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Retinopathy of Prematurity in Infants Weighing Less Than 500 Grams at Birth Enrolled in the Early Treatment for Retinopathy of Prematurity Study

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Abstract

Purpose—To describe patient characteristics, classification and onset of prethreshold retinopathy of prematurity (ROP), and ocular findings at 6 months corrected age in infants with birth weights <500 grams enrolled in the Early Treatment for Retinopathy of Prematurity (ETROP) Study.

Design—Multicenter randomized clinical trial.

Participants—63 infants with birth weights <500 grams who developed ROP and were enrolled in the ETROP Study.

Methods—Infants <1251 grams at birth were logged at 26 study centers from 10/1/00 to 9/30/02 and underwent examinations for ROP. Infants who developed ROP and whose parents/legal guardians consented were enrolled in the ETROP Study. Infants who developed high-risk

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prethreshold ROP were randomized; one eye was treated early with peripheral retinal ablation and the other eye managed conventionally, or, in asymmetric cases, the high-risk eye was randomized to either early peripheral retinal ablation or conventional management. All eyes reaching prethreshold ROP (either low-risk or high-risk) were examined when infants reached 6 months corrected age.

Main Outcome Measure—ROP incidence, characteristics and ocular findings among participants.

Results—34 infants reached prethreshold or worse severity in one or both eyes. ROP was located in zone I in 43.3% of all prethreshold eyes and plus disease was present in 46.7%. Median postmenstrual age for diagnosis of all prethreshold ROP was 36.1 weeks, but earlier (35.1 weeks) for eyes that developed high-risk prethreshold ROP. In the 27 surviving infants with prethreshold ROP (either high-risk or low-risk), ophthalmic examination at 6 months corrected age showed a normal posterior pole in 22 (81.5%), a favorable structural outcome with posterior pole abnormalities in 4 (14.8%), and an unfavorable structural outcome (stage 4B) in 1 (3.7%). One infant was diagnosed with amblyopia, 4 with nystagmus, 4 with strabismus, and 8 with myopia >-5.00 diopters.

Conclusions—This is the first report on characteristics of prethreshold ROP in infants with birth weights <500 grams. These infants are at high risk for developing prethreshold ROP although many initially achieve a favorable structural outcome. In the longer term, they are at risk of developing strabismus, nystagmus, high myopia, and abnormal retinal structure and should therefore receive continued long-term follow-up.

Retinopathy of prematurity (ROP) is a disease of the retinal vasculature that can cause significant impairment of vision. In premature infants, both the incidence and the severity of ROP increase with decreasing birth weight and gestational age. Data from the multicenter Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study indicated that the incidence of ROP increased from approximately 40% in infants with birth weights 1,101-1,200 g to more than 90% in those with birth weights 501-600 g.[1,2] It increased from approximately 35% in infants with gestational age of 31 weeks to more than 95% in those with gestational age of 24 weeks.[1,2] The incidence of significant (prethreshold) ROP increased from approximately 5% in infants with birth weights 1,101-1,200 g to approximately 50% in those with birth weights 501-600 g. It increased from approximately 3% in infants with gestational age of 31 weeks to approximately 45% in those with a gestational age of 24 weeks.[1,2]

Advances in neonatal care, including improved ventilation techniques and intravenous nutrition, have improved the survival rates of extremely premature infants. Although morbidity is high in extremely immature infants[3,4] and most develop at least some ROP,[1,2] no large studies have analyzed retinal or visual outcomes in infants with birth weights <500 grams.

Interest in the effectiveness of peripheral retinal ablation in the prevention of visual impairment and retinal detachment in eyes with very severe (threshold) ROP led to the multicenter CRYO-ROP Study, which enrolled 291 infants from 1986 through 1987 and followed them to age 15 years, Results indicated a significant benefit of peripheral retinal

ablation with cryotherapy for the prevention of severe visual impairment and retinal detachment in eyes with threshold ROP.[5-7] This positive outcome led clinicians to question whether earlier treatment of ROP, prior to the development of threshold severity, could lead to even better visual and retinal structural outcomes. The Early Treatment for Retinopathy of Prematurity (ETROP) Study tested this hypothesis by comparing results of peripheral retinal ablation at prethreshold ROP that was determined by a risk-analysis model[8] to be at high risk for unfavorable outcome versus conventional management, which involved monitoring ROP status and treating only if ROP of threshold severity developed.[9] Over 400 infants were enrolled in this multicenter study from 2000 to 2002, and results indicated a benefit of earlier treatment, shown by assessment of grating visual acuity and retinal structure at 9 months corrected age.[10]

The ETROP Study enrolled 63 patients with birth weights <500g. The purpose of the present report is to provide descriptive information on ROP in this cohort. We also provide follow-up data at 6 months corrected age for those infants who developed prethreshold ROP in one or both eyes.

Methods

A detailed description of the study protocol has been published previously.[9] From October 1, 2000 to September 30, 2002, ETROP personnel at 26 sites maintained a log of all infants with birth weights <1251 g. Infants who showed ROP in one or both eyes, based on an eye examination conducted by a study-certified ophthalmologist when the infant was between 28 and 42 days of life, were enrolled in the ETROP Study after the parent provided written informed consent. Examiners conducted serial examinations at intervals of 2 weeks. If the child developed “near-prethreshold” (a study term defined as zone II stage 2 with zero to one quadrant dilated and tortuous vessels or immature vascularization in zone 1) or prethreshold ROP, exams were conducted weekly. The ophthalmologist classified ROP in each eye according to the International Classification for Retinopathy of Prematurity (ICROP).[11] Prethreshold ROP was defined as: (a) zone I any ROP; (b) zone II stage 2 with plus; (c) zone II stage 3 no plus; or (d) zone II stage 3 with plus but fewer clock hours than required for threshold ROP. Threshold ROP was defined as zone I or II, five contiguous or eight composite clock hours of stage 3 with plus disease.[5] In this study, plus disease was defined as dilated and tortuous vessels in two or more quadrants.

If an examination indicated that an infant had prethreshold ROP in one or both eyes, demographic and disease-related data were entered into the RM-ROP2 risk management program[8] to determine whether the eye was “high risk” (i.e., having a risk of unfavorable structural outcome ≥15% at 3 months post-term if untreated) or “low risk” (i.e., having a risk of unfavorable outcome <15%). Following written informed parental consent, an infant with high risk prethreshold ROP was entered into the randomized (surgical) portion of the study. If high-risk prethreshold ROP developed bilaterally, one eye was randomized to receive peripheral retinal ablation within 48 hours, while the fellow eye was managed conventionally, with peripheral retinal ablation if threshold ROP developed. If an infant developed high-risk prethreshold ROP in only one eye, that eye was randomized to either earlier treatment or conventional management.

Infants with low risk prethreshold ROP in the worse eye underwent re-examination at 2- to 4-day intervals for up to 2 weeks. If high-risk prethreshold ROP developed and parents consented, the infant entered the randomized trial. If the ROP did not advance to high-risk prethreshold disease during two weeks of examinations at 2- to 4-day intervals, the interval between examinations could be extended, with examinations conducted as clinically indicated.

All study infants with a history of prethreshold ROP were examined at six months corrected age by a study-certified ophthalmologist. Retinal status was classified by the examining ophthalmologist as normal, straightened temporal vessels, macular ectopia, retinal fold not involving the macula, partial retinal detachment not including the macula (stage 4A), retinal fold involving the macula, partial retinal detachment including the macula (stage 4B), total retinal detachment (stage 5), or unable to grade. Also documented were presence or absence of strabismus, nystagmus, refractive error and amblyopia (defined as abnormal fixation behavior in one eye in the absence of an unfavorable anatomic outcome or any other abnormality noted on fundus exam to explain it).

The protocol was approved by the Institutional Review Boards at each participating institution, and written informed consent was obtained from parents or guardians for all study procedures.

Data Analysis

All 63 infants with birth weights <500 g who were enrolled in the study were included in the analysis of baseline characteristics. For the 34 infants whose ROP progressed to prethreshold in one or both eyes, results are presented for one eye only. If neither eye received early treatment, then the eye to be included was selected at random. If one eye received early treatment, then the fellow eye, which was managed conventionally, was selected. While it would be interesting to know if outcomes of early treatment were similar in these extremely low birth weight infants to those obtained in the ETROP cohort as a whole, this analysis was not possible. Many variables were used by the risk analysis program[8] to determine whether an eye had high risk prethreshold ROP, the status that was required for randomization to early treatment versus conventional management. Thus, any differences observed could be related to factors other than birth weight. Furthermore, there were too few early treated eyes in this group of infants with birth weights <500 g to allow a meaningful analysis of results.

Eyes were classified as having an “unfavorable” structural outcome if there was a retinal fold involving the macula, a partial retinal detachment including the macula (stage 4B), or total retinal detachment (stage 5).[5,9]

Results

Study cohort

Figure 1 summarizes the derivation of the cohort for this study. At the 26 study centers, 9,721 infants with birth weights <1251 g were logged between October 1, 2000 and September 30, 2002. Three hundred sixty-nine (369) had birth weights <500 g. Of this

number, 306 infants were not enrolled in the ETROP study due to death (n=237), transfer or discharge (n=13), ineligibility due to systemic or ocular abnormalities (n=19), absence of ROP on all examinations (n=6), or failure to obtain consent for study examinations (n=31). Among the 63 consented and enrolled infants, 34 developed prethreshold or worse ROP in the worse eye, 22 developed near-prethreshold disease (Zone II, stage 2) in the worse eye, and 7 developed mild ROP in the worse eye. Table 1 displays the baseline demographic characteristics of the study cohort.

Characteristics of prethreshold ROP in study infants

Table 2 summarizes the disease classification features for one eye of each patient who developed prethreshold disease. ROP was present in zone I in 43.3% of eyes with prethreshold disease and plus disease was present in 46.7%. Presence of aggressive posterior ROP was not recorded, as it had not yet been defined when the ETROP Study was designed.

Table 3 provides information on timing of onset of prethreshold ROP and high risk prethreshold ROP in the selected eye for each patient. Among the subset of 25 eyes that developed high-risk prethreshold disease, the median postmenstrual age of onset of prethreshold ROP (35.1 weeks) is approximately one week earlier than the median postmenstrual age of onset of prethreshold ROP (36.1 weeks) for the entire group of 30 eyes that developed prethreshold disease. Similarly, among the 25 eyes that developed *high-risk* prethreshold disease, the median chronological age of onset of prethreshold ROP (10.1 weeks) is approximately one week earlier than the median chronological age of onset of prethreshold ROP (11.4 weeks) for all eyes that developed prethreshold disease. Out of the 25 high-risk eyes, 3 were from patients who refused to join the early treatment trial. The remaining 22 high-risk eyes were managed conventionally (i.e., were treated if they reached threshold or were observed until the ROP regressed without needing treatment). 17 of these 22 high-risk control eyes (77%) progressed to threshold ROP and were treated with laser at threshold, only one eye had an unfavorable structural outcome at 6 month exam; 5 of 22 high-risk eyes (23%) that were managed conventionally regressed without any laser treatment, all of these eyes had favorable structural outcomes at 6 month exam.

Six-month structural outcomes and ocular findings

Table 4 displays the structural outcomes found at the six-month examination for the selected eye of each patient included in this analysis. An unfavorable structural outcome (retinal detachment involving the macula) was seen in only one eye (3.7% of the 27 eyes that developed prethreshold ROP; 4.5% of the 22 eyes that developed high-risk prethreshold ROP). Table 5 presents the prevalence of amblyopia (4.2%), nystagmus in both eyes (17.4%), strabismus (17.4%), and high myopia (32.0%) in these patients. The most frequently occurring ocular condition was myopia of -5.00 diopters (D) or greater, which was found in 8 patients, followed by nystagmus and strabismus, both of which were found in four of the 27 patients with prethreshold ROP.

Data based on a comparison of earlier treatment vs conventional management of eyes with high-risk prethreshold ROP are not provided, and we also have not compared this group of infants to other subgroups or the rest of the group of infants in the study. Such comparisons

could be potentially interesting, but also run the risk of scientific inaccurate because infants were randomized into the study on the basis of many factors, one of which was birthweight.

Discussion

Relatively little has been published about the ROP characteristics of infants weighing less than 500 grams at birth. The survival of these infants, at the lower end of the extremely low birth weight range (401 to 1000 grams), continues to improve due to advances in neonatal care. Improved survival of these particularly immature infants has resulted in a larger cohort of infants at risk for developing vision-threatening ROP.[1,2]

Despite an improved prognosis for infants weighing less than 500 grams at birth, many do not survive long enough to develop ROP. Of 369 such infants logged into the ETROP study, 237 (64.2%) died prior to undergoing an ROP examination at 28 to 42 days of life. However, of the 100 infants who received ROP examinations through resolution of the acute phase, only six (6%) failed to develop any ROP. Of the 63 infants with birth weights less than 500 grams who developed ROP and whose parents consented to enrollment in the ETROP study, seven developed mild ROP in the worse eye, while the remaining 56 developed near-prethreshold or prethreshold disease. Of the 30 infants whose ROP reached prethreshold in one or both eyes, 13 (43.3%) developed ROP in zone I and 14 (46.7%) had plus disease. Thus, most of these tiny infants do develop ROP.

Among the 63 patients reported in this paper, there were no demographic factors that significantly correlated with ROP severity (less-than-prethreshold vs prethreshold or worse ROP), including race, sex, inborn vs. outborn status, single vs. multiple gestation, birth weight and gestational age. The racial distribution and percent born at a study hospital in the 63 infants with birth weights <500 g was similar to that of the entire group of 2,320 infants with birth weights <1251 g who developed ROP and were enrolled in the ETROP Study.[12] However, fewer of the <500 g cohort were male (33.3% vs 50.6%), and more were singleton births (85.7% vs 70.1%); these results are expected given the lower survival rates of male infants and multiple births.

Mean birth weight in this cohort was 454.5 grams and mean gestational age was 25.1 weeks. Other reports have focused on ROP in extremely premature infants,[13,14] but comparisons to this report are limited because inclusion criteria differed, the studies were retrospective, or ROP screening procedures varied. A strength of the cohort reported herein is that the infants were evaluated prospectively in a manner determined by a set protocol. However, comparison of the present subgroup of 63 patients with birth weights <500 g in the ETROP Study with the rest of the ETROP Study cohort is not feasible, because birth weight is only one of many potential differences, including differences in neonatal complications (which were not recorded as part of the study), between the subgroup and the entire cohort. Thus, if differences in the course of their ROP were in reality due to more neonatal complications, for instance, it would be incorrect to attribute these differences to birth weight alone.

As noted above, a fairly high proportion (43.3%) of prethreshold ROP in this group occurred in zone I, which is not surprising given the immaturity of retinal vessel development in low

gestational age infants. However, timing of the onset of prethreshold ROP in infants with birth weights <500 g, at a median postmenstrual age of 36.1 weeks, was identical to that reported for the CRYO-ROP Study,[15] which enrolled infants with birth weights <1251 g from January, 1986 through November, 1987, and identical to that for the entire ETROP Study cohort of infants with birth weights <1251 g.[12] As noted in previous reports of extremely premature infants,[12],[16] the onset of prethreshold ROP occurred one week earlier, at 35.1 weeks postmenstrual age, in eyes that developed high risk prethreshold disease. However, current ROP screening guidelines ensure that premature infants are examined prior to this age (average postnatal age for treatment, 10.1 weeks).[17]

In the 27 eyes with prethreshold ROP that were examined at 6 months corrected age, the majority (81.5%) had a normal posterior pole, and in 26 (96.3%), the structural outcome was favorable. Among the subset of 22 eyes that developed high risk prethreshold disease, results were nearly as good; 17 (77.3%) had a normal posterior pole at 6 months corrected age, and in 20 (95.5%), structural outcome was favorable. The eye examination showed myopia of -5.00 D or greater in eight patients, bilateral nystagmus in four patients, and strabismus in four patients. These results are not surprising, as nystagmus, strabismus, and high myopia are known to occur more frequently in premature infants than in full-term infants.[18-20]

It is of interest that a small number of infants with birth weights <500 g developed either no ROP (n=6) or mild ROP (n=7) and that the majority of patients in this series achieved a favorable structural outcome. The spectrum of ROP severity among infants with similar known risk factors has led some authors to propose a role for a genetic basis for ROP.[21] An improved understanding of ROP genetics may lead to earlier and more effective intervention. Better strategies to prevent blindness from ROP will be increasingly important in developing countries, which are poised to experience a sharp increase in the survival of premature infants.

It is likely that there will be increasing numbers of surviving infants with birth weights less than 500 grams. This report is the first of its kind to describe characteristics of ROP in this group. Fortunately, the data of the present report, although based on a limited sample size, indicate that current screening guidelines and treatment recommendations appear to be appropriate for these tiny infants.

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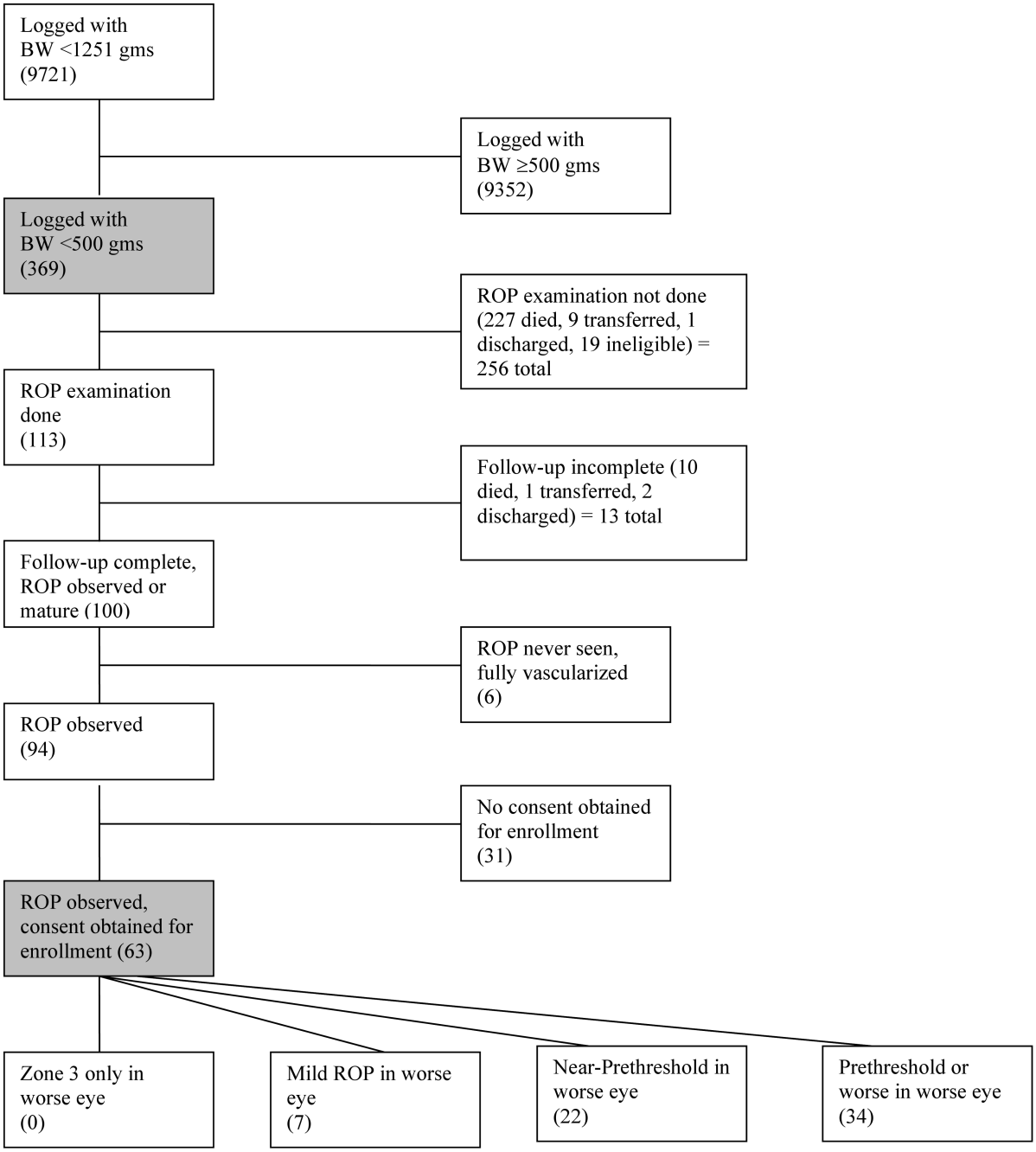

Figure 1.

Derivation of study cohort of Early Treatment for Retinopathy of Prematurity (ETROP) Study infants with birth weight < 500 grams, from among all infants < 1251 grams birth weight (BW) who were examined for retinopathy of prematurity (ROP) at participating centers.

Table 1

Baseline characteristics of Early Treatment for Retinopathy of Prematurity Study infants with birth weight <500 grams who developed retinopathy of prematurity and whose parents consented for enrollment.

		Less Than Prethreshold* (N = 29)		Prethreshold or Worse* (N = 34)		Total (N = 63)	
		n	%	n	%	n	%
Born in study hospital		28	(96.6)	29	(85.3)	57	(90.5)
Male		12	(41.4)	9	(26.5)	21	(33.3)
Race							
White (non-Hispanic)		18	(62.1)	25	(73.5)	43	(68.3)
African-American		8	(27.6)	6	(17.6)	14	(22.2)
Hispanic		2	(6.9)	2	(5.9)	4	(6.3)
Others		1	(3.4)	1	(2.9)	2	(3.2)
Multiple births							
Single		23	(79.3)	31	(91.2)	54	(85.7)
Twins		5	(17.2)	3	(8.8)	8	(12.7)
Others		1	(3.4)	0	(0.0)	1	(1.6)
Birth weight (grams)	Mean		456.2		453.1		454.5
	SD		(49.0)		(35.7)		(42.0)
Gestational age (weeks)	Mean		25.3		25.0		25.1
	SD		(1.6)		(1.5)		(1.5)

SD = standard deviation

*Data are categorized based on the highest severity of retinopathy of prematurity (ROP) observed in either eye.

Table 2

Disease classification among Early Treatment for Retinopathy of Prematurity Study eyes in the 30 infants with birth weight <500 grams who developed prethreshold or worse retinopathy of prematurity in one or both eyes.

Disease Classification*	Number of Eyes**	Percent
Z I, S 3+	3	10.0
Z I, S 3-	1	3.3
Z I, S 1/2+	2	6.7
Z I, S 1/2-	7	23.3
Z II, S 3+	7	23.3
Z II, S 3-	8	26.7
Z II, S 2+	2	6.7

Key: Z=zone, S=stage, +/- = presence or absence of plus diseases

* If prethreshold retinopathy of prematurity (ROP) was documented on more than one examination for a patient, the examination was selected that had the highest risk profile based on a computerized risk model (RM-ROP2).[8]

** Data for three patients with prethreshold or worse ROP in one eye are not included because the selected eye did not reach prethreshold disease, and data were not included for one patient in whom the onset of prethreshold ROP was not documented before threshold disease was diagnosed.

Table 3

Onset of prethreshold retinopathy of prematurity (ROP) in all 30 Study infants with birth weight <500 grams who developed prethreshold ROP and in the subset of 25 infants who developed high risk prethreshold ROP.

	Prethreshold ROP (N=30)	High Risk Prethreshold ROP (N=25)
Chronologic age, wks		
Median	11.4	10.1
Minimum	6.3	6.3
Maximum	15.1	13.7
Postmenstrual age, wks		
Median	36.1	35.1
Minimum	31.3	31.3
Maximum	41.4	40.7

Table 4

Structural outcomes at 6 months corrected age among eyes of all infants with birth weight <500 grams who developed prethreshold retinopathy of prematurity (ROP) and in the subset of infants who developed high risk prethreshold ROP.

	Presthreshold ROP (N=27)*		High Risk Presthreshold ROP (N=22)*	
	n	%	n	%
Favorable outcome				
Normal posterior pole	22	(81.5)	17	(77.3)
Abnormal angle of temporal vessels	3	(11.1)	3	(13.6)
Macular ectopia	0	(0.0)	0	(0.0)
Retinal detachment not involving macula (Stage 4A)	1	(3.7)	1	(4.5)
Unfavorable outcome				
Retinal detachment involving macula (Stage 4B)	1	(3.7)	1	(4.5)

* Three patients died before the 6 month exam

Table 5

Ocular findings at 6-month outcome examination in Early Treatment for Retinopathy of Prematurity Study infants with birth weight <500 grams who developed prethreshold retinopathy of prematurity.

Ocular Condition	Present	Absent	UG	Not recorded
Amblyopia*	1 (4.2%)	23 (95.8%)	3	0
Nystagmus OU	4 (17.4%)	19 (82.6%)	1	3
Strabismus	4 (16.0%)	21 (84.0%)	2	0
High Myopia †	8 (32.0%)	17 (68.0%)	2	0

UG = unable to grade; OU = both eyes

*Abnormal fixation behavior in one eye in the absence of unfavorable anatomic outcome or any other abnormality noted on fundus exam to explain it in one or both eyes.

†Myopia of -5.00 diopters or worse in one or both eyes