

Retinopathy of Prematurity

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Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder unique to premature infants. As premature births increase in many areas of the world, ROP has become a leading cause of childhood blindness. A better understanding of the pathogenesis of ROP, adherence to strict screening guidelines, and evolution of treatment options have reduced the number of sight-threatening complications from ROP.

Retinopathy of prematurity (ROP) is a disorder of retinal blood vessel development in low birth weight preterm infants and is the second leading cause of childhood blindness in the United States behind cortical visual impairment [1]. ROP is a complex disease process initiated in part by a lack of complete retinal vascularization in premature infants. Retinal vascular development begins during week 16 of gestation, proceeding from the optic disc centrifugally to the retinal periphery. In almost all term infants, the retina and retinal vasculature are fully developed, and ROP cannot occur. However, in preterm infants, the development of the retina is incomplete. The degree of retinal immaturity depends on the degree of prematurity at birth. The absence of retinal vessels in the immature retina can result in retinal ischemia, leading to the release of vascular growth factors [2]. Earlier stages of the disease may regress spontaneously at any time. If the disease progresses, vitreous hemorrhage, tractional retinal detachment, and blindness can occur [3].

ROP was initially described by T. L. Terry as retrolental fibroplasia (RLF) in 1942 when he noted a dense, white, fibrovascular plaque behind the lens in a series of preterm infants [4]. This finding was eventually understood to be a complete tractional retinal detachment, which is the end stage of this disease. In the 1950s, RLF became the leading cause of infant blindness in developed countries with organized and well-funded health care. It was suggested that oxygen toxicity caused the disease, as babies born prematurely in developed countries were treated in incubators with artificially high levels of oxygen [5]. The incidence of ROP decreased in the 1960s with limitation of oxygen for preterm infants. Unfortunately, this also led to an increase in preterm infant deaths and cerebral palsy [6].

Epidemiology and Risk Factors

Each year in the United States, about 14,000 preterm infants are affected by ROP. Of these infants, approximately

90% experience spontaneous regression, and between 1,100 and 1,500 develop disease severe enough to require medical treatment [7]. The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Cooperative Group determined that ROP occurred in 66% of infants with a birth weight of 1,250 g or less and in 82% of infants with a birth weight of less than 1,000 g [3]. Despite appropriate medical interventions, 400 to 600 infants each year in the United States become legally blind from ROP [7].

Gestational age and birth weight, the two greatest risk factors for ROP, are inversely correlated with the development of ROP. Specifically, smaller babies and those born at an earlier gestational age are at higher risk. Between 1986 and 2013, the birth weight and gestational age of infants enrolled in ROP studies in the United States decreased, whereas ROP prevalence and incidence remained stable [8]. In regions of the world where resources are limited, there is an increasing incidence of ROP corresponding to neonatal interventions to treat premature infants who would not previously have survived. In such cases, there is a disparity between saving premature infants and successfully diagnosing and managing their ROP [1].

The use of supplemental oxygen is a known risk factor for ROP. There is evidence that maintaining oxygen saturation levels at a lower level prior to 34 weeks' post-menstrual age can reduce the incidence of ROP. However, it is unclear whether this benefit justifies the systemic risks to preterm infants [9].

Low early levels of insulin-like growth factor-1 (IGF-1) are associated with slower weight gain and more severe ROP. The weight, IGF-1, neonatal ROP (WINROP) algorithm uses gestational age, serum IGF-1 levels, and infant weight gain to identify babies at high risk for development of type 1 ROP [10].

Other specific postnatal factors that increase the risk for ROP include sepsis, blood transfusion, and intraventricular hemorrhage [11].

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Terminology and Classification

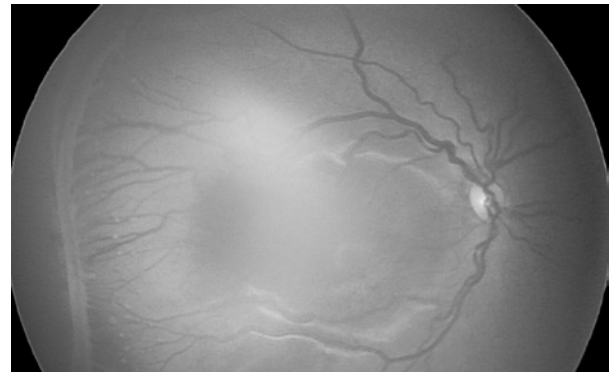
The International Classification of Retinopathy of Prematurity was developed for the purpose of consistently describing, staging, and studying ROP (see Table 1). The classification describes the disease by location or retinal zone of involvement, disease severity or stage, extent of disease in clock hours, and whether or not *plus disease* is present. Plus disease refers to marked arteriolar tortuosity and venous engorgement of the posterior retinal vasculature (see Figure 1). *Pre-plus disease* refers to dilation and tortuosity that is abnormal but less than that seen in plus disease (see Figure 2). *Aggressive posterior ROP* is a severe form of ROP where vascularization ends in zone I or posterior zone II and is accompanied by plus disease. *Threshold disease* refers to more than 5 contiguous or 8 cumulative clock hours of extraretinal neovascularization (stage 3) in zone I or II with plus disease (see Figure 1). *Prethreshold disease* is terminology from the Early Treatment for Retinopathy of Prematurity (ETROP) study, further divided into *type 1* (high risk prethreshold ROP) and *type 2* (lower risk prethreshold ROP). *Type 1 ROP* refers to zone I, any stage ROP with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 ROP with plus disease. *Type 2 ROP* refers to zone I, stage 1 or 2 ROP without plus disease; or zone II, stage 3 ROP without plus disease [12].

An eye is classified according to the most advanced stage of disease noted. Careful documentation of all observed stages, zones, and extent of ROP is required. The higher the stage of ROP, the more severe the disease is. The more posterior the zone of ROP, the more non-perfused retina there is anteriorly and the worse the prognosis. Management and treatment decisions are made based on ROP stage and severity [7, 12].

TABLE 1.
International Classification for Acute Retinopathy of Prematurity

| Location |
|--|
| Zone I: Posterior retina within a 60° circle centered on the optic nerve |
| Zone II: Extends from the edge of zone I centrifugally to the nasal ora serrata |
| Zone III: Residual crescent of retina anterior to zone II |
| Extent: Number of clock-hours involved |
| Severity |
| Stage 0: immature retinal vasculature with no ROP |
| Stage 1: Demarcation line between vascularized and avascular retina |
| Stage 2: Ridge (demarcation line with height, width, and volume) +/- small tufts of neovascular tissue |
| Stage 3: Ridge with extraretinal fibrovascular proliferation |
| Stage 4: Partial retinal detachment |
| 4A: extrafoveal detachment |
| 4B: retinal detachment includes fovea |
| Stage 5: Total retinal detachment |
| Plus disease: Vascular dilatation (venous) and tortuosity (arteriolar) of posterior retinal vessels in at least 2 quadrants of the retina |

FIGURE 1.
Zone II stage 3 ROP with Plus Disease



Source. Courtesy of Sharon Freedman, MD.

Pathophysiology of ROP

While not entirely understood, the pathophysiology of ROP is thought to be a two-phase process. The first phase occurs between 22 to 30 weeks' postconceptional age when a preterm infant is born and begins to breathe. The developing retina becomes hyperoxic relative to intrauterine oxygen levels. Increased oxygen tension in the retina leads to decreased production of vascular endothelial growth factor (VEGF) and IGF-1. Low levels of VEGF and IGF-1 lead to cessation of retinal blood vessel growth. The second phase begins between 31 to 34 weeks' postconceptional age and is characterized by disorganized retinal vascular growth. This process is due to abundant growth factors secreted by the ischemic retina (particularly VEGF and IGF-1) as well as oxidative damage to endothelial cells. Initially, a visible line between vascular and avascular retina forms (stage 1), followed by a ridge of tissue (stage 2). As the disease progresses, abnormal vessels proliferate along the ridge and into the vitreous cavity (stage 3). Progressive cicatricial contraction of the abnormal blood

FIGURE 2.
Zone II stage 2 ROP with Pre-Plus Disease



Source. Courtesy of Sharon Freedman, MD.

vessels and vitreous gel produces tractional retinal detachment (stages 4 and 5) [2, 13].

Associated Conditions and Late Sequelae of ROP

Myopia (nearsightedness) is a common sequela of regressed or treated ROP. High myopia may cause amblyopia as well as strabismus. Macular scarring can occur, which leads to reduced central visual acuity. It is also common to see temporal dragging of the macula, which results in the appearance of exotropia (pseudostabismus). Conventional treatment of ROP involves ablation of the peripheral avascular retina, which leads to variable peripheral visual field defects. Less common complications of severe ROP include cataract and glaucoma. Older children and adults with a history of ROP require periodic ophthalmic examinations throughout their lifetime, due to the risk for late complications including retinal detachment [14].

Screening Guidelines

In the United States, dilated funduscopy examination by a qualified ophthalmologist using binocular indirect ophthalmoscopy is recommended for all infants with a birth weight of less than 1,500 g or gestational age of 30 weeks or less. Screening is also recommended for infants with a birth weight between 1,500 g and 2,000 g or a gestational age greater than 30 weeks who have had an unstable clinical course or who are otherwise believed to be at high risk by the attending neonatologist. Examination of the eyes is performed after dilation of the pupils (often with a 0.2% cyclopentolate and 1.0% phenylephrine solution). Sterile instruments are used, including an eyelid speculum and scleral depressor. A nurse or other qualified assistant should be present in order to swaddle the infant and stabilize the head as well as to intervene if the infant experiences apnea or bradycardia during the examination [7].

The first examination is performed between 4 and 6 weeks' postnatal age or 31 weeks' postmenstrual age, whichever is later. After each examination, the follow-up interval is determined based on the presence or absence of ROP and the disease features, as outlined in Table 2. More severe disease indicates a need for shorter follow-up intervals. Retinal screening exams may be discontinued when zone III retinal vascularization is attained without previous zone I or II ROP or with complete regression of ROP. Exams may also be discontinued at post-menstrual age of 50 weeks if no prethreshold disease (or worse ROP) is present. Caregivers must be educated about ROP prior to their baby's discharge from the neonatal intensive care unit, as it is not uncommon for infants to be sent home from the hospital before their ROP has resolved or before their retinal vasculature is mature. These infants require continued screening exams on an outpatient basis [7].

Digital retinal photography has been shown to be accurate for detecting clinically significant ROP. Telemedicine involving retinal image-based ROP screening has been used,

largely in areas where a qualified ophthalmologist is not available to perform conventional screening examinations [15].

It is important to note that affected infants in developing countries are generally larger and of older gestational age than infants in the United States in whom ROP develops. Screening criteria for ROP should be modified in developing countries [1].

Treatment

In 1988, the CRYO-ROP study demonstrated that cryoablation of the peripheral avascular retina in eyes with threshold ROP resulted in a 50% reduction of unfavorable outcomes, including macular dragging and retinal detachment [3]. Diode laser ablation was used in later studies following the same guidelines as those in the CRYO-ROP trial, and was shown to be equally effective in inducing regression of ROP and more effective in preventing adverse visual and structural sequelae (see Figures 3 and 4) [16]. The ETROP trial in 2003 demonstrated that earlier treatment for high risk eyes (type 1) resulted in better structural and visual outcomes than conventional treatment for threshold ROP. Laser treatment is recommended for eyes with type 1 ROP, while eyes with type 2 ROP should be closely observed for progression. Clinical judgment and consideration of other risk factors for progression are required for optimal management [17].

The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study evaluated the use of anti-angiogenic medication injected into the vitreous for the treatment of zone I or posterior zone II stage 3 ROP with plus disease. Compared with conventional laser therapy, a statistically significant treatment benefit for bevacizumab was demonstrated for zone I ROP, whereas zone II disease had similar outcomes with either treatment. Normal peripheral retinal vascularization continued after treatment with

TABLE 2.
Recommended Intervals of Follow-Up Eye Examinations for ROP

| |
|---|
| 1 week or less |
| Immature vascularization in zone I or posterior zone II |
| Stage 1 or 2 ROP in zone I |
| Stage 3 ROP in zone II |
| Suspected or present aggressive posterior ROP |
| 1 to 2 weeks |
| Immature vascularization in posterior zone II |
| Stage 2 ROP in zone II |
| Unequivocally regressing ROP in zone I |
| 2 weeks |
| Stage 1 ROP in zone II |
| Immature vascularization in zone II |
| Unequivocally regressing ROP in zone II |
| 2 to 3 weeks |
| Stage 1 or 2 ROP in zone III |
| Regressing ROP in zone III |

intravitreal bevacizumab, whereas laser therapy produced permanent destruction of the peripheral avascular retina. However, recurrence of ROP requiring retreatment occurred on average 16 weeks after treatment with bevacizumab, and late-onset retinal detachments have been reported [18]. In addition, a reduction in serum VEGF has been demonstrated in infants after intravitreal injections, which raises concerns for the effects of antiangiogenic drugs on the developing vasculature in other areas of the body [19].

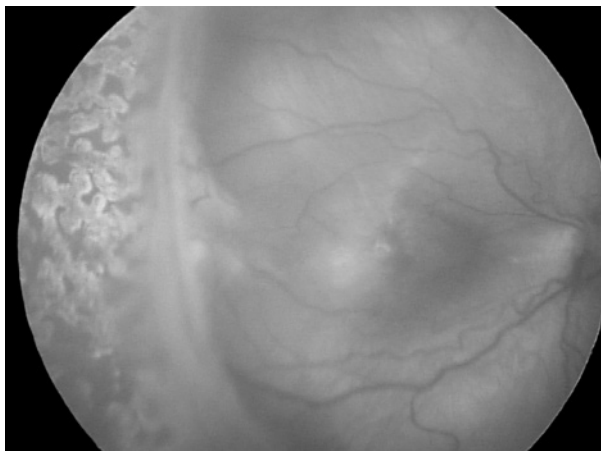
Eyes with stage 4 or 5 ROP require additional surgical intervention such as scleral buckling and/or vitrectomy to alleviate the vitreoretinal traction that causes retinal detachment. More favorable outcomes are noted in eyes undergoing surgery at stage 4A (macula attached) than at stage 4B (macula detached) [20]. For eyes with stage 5 ROP (total retinal detachment), vitrectomy has been successful in reattaching the retina in approximately 30% of eyes, and 25% remain attached 5 years later. Unfortunately, only 10% of these patients have ambulatory vision (able to see large objects at close range) [21].

Conclusion

The most important risk factors for the development and progression of ROP are extremely low birth weight and gestational age 30 weeks and under. Therefore, preventing ROP begins with preventing prematurity through optimal prenatal care. Reducing subsequent post-natal risk factors depends on optimal perinatal and postnatal care, as well as adhering to strict ROP screening guidelines. Screening criteria and risk factors that are recognized in one country do not necessarily apply in another country where available perinatal care may not be comparable. Recognizing and treating ROP in a timely fashion is critical for achieving the best visual outcome. ROP and its sequelae can cause problems throughout a patient's life; therefore, long-term monitoring by an ophthalmologist is crucial. NCMJ

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FIGURE 3.
Zone II stage 4A After Diode Laser Treatment



Source. Courtesy of Sharon Freedman, MD.

FIGURE 4.
Sedated Infant Undergoing Diode Laser Treatment for ROP in the NICU



Source. Courtesy of Sharon Freedman, MD.

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