management group.[8]

Results

Prevalence of Myopia and High Myopia

Table 1 presents the percentage of ET and CM eyes with myopia and high myopia at ages 4, 5, and 6 years of age. In both the ET and CM groups, more than 60% of eyes had a myopic spherical equivalent of ≥0.25 D, and more than a third of the eyes had ≥5.00 D of myopia. The right two columns of this table further divide the group of CM eyes into CM eyes that progressed to threshold severity and were treated and those CM eyes that regressed without treatment. More than three-quarters of CM eyes that were treated developed a myopic spherical equivalent of ≥0.25 D compared to less than half of those CM eyes that regressed.

Figures 1A and 1B show the percentage of eyes with myopia or high myopia from the 6 month post-term examination to the final examination of the ETROP study at age 6 years. The percentage of eyes with myopia or high myopia increased early in life but was stable at the 4-, 5-, and 6-year examinations. Using the Theil regression, the median slopes (rate of change per month) for myopia ≥0.25 D (Figure 1A) were 0.08 (95% CI, −0.05 to 0.38) among ET eyes and 0.00 (95% CI, −0.19 to 0.21) among CM eyes (Sen-Adichie statistic, 1.6150; $P = 0.20$). Similarly, median slopes for myopia ≥5.00 D (Figure 1B) were 0.33 (95% CI, 0.04 to 0.54) for ET eyes and 0.21 (95% CI, −0.01 to 0.51) for CM eyes (Sen-Adichie statistic, 0.0178; $P = 0.89$). Thus there was no difference in the median monthly rate of change between ET and CM eyes.

Distribution of Refractive Error at Ages 4, 5, and 6 Years

Figure 2 shows the distribution of refractive errors for ET eyes at 4-, 5-, and 6-year examinations compared to the distribution at the first examination at 6 months post-term. By the examination at 4 years, the prevalence of myopia of >8.00 D had increased from around 5% to more than 20%. Further details are in e-Supplement 2 (available at jaapos.org).

Myopia and High Myopia versus Zone or Plus Disease

The two left-hand columns of Tables 2A and 2B show the percentage of eyes with myopia and high myopia at 4, 5, and 6 years of age for ET and CM eyes based on the zone of acute phase retinopathy at the time of randomization. Among zone 1 eyes, approximately 3 of 4 of the ET eyes and 2 of 3 of the CM eyes were myopic. Of zone 2 eyes, approximately 2 of 3 eyes in both the ET and CM groups were myopic (Table 2A). Among zone 1 eyes, more ET eyes at ages 4, 5, and 6 years had high myopia than CM eyes (Table 2B). Of zone 2 eyes, the percentage of eyes with high myopia varied from 29.9% to 43.2% for ET eyes and 33.6% to 35.1% for CM eyes.

The two right hand columns of Table 2 show the percentage of eyes with myopia and high myopia at 4, 5, and 6 years of age for ET and CM eyes based on the presence or absence of plus disease at the time of randomization. Among the ET and CM eyes with plus disease, approximately 2 of 3 eyes had myopia at all three test ages and just over 1 out of 3 had high myopia. When myopia was considered for eyes without plus disease, there was a slightly higher percentage of ET eyes with myopia than CM eyes.

Myopia and High Myopia in Eyes with Type 1 and with Type 2 ROP

The prevalence of myopia in ET and CM eyes with type 1 ROP at 6 years was 67.8% and 69.6%, respectively. For eyes with type 2 ROP, the prevalence of myopia was 75% for ET eyes and 61.6% for CM eyes. High myopia was found in 37.2% of ET eyes and 38.0% of CM eyes with type 1 ROP and 45% of ET eyes and 35.6% of CM eyes with type 2 ROP.

Discussion

The results of the ETROP study at 6 years of age indicated that earlier treated eyes with high-risk prethreshold ROP were not statistically different in terms of visual function when compared to the group of eyes that were conventionally managed (ie, eyes with high-risk prethreshold ROP that were treated only if they progressed to threshold ROP).[9] However, in 2003, based on the Teller acuity results, the study showed a benefit in favor of early treatment. The ETROP investigators developed a clinically useful algorithm that defined eyes with prethreshold ROP that would benefit from earlier treatment based solely on the ROP status of the eye at a single examination, that is, eyes with type 1 ROP.[2] Using this clinical algorithm, the visual function result at 6 years showed that type 1 eyes had a significant benefit from early treatment compared to conventional management with treatment if threshold ROP developed.[9]

Previous reports on refractive error development from the ETROP study[4,5,10,11] showed no treatment-related difference in the prevalence of myopia or high myopia during the first 3 years, although the prevalence of myopia had increased in both the ET and CM groups of eyes during this period. The results of the present study extend this finding with no treatment-related difference between ET and CM eyes into early preschool and school years for the ETROP population. In addition, the prevalence of myopia and high myopia did not continue to increase in either the ET or CM groups of eyes. Furthermore, the results found that the rate of refractive error development (change per month) did not differ significantly between the ET and CM groups. The results also confirm that CM eyes in which the ROP progresses to require peripheral retinal ablation are more likely to develop myopia and high myopia than those CM eyes in which ROP regressed. As described previously in the ETROP study,[4] this relation to severity of ROP was also noted in a report of refractive error at earlier ages in ETROP subjects. Furthermore, the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study documented that severity of disease[7] and not treatment[12] was likely the cause of myopia.

Previous reports of refractive error development in the ETROP cohort[4,5] showed that, in contrast to eyes in the CRYO-ROP study in which refractive error was relatively static after 9 months post-term,[6,7] the prevalence of myopia and of high myopia increased up to age 3 years. There was concern that this increase in prevalence might continue to 6 years of age; results of the present study indicate, however, that the prevalence of myopia and high myopia are relatively unchanged after age 3 years in both ET and CM eyes (Table 1 and Figure 1).

In conclusion, the results of the present study indicate that approximately two-thirds of eyes that had high-risk prethreshold ROP during the neonatal period are likely to be myopic into

the preschool and early school years; furthermore, the increase in the proportion of eyes with high myopia that had been observed in both ET and CM eyes between ages 6 months and 3 years does not appear to continue to increase thereafter, at least to 6 years of age. The present study showed no evidence that earlier treatment of eyes with high-risk prethreshold ROP influenced refractive error development, although it does appear that the prevalence of myopia or high myopia varied between ET and CM eyes when the zone of ROP or the presence of plus disease was considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Hardy RJ, Palmer EA, Dobson V, et al. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Risk analysis of prethreshold retinopathy of prematurity. Arch Ophthalmol. 2003; 121:1697–1701. [PubMed: 14662587]
2. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003; 121:1684–1696. [PubMed: 14662586]
3. The Early Treatment for Retinopathy of Prematurity Cooperative Group. The Early Treatment for Retinopathy Of Prematurity Study: Structural findings at age 2 years. Brit J Ophthalmol. 2006; 90:1378–1382. [PubMed: 16914473]
4. Davitt BV, Dobson V, Good WV, et al. the Early Treatment for Retinopathy of Prematurity Cooperative Group. Prevalence of myopia at 9 months in infants with high-risk prethreshold retinopathy of prematurity. Ophthalmology. 2005; 112:1564–1568. [PubMed: 16023214]
5. Quinn GE, Dobson V, Davitt BV, et al. Early Treatment for Retinopathy of Prematurity Cooperative Group. Progression of myopia and high myopia in the Early Treatment for Retinopathy of Prematurity Study: Findings to 3 years of age. Ophthalmology. 2008; 115:1058–1064. [PubMed: 18423871]
6. Quinn GE, Dobson V, Repka MX, et al. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Development of myopia in infants with birth weights less than 1251 grams. Ophthalmology. 1992; 99:329–340. [PubMed: 1565444]
7. Quinn GE, Dobson V, Kivlin J, et al. Prevalence of myopia between 3 months and 5½ years in preterm infants with and without retinopathy of prematurity. Ophthalmology. 1998; 105:1292–1300. [PubMed: 9663236]
8. Hollander, M.; Wolfe, DA. Nonparametric Statistical Methods. 2nd ed.. New York: Wiley Series in Probability and Statistics; 1999.
9. Early Treatment for Retinopathy of Prematurity Cooperative Group. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2010; 128:663–671. [PubMed: 20385926]
10. Davitt BV, Dobson V, Quinn GE, Hardy RJ, Tung B, Good WV. Early Treatment for Retinopathy of Prematurity Cooperative Group. Astigmatism in the Early Treatment for Retinopathy of Prematurity Study: Findings to 3 years of age. Ophthalmology. 2009; 116:332–339. [PubMed: 19091409]
11. Davitt BV, Quinn GE, Wallace D, et al. on behalf of Members of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Astigmatism progression in the Early Treatment for Retinopathy of Prematurity Study to 6 years of age. Ophthalmology. 2011; 118:2326–2329. [PubMed: 21872933]

12. Quinn GE, Dobson V, Siatkowski RM, et al. for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Does cryotherapy affect refractive error? Results from treated versus control eyes in the Cryotherapy for Retinopathy of Prematurity trial. Ophthalmology. 2001; 108:343–347. [PubMed: 11158812]

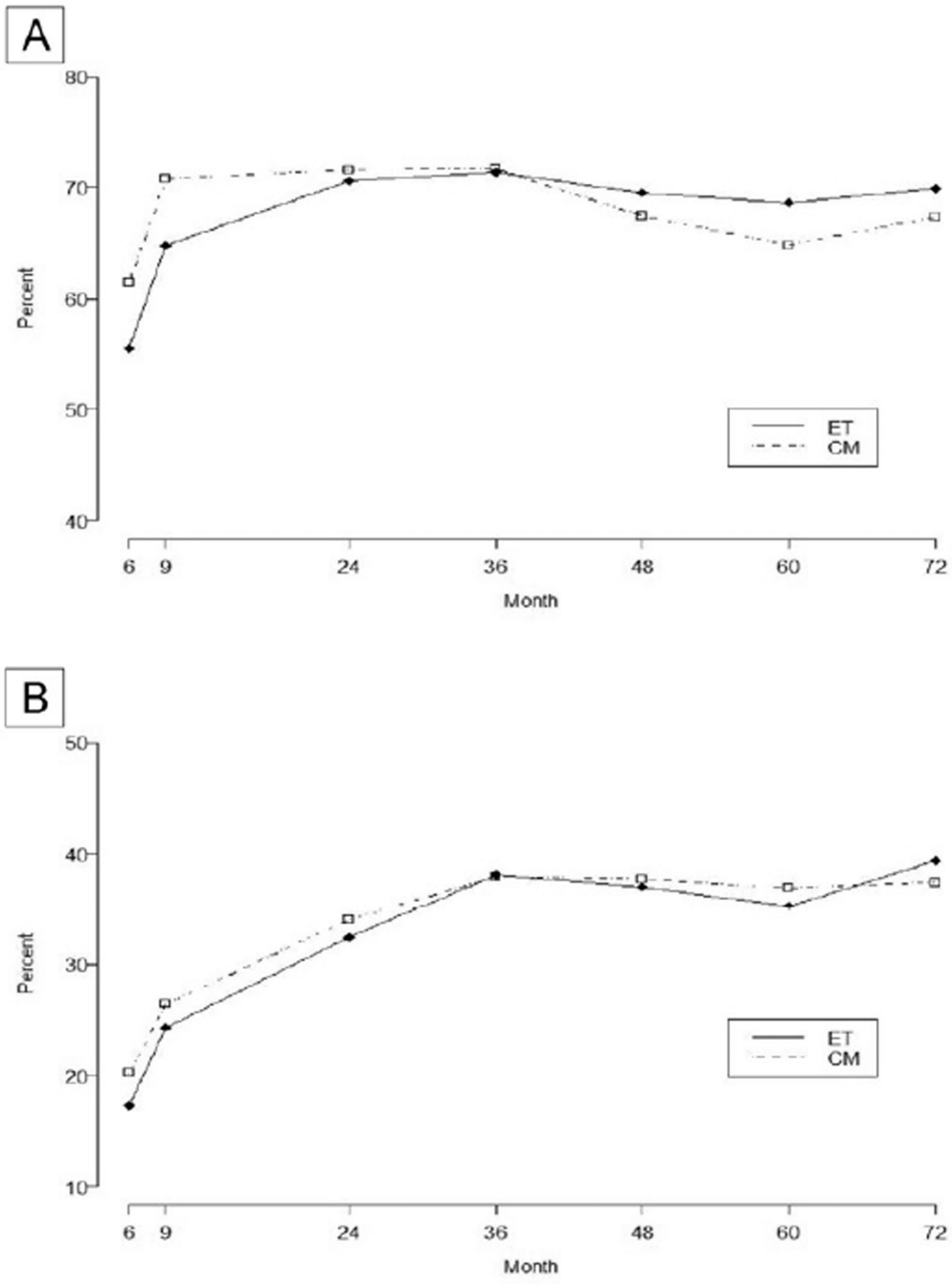

FIG 1.

Prevalence of myopia (A), ≥0.25 D, and high myopia (B), ≥5.00 D, at seven ages for eyes in the earlier treated (ET) and conventionally managed (CM) groups. Numbers of eyes in each group at the test ages, 6 months, 9 months, and 2, 3, 4, 5, and 6 years: ET: 283, 304, 281, 268, 262, 255, 279; CM: 272, 280, 253, 243, 239, 233, 257, respectively.

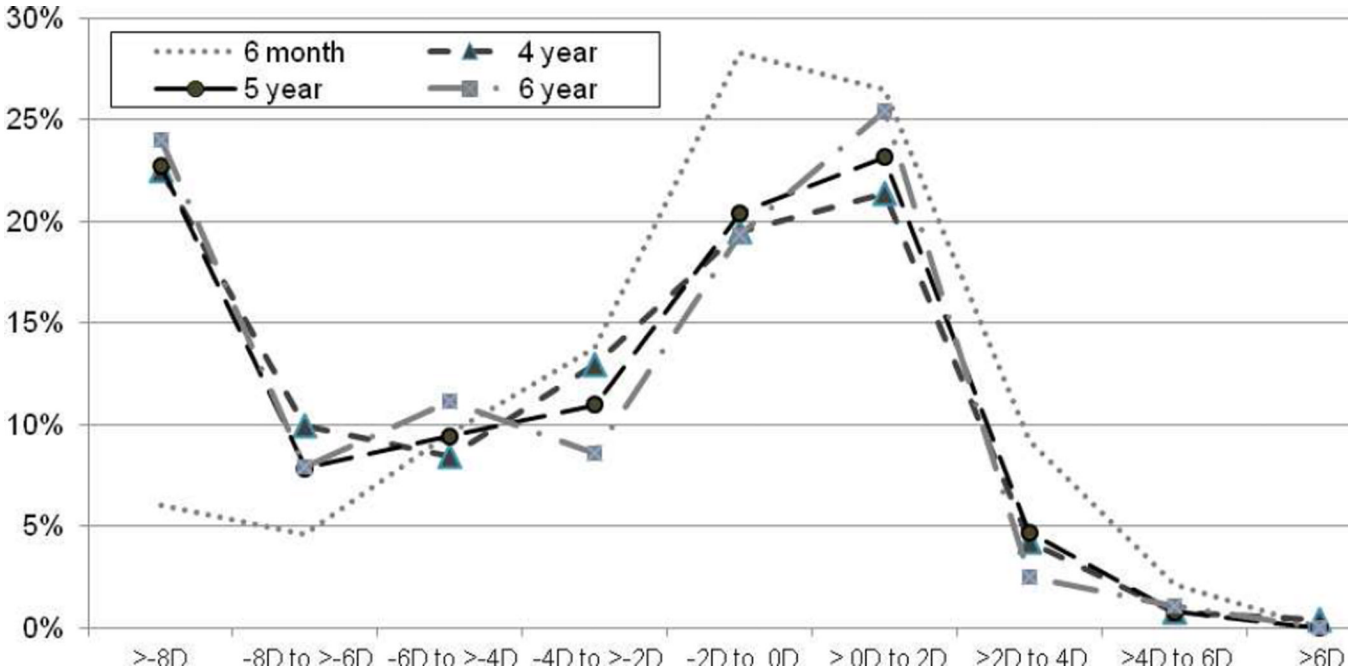

FIG 2.

Distribution of refractive error (spherical equivalent) in ET eyes at four ages, plotted in 2 D steps, from −8.00 D to +6.00 D (n = 283 at 6 months, 262 at 4 years, 255 at 5 years, and 279 at 6 years).

Table 1

Percentage of eyes with myopia and high myopia at 4, 5, and 6 years postnatal age

Refractive status	Postnatal age, years	Treatment at high-risk prethreshold, n/N[a] (%)	Conventionally managed high-risk eyes		
			Total conventionally managed high-risk eyes, n/N[b] (%)	Treatment at threshold, n/N (%)	Regressed, no treatment, n/N (%)
Myopia ≥0.25 D	4	182/262 (69.2)	161/239 (67.4)	118/145 (81.4)	43/94 (45.7)
	5	175/255 (68.6)	151/233 (64.8)	110/141 (78.0)	41/92 (44.6)
	6	195/279 (69.9)	173/257 (67.3)	128/157 (81.5)	45/100 (45.0)
Myopia ≥5D	4	97/262 (37.0)	90/239 (37.7)	72/145 (49.7)	18/94 (19.1)
	5	90/255 (35.3)	86/233 (36.9)	71/141 (50.4)	15/92 (16.3)
	6	110/279 (39.4)	96/257 (37.4)	79/157 (50.3)	17/100 (17.0)

[a]Refractive error data unavailable due to retinal detachment, media opacity, pupillary miosis, or other difficulty in refracting (14 eyes at 4 years, 14 eyes at 5 years, and 15 eyes at 6 years) and due to exclusion of eyes that underwent vitrectomy, scleral buckling procedures, iridectomy, glaucoma procedures, or cataract surgery in an additional 13 eyes at 4 years, 16 eyes at 5 years, and 16 eyes at 6 years.

[b]Refractive error data unavailable due to retinal detachment, media opacity, pupillary miosis, or other difficulty in refracting (25 eyes at 4 years, 23 eyes at 5 years, and 26 eyes at 6 years) and due to exclusion of eyes that underwent vitrectomy, scleral buckling procedures, iridectomy, glaucoma procedures, or cataract surgery in an additional 18 eyes at 4 years, 20 eyes at 5 years, and 20 eyes at 6 years.

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Table 2

A. Percentage of eyes with myopia in which ROP occurred in zone 1 versus zone 2 and the percentage of eyes with myopia in which plus disease was present or absent					
Group	**Age, years**	**Zone of ROP**		**Presence of plus disease**	
		Zone 1, n/N (%)	**Zone 2, n/N (%)**	**Plus n/N (%)**	**No plus n/N (%)**
Treated at high-risk prethreshold ROP	4	79/105 (75.2)	103/157 (65.6)	119/176 (67.6)	63/86 (73.3)
	5	76/101 (75.2)	99/154 (64.3)	112/170 (65.9)	63/85 (74.1)
	6	87/111 (78.4)	108/168 (64.3)	124/186 (66.7)	71/93 (76.3)
Conventionally managed, with treatment at threshold, if reached	4	59/88 (67.0)	102/151 (67.5)	116/165 (70.3)	45/74 (60.8)
	5	57/87 (65.5)	94/146 (64.4)	106/159 (66.7)	45/74 (60.8)
	6	64/95 (67.4)	109/162 (67.3)	123/176 (69.9)	50/81 (61.7)

B. Percentage of eyes with high myopia in which ROP occurred in zone 1 versus zone 2 and the percentage of eyes with high myopia in which plus disease was present or absent					
Group	**Age, years**	**Zone of ROP**		**Presence of pus disease**	
		Zone 1, n/N (%)	**Zone 2, n/N (%)**	**Plus, n/N (%)**	**No plus, n/N (%)**
Treated at high-risk prethreshold ROP	4	50/105 (47.6)	47/157 (29.9)	61/176 (34.7)	36/86 (41.9)
	5	44/101 (43.6)	46/154 (29.9)	59/170 (34.7)	31/85 (36.5)
	6	55/111 (49.5)	41/95 (43.2)	69/186 (37.1)	41/93 (44.1)
Conventionally managed, with treatment at threshold, if reached	4	37/88 (42.0)	53/151 (35.1)	64/165 (38.8)	26/74 (35.1)
	5	37/87 (42.5)	49/146 (33.6)	59/159 (37.1)	31/85 (36.5)
	6	55/168 (32.7)	55/162 (34.0)	67/176 (38.1)	29/81 (35.8)