

# Current screening and treatments in retinopathy of prematurity in the US

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**Abstract:** Retinopathy of prematurity (ROP) is a complex disease characterized by an aberrant developmental retinal angiogenesis in preterm infants and can carry significant visual morbidity, including retinal detachment and blindness. Though large scale, randomized clinical trials have improved our understanding of the pathophysiology and progression of the disease, the management of ROP remains a challenge for ophthalmologists. This review addresses the up-to-date screening approach, diagnosis, and treatment guidelines for ROP in the US.

**Keywords:** retinopathy of prematurity, retinal vascular development, vascular endothelial growth factor, ETROP, BEAT-ROP, eROP

## Introduction

Retinopathy of prematurity (ROP) was first described in 1940s when high saturation of oxygen supplementation improved the survival of preterm infants but contributed to blindness.<sup>1</sup> At that time, Terry<sup>2</sup> used the term “retrolental fibroplasia,” which we now know corresponds to end-stage ROP. ROP is characterized by a delay in physiologic retinal vascular development followed by abnormal proliferation into the vitreous.

Limiting the inspired oxygen concentration has decreased the incidence of ROP but has caused a higher mortality and cerebral palsy in the surviving newborns. Though unregulated oxygen is a clear risk factor for ROP, in modern neonatal practice, with tight regulation and control of oxygen saturation, the relationship between oxygen and development of ROP is complex and incompletely understood. Today, young gestational age (GA) and low birth weight are the uniformly recognized risk factors for developing ROP, and other variables such as low insulin-like growth factor 1 (IGF-1) levels, postnatal weight gain, hyperglycemia, blood transfusions, use of surfactant, and prolonged artificial ventilation have also been identified.<sup>3-6</sup>

Improvement of neonatal care has led to the survival of younger preterm infants of very low GA and birth weight<sup>7,8</sup> who are at high risk for developing ROP. Moreover, more premature infants are also surviving in developing countries, where uncontrolled oxygen delivery is still being used, causing an increase in ROP cases in developing countries around the world.

Despite improved screening and treatment guidelines, ROP remains a leading cause of visual impairment in premature infants in the US.<sup>9</sup>

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# Pathophysiology of ROP

Until the fourth month of gestation, the retina remains avascular and the developing retina obtains its nutrients from the hyaloid vasculature. At 16 weeks, the angioblasts near the hyaloid artery invade the nerve fiber layer. The first retinal vessels sprout from the optic nerve head and migrate toward the periphery extending to the ora serrata nasally by 36 weeks and temporally by 40 weeks. The microglia and astrocytes secrete vascular endothelial growth factor (VEGF) and IGF-1. The delicate balance and gradient of growth factors play an important role in the development of the superficial and deep layers of the retinal vasculature.<sup>9</sup>

Increasing evidence points to the fact that the mechanism of retinal vascularization is similar to that of vascularization of the brain during development. Retina and central nervous system vascular networks originate from existing vessels by angiogenesis; periventricular leukomalacia and ROP may develop in preterm infants and altered oxygen conditions is a risk factor for both.<sup>10</sup>

During the second half of pregnancy, there is relative intrauterine hypoxia (oxygen tissue tension of 25–35 mmHg) compared to 95–100 mmHg in room air after birth. ROP can be seen as a delay of normal retinal neuronal and vascular development in preterm infants, which causes pathological compensatory mechanisms that lead to aberrant vascularization. Pathogenesis can be separated into two different postnatal phases that differ in the expression of VEGF. The first phase is characterized by an arrest of the normal retinal development because of relative environmental hyperoxia and downregulation of VEGF, IGF-1, erythropoietin, and  $\omega$ -3 polyunsaturated fatty acids. The second phase occurs between 32 and 36 weeks post-GA. As the infant retina matures and metabolic demands increase, relative hypoxia of the avascular retina results, causing an overexpression of VEGF, IGF-1, and oxidative damage. Vasoproliferation is the hallmark of the second phase, but is a disorganized vascular growth into the vitreous at the border of the avascular retina. If ROP continues to progress, it can lead to a tractional retinal detachment, considered the fibrovascular phase.

Animal models have helped in the understanding of the pathogenic mechanism of the disease. In 1953, Patz et al<sup>11</sup> described for the first time the association between ROP and administration of high doses of oxygen. Aston<sup>12</sup> was the first in reporting the two postnatal phases in premature infants and further described through experimental work in kittens the closure of newly formed capillaries related to oxygen-toxicity (Phase I) followed by hypoxia-mediated vasoproliferation (Phase II) when kittens were transferred to

room air.<sup>13</sup> However, animal models have several limitations. First, animal retinas normally vascularize after birth, unlike human retinas that vascularize prenatally. Second, animal models have no other comorbidities such as lung pathology, sepsis, and anemia.

# Classification

The original International Classification of ROP was a consensus of 15 international experts in ROP, published in 1984<sup>14</sup> and was last updated in 2005.<sup>15</sup> It has facilitated the development of large multicenter clinical trials, helped in the understanding of the natural course of the disease as well as classified infants with ROP into prognostic subgroups of higher risk of unfavorable outcomes.

The classification of ROP describes three locations (zones I–III), five stages (stages 0–5), and the presence of plus disease (Table 1).

The zone is the extent of physiologic vascularization completed in utero; therefore, lower zone implies worse disease. The stage is defined by the appearance of the junction between the vascular and avascular retina. If more than one stage is present, the staging is determined by the most severe stage identified. Plus disease is the dilation and tortuosity of retinal arteries and veins in the posterior pole compared to a standard photograph.<sup>15</sup> The presence of plus disease increases the likelihood of disease progression and risk of poor visual outcome.

Aggressive posterior ROP is a subtype of ROP that behaves very aggressively and unpredictably. It describes posterior disease (in zone I or posterior zone II) with plus disease out of proportion to that characteristically presenting

**Table 1** Classification of retinopathy of prematurity

Location
Zone I: posterior retina within a 60° circle centered on the optic nerve
Zone II: from zone I to a 360° circle encompassing the nasal ora
Zone III: remaining temporal peripheral retina
Severity
Stage 1: a flat demarcation line that differentiates vascular from avascular retina
Stage 2: elevated ridge between the vascular and avascular retina with or without small tufts of fibrovascular proliferation (“popcorn”)
Stage 3: neovascular vessels growing along the ridge into the vitreous
Stage 4: partial retinal detachment
4A: extrafoveal
4B: including fovea
Stage 5: total retinal detachment, usually with funnel configuration
Plus disease: arteriolar tortuosity and venous engorgement in the posterior pole, a sign of progressive disease
Preplus disease: dilation and tortuosity that are insufficient for the diagnosis of plus disease

with a flat neovascularization at the vascular–avascular junction. This ROP phenotype is seen in the lowest birth weight infants and carries a higher risk of poor visual outcome and retinal detachment.<sup>15</sup>

The Early Treatment for Retinopathy of Prematurity (ETROP) study reclassified ROP into type 2 (to be closely monitored) and type 1 (requires treatment)<sup>16</sup> (Table 2).

## Diagnosis and screening recommendations

Fortunately, between 92% and 96% of ROP regresses spontaneously without any intervention. It is estimated that less than 10% of infants screened develop severe forms of the disease and require treatment.<sup>17</sup>

Current US guidelines, updated in 2013, recommend screening for infants with birth weight of 1,500 g or less or GA of 30 weeks or less.<sup>18</sup> A third criterion for ROP screening includes more mature infants with a complicated postnatal course or at risk for ROP at the discretion of the neonatologist, especially in the presence of necrotizing enterocolitis, intraventricular hemorrhage, sepsis, or bronchopulmonary dysplasia.

The first screening examination should take place at 4–6 weeks postpartum or at 31 weeks GA, whichever is later. Special attention to those infants born before 25 weeks GA with screening at 6 weeks postpartum permits the early detection of aggressive posterior ROP.

The fundus exam in a preterm infant may reveal one of three findings: mature retina, immature retinal vasculature, or ROP. ROP screening can be discontinued if: 1) Zone III retinal vascularization is present without previous zone I or zone II ROP. 2) There is no evidence of prethreshold disease or worse ROP by 50 weeks postmenstrual age. 3) There is regressing ROP in zone III without abnormal vascular tissue that can reactivate in zone II or III.<sup>18</sup>

Screening preterm infants at risk of ROP requires serial funduscopic examinations by skilled ophthalmologists. This

is done after pupillary dilation using a binocular indirect ophthalmoscope and a scleral depressor, and may be stressful to a preterm infant even in the hands of an experienced examiner.

A national survey revealed that more than a third of the providers who perform ROP examinations are general ophthalmologists, nonfellowship trained.<sup>19</sup> As more premature babies are surviving, there is a growing demand for ROP evaluations. The overall paucity of skilled examiners linked to the increasing frequency of ROP examinations as per revised recommendation guidelines<sup>18</sup> can make a timely evaluation a real challenge, especially in underserved areas of the US and middle-income countries. An appropriately timed examination and treatment of ROP has a major impact on visual outcome. Despite improving screening guidelines and increased number of therapies, the main cause of childhood blindness in middle-income countries is the shortage of trained ophthalmologists willing to screen and treat ROP infants.<sup>20</sup>

In order to decrease the burden of examinations and detect infants who will progress to treatment requiring ROP, the WINROP algorithm was developed. It incorporates the weekly weigh gain postpartum, GA, and birth weight to predict progression to type 1 ROP.<sup>21</sup>

Telemedicine is another promising methodology that has gained popularity in recent years. Infants' retinas are photographed by nonphysicians using a RetCam System (Clarity Medical Systems, Pleasanton, CA, USA) and interpreted at an off-site reading center. Remote ROP screening has been shown to be an alternative to an ROP specialist examining every infant at risk for ROP using indirect ophthalmoscopy, especially in underserved areas of the US<sup>22</sup> and middle-income countries. It is reproducible and decreases the inter-observer discrepancy. The disadvantages of retinal imaging are that it requires an excellent pupillary dilation (more than 7–8 mm); difficulty visualizing zone III; and the difficulty photographing older infants.

The use of telemedicine was validated in the recent eROP study, which was a multicenter trial funded by the National Eye Institute that compared screening results from wide-field digital retinal images obtained by nonphysician certified ROP imagers using a standardized imaging protocol and conventional retinal exams by trained ophthalmologists for acute ROP screening. This study showed that wide field imaging has an excellent inter- and intragrader agreement for ROP diagnosis compared to standard of care<sup>23</sup> and may provide an objective way to standardize ROP protocols and guidelines.<sup>24,25</sup>

**Table 2** Clinical phenotypes of retinopathy of prematurity (ROP) as per the Early Treatment of Retinopathy of Prematurity (ETROP) cooperative group classification

Type 1 ROP (high-risk prethreshold disease) – treat (within 48–72 hours)
Zone I, any stage with plus disease
Zone I, stage 3 without plus disease
Zone II, stage 2 or 3 with plus disease
Type 2 ROP (low-risk prethreshold disease) – watch closely (within 1 week)
Zone I, stage 1 or 2 without plus disease
Zone II, stage 3 without plus disease

In rural areas of India, the availability of ophthalmologists experienced in ROP management is especially pronounced. The KIDROP program initiated in 2008 has the aim of training technicians to perform and interpret retinal imaging obtained by RetCam or cell phones. Infants that fulfill criteria for laser ablation as per the ETROP study undergo laser locally without the need to travel to the city.<sup>26</sup>

Multiple prospective and retrospective studies have shown that digital photography may be a valuable tool to detect clinically significant ROP and referral-warranted ROP,<sup>27–29</sup> although it does not replace indirect ophthalmoscopy, the gold standard.<sup>30</sup> The different sensitivity, specificity, and positive predictive value of the RetCam compared to ophthalmic examination may reflect discrepancy in training level of examiners and differences in methodology.<sup>31</sup>

## Prevention and risk factors

Prevention of preterm birth is the most important preventive factor for ROP development.

Current research efforts are focused on the detection of pre- and postnatal risk factors for ROP progression.

The STOP-ROP multicenter study showed no significant difference between maintaining an oxygen saturation level of 96%–99% versus 89%–94% for prethreshold ROP.<sup>32</sup>

A higher survival rate of infants younger than 28 weeks with 91%–95% oxygen saturation was found in the BOOST II study, although there is an increase of incidence of ROP shown at this oxygen rate in other studies.<sup>33</sup>

A recent study showed significant differences in IGF levels in black mothers compared to other races.<sup>34</sup>

Genetic factors may explain difference in incidence in twins. Several gene variants such as those of the *wnt* pathway (frizzled 4, lipoprotein-related receptor-related protein 5, and Norrie Disease Protein) have been implicated.<sup>35</sup>

## Treatment

Prior to the 1980s, the only standardized modality for treatment of ROP was surgery for retinal detachment in the advanced stages of disease. Cryotherapy emerged in the treatment of ROP around this time as it ablates peripheral ischemic retina; however, there were no guidelines for its use based on severity of disease.

The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study sought to determine the point at which retinal neovascularization was equally likely to progress to retinal detachment or regress. Carried out from the mid-1980s, this seminal trial in ROP and ophthalmology involved 23 centers

and followed patients for 20 years.<sup>36</sup> CRYO-ROP introduced a unified classification of ROP, including a standardized photograph of plus disease and the concept of threshold disease, defined as five contiguous clock hours or eight noncontiguous clock hours of stage 3 ROP with plus disease in zone I or zone II. The study demonstrated a significant reduction in unfavorable anatomic outcome, such as retinal detachment, posterior folds in the retina, or development of retrolental fibrous tissue (primary outcome). At 15-year follow-up, the final report from CRYO-ROP, 30% of treated eyes and 52% of control eyes had unfavorable structural outcomes. Unfavorable visual acuity outcomes (defined as Snellen visual acuity equivalent of 20/200 or worse) were seen in 45% of treated eyes versus 64% of control eyes at 15-year follow-up.<sup>37</sup>

The CRYO-ROP study was terminated early because of the significant reduction in unfavorable outcomes in treated eyes<sup>36</sup> and it was felt that treatment should not be withheld in the control group. Much of our current understanding of the natural history of ROP derives from the control group in the CRYO-ROP study.

The CRYO-ROP established the benefits of treating ROP at threshold, and a subsequent study, the ETROP, was designed to investigate if treatment prior to threshold disease would further decrease unfavorable anatomic outcomes. The ETROP defined “prethreshold disease” as type 1 and type 2 ROP. It was calculated that type 1 eyes had a 15% or greater chance of unfavorable anatomic outcome versus less than 15% chance for type 2 eyes. ETROP demonstrated the benefit of peripheral laser ablation in type 1 ROP and frequent observation in type 2 disease. At this point, ablation of the avascular retina was done with diode laser as opposed to cryotherapy.<sup>38</sup> Though types 1 and 2 disease were defined in the ETROP study by a multivariate logistic regression model based on natural history data from CRYO-ROP, clinically, type 1 disease was found to correspond to zone I ROP of any stage with plus disease, zone 1 stage 3 disease without plus, and zone 2 stage 2 or 3 disease with plus. Type 2 ROP was found to correspond to zone 1, stage 1 or 2 without plus, or zone 2 stage 3 without plus. At 6-year follow-up, 9% of early treated eyes had unfavorable structural outcomes compared to 15% in the conventional treatment group.<sup>16</sup>

The results of the ETROP trial form the framework for modern surveillance and treatment of ROP in the US and worldwide. Current guidelines in the US recommend peripheral laser ablation to the avascular retina for type 1 ROP, performed within 72 hours of diagnosis. Complete laser



treatment from the ridge to the ora serrata is administered, with half burn width apart spacing of laser spots. After treatment, infants are followed closely for resolution of disease or additional laser to any “skip areas” or areas that were not adequately treated initially.

Laser treatment has many ocular and systemic advantages over cryotherapy<sup>39</sup>: laser decreases the requirements for general anesthesia, allows treating more posterior retina, and has a lower rate of systemic complications (eg, apnea, bradycardia, cardiopulmonary arrest requiring resuscitation).<sup>40</sup> Ocular complications include vitreous hemorrhage, cataract, elevated intraocular pressure, choroidal effusions, and postoperative inflammation. Topical cycloplegics and steroids may be administered for a short time after treatment to minimize these complications.

With the recent increase in intravitreal anti-VEGF therapy in adults for the treatment of various vasoproliferative disorders and given the role of VEGF in angiogenesis, anti-VEGF therapies have been successfully utilized in the treatment of ROP. The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study randomized ROP patients to receive a single intravitreal injection of bevacizumab at 0.625 mg in 0.025 mL. This study concluded that intravitreal bevacizumab reduced the recurrence of stage 3 ROP in zone I as compared to laser; 42% in the group of laser therapy compared to 6% in the bevacizumab group. Posteriorly, Reynolds et al suggested that bevacizumab may be superior to laser therapy for stage 3+ zone I but not for zone II posterior disease.<sup>41,42</sup> Interestingly, recurrence of ROP in patients treated with intravitreal bevacizumab was found to occur later than recurrence after laser ablation therapy (16±4.6 weeks with bevacizumab versus 6.2±5.7 weeks with laser), necessitating longer follow-up. Once bevacizumab is administered, patients need to be followed up until full vascularization of the retina. Intravitreal bevacizumab is not US Food and Drug Administration-approved for the treatment of ROP. Although anti-VEGF therapy is a promising therapy in infants with ROP, its use is still controversial given the unknown systemic risks and cases of poor clinical outcome with bevacizumab treatment.<sup>43</sup> Systemic inhibition of VEGF for up to 8 weeks after a single intravitreal injection has been reported<sup>44</sup> and the effects of systemic VEGF inhibition on other developing vascular beds such as the lungs are unknown. Treatment failure and adverse events such as persistent avascular retina, retinal detachment, and blindness have also been reported.<sup>41,45,46</sup> The selection of anti-VEGF agent and optimal dosage are unknown and remain the subject of investigation.

Despite treatment, ~16% of patients with type 1 ROP developed a retinal detachment.<sup>16</sup> Once an advancing stage 4 detachment is diagnosed, treatment with lens sparing vitrectomy (LSV) is recommended. In one large series, the reattachment rate after one LSV was 82% for stage 4A disease, 70% for stage 4B, and 43% for stage 5.<sup>47</sup> Scleral buckles can also be used in the treatment of ROP detachments but often need to be divided to avoid significant induced refractive changes.

In a small series, the combination of LSV and scleral buckling was not superior to LSV alone.<sup>48</sup> The visual outcomes in stage 5 detachments are extremely poor; therefore, the goal of ROP care is to prevent their development by screening appropriately and treating progressing disease.<sup>49</sup>

Patients with ROP can also develop effusive or serous detachments, which are caused by leakage from vascular structures. These are usually posterior to the ridge and convex shaped. Effusive detachment may resolve spontaneously, and there are reports of successful resolution after intravitreal bevacizumab administration<sup>50</sup>; however, surgical intervention may be needed in select cases.

## Summary

Our understanding of the pathophysiology of ROP and approach to management is evolving but many questions remain. Knowledge from ongoing studies will hopefully lead to the decrease of vision loss in ROP as well as better screening methods, better predictive algorithms, and new treatments.

## Disclosure

The authors report no conflicts of interest in this work.

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