# Retinopathy of Prematurity

# 29

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**Abstract**

Retinopathy of prematurity (ROP) is a proliferative disorder involving the developing vasculature of premature infants that can result in retinal detachment and blindness. Timely screening for ROP and prompt treatment of severe ROP can decrease the prevalence of unfavorable retinal structural and poor visual outcome. The criteria for treatment of ROP has evolved from classic threshold ROP, as defined in the Multicenter Trial of Cryotherapy for ROP, to type 1 prethreshold ROP, as defined in the Early Treatment of ROP randomized trial, with incremental improvement in the overall treatment outcome. The mode of treatment has also transitioned from the use of cryotherapy to laser photocoagulation. The mouse model of oxygen-induced retinopathy has elucidated the pathogenesis of ROP and led to new interventions and screening approaches. Pharmacotherapy using the intravitreal injection of bevacizumab, an antibody to vascular endothelial growth factor, appears to be superior to laser photocoagulation for type 1 ROP in zone I but equivalent to laser therapy for type 1 ROP in zone II. However, the systemic risks associated with bevacizumab are uncertain. New screening algorithms based on the rate of postnatal growth of at risk infants are being developed in order to reduce the percentage of infants screened while maintaining efficacy. Digital fundus photography has a high degree of accuracy for the detection of treatment warranting ROP. Validation studies for the reliability and accuracy of telemedicine for ROP are under way.

**Keywords**

Retinopathy of prematurity • Screening • Laser • Cryotherapy • VEGF • Bevacizumab • Algorithms • Telemedicine

## Abbreviations

| | |
|---|---|
| AP-ROP | Aggressive posterior ROP |
| BEAT-ROP | Bevacizumab eliminates the angiogenic threat of ROP randomized trial |
| BW | Birth weight |
| CHOP | Children's Hospital of Philadelphia |
| CRYO-ROP | Multicenter trial of cryotherapy for ROP |
| EGA | Estimated gestational age |
| e-ROP | Telemedicine approaches to evaluating acute-phase ROP study |

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| | |
|---|---|
| ETROP | Early treatment for ROP randomized trial |
| G-ROP | Postnatal growth in ROP studies |
| ICROP | International classification of ROP |
| IGF-1 | Insulin-like growth factor 1 |
| IVB | Intravitreal injection of bevacizumab |
| PMA | Postmenstrual age |
| RM-ROP2 | Risk models for ROP version 2 |
| ROP | Retinopathy of prematurity |
| VEGF | Vascular endothelial growth factor |
| WINROP® | Weight insulin-like growth factor I, neonatal ROP algorithm |

## Background

Retinopathy of prematurity (ROP) is a proliferative disorder involving the retinal vasculature of premature infants that can result in retinal detachment and blindness. Retinal vessels develop from the optic nerve beginning at 14–15 weeks of gestation and proceed peripherally to fully vascularize the retina to the ora serrata nasally and temporally by 32 weeks and approximately 40 weeks postmenstrual age (PMA), respectively [1].

In the currently accepted model of ROP pathogenesis (Table 29.1), the vascularization of the retina is dependent upon both insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) and may be divided into two phases [2, 3]. In phase I, premature birth disrupts the normal retinal vascularization process by depriving the premature infant of IGF-1, which is normally derived from the placenta and amniotic fluid in utero. VEGF, in the absence of IGF-1, is not sufficient to promote maximum retinal angiogenesis. In addition, VEGF expression is downregulated by the relatively higher oxygen environment outside the womb. Consequently, normal retinal vascularization during phase I is diminished.

Several weeks after birth, during phase II of ROP, the metabolic demand of the maturing retina increases. Relative hypoxia of the avascular retina develops and results in an up-regulation of VEGF. However, the higher levels of VEGF alone are not effective in promoting vascularization of the retina unless sufficient IGF-1 is also present. In the premature infant, low IGF-1 levels are associated with poor nutritional intake and poor weight gain [4]. As the infant gains weight postnatally over several weeks, IGF-1 levels also rise to a threshold level which then has a permissive effect on VEGF-stimulated retinal angiogenesis. If retinal vascular development up to this point has been sufficiently blunted by the previously low expression of VEGF and IGF-1, extraretinal neovascular proliferation may occur. This abnormal proliferative process may regress if retina vascularization continues such that hypoxia is diminished and VEGF expression reduced. But the persistence of hypoxia can result in continued fibrovascular proliferation and ultimately lead to a retinal detachment.

**Table 29.1** Simplified model of the pathogenesis of retinopathy of prematurity

| In utero (normal vessel growth) | Premature birth (vessel growth stops) | Maturing retina (becomes hypoxic) | Retinal neovascularization[a] |
|---|---|---|---|
| IGF-1 normal | ↓ IGF-1 | Slow ↑ IGF-1 | ↑ IGF-1 to "threshold" |
| VEGF normal | ↓↓ VEGF | ↑↑ VEGF | ↑↑ VEGF |

*IGF-1* insulin-like growth factor 1, *VEGF* vascular endothelial growth factor (adapted from Hellstrom et al. 2001) [3]

[a]Subsequently, the retinal neovascularization either regresses with the normalization of vitreous levels of VEGF, or the proliferative process continues and can result in a retinal detachment.

## Clinical Appearance and Classification of ROP

Timely screening for and prompt treatment of severe ROP can prevent the development of unfavorable retinal structural outcome and visual loss. The International Classification for ROP (ICROP), first developed in 1984 and revised in 2005 [5, 6], enabled clinicians and researchers to describe ROP using a common scheme, which also facilitated the conduct of clinical trials. ROP is classified on the basis of location (zones I–III), severity (stages 1–5), and the extent or number of clock hours of involvement. In general, the more posterior the location, the greater the extent of involvement, and the higher the stage, the more severe the ROP.

As shown in Fig. 29.1, the zones defined by ICROP are as follows:

- Zone I is a circle centered upon the optic nerve with a radius that is twice the disc to macula distance.
- Zone II is the region outside of zone I and inside a circle centered upon the optic nerve with a radius defined by the distance from the optic disc to the nasal ora serrata.
- Zone III is the remaining temporal crescent provided that the nasal retina is fully vascularized to the ora serrata for at least 2 clock hours.

The stages of ROP are defined as follows:

- Stage 0—immature vascularization
- Stage 1—demarcation line
- Stage 2—ridge (demarcation line with height and width)
- Stage 3—extraretinal fibrovascular proliferation
- Stage 4—partial retinal detachment
  - 4A—not macula involving
  - 4B—macula involving

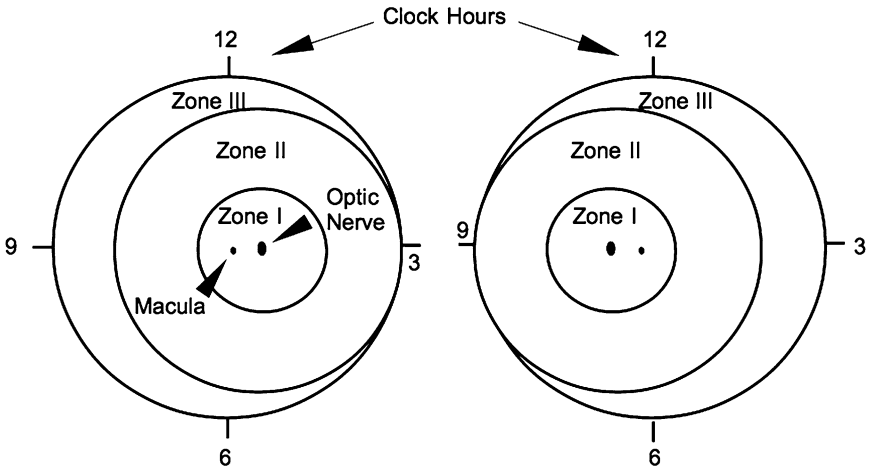


**Fig. 29.1** Zones for the classification of retinopathy of prematurity. Adapted from the International Classification of Retinopathy of Prematurity [5, 6]

**Table 29.2** Subgroups of severe retinopathy of prematurity

| Category | Definition |
|---|---|
| Threshold ROP | ≥5 contiguous or ≥8 cumulative clock hours of stage 3 in zone I or II with plus disease |
| Prethreshold ROP | Zone I stage 1, 2, or 3[a] with or without plus disease, zone II stage 2 with plus disease, or zone II stage 3[a] with or without plus disease |
| Type 1 prethreshold | Zone I stage 1, 2, or 3[a] with plus disease, zone I stage 3 without plus disease, or zone II stage 2 or 3[a] with plus disease |
| Type 2 prethreshold | Zone I stage 1 or 2 without plus disease or zone II stage 3 without plus disease |

[a]The extent of stage 3 involvement in eyes with plus disease is less than for threshold ROP. Threshold and prethreshold ROP were defined in the Multicenter Trial of Cryotherapy for ROP; [8] type 1 and type 2 prethreshold ROP were defined in the Early Treatment for ROP randomized trial [9]. *ROP*, retinopathy of prematurity

- Stage 5—total retinal detachment, which is funnel shaped and described based on the anterior and posterior configurations as open-open, open-closed, closed-open, or closed-closed.

In addition, plus disease, which usually develops with stage 3 ROP but may occur with other stages of ROP, is defined as venous dilation and arteriolar tortuosity in the posterior pole. Currently, the diagnosis of plus disease requires at least two quadrants of vessel dilation and tortuosity consistent with a standard reference photograph [6]. However, there is a subjective element in the examiner's perception of vessel dilatation and tortuosity and, consequently, in the diagnosis of plus disease [7]. Care should be taken to differentiate plus disease from pre-plus disease in which the posterior vessel abnormalities are insufficient to warrant the diagnosis of plus disease [6].

Besides the standard zone-stage-plus disease combinations, subgroups of ROP have been defined in various clinical trials [6, 8, 9]. As shown in Table 29.2, these include classic threshold ROP and prethreshold ROP (types 1 and 2). In addition, aggressive posterior ROP (AP-ROP) describes a severe, rapidly progressing form of ROP that occurs mostly in zone I but may also appear in posterior zone II. It is characterized by a severity of plus disease out of proportion to the observed peripheral retinopathy. The typical progression from stage 1 to 3 ROP does not occur. Instead, a "deceptively featureless" flat neovascularization may occur at the junction of vascularized and nonvascularized retina, where a circumferential vessel often appears. If not treated promptly, AP-ROP usually progresses to a total retinal detachment [6].

ROP examination pearls are detailed in Appendix J.

## Screening for ROP

The details of the currently recommended screening guidelines for ROP in the USA are provided in Appendix K [10]. Premature infants ≤1500 g birth weight (BW) or ≤30 weeks of estimated gestational age (EGA) are identified for screening. The recommended timing of initial screening for ROP and the subsequent intervals of screening are also described in Appendix K. Recent studies suggest, however, that postnatal weight gain, which is associated with postnatal IGF-1 levels, is an important predictor of infants developing severe ROP [2–4]. Different screening algorithms based on postnatal weight gain have been developed in an attempt to reduce the percentage of infants screened while maintaining efficacy. The Weight, Insulin-like growth factor I, Neonatal ROP algorithm (WINROP®), developed in Sweden and Boston, has a sensitivity of 98.6 % in detecting type 1 prethreshold ROP when assessed in a multicenter cohort of premature infants [11]. The Children's Hospital of Philadelphia (CHOP) ROP algorithm [12] is being evaluated in the postnatal growth in ROP studies (G-ROP) to determine if a sensitivity >99 % can be achieved for the detection of type 1 prethreshold ROP and whether the approach is cost effective.

Remote screening for ROP using wide-angle digital fundus photography, i.e., telemedicine, has a high degree of accuracy and already complements standard ROP examinations in many institutions [13]. The multicenter Telemedicine Approaches to Evaluating Acute Phase ROP study (e-ROP) will provide important data regarding the validity, reliability, feasibility, and cost-effectiveness of digital retinal imaging by comparing it with diagnostic examinations by ophthalmologists performed on the same eyes.

## Major Clinical Trials

### The CRYO-ROP Study

The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP, 1986–1987) evaluated cryotherapy of the peripheral avascular retina for the treatment of classic threshold ROP as defined in Table 29.2 [8]. Cryotherapy, performed within 72 h of diagnosis, resulted in a 39.5 % reduction in the incidence of unfavorable retinal structural outcome at 3 months as compared with observation. During the 15 years of follow-up of the CRYO-ROP study, the beneficial effects of cryotherapy in reducing the proportion of eyes with unfavorable structural and visual outcome, as compared with observation, have remained consistent [14]. Subsequently, in the 1990s, cryotherapy was gradually replaced by laser therapy, which seemed to yield better structural and functional outcomes [15]. Ablation of the avascular retina has been found to reduce the expression of retinal VEGF mRNA, which has a critical role in the abnormal proliferative process in ROP [16].

### The ETROP Study

The CRYO-ROP study showed that eyes with threshold disease in zone I had a particularly high rate of progressing to an unfavorable retinal structural outcome despite treatment (78 % for cryotherapy versus 94 % for observation) [8]. This led investigators to consider whether treatment at a lower severity of disease, namely prethreshold ROP (Table 29.2), prior to the onset of threshold ROP would improve outcome. In the Early Treatment for ROP (ETROP) randomized trial, a multiple logistic regression formula was used to categorize the prethreshold ROP eyes of infants enrolled in the ETROP study as either high or low risk [9, 17]. The formula, also known as risk models for ROP version 2 (RM-ROP2), was developed using information regarding untreated prethreshold ROP eyes from the CRYO-ROP study that developed an unfavorable retinal structural outcome at 3 months. It was comprised of prognostic variables that included "baby" characteristics, such as birth weight, gestational age, race, location of birth, and multiple birth status, as well as eye characteristics, such as the age at which the initial detection of ROP occurred or the interval of time between the onset of ROP and prethreshold ROP. Using this formula, high-risk prethreshold ROP eyes in ETROP were randomized to early treatment within 48 h of diagnosis or to conventional management in which treatment occurred only if the eyes progressed to classic threshold ROP [9]. By contrast, low-risk prethreshold ROP eyes were reexamined and reassessed for risk at the appropriate intervals and triaged accordingly. At 9 months after treatment, early treatment had reduced the proportion of eyes with unfavorable retinal structural outcome and with unfavorable visual acuity from 15.6 % to 9.1 % and from 19.5 % to 14.5 %, respectively, as compared with conventional management [9].

While the results for the early treatment of high-risk prethreshold ROP eyes were compelling, the ETROP investigators also performed a post hoc analysis in which they evaluated the eye outcome of early treatment versus conventional management for various zone-stage-plus disease combinations of high-risk prethreshold ROP. Based on these results, they recommended the early treatment of those zone-stage-plus disease combinations defined as type 1 prethreshold ROP and conventional management of those combinations defined as type 2 prethreshold ROP (Table 29.2) [9]. It should be emphasized that the ETROP was not designed to evaluate the benefits of early treatment versus conventional management of type 1 or type 2 prethreshold ROP but rather of high-risk prethreshold ROP as calculated by RM-ROP2. Even though the early treatment of type 1 prethreshold ROP may have become the de facto standard of care, there has been controversy with some clinicians advocating early treatment for only zone I type 1 prethreshold ROP [18–21]. To their credit, the ETROP authors acknowledged that the type 1 versus type 2 prethreshold ROP distinction was in part for the benefit of those clinicians who did not wish to use the RM-ROP2 formula to determine if a prethreshold ROP eye was at high risk. Moreover, rather than mandating treatment at the onset of type 1 prethreshold ROP, they saw the development of type 1 prethreshold ROP as opening a time window of opportunity until the onset of threshold ROP, during which early treatment should be seriously considered [21].

### The BEAT-ROP Study

The mouse model for the pathogenesis of ROP had suggested that the injection of anti-VEGF antibodies into the vitreous could be used to reverse the manifestations of oxygen-induced retinopathy [22]. The Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) randomized trial compared the intravitreal injection of 0.625 mg

bevacizumab (IVB) with laser treatment for type 1 prethreshold ROP [23]. With respect to the proportion of eyes that developed a recurrence of neovascularization by 54-week PMA, IVB was superior to laser for the treatment of type 1 prethreshold ROP in zone I (6 % vs. 42 %, $p=0.003$) but not different from laser for the treatment of type 1 prethreshold ROP in zone II (5 % vs. 12 %, $p=0.27$). In addition, IVB-treated eyes showed progressive vascularization of the immature retina beyond the original vascular-avascular junction at the time of therapy, an area that would otherwise have been destroyed by laser photocoagulation. Since recurrence of neovascularization generally occurred later in eyes receiving IVB as compared with laser treatment ($16.0 \pm 4.6$ vs. $6.2 \pm 5.7$ weeks), infants treated with IVB should be monitored for a longer period of time than those receiving laser therapy. However, there is currently no consensus on the intervals and duration of posttreatment follow-up examinations or on the use of laser as an adjunctive treatment in eyes previously treated with IVB, which have had regression of neovascularization, but nevertheless still possess persistent avascular areas in the peripheral retina.

With respect to safety, BEAT-ROP was not sufficiently powered to evaluate the risk of mortality [23]. Thus, it was not possible to determine if the number of infant deaths in the group receiving IVB was significantly higher than the group receiving laser therapy (5 vs. 2). However, in animal and human studies, bevacizumab appears to escape from the eye as indicated by either an elevation in the serum concentration of bevacizumab or a reduction in the level of VEGF in the peripheral circulation after IVB [24, 25]. These findings are concerning as VEGF is important in the development of the brain, lungs, kidney, and bones. Since the current dose of IVB is theoretically capable of neutralizing all VEGF in the vitreous in excess of 5000-fold [24], it may be possible to reduce the dose of IVB without loss efficacy for the treatment of type 1 prethreshold ROP while lowering the infant's systemic exposure to the drug. A forthcoming Phase 1 trial by the Pediatric Eye Disease Investigator Group is designed to answer this question.

## Case Studies

### Case Study 1

The RetCam® (Clarity Medical Systems, Pleasanton, CA) fundus photographs in Fig. 29.2 are from a Caucasian male premature infant, who was born at 24-week EGA with 650 g BW. The infant was screened initially at 32-week PMA and found to have immature vascularization (stage 0) in zone I of both eyes. By 35-week PMA, the patient had developed plus disease and significant arteriovenous shunting. Flat neovascularization with hemorrhage as well as circumferential vessels along the border of the vascular-avascular junction were present in both eyes. The findings fulfilled the definition of either type 1 zone I ROP or AP-ROP. Both eyes were treated with laser photocoagulation within 24 h. In the ensuing weeks, the plus disease and flat neovascularization completely regressed leaving a favorable retinal structural outcome.

#### Key Points

- It may be debated whether plus or pre-plus disease is present in Fig. 29.2. Excessive pressure on the eye during RetCam® photography can compress retinal vessels and thus damp or mask the presence of extraretinal neovascularization or plus disease [26].
- Even though the ETROP study allowed for treatment within 48 h of diagnosis, consideration should be given to treating zone I disease, especially AP-ROP within 24 h.
- After treatment, one should see, at the very least, *no progression* at the 1-week posttreatment examination and significant regression of plus disease and neovascularization by week 2. If the treated ROP appears to be worsening and no untreated areas of avascular retina are available for supplemental laser treatment, consideration should be given to intravitreal bevacizumab as adjunctive therapy.
- Based on the results of BEAT-ROP, this patient would have been a candidate for treatment with bevacizumab [23]. The potential systemic risks associated with IVB, the need for longer follow-up examinations due to late recurrence of neovascularization, and the potential need for subsequent laser therapy should be explained to the parents as part of the consent process.
- After IVB, one should expect a dramatic improvement in the plus disease as early as 1–2 days with significant regression of extraretinal neovascularization within a few days to 1 week.

(continued)

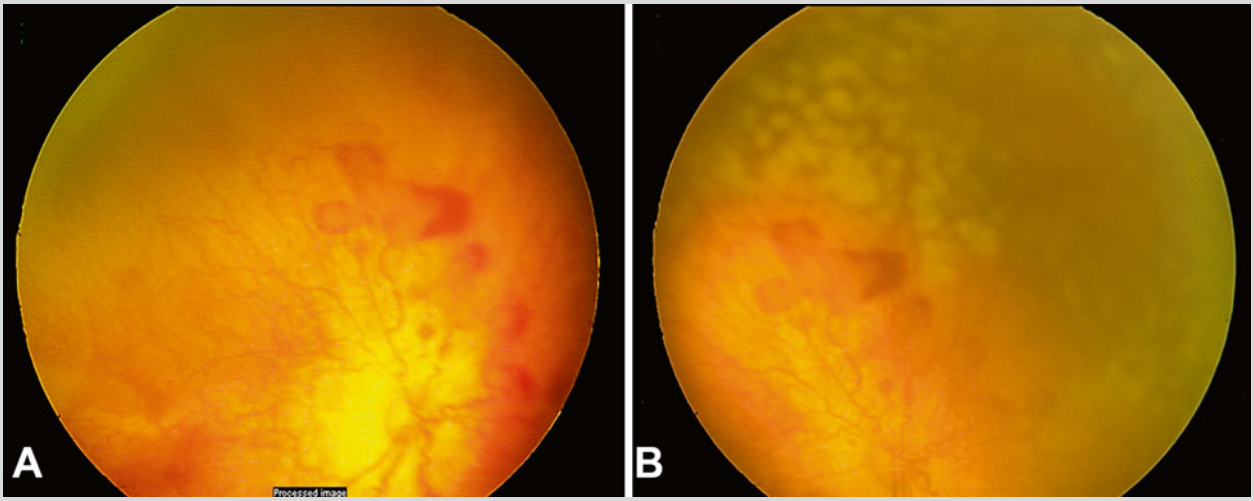


**Fig. 29.2** Right eye of an infant with aggressive posterior ROP in zone I immediately (**a**) before and (**b**) after laser treatment

## Case Study 2

The fundus photograph in Fig. 29.3 was from an African-American female premature infant who was of twin birth and born at 26-week EGA with 690 g BW. At 37-week PMA, both eyes developed stage 3 ROP in mid-zone II but without plus disease. By 39-week PMA, the stage 3 ROP in both eyes had progressed to involve all 12 clock hours (360°) of retina but still without plus disease. This was an unusual case because based on the revised ICROP guidelines, the patient did not have type 1 prethreshold ROP at this point. No treatment was offered until 40-week PMA when plus disease developed, which converted the eye status simultaneously to type 1 prethreshold ROP as well as classic threshold ROP. Laser photocoagulation was performed in both eyes with subsequent complete regression of disease.

### Key Point

- Again, it may be argued that this patient has pre-plus, instead of plus, disease. However, given the presence of 12 clock hours of stage 3 neovascularization, this patient would likely have progressed to unequivocal plus disease soon afterward. Then the large extent of stage 3 present would have increased the risk for unfavorable outcome after treatment, though the patient's black race may somewhat lessen that risk [8].

Additional ROP examination and treatment pearls are given in Appendix J.

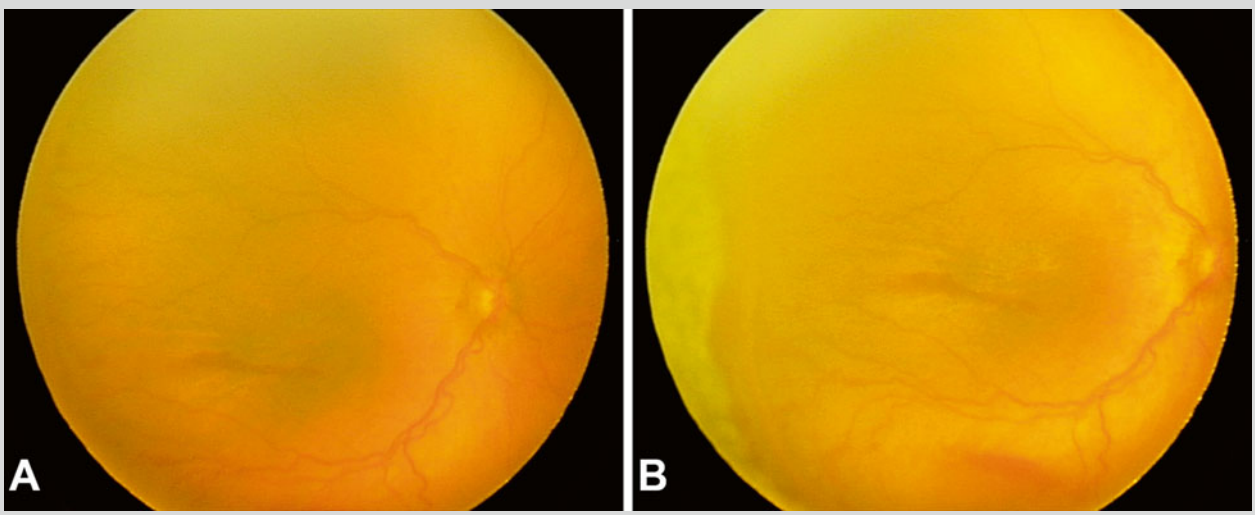


**Fig. 29.3** Right of a patient with 360° of stage 3 neovascularization with plus, or possibly pre-plus, disease immediately (**a**) before and (**b**) after laser treatment

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