

# Risk Analysis of Prethreshold Retinopathy of Prematurity

ARCHIVES EXPRESS

Robert J. Hardy, PhD; Earl A. Palmer, MD; Velma Dobson, PhD; C. Gail Summers, MD; Dale L. Phelps, MD; Graham E. Quinn, MD, MSCE; William V. Good, MD; Betty Tung, MS; for the Cryotherapy for Retinopathy of Prematurity Cooperative Group

**Objective:** To present a new multifactorial algorithm to integrate important risk factors for unfavorable retinal outcome in eyes that reached prethreshold retinopathy of prematurity (ROP) in the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study. A computerized risk model (RM-ROP2) was developed from this algorithm to identify high-risk prethreshold eyes for enrollment in the Early Treatment for Retinopathy of Prematurity randomized trial.

**Methods:** Data were analyzed from 613 eyes (1 eye per infant) in the natural history cohort of the Multicenter Trial for Cryotherapy for Retinopathy of Prematurity. These eyes were selected from infants in whom 1 or both eyes progressed to prethreshold ROP. Eyes that progressed to threshold ROP and were randomized to cryotherapy were excluded from this study, but control eyes that reached threshold ROP were included. The course of ROP for 1 prethreshold eye for each infant was tracked until the evaluation of its structural outcome at 3 months' postterm. Tables present structural outcome by se-

lected risk characteristics. A multiple logistic risk model is used to summarize the combined effect of all of these known prognostic risk factors as they relate to structural outcome.

**Results:** Eyes were classified by predicted outcome into 10 risk categories, lowest to highest. Both the observed and predicted outcomes in each category showed an increasingly unfavorable outcome when viewed from lowest to highest risk. Prethreshold ROP eyes were then divided into 2 groups, high-risk, eyes (risk, 0.15-1.0) and low-risk eyes (risk, <0.15). High-risk eyes had an unfavorable outcome of 36% at 3 months' postterm; whereas, only 5% of the low-risk eyes had an unfavorable outcome.

**Conclusion:** The model effectively identifies prethreshold ROP eyes that have a relatively high risk and eyes that have a lower risk of an unfavorable structural outcome at 3 months.

*Arch Ophthalmol.* 2003;121:1697-1701

**I**N 1991, the Cryotherapy for Retinopathy of Prematurity Cooperative Group (CRYO-ROP) published detailed incidence figures for ROP by severity of disease and also tabulated them by an array of patient subgroups such as birth weight, race, and others.<sup>1</sup> In 1993, we reported the results of multiple logistic regression analysis of numerous independent variables, both for baseline characteristics of infants and by ROP classification features.<sup>2</sup> That article quantified, for the first time, the risk effect of these variables on the likelihood of an eye reaching the threshold ROP (**Table 1**) for treatment, and the likelihood that an eye that reached threshold ROP and was untreated would progress to an unfavorable outcome 3 months later.<sup>2</sup> We also have published outcome statistics for untreated ROP tabulated by baseline infant characteristics and numerous severity categories.<sup>3,4</sup>

While the published risk analysis data lent objectivity to estimating prog-

nosis, it remained difficult for physicians to quantify the risk for an individual infant. Major progress in that direction was achieved through the development of a mathematical algorithm, converted into a risk analysis computer program known as RM-ROP.<sup>5</sup>

*See also pages 1684  
and 1769*

As originally described, RM-ROP consists of 5 mathematical equations that provide a relationship among risk factors observed about the infant and the infant's retina as they correlate with structural outcome. The program is based on data from 4099 infants who weighed less than 1251 g at birth who composed the natural history cohort of the Multicenter Trial for Cryotherapy for Retinopathy of Prematurity.<sup>1,2</sup> The RM-ROP analyzes data acquired during acute-phase ROP to calcu-

Author affiliations are listed at the end of this article. The authors have no relevant financial interest in this article. A list of the members of the Cryotherapy for Retinopathy of Prematurity Cooperative Group can be found at <http://www.nei.nih.gov/nejtrials/static/study32.htm#ClinicalCenters>.

**Table 1. Definitions of Prethreshold ROP, Threshold ROP, and Unfavorable Physician's Summary Diagnosis**

Category	Inclusion Criteria
Prethreshold ROP	Zone I, any ROP Zone II, stage 2 ROP with plus disease (defined as dilation and tortuosity of posterior pole retinal vessels); zone II, any amount of stage 3 ROP without plus disease; or zone II, stage 3 with plus disease but fewer than 5 contiguous or 8 cumulative clock hours
Threshold ROP	Zones I or II with 5 contiguous or 8 cumulative clock hours of stage 3 with plus disease
Unfavorable summary diagnosis	Retinal fold involving the macula; retrolental opacity blocking the visual axis and/or partial retinal detachment involving the macula; or total retinal detachment, or total papillary occlusion by fibrovascular membrane

Abbreviation: ROP, retinopathy of prematurity.

late 2 risk estimates: (1) that an individual infant's eye will develop threshold ROP, and (2) if threshold is reached, that the eye with or without treatment will develop an unfavorable structural outcome (and very likely, blindness) 3 months later.

We have developed a different version of the program that calculates the risk of an unfavorable 3-month outcome for eyes at prethreshold ROP severity (Table 1), rather than waiting until the eye reaches threshold ROP. This new risk model, RM-ROP2, is the subject of this article. The RM-ROP2 has been used to select high-risk prethreshold ROP eyes for enrollment in a clinical trial, the Early Treatment for Retinopathy of Prematurity study sponsored by the National Eye Institute, National Institutes of Health, Bethesda, Md.<sup>6</sup>

## METHODS

### STUDY POPULATION

A group of infants was selected as follows from the natural history cohort of the CRYO-ROP study.<sup>3</sup> The full natural history cohort consists of 4099 subjects who were enrolled from January 1, 1986, through November 30, 1987, as newborns with birth weights less than 1251 g. Beginning at 4 through 6 weeks of age, they were examined by specially trained and certified ophthalmologists every 2 weeks for the development of ROP, and later for outcome 3 months' postterm or after randomization. If ROP progressed to the prethreshold level, the examination interval was shortened to within 7 days. Data from the 731 infants who developed prethreshold or worse ROP in 1 or both eyes were eligible for inclusion in this study. (The remaining 3368 infants either had no ROP or developed ROP that remained less severe than the prethreshold category.) One eye of each infant was selected for the present analysis.

In cases in which only 1 eye reached prethreshold or worse ROP during the course of acute-phase ROP, that eye was chosen for study. For infants with both eyes reaching prethreshold ROP, the following selection criteria were used: (1) if neither eye reached the treatment threshold, 1 eye was selected at random; (2) if both eyes eventually reached threshold ROP, the eye randomized in the CRYO-ROP study to not receive cryotherapy (control eye) was included; and (3) if only 1 eye eventually reached threshold ROP severity and was randomized to serve as the control eye, that eye was included; conversely, if the eye was randomized to receive cryotherapy, the untreated prethreshold fellow eye was included. Following the eyes in groups 1 through 3 produces a natural history of untreated eyes through onset of prethreshold ROP, including those eyes that progressed to treatment threshold ROP but were untreated. This allows the risk model to properly estimate the risk of an unfavorable 3-month outcome.

These data are presented in tabular form by infant and eye characteristics. The multiple logistic risk model was used to examine the prognostic factors related to an unfavorable structural outcome. The multiple logistic equation is described and the coefficients of each of the factors included in the model are given. Calculation of the multiple logistic risk model was done using *Stata Statistical Software: Release 7.0*.<sup>7</sup>

## RESULTS

Of the 731 infants who constituted the prethreshold CRYO-ROP study population, a subgroup of 613 infants had their outcome determined at 3 months. Outcomes were unavailable from the remaining 118 infants for the following reasons: (1) 43 died before the 3-month examination, (2) 66 were not examined because of parental refusal (n=27) or loss of contact with the family (n=39), and (3) 9 were examined but the examiner was unable to classify the outcome. The baseline characteristics of both the entire cohort and the subgroup of 613 eyes with 3-month outcome data are summarized in **Table 2**. The subgroup of infants with 3-month outcome data is overall remarkably similar to the base natural history cohort.

The rates of unfavorable fundus outcome are given in **Table 3** by various characteristics of the infants and their selected eyes. As expected from previously published risk factors, infants born in 1 of the participating hospitals had a lower rate of an unfavorable outcome than those born in nonparticipating hospitals (15.5% vs 21.1%,  $P=.13$ ). Likewise, black infants had lower rates of unfavorable outcome than nonblack infants (8.6% vs 19.7%,  $P<.001$ ). Singleton infants had an unfavorable outcome rate of 17.5%, whereas multiple-birth infants had a slightly lower rate of 14.5% ( $P=.44$ ). The unfavorable outcome rate for female infants was 18.4%, while male infants had a slightly lower rate of 15.1% ( $P=.28$ ). By birth weight categories, the unfavorable outcome rates vary from 23.7% for infants weighing less than 750 g at birth down to 9.0% for infants weighing 1000 to 1250 g at birth. Similarly, infants born more prematurely had higher rates of unfavorable outcome than infants born later in gestation.

Table 3 also gives the outcome of the eyes categorized by the clinical findings at the time of designation as prethreshold ROP. Within each zone of disease, eyes with plus disease (defined as dilation and tortuosity of posterior pole retinal vessels) had a higher rate of unfavorable outcome than eyes without plus disease. Note that for ROP in zone II, eyes with stage 2 with plus disease had more unfavorable outcomes than eyes with stage 3

**Table 2. Baseline Risk Characteristics\***

Risk Characteristic	All Patients With Prethreshold ROP (n = 731)	Patients With Prethreshold ROP With 3-Month Outcome (n = 613)
Born in the study hospital	75.4	76.8
Race		
Black	28.6	26.4
Nonblack	71.4	73.6
Multiple birth status		
Single	78.4	77.5
Multiple	21.6	22.5
Birth weight, mean (SD), g	831 (175)	829 (175)
Gestational age, mean (SD), wk	26.5 (1.8)	26.5 (1.8)
Onset of ROP, median, postmenstrual wk	34.0	34.0
At first sign of ROP, was ROP in zone I	7.4	6.7
Interval for ROP to prethreshold level, median, wk	2.0	2.0
Plus disease† at first prethreshold ROP examination	38.3	38.3
Stage 3 ROP	81.3	83.0

Abbreviation: ROP, retinopathy of prematurity.

\*Data are given as percentage of patients unless otherwise indicated.

†Defined as dilation and tortuosity of posterior pole retinal vessels.

without plus disease. The percentage of unfavorable eyes varied only slightly with postconceptional time of onset of ROP; however, it decreased with increasing duration from the onset of ROP to prethreshold level, ranging from 27.4% when that interval was 1 week, to 6.4% when the interval was longer than 3 weeks.

To further evaluate these risk factors individually as well as their simultaneous influence on the outcome of ROP, a logistic risk analysis was applied to these data. The multiple logistic risk model RM-ROP2 for prethreshold eyes has the following mathematical form:

$$p = \{1 + \exp[-(\alpha + \beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k)]\}^{-1}.$$

Each  $x_i$  is an infant or eye factor that increased (or decreased) the risk  $p$ , of having an unfavorable outcome. The  $\beta_i$  and  $\alpha$  are coefficients in the risk model that are estimated from these data. The  $\beta_i$  is the coefficient associated with  $x_i$  and  $\alpha$  is a constant term. The function  $\exp$  raises the expression in brackets to the base  $e=2.71828$ . . . .

The results, given in **Table 4**, are summarized in terms of the regression coefficients and odds ratio for each factor. For example, the odds of an unfavorable outcome,  $p/(1-p)$ , for infants who have plus disease at the first prethreshold examination are 8.6 times higher than for those who do not have plus disease. Both birth weight and gestational age were important; however, neither reached statistical significance in the multiple variable analyses. Because these 2 factors are biologically related, they should be considered jointly rather than separately. When considered together as an indicator of prematurity, they become statistically significant ( $P=.002$ )

**Table 3. Unfavorable Outcome Rates at 3 Months for 613 Eyes That Had Untreated Prethreshold ROP**

Variable	No. of Eyes With Unfavorable Outcome	Total No. of Eyes	Eye With Unfavorable Outcome, %
Born in the study hospital			
Yes	73	471	15.5
No	30	142	21.1
Multiple birth status			
Single	83	475	17.5
Multiple	20	138	14.5
Race			
Black	14	162	8.6
Nonblack	89	451	19.7
Sex			
Male	46	304	15.1
Female	57	309	18.4
Birth weight, g			
<750	52	219	23.7
750-999	41	283	14.5
1000-1250	10	111	9.0
Gestational age, wk			
≤27	86	441	19.5
28-31	17	168	10.1
≥32	0	4	0.0
Zone I			
Stage 3+	4	5	80.0
Stage 1+, 2+	3	6	50.0
Stage 1, 2	9	30	30.0
Zone II			
Stage 3+	58	156	37.2
Stage 3	17	348	4.9
Stage 2+	12	68	17.6
Onset of ROP, postmenstrual age, wk			
≤32	12	75	16.0
32-34	45	242	18.6
35-36	32	204	15.7
>36	14	92	15.2
Interval for ROP to prethreshold level, wk			
≤1	59	215	27.4
1-2	20	147	13.6
2-3	13	78	16.7
>3	11	173	6.4

Abbreviations: ROP, retinopathy of prematurity; +, with plus disease (defined as dilation and tortuosity of posterior pole retinal vessels).

as predictive of unfavorable outcome. Black race was an important predictor of reduced risk. When clinical characteristics of ROP in each eye were studied, zone and stage of disease were important factors along with plus disease. Also, the interval of ROP progression from onset to prethreshold level played a major role in the prognosis. All ROP characteristics that classified an eye at the prethreshold level were important indicators of outcome prognosis. However, the presence of zone I disease and the presence of plus disease were particularly strong indicators of a poor prognosis.

The multiple logistic model summarizes the experience of this group of prethreshold eyes. The **Figure** shows the fit of the model in 10 risk categories each containing approximately one tenth of the sample. Hence, there are approximately 60 eyes in each risk category (lowest to highest). Both the observed and expected percentages of

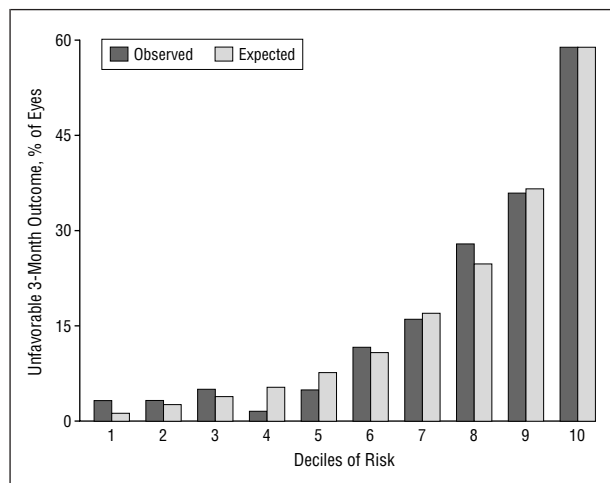
**Table 4. Multiple Logistic Coefficients for 613 Natural History Eyes (Untreated) in the CRYO-ROP Study**

Variables	$\beta$ Coefficient*	Odds Ratio	P Value	95% Confidence Interval
Birth weight (per 100 g)	-0.134	0.87	.16	0.73-1.05
Gestational age, wk	-0.174	0.84	.13	0.67-1.05
Race (black = 1, other = 0)	-0.934	0.39	.006	0.20-0.76
Born in the study hospital (yes = 1, no = 0)	-0.399	0.67	.16	0.39-1.16
Multiple-birth status (single = 1, multiple = 0)	0.216	1.24	.48	0.68-2.28
Onset of ROP, postmenstrual age, wk	-0.042	0.96	.61	0.82-1.13
At first sign of ROP, was ROP in zone I (zone I = 1, zone II = 0)	2.205	9.07	<.001	3.14-26.20
Interval for ROP to prethreshold level, wk	-0.204	0.82	.008	0.70-0.95
Plus disease† at first prethreshold ROP examination (plus = 1, no plus = 0)	2.152	8.60	<.001	4.92-15.06
Stage 3 ROP (stage 3 = 1, no stage 3 = 0)	0.952	2.59	.008	1.28-5.23

Abbreviations: CRYO-ROP, Cryotherapy for Retinopathy of Prematurity Cooperative Group; ROP, retinopathy of prematurity.

\* $\alpha = 4.083$ .

†Defined as dilation and tortuosity of posterior pole retinal vessels.



Observed and expected percentage of eyes with unfavorable 3-month outcome by decile of risk (10 risk categories). The number of eyes with retinopathy of prematurity studied was 613 with approximately 60 eyes per decile. Both the observed and expected percentage of eyes that had an unfavorable 3-month outcome increased from the lowest to the highest decile of risk.

eyes that had an unfavorable outcome increased from the lowest to the highest decile of risk. They are also similar within each decile category ( $\chi^2_8=5.43$ ,  $P=.71$ ).

A further evaluation of the results was obtained by dividing the prethreshold ROP eyes into 2 groups using a cutoff point for the risk at 0.15. On the upper side of risk were those with a risk of an unfavorable outcome of 0.15 to 1.00 vs those with a risk less than 0.15. During the planning of the Early Treatment for Retinopathy of Prematurity study, the span of cutoff point values between 0.10 and 0.20 was examined. The value of 0.15 was chosen as the enrollment level of risk for the study because it included within the high-risk group of 235 eyes, 68% that progressed to threshold ROP and/or an unfavorable outcome. It also appeared to minimize assigning the eyes for early treatment that did not progress to threshold ROP or an unfavorable outcome by reducing this to 32% (other cutoff point information available from the corresponding author).

Data showing the results for these 2 risk groups are given in **Table 5**, further classifying eyes according to International Classification of ROP categories. For eyes with a risk 0.15 to 1.00, 36% had an unfavorable 3-month

structural outcome. When the risk was less than 0.15, 5% had an unfavorable 3-month structural outcome. This striking separation in the unfavorable structural outcome rate was fairly consistent across the International Classification of ROP categories, with high-risk eyes showing more adverse outcomes than low-risk eyes. If we look at the progression to conventional threshold ROP, for eyes designated as high risk, 63% progressed to the conventional threshold ROP for treatment and for eyes designated as low risk, 14% progressed to threshold ROP.

#### COMMENT

The CRYO-ROP study has reported various prognostic factors that play a role in acute-phase ROP.<sup>2</sup> A further article from the CRYO-ROP study described using the profile of these factors to develop a series of risk models.<sup>6</sup> These RM-ROP models were designed as part of a novel system to aid physicians in assessing the risk of ROP in individual infants. The risk of reaching threshold ROP could be calculated with RM-ROP at birth, at onset of ROP, and at onset of prethreshold ROP. Then, at threshold ROP the risk of an unfavorable outcome at 3 months with or without treatment could be calculated.

In this article, again using data from the CRYO-ROP multicenter trial, we focus on a newer computer program (RM-ROP2) based on the natural history of the latter part of acute-phase ROP, from the time an eye is identified as having prethreshold ROP until the ROP either resolves or progresses to an unfavorable structural outcome at 3-months' follow-up. Using RM-ROP2 in a clinical setting requires a biweekly schedule of eye examinations by an experienced and knowledgeable examiner, beginning at 4 through 6 weeks of life and continuing until prethreshold ROP develops. Data on an infant's demographic characteristics and the progression of ROP are used to calculate the risk that the infant's eye would have an unfavorable fundus outcome at 3 months without surgical intervention for threshold ROP. The RM-ROP2 integrates all the information about the infant and the ROP observed in the eye examination into a single risk estimate. The coefficients in Table 4 provide the relative weighting of the demographic and clinical factors that was mathematically derived from the database.

**Table 5. Outcome for High-Risk and Low-Risk Eyes With ROP by ICROP Classification at First Determination of Prethreshold ROP\***

Zone	ICROP		High-Risk Eyes (0.15-1.00)	Low-Risk Eyes ( $<0.15$ )	% of High-Risk Eyes
	Stage	Plus Disease†			
I	3	Present	5 (80)	0	100
I	1 or 2	Present	6 (50)	0	100
I	1 or 2	Absent	23 (39)	7	77
II	3	Present	145 (39)	11 (18)	93
II	3	Absent	14 (21)	334 (4)	4
II	2	Present	42 (21)	26 (12)	62
<b>Total</b>			<b>235‡ (36)</b>	<b>378§ (5)</b>	<b>38</b>

Abbreviations: ICROP, International Classification of Retinopathy of Prematurity; ROP, retinopathy of prematurity.

\*Data are given as the number (percentage of eyes with an unfavorable 3-month outcome) of eyes unless otherwise indicated.

†Defined as filiation and tortuosity of posterior pole retinal vessels.

‡Sixty-three percent of these eyes progressed to threshold ROP.

§Fourteen percent of these eyes progressed to threshold ROP.

The clinical course and visual outcome are generally favorable for eyes that do not progress to prethreshold ROP.<sup>4</sup> However, variability in outcome occurs once an eye reaches prethreshold ROP, making RM-ROP2 useful in predicting risk. To illustrate the use of RM-ROP2, presume that an infant has reached prethreshold ROP. At this point an assessment of risk becomes desirable because of the wide range of possible risk levels and the potential for reaching the standard treatment threshold. Further, suppose that the infant is white, born in a participating CRYO-ROP center, a singleton birth, with a birth weight of 640 g and a gestational age of 26 weeks. The ROP began at 34 weeks, and prethreshold ROP was first observed at 36 weeks in the form of stage 3 with plus disease in zone II, but without the requisite number of clock hour sectors to comprise threshold ROP. All this demographic and clinical information are entered into the RM-ROP2 system. The RM-ROP2 uses its mathematical risk model to simultaneously consider the pertinent characteristics of the infant at birth and later ocular characteristics at prethreshold ROP (Tables 2 and 4). Based on the assumed information in the example, RM-ROP2 provides an estimate that the risk of the eye's having an unfavorable outcome is 0.45.

The Early Treatment for Retinopathy of Prematurity study used the RM-ROP2 system to identify a select group of prethreshold ROP infants with a relatively high risk of an unfavorable outcome. These selected high-risk prethreshold eyes were randomized to either receive immediate peripheral laser ablation, or to have prethreshold ROP managed in the conventional way, with treatment only if the retinopathy progressed to threshold ROP severity. Based on analyses of the CRYO-ROP data, a cutoff point of 0.15 was chosen as the minimum risk level to test the efficacy of earlier intervention at prethreshold level vs later treatment (if required, at threshold). The selection of the cutoff point and the RM-ROP2 model were solely based on prethreshold ROP eyes in the CRYO-ROP study. A companion article in this issue of the ARCHIVES reports the application of the RM-ROP2 model and the results of the Early Treatment for Retinopathy of Prematurity multicenter clinical trial.<sup>8</sup>

Submitted for publication August 27, 2003; final revision received October 7, 2003; accepted October 9, 2003.

From the School of Public Health, University of Texas–Houston (Dr Hardy and Ms Tung); Casey Eye Institute, Oregon Health & Science University, Portland (Dr Palmer); Department of Ophthalmology, University of Arizona, Tucson (Dr Dobson); Departments of Ophthalmology and Pediatrics, University of Minnesota, Minneapolis (Dr Summers); Departments of Pediatrics and Ophthalmology, University of Rochester, Rochester, NY (Dr Phelps); Division of Pediatric Ophthalmology, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia (Dr Quinn); and the Smith-Kettlewell Eye Research Institute, San Francisco, Calif (Dr Good).

This study was supported by grant U10 EY05874, from the National Eye Institute, National Institutes of Health, Bethesda, Md.

Corresponding author and reprints: Robert J. Hardy, PhD, University of Texas–Houston Health Science Center, School of Public Health, Coordinating Center for Clinical Trials, 1200 Herman Pressler St, Room E827, Houston, TX 77030.

## REFERENCES

- Palmer EA, Flynn JT, Hardy RJ, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. *Ophthalmology*. 1991;98:1628-1640.
- Schaffer DB, Palmer EA, Plotsky DF, et al, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Prognostic factors in the natural course of retinopathy of prematurity. *Ophthalmology*. 1993;100:230-237.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group. The natural ocular outcome of premature birth and retinopathy: status at one year. *Arch Ophthalmol*. 1994;112:903-912.
- Editorial Committee, for the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Natural history ROP: Multicenter Trial of Cryotherapy for Retinopathy of Prematurity: ocular outcome at 5½ years in premature infants with birth weights less than 1251g. *Arch Ophthalmol*. 2002;120:595-599.
- Hardy RJ, Palmer EA, Schaffer DB, Phelps DL, Davis BR, Cooper CJ, for the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity Cooperative Group. Outcome-based management of retinopathy of prematurity [published correction appears in *J AAPOS*. 1977;1:137]. *J AAPOS*. 1997;1:46-54.
- Good WV, Hardy RJ, for the ETROP Multicenter Study Group. The Multicenter Study of Early Treatment for Retinopathy of Prematurity (ETROP) [guest editorial]. *Ophthalmology*. 2001;108:1013-1014.
- Stata Corp. *Stata Statistical Software: Release 7.0*. College Station, Tex: Stata Corp; 2001.
- 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.