# Diagnostic and Treatment Advances in Retinopathy of Prematurity

*a report by*
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*Duke University Eye Center DOI: 10.17925/USOR.2007.02.00.18*

There have been several recent advances in the care of infants with retinopathy of prematurity (ROP). These include the revision of the International Classification of ROP, the application of results from the Early Treatment for ROP (ETROP) clinical trial, and computer-assisted analysis of plus disease.

## The International Classification of Retinopathy of Prematurity Revisited

The International Classification of ROP (ICROP) includes zone, stage, and the presence or absence of plus disease.[1] Zone refers to the location of disease, and zone I is defined as a circle with radius equal to twice the disc–fovea distance. Stage refers to severity of ROP, and the extent of disease is described by clock hours. Stage 1 is a demarcation line between vascular and avascular retina. Stage 2 is a ridge with thickness and elevation. Stage 3 is extra-retinal non-vascular tissue extending into the vitreous. Stage 4A refers to a partial retinal detachment not involving the fovea, and Stage 4B is a partial retinal detachment involving the fovea. Stage 5 is a total retinal detachment.

The Committee to Revisit ICROP provided three major additions to ICROP—aggressive posterior ROP (AP-ROP), pre-plus disease, and a clinical pearl for estimating the extent of zone I.[2] AP-ROP describes rapidly progressing ROP in zone I with plus disease. Stage 3 of AP-ROP is often intra-retinal and can be deceptively featureless. It is a rapidly progressive form of ROP that is observed in the smallest premature infants, and it requires prompt laser treatment.

Pre-plus disease describes an intermediate level of plus disease between normal and plus disease. Examiners recognize that there is a spectrum of abnormality in posterior pole dilation and tortuosity.[3] The committee defined pre-plus disease as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease, but that demonstrate more arterial tortuosity and more venous dilatation than normal. A new category was needed to clarify that 'plus disease' refers only to eyes with at least two quadrants of dilation as well as tortuosity meeting or exceeding that in the standard photograph of plus disease.[4] It also helps to avoid potentially confusing terminology such as 'mild plus,' for which it is unclear whether the abnormality is or is not as severe as that seen in the standard photograph.

Finally, the Committee to Revisit ICROP provided a clinical pearl for estimating the extent of zone I. When a 25- or 28-diopter (D) lens is used to view the posterior pole, it can be placed so that the optic nerve is barely visible on one edge of the field of view. If any ROP is evident in the entire field of view, the ROP must be in zone I, because the view with a 25 or 28D lens subtends an angle roughly equivalent to the radius of zone I.

## Results from the Early Treatment for Retinopathy of Prematurity Clinical Trial

The ETROP study tested the hypothesis that earlier treatment of high-risk infants would result in a better visual outcome than conventional treatment at threshold.[5,6] Earlier treatment was defined as ablation of the avascular retina in high-risk, pre-threshold eyes. High risk was determined using a computer program (RM-ROP2) based on data from the Cryotherapy for ROP (CRYO-ROP) natural history cohort. Pre-threshold eyes included those with any ROP in zone I, those with plus disease but without stage 3 or with insufficient stage 3 for threshold, and eyes with stage 3 but without plus disease.

Of 828 infants identified at pre-threshold, 499 were determined to be high risk. Of these, 401 were randomized—317 were bilateral cases and 84 were asymmetric cases in which the one eye was randomized to treatment or control. Treatment was ablation of the peripheral avascular retina at high-risk pre-threshold, and those in the control group were observed and treated only if threshold was reached. The primary outcome was unfavorable visual acuity at nine months. Of 330 eyes treated at high-risk pre-threshold (14.5%), 48 had an unfavorable visual acuity at nine months, whereas 63 of 323 (19.5%) conventionally managed eyes had an unfavorable visual outcome (p=0.01). A secondary outcome was unfavorable retinal structure at nine months, which was defined as either a posterior retinal fold involving the macula, retinal detachment involving the macula, retrolental tissue or mass, or the need for a vitrectomy or scleral

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buckle. Unfavorable retinal structure at nine months occurred in 30 of 331 eyes treated at high-risk pre-threshold (9.1%) and in 51 of 326 conventionally managed eyes (15.6%; p<0.001).

Because clinicians are unlikely to utilize a computer program to determine high-risk status, a subgroup analysis was carried out based on the ICROP to identify which infants would benefit from earlier-than-usual treatment. It was noted that some subgroups, when managed conventionally, were unlikely to reach threshold or an unfavorable visual outcome. For example, only 41% of eyes with zone I, stage 1 or 2 without plus disease reached threshold or an unfavorable outcome, and only 16% of eyes with zone II, stage 3 without plus disease reached threshold or an unfavorable outcome.[6] Therefore, it is not recommended that these eyes receive early treatment.[7]

Revised treatment guidelines based on results of ETROP are that 'type 1' ROP should be treated promptly. These eyes include: zone I, any stage with plus disease; zone I, stage 3 without plus disease; and zone II, stage 2 or 3 with plus disease. It is recommended that 'type 2' ROP should be observed closely. These eyes include zone I, stage 1 or 2 without plus disease; and zone II, stage 3 without plus disease.[6]

## Computer-assisted Quantification of Plus Disease

Much progress has been made in recent years in computer-assisted measurement of plus disease. Following the results of ETROP, plus disease is arguably the most important sign in ROP, since it is a major component of type 1 ROP. However, the assessment of plus disease is hampered by subjectivity. The diagnosis of plus disease is based on comparison with the standard photograph that was first used for the CRYO-ROP study.[4] However, examiners utilize and interpret this photograph in different ways. Freedman and associates found that three principal investigators in the CRYO-ROP study disagreed on the presence of plus disease in 29 of 72 images (40%).[8] Chiang found that 22 experts all agreed on the presence or absence of plus disease in only four of 34 images (12%).[9] Therefore, even for experts, the assessment of plus disease is often an educated guess. The CRYO-ROP study group wrote that there is a need for a practical way to quantify plus disease that would permit further exploration of the effect of plus disease on ROP outcome.[10]

We have developed a computer program, called 'ROPtool,' that automatically traces retinal blood vessels and measures their tortuosity.[11] It expresses tortuosity as 'tortuosity index,' and a tortuosity index greater than 10 has more tortuosity than the average of all vessels in the standard photograph of plus disease. In a pilot study of ROPtool, we found that inter-user agreement was at least as good as inter-examiner judgment. This pilot study also allowed us to determine appropriate numeric thresholds for plus tortuosity and pre-plus tortuosity using the consensus of two examiners as the reference standard. ROPtool had a sensitivity of 100% (11/11) and a specificity of 78% (7/9) in the detection of tortuosity sufficient for plus disease, and its overall accuracy was 90% (18/20).[11]

This pilot study showed that ROPtool is a promising technology for reducing the subjectivity of plus disease assessment. The computer program needs to be validated with more images and its measurement of dilation needs to be improved. It is also unknown how well ROPtool will work with video images. If it will accurately measure vascular abnormality in videos obtained during routine indirect ophthalmoscopy, this technology could easily be applied at the bedside. In the future, ROPtool may be useful to augment expert judgment of plus disease as part of medical consultations. Several studies have shown that remote screening for ROP is feasible.[12–14] The precise degree of vascular dilation and tortuosity will be useful for studying the evolution and mechanism of plus disease. It could also correlate with prognosis, affect treatment decisions, and influence follow-up intervals.

## Conclusions

In conclusion, many advances have been made in ROP diagnosis and treatment over the past decade; however, many challenges remain. Despite promising results from the ETROP study, severe cases of ROP that are relatively unresponsive to laser treatment still exist. Could there be a role for anti-vascular endothelial growth factor (VEGF) agents in the management of these difficult cases?[15] It is also unknown whether curtailing supplemental oxygen will have a beneficial effect on ROP without causing other morbidities.[16,17] Finally, other methods for preventing ROP will be studied, such as the administration of inositol.[18] ■


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