Predictive Value of Pre-plus Disease in Retinopathy of Prematurity

David K. Wallace, MD, MPH; Sharon F. Freedman, MD; M. E. Hartnett, MD; Graham E. Quinn, MD, MSCE

Objectives: To investigate prospectively whether the presence of pre-plus disease predicts progression to severe retinopathy of prematurity (ROP) requiring laser treatment.

Methods: Posterior retinal video recordings were obtained during 710 indirect ophthalmoscopy examinations of 214 premature infants over a period of 5 years. Two masked experts reviewed short video recordings and determined whether there was plus disease, pre-plus disease, or neither. The primary analysis included results of one examination of the right eye at 33 to 34 weeks' postmenstrual age. The primary outcome was a comparison of the proportion of eyes subsequently requiring laser treatment between the group graded as having pre-plus disease vs the group graded as having neither plus disease nor pre-plus disease.

Results: Of 10 eyes with pre-plus disease at 33 to 34 weeks’ postmenstrual age, 7 (70%) subsequently required laser treatment; of 154 eyes without pre-plus disease or plus disease at 33 to 34 weeks’ postmenstrual age, 14 (9%) subsequently required laser treatment (risk ratio, 7.7; 95% confidence interval, 4.1-14.8; \( P = .001 \)). The mean time between the examination diagnosing pre-plus disease and laser treatment was 1.6 weeks (range, 1.0-2.4 weeks). When adjusting for birth weight, gestational age, ROP location (zone), and ROP severity (stage), the presence of pre-plus disease at 33 to 34 weeks' postmenstrual age independently predicted the need for laser treatment (adjusted odds ratio, 7.6; 95% confidence interval, 1.4-42.3; \( P = .02 \)).

Conclusions: Pre-plus disease observed early during the course of ROP is strongly associated with the development of severe ROP requiring laser treatment. The diagnosis of pre-plus disease has prognostic value beyond that already provided by birth weight, gestational age, ROP zone, and ROP stage. Eyes with pre-plus disease should be closely observed to allow optimal timing of intervention.


Retinopathy of Prematurity (ROP) is the second leading cause of severe pediatric visual impairment in the United States. Plus disease is an important marker of severe, potentially sight-threatening ROP, and it is characterized by severely abnormal dilation and tortuosity of central posterior retinal blood vessels. Plus disease is diagnosed when an eye has at least as much dilation and tortuosity of its posterior vessels as in the standard photograph first used in the Cryotherapy for Retinopathy of Prematurity clinical trial. Another category of posterior pole vessel abnormality, pre-plus disease, was included in the revision of the International Classification of Retinopathy of Prematurity. Pre-plus disease is defined as “vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arteriolar tortuosity and more venular dilatation than normal.” However, few data describe the natural history or prognostic significance of pre-plus disease. Our objective was to investigate prospectively whether the presence of pre-plus disease predicts progression to severe ROP requiring laser treatment. We also sought to determine if a diagnosis of pre-plus disease increases the prognostic value beyond that already provided by the established ROP descriptors of location (zone) and severity (stage).

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STUDY DESIGN

The study protocol and Health Insurance Portability and Accountability Act of 1996–compliant consent form were approved by the institutional review board of Duke University. Parents of participants gave written informed consent for the use of their infants’ reti-
nal video recordings. Some parents could not be contacted, and our institutional review board granted permission for the use of their infants’ data. Consecutive infants weighing less than 1250 g were prospectively enrolled over a 5-year period. As part of our routine screening for ROP, we videotaped every examination using a video indirect ophthalmoscopy system (Heine, Herrsching, Germany) and a 28-diopter condensing lens. All examinations were performed by 1 of us (D.K.W. or S.F.F.) Examinations began at 4 to 6 weeks of age, and follow-up examinations were performed at least biweekly according to published guidelines. Our criterion for laser treatment was the presence of type 1 ROP based on the results of indirect ophthalmoscopic examination.

Infants were eligible for inclusion in the study if they were followed up at least biweekly until (1) retinal vascularization was complete or in zone III, (2) they had laser treatment, or (3) they were at least 40.5 weeks’ postmenstrual age (PMA). The age of 40.5 weeks was chosen as the minimum time for follow-up because it rounds up to 41 weeks, and by this time approximately 95% of eyes requiring treatment will have been treated. Medical records were reviewed to obtain the following data: date of birth, estimated gestational age at birth, birth weight, race/ethnicity, inborn (at study center) vs outborn status, and single vs multiple birth. For each eye examination, the following data were collected as part of routine care: date of examination, ROP zone (location of disease), ROP stage (severity of disease), circumferential extent of highest stage (clock hours), and presence or absence of plus disease.

A research assistant transferred video clips to a computer using a video capture board. The research assistant then selected the best digital image frame for each eye. Only 1 eye of each infant was included in the study to allow the use of standard statistical tests without adjustment for intereye correlation. The right eye was included unless images from the left eye were clearly superior. At least 2 months (and in most cases years) after the images were collected, the research assistant inspected each image and graded each quadrant for dilation and tortuosity separately using a scale of 0 to 9 (Table 1). When determining whether there was plus disease, pre-plus disease, or neither, the masked graders relied on the standard definitions of plus disease and pre-plus disease. In addition, all graders were given color images of the standard photograph of plus disease and examples of pre-plus disease from “The International Classification of Retinopathy of Prematurity Revisited” article. Using the individual quadrant grades, an overall grade was assigned to each eye. This overall assessment was based on the guideline that, for an eye to have plus disease, at least 2 quadrants must have tortuosity sufficient for plus disease and at least 2 quadrants must have dilation sufficient for plus disease (the same rule was used for pre-plus disease). Each image was examined by 2 graders; if they disagreed, the third grader examined the image, and the final grade was based on majority vote.

All 3 graders served as 1 of 2 primary graders for some images and as the tiebreaking grader for other images. The 2 of us who performed the diagnostic examinations and served as graders agreed to report if we recognized any of the images as being taken from a particular infant, but this did not occur.

Based on date of examination and date of birth, PMA at each examination was calculated. One examination from each infant was included for analysis in each of the following PMA groups: 31 to 32, 33 to 34, 35 to 36, 37 to 38, 39 to 40, and 41 to 42 weeks. Weeks of age were rounded to the nearest whole number; so that the category of 33 to 34 weeks, for example, included examinations performed between 32 weeks plus 4 days and 34 weeks plus 3 days. If 2 or more examinations for 1 infant were performed during a single period, the examination closest to the midpoint for the category (eg, 33.5 weeks) was included. The age group of 33 to 34 weeks was chosen a priori for the primary analysis because, in one of our pilot studies, this age stratum had the highest proportion of eyes with pre-plus disease that later needed laser treatment. In addition, infants at this age were young enough that few of them would likely be excluded based on already having received laser treatment. For the primary analysis (33-34 weeks) and for each age-specific analysis (eg, 35-36 weeks), infants were excluded if the need for laser treatment was determined at the same time as the examination, if plus disease was present (as determined by masked graders), or if video recordings had insufficient quality to allow determination of plus disease or pre-plus disease. For the primary analysis, if the video recording from the examination closest to 33.5 weeks had inadequate quality for grading, then another examination performed between 32.5 and 34.5 weeks was used if available.

A secondary analysis determined whether pre-plus disease that was present at any study examination (ie, present at ≥1 examinations for a given eye) predicted the need for laser treatment. For this analysis, study examinations included only those examinations closest to the midpoint for the category (eg, 33.5 weeks) and usually did not include every inpatient examination for a given infant. If pre-plus disease was not observed during any study examinations, then it was necessary to have at least 1 examination at 35 weeks’ PMA or later so as to be included in this analysis of whether pre-plus disease was present at any one of an infant’s multiple study examinations. Those without a study examination after 35 weeks were excluded for this analysis only because they were more likely to have pre-plus disease that was unobserved and to be misclassified as never having pre-plus disease.

### SAMPLE SIZE CALCULATIONS AND STATISTICAL ANALYSIS

Based on pilot data, we expected that 35% of those classified as having pre-plus disease at 33 to 34 weeks’ PMA would eventually require laser treatment, while 6% of those classified as having neither plus disease nor pre-plus disease would need laser treatment. Using a 2-sided Fisher exact test with a statistical significance level of .05, we calculated that 150 total participants for the primary analysis would provide 91% power to find a difference between groups. Comparisons between proportions were performed using the Fisher exact test. Logistic regression models were used to determine...
mine if pre-plus disease independently predicted the need for laser treatment when also considering concurrent examination findings of ROP zone and stage. Additional models were constructed that included pre-plus disease, zone, stage, birth weight, and gestational age as predictors of laser treatment. All analyses were performed using commercially available statistical software (SAS, version 9.1; SAS Institute, Cary, North Carolina).

RESULTS

DESCRIPTION OF COHORT

Seven hundred ten total video recordings from 1 eye of 214 infants were included. No parents of eligible infants refused consent, and all eligible infants were included. Eighty-one of 710 posterior retinal video recordings (11%) from 64 infants could not be graded because of inadequate image quality (typically poor focus or hazy media). At least 1 recording could be graded for all but 1 of 214 infants. Video 1, video 2, and video 3 (http://www.archophthalmol.com) show study eyes with plus disease, pre-plus disease, and neither, respectively. Table 2 gives characteristics of the infants in our cohort. Infants with pre-plus disease in the right eye at 33 to 34 weeks had a lower mean birth weight and a younger mean gestational age than infants without pre-plus disease. Infants with pre-plus disease were also more likely to be of white race/ethnicity, be the product of a multiple birth, have ROP in zone I, and have stage 3 disease.

PRIMARY ANALYSIS

One hundred sixty-four eyes of 164 infants were examined at 33 to 34 weeks' PMA and were included in the primary analysis. Of 10 eyes with pre-plus disease at 33 to 34 weeks' PMA, 7 (70%) subsequently required laser treatment; of 154 eyes without pre-plus disease or plus disease at 33 to 34 weeks, 14 (9%) subsequently required laser treatment (risk ratio, 7.7; 95% confidence interval [CI], 4.1-14.8; odds ratio, 23.7; 95% CI, 5.5-101.9; P < .001). For eyes with pre-plus disease at 33 to 34 weeks' PMA that progressed to severe disease requiring laser treatment, the mean time to laser treatment was 1.6 weeks (range, 1.0-2.4 weeks; median, 1.3 weeks). For eyes without pre-plus disease at 33 to 34 weeks' PMA that progressed to disease requiring laser treatment, the mean time to laser treatment was 3.1 weeks (range, 1.0-7.0 weeks; median, 2.6 weeks). Four patients (2.4%) were excluded from the primary analysis because plus disease was present or the need for laser treatment was determined at the time of that examination, and 5 patients (3%) were excluded because the video recordings had insufficient quality to allow determination of plus disease or pre-plus disease. Disagreement occurred between 2 graders for 5 images (3%) included in the primary analysis, requiring a tiebreaking assessment by the other grader.

SECONDARY ANALYSES

Table 3 gives results for each PMA stratum. Of 14 eyes with pre-plus disease at 33 to 36 weeks' PMA, 6 (42%) later required laser treatment; of 120 eyes without pre-plus disease at 35 to 36 weeks, 5 (4%) later required laser treatment (risk ratio, 10.3; 95% CI, 3.6-29.4; odds ratio, 17.3; 95% CI, 4.3-69.0; P < .001). For other PMA strata, the presence of pre-plus disease did not predict the need for laser treatment.

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<td>Birth weight, mean, g</td>
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Abbreviation: ROP, retinopathy of prematurity.

aThe total numbers of infants differ because infants were excluded from the primary analysis at 33 to 34 weeks' postmenstrual age if there was no videotaped inpatient examination during that time, and they were excluded from the analysis “at any study examination” if there was no videotaped inpatient examination at 35 weeks' postmenstrual age or later.
The "International Classification of Retinopathy of Prematurity Revisited" article expanded the classification of posterior pole vascular appearance to include pre-plus disease, an intermediate grade of vascular abnormality between plus disease and normal posterior pole vessels. The prognostic significance of plus disease has been firmly established; however, the predictive value of pre-plus disease has not been previously established. When planning this study, we reasoned that if pre-plus disease had prognostic significance, its presence would aid clinicians in predicting disease progression and choosing appropriate follow-up intervals. Indeed, we found that pre-plus disease noted between 33 and 36 weeks' PMA was predictive of progression to severe ROP requiring laser treatment. We had determined a priori based on pilot data that the primary analysis would include only examinations performed at 33 to 34 weeks. We found that 70% of eyes with pre-plus disease at 33 to 34 weeks' PMA eventually needed laser treatment, whereas only 9% of eyes without pre-plus disease at that time progressed to require laser treatment. These prospective data are in agreement with pilot data from a small retrospective study. In that study, 5 of 8 eyes with mild vascular dilation and tortuosity insufficient for plus disease progressed to laser treatment, whereas none of the 24 eyes without mild vascular changes progressed to laser treatment (P < .001).

Clinicians consider many factors beyond posterior pole appearance when planning and performing serial diagnostic examinations of premature infants, including birth weight, gestational age, and concurrent examination findings of ROP zone and stage. Assuming that these factors...
are known and considered in an infant without plus disease, we sought to understand if there is any prognostic value added by distinguishing between the presence vs the absence of pre-plus disease. Results of logistic regression analysis showed that pre-plus disease at 33 to 34 weeks’ PMA is independently associated with future need for laser treatment, even after adjusting for zone and stage in one model and for birth weight, gestational age, ROP zone, and ROP stage in a second model. These results reaffirm that pre-plus disease vascular changes early in the disease course should alert examiners to the possibility of progression to severe disease. Pre-plus disease noted later in the disease course (ie, ≥37 weeks) was not associated with the need for laser treatment. A possible explanation is that eyes that first develop pre-plus disease at 37 weeks or beyond or eyes that have persistent pre-plus disease that has not worsened to plus disease by 37 weeks have a more indolent course than those that develop pre-plus disease earlier.

There is value to using the term pre-plus in addition to its prognostic significance. Plus disease refers specifically to severe vascular dilation and tortuosity, requiring at least 2 quadrants with vascular abnormalities that meet or exceed those of a standard photograph used for multiple clinical trials.3,12 There is a spectrum of posterior pole vascular appearance from normal to mild dilatation and/or tortuosity to the more severe changes characteristic of plus disease. Confusion can arise when clinicians use phrases such as “mild plus,” as it is unclear whether expression refers to plus disease that barely meets severity requirements or to vascular abnormalities that are insufficient for true plus disease. The former requires laser treatment, whereas the latter does not. The term pre-plus fills this void and allows more accurate written and verbal communication between ophthalmologists and neonatologists.

We found that a large proportion of eyes with pre-plus disease later required laser treatment, especially eyes with pre-plus disease at 33 to 36 weeks’ PMA. However, some eyes with pre-plus disease never progress to plus disease and never require laser treatment. Is it possible to predict which eyes with pre-plus disease are most likely to progress to laser treatment? Ghodasra et al13 measured vessel tortuosity and width using computer-assisted image analysis of the retina and reported that eyes with pre-plus disease that progressed had more vessel tortuosity and dilation than did eyes with pre-plus disease that regressed. They concluded that, because vascular abnormalities in ROP are a continuum and clinical diagnosis is subjective, quantitative measurement of retinal vessel tortuosity and width by image analysis algorithms may improve risk stratification of eyes with ROP.

Our study has some limitations. First, the establishment of “truth” using the judgment of 3 experts is somewhat subjective, and studies14,15 have shown that experts frequently disagree when diagnosing plus disease or pre-plus disease from digital images. Instead of still images, we used videos from indirect ophthalmoscopy, and judgment by examiners performing indirect ophthalmoscopy is standard in ROP diagnosis. We cannot know with certainty that overall eye grades based a quadrant scale of 0 to 9 given after review of video clips would match eye grades of plus disease, pre-plus disease, or neither during a bedside examination; however, such a study is planned for these same images. If video grading of plus disease by masked examiners is considerably less accurate than bedside examination, pre-plus disease could have been misclassified. However, the bias introduced in this scenario (even if pre-plus disease is “overcalled”) would be in the direction of finding no association between pre-plus disease and need for laser treatment. It will also be useful in future studies to substantiate our findings using a more objective measure of vascular width and tortuosity, such as computer-assisted analysis of images.16-19 A second limitation is that we could enroll only infants who had sufficient follow-up (to ≥40.5 weeks’ PMA) to be reasonably sure that they did or did not develop type 1 ROP and require laser treatment. Nevertheless, we believe that our findings are generalizable to infants with ROP. Infants who are discharged home or transferred early to a local nursery tend to be healthy and are unlikely to develop severe ROP, and these infants likely have a low incidence of pre-plus disease. Even when these generally healthy infants develop pre-plus disease, we have no reason to believe that they would be any more or less likely to progress from pre-plus disease to severe ROP than infants in our nursery of the same age. A third limitation is that some of our secondary analyses were limited by sample size or by our study’s practical design to videotape only inpatient examinations. A fourth possible limitation is that we required at least 2 quadrants of pre-plus dilation and 2 quadrants of pre-plus tortuosity to designate an eye as having pre-plus disease. This level of detail is not included in the published definition of pre-plus disease, which is simply “vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arteriolar tortuosity and more venular dilatation than normal.”6(p995) We chose to require 2 quadrants of abnormality to make assessment of pre-plus disease analogous to that of plus disease and to render it unlikely that mild abnormalities in 1 quadrant alone, either real or perceived by a masked examiner viewing a video segment, would drive the diagnosis of pre-plus disease.

In conclusion, pre-plus disease observed between 33 and 36 weeks’ PMA is associated with eventual need for laser treatment, with the strongest association at examinations between 33 and 34 weeks’ PMA. Pre-plus disease at this age has prognostic value beyond that already provided by birth weight, gestational age, ROP zone, and ROP stage. Infants with pre-plus disease early in the course of ROP have increased risk to require laser treatment and should be followed up closely to allow optimal timing of intervention, particularly if other ROP risk factors are present.

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