Retinopathy of prematurity (ROP): Risk factors, classification, and screening

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INTRODUCTION

Retinopathy of prematurity (ROP) is a developmental vascular proliferative disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. ROP is an important cause of severe visual impairment in childhood.

This topic will review the pathogenesis, epidemiology, classification, and screening for ROP. The management and prognosis of ROP are discussed separately. (See "Retinopathy of prematurity (ROP): Treatment and prognosis".)

Other common eye problems in preterm infants include amblyopia, strabismus, and refractive errors. These are discussed separately:

- (See "Amblyopia in children: Classification, screening, and evaluation".)
- (See "Evaluation and management of strabismus in children".)
- (See "Refractive errors in children".)

THE PRETERM INFANT'S EYE

The size and characteristics of the eye differ in preterm and term infants:

- The globe diameter is approximately 10 to 14 mm at 28 weeks gestation, compared with 16 to 17 mm at term.

- The ocular media are frequently hazy in preterm infants and impede visualization of the fundus. Small peripheral lens vacuoles are common. In addition, an incompletely involuted hyaloid artery may appear as a white or red strand in the vitreous.
- The blood vessels in the anterior vascular capsule of the lens regress in a consistent pattern and correlate well with gestational age between 27 and 34 weeks [1].
- Pupillary size in preterm infants is approximately 3 to 4 mm, slightly smaller than at term. Constriction of the pupils in response to light starts at approximately 30 to 32 weeks gestation and is consistently present after 35 weeks [2].
- Tear production is reduced in preterm infants and may result in drying of the corneas during an eye examination and increased absorption of topically applied medications [3].

PATHOGENESIS

Normal vascularization — The sequence of vascularization of the eye is important in understanding the pathogenesis of ROP. No blood vessels are present in the retina before approximately 16 weeks gestation. From approximately the sixth week, the anterior segment of the eye receives its vascular supply from the hyaloid artery. This artery extends from the optic cup, passes through the vitreous, and supplies vessels to both surfaces of the lens and iris. These vessels usually are resorbed by 34 weeks of gestation.

Retinal vascularization normally begins at 15 to 18 weeks gestation. Retinal blood vessels extend out from the optic disc (where the optic nerve enters the eye) and grow peripherally. Vascularization in the nasal retina is complete at approximately 36 weeks. Vascular development usually is complete in the temporal retina by 40 weeks, although maturation may be delayed until 48 to 52 weeks postmenstrual age (PMA) in preterm infants (figure 1).

Vascularization in retinopathy of prematurity — The pathogenesis of ROP is thought to involve two stages. An initial injury caused by factors such as hypotension, hypoxia, or hyperoxia, with free radical formation, injures newly developing blood vessels and disrupts normal angiogenesis. Following this disruption, vessels either resume normal growth or new vessels grow abnormally out from the retina into the vitreous. Increased permeability of these abnormal new vessels (neovascularization) can result in retinal edema and hemorrhage. Abnormal fibrovascular tissue may develop along with the neovascularization and later contract, producing traction on the retina. In some severe cases, this results in retinal distortion or retinal detachment. However, in most instances, the abnormal vascular tissue regresses with little residual effect.

Regulation of the expression of vascular endothelial growth factor (VEGF) and other cytokines appear to contribute to both normal retinal vessel growth and abnormal vascular disruption and subsequent neovascularization [4-10]. The mechanisms that determine whether initial disruption of normal angiogenesis in ROP will be followed by resumption of normal vascular development or progression of pathologic neovascularization are unknown.

Insulin-like growth factor-1 (IGF-1) supports normal retinal vascular growth and interacts with VEGF [11-13]. The possible role of IGF-1 in ROP has been evaluated in several series of preterm infants who had serial blood samples and retinal examinations. In each of these series, decreased serum concentrations of IGF-1 were associated with the development of ROP [14-18]. With low IGF-1, vessels cease to grow, the maturing avascular retina becomes hypoxic, and VEGF accumulates. Later, as IGF-1 levels rise during maturation and reach a critical level, neovascularization ensues. Activation of a specific VEGF receptor may protect developing retinal vessels and prevent retinal ischemia induced by oxygen. This was investigated in a study in newborn mice, in which activation of the VEGF receptor VEGFR-1 by placental growth factor-1 (PGF-1) decreased the obliteration of retinal vessels by hyperoxia (22 versus 5 percent) and did not induce neovascularization [19]. Stimulation of another VEGF receptor, VGEFR-2, had no effect on blood vessel survival.

Photoreceptor development — ROP appears to affect photoreceptor development. An observational study in which retinal sensitivity and retinal responsivity were assessed by electroretinography between 30 and 72 weeks PMA suggests that photoreceptor development is altered in prematurity (with or without ROP), that conditions that affect the photoreceptor cells (eg, ROP, ROP treatment) appear to reduce sensitivity, and that retinal neuronal behavior may be influenced by extrauterine experience [20,21].

INCIDENCE

ROP affects a substantial number of preterm infants worldwide [22]. Both the incidence and severity of ROP increase with decreasing gestational age (GA) and birth weight (BW) [23-28]. ROP is rarely diagnosed in infants ≥32 weeks GA.

Among very preterm (VPT) and very low birth weight (VLBW) infants (ie, GA <32 weeks and/or BW <1500 g), reported incidence rates of ROP of any severity range from 25 to 40 percent [23,28].

Most infants who develop ROP have mild disease that does not require treatment. Severe ROP (defined as stage ≥3 (figure 2)) accounts for approximately 15 to 20 percent of cases. Thus,

approximately 6 to 10 percent of VPT and VLBW infants develop severe ROP [23,25,27,28].

In a large multicenter prospective study carried out over ten years (1992 to 2002), rates of severe ROP according to GA category were as follows [27]:

- 22 to <25 weeks GA – 43 percent
- 25 to <27 weeks GA – 21 percent
- 27 to 30 weeks GA – 3 percent

These estimates reflect rates of ROP among neonates managed in resource-abundant settings. In resource-limited settings, ROP rates may be higher and ROP tends to occur in more mature infants with higher BW [22,29].

The epidemiology of ROP has shifted over time coinciding with advances in neonatal practice. The overall incidence of ROP appears to be increasing [30]. This is likely due to increased diagnosis through routine screening and increased survival of the most preterm neonates (ie, GA <26 weeks) who are at greatest risk of ROP. However, among more mature preterm infants (GA ≥27 weeks), rates of ROP have decreased since the late 1990s. This was illustrated in a single-institution study that included >7000 VPT and VLBW infants cared for over a 30-year period (1990 to 2019) [28]. Among infants <27 weeks GA, rates of ROP increased slightly over the study period (54 percent in the 1990s versus 58 percent in the 2000s versus 60 percent in the 2010s). Among infants 27 to 32 weeks, rates of ROP declined from 24 percent in the 1990s to 13 percent in the 2010s. The decline in ROP among infants 27 to 32 weeks GA may reflect advances in respiratory care practices during the study period (ie, increasing use of noninvasive respiratory support, less mechanical ventilation) since mechanical ventilation and oxygen exposure are important risk factors for ROP.

RISK FACTORS

The most important risk factor for developing ROP is degree of prematurity. However, >50 separate risk factors have been identified.

- **Factors associated with increased risk** – Factors that are associated with higher rates of ROP include [31-44]:
  - Low BW
  - Low GA
  - Mechanical ventilation for >1 week
  - Hyperoxemia (elevated oxygen tension)

- Bronchopulmonary dysplasia
- Surfactant therapy
- High blood transfusion volume
- High severity of illness score
- Sepsis, particularly fungal sepsis
- Necrotizing enterocolitis
- Poor weight gain and/or low caloric intake
- Hyperglycemia and/or need for insulin therapy
- Fluctuations in blood gas parameters
- Intraventricular hemorrhage
- Hydrocephalus

It is unclear whether use of erythropoiesis stimulating agents (ESAs) increases the risk of ROP. Early trials suggested a possible increased risk, but this finding has not been borne out in larger trials and meta-analyses. (See "Anemia of prematurity (AOP)", section on 'Erythropoiesis stimulating agents (ESAs)'.)

- **Protective factors** – Factors associated with reduced rates of ROP include:
  - Breastmilk feeding [45,46]. (See "Infant benefits of breastfeeding".)
  - Supplementation of feeding with long-chain polyunsaturated fatty acids (LCPUFAs). (See "Long-chain polyunsaturated fatty acids (LCPUFA) for preterm and term infants", section on 'Very low birth weight infants'.)
  - Infants with trisomy 21 appear to be at a lower risk for ROP compared with other infants [47].

CLASSIFICATION

The International Classification for Retinopathy of Prematurity (ICROP) provides a uniform approach to documenting the extent and severity of disease as summarized in the figure (figure 2) [48]. The ICROP system ensures consistent communication among care providers and in clinical research studies. Four features are characterized in the ICROP classification schema:

- Zone – Describes the disease location on the retinal surface in relation to the disc, from the central posterior zone (I) to the outer crescent (zone III).

- Stage – Describes the severity from mildest disease (flat white line of demarcation [stage 1]) to most severe (total retinal detachment [stage 5]).
- Extent – Described by dividing the retinal surface in 12 sections, similar to hours of a clock.
- Presence or absence of plus disease, the most important indicator of disease severity. Plus disease is characterized by abnormal dilation and tortuosity of vessels in zone I. Preplus disease is an intermediate state between normal zone I vessels and plus disease.

"Threshold ROP" is a term that was previously used to describe the threshold at which treatment was recommended. However, treatment is now initiated when the infant develops high-risk prethreshold ROP, also called "type I ROP."

Type I ROP is defined as **any** of the following:

- Any stage ROP in zone I with plus disease
- Stage 3 ROP in zone I without plus disease
- Stage 2 or 3 ROP in zone II with plus disease

Indications for treatment are discussed in greater detail separately. (See "Retinopathy of prematurity (ROP): Treatment and prognosis", section on 'Treatment'.):

NATURAL HISTORY

The course of ROP is more correlated with postmenstrual age (PMA) than postnatal age. ROP typically begins approximately 34 weeks PMA, although it may be seen as early as 30 to 32 weeks [24]. In a large natural history study, stages 1, 2, and 3 ROP (figure 2) occurred at a median PMA of 34.3, 35.4, and 36.6 weeks, respectively [24].

ROP advances irregularly until 40 to 45 weeks PMA but resolves spontaneously in the majority of infants. In a natural history study, in which two-thirds of infants with birth weight (BW) ≤1250 g developed some degree of ROP, treatment for severe disease was needed in only 6 percent [24].

Regression of ROP also depends upon PMA and the location of disease. In one report of 766 children from the natural history study, involution began at a mean PMA of 38.6 weeks, and before 44 weeks in 90 percent of patients [49]. The outcome was favorable in 99 percent of infants when ROP resolved by moving from zone II to III. Partial or total retinal detachment was never seen when ROP was limited to zone III in serial examinations.

Ocular outcome is typically poor in infants with severe untreated ROP. This was evaluated at 5.5 years corrected age in infants with BW ≤1250 g who were enrolled in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity [50]. Among untreated eyes, poor structural outcomes (eg, central retinal fold, severe retinal detachment) occurred in 3.1 percent of eyes, and poor Snellen visual acuity (20/200 or worse) occurred in 5.1 percent of eyes. All infants with a poor structural outcomes and nearly all poor visual acuity outcomes had a history of severe ROP (zone II ROP involving >6 clock hours of stage 3+ disease or zone I ROP). Poor visual acuity occurred in only 2 of 110 eyes (1.8 percent) when ROP was observed only in zone III.

SCREENING

Screening criteria — We suggest screening **all** infants with birth weight (BW) ≤1500 g or gestational age (GA) ≤30 weeks, as well as those with BW between 1500 g and 2000 g or GA >30 weeks whose clinical course places them at increased risk for ROP (as determined by the neonatologist). This practice is consistent with the recommendations of the American Academy of Pediatrics (AAP), the American Academy of Ophthalmology (AAO), the American Association for Pediatric Ophthalmology and Strabismus (AAPOS), and the American Association of Certified Orthoptists (AACO) [51]. The Royal College of Paediatrics and Child Health, the Royal College of Ophthalmologists in the United Kingdom, and the Canadian Paediatric Society have made similar recommendations, suggesting screening for infants with birth weight ≤1250 g and infants with GA <31 weeks regardless of BW [52,53].

Screening for ROP is a labor-intensive process with a relatively low yield; <10 percent of infants who are screened require treatment [54]. The optimal criteria for screening remain uncertain. In a Canadian study, screening infants with a BW ≤1200 g was the most cost-effective strategy [55]. Incorporation of postnatal risk factors into the screening guidelines may increase the yield of screening. Research has focused on developing prediction models to identify high-risk infants with the hope of reducing the number of infants requiring ophthalmologic examinations. However, these methods require additional validation in broad populations before changes to the screening recommendations can be made. Several models using various combinations of GA, BW, postnatal weight gain, and serum IGF-1 levels to predict increased risk of severe ROP have been developed [40,41,56-59]. In initial validation studies, the sensitivity of these models approached 100 percent, and the specificity ranged from 32 to 84 percent. However, in a subsequent retrospective validation study from Mexico involving 192 infants born at <32 weeks gestation, the sensitivity of one such model using weight and IGF-1 level in detecting severe ROP was only 84.7 percent [60].

Screening examination — The screening evaluation consists of a comprehensive eye examination performed by an ophthalmologist with expertise in neonatal disorders [51]. The pupil must be dilated in order to visualize the vitreous and retina. We suggest using a combination eyedrop (eg, Cyclomydril, which contains weak concentrations of phenylephrine and cyclopentolate) 30 minutes or more before the examination. Both manipulation of the eye and the cycloplegic eyedrops can produce adverse cardiorespiratory and gastrointestinal effects (eg, bradycardia, arrhythmia, apnea, desaturation, emesis) [61-64]. Therefore, it is essential to carefully monitor the infant during and after the examination procedure. Topical anesthetic can be used based on the preference of the examining clinician [65].

The retina is examined by looking through the pupil with an indirect ophthalmoscope with a 20 or 28 diopter or other condensing lens while the eyelids are retracted with a speculum. ROP is most commonly visualized in the peripheral retina, which often is obscured by the iris. In order to completely view this area, a scleral depressor is used to indent the eye externally. ROP, if present, is described using the standardized classification (figure 2). (See 'Classification' above.)

Alternatively, telemedicine systems can be used to identify infants with potentially severe ROP. (See 'Telemedicine screening' below.)

Examination schedule — We initiate retinal examinations at 31 weeks postmenstrual age (PMA) for infants born at 22 to 27 weeks and at four weeks of chronologic age for infants born at ≥28 weeks (table 1). This schedule is supported by natural history data from three large randomized trials [66-68], in which retinal conditions associated with poor outcome were not observed before 31 weeks PMA or four weeks postnatal age in 99 percent of infants. This practice is consistent with guidance from the AAP/AAO/AAPOS/AACO joint statement [69]. Although treatable ROP rarely occurs before 32 weeks PMA, we initiate screening at 31 weeks PMA to account for the possibility of errors in dating, examination delays due to medical status, and to permit flexibility in scheduling.

Additional examinations are performed at intervals of one to three weeks until the retinal vessels have completely grown out to the ora serrata (periphery of the retina). If ROP develops, the eye may be examined more frequently, depending upon the severity of disease and rate of progression. The AAP/AAO/AAPOS/AACO joint statement suggests follow-up examinations according to the following schedule [51].

Follow-up within one week is recommended for infants with any of the following [51,70]:

- Immature vascularization in zone I, without ROP
- Immature retina that extends into posterior zone II, near the boundary of zone I

- Stage 1 or 2 ROP in zone I
- Stage 3 ROP in zone II
- Suspected aggressive ROP

Follow-up within one to two weeks is recommended for infants with any of the following:

- Immature vascularization in posterior zone II
- Stage 2 ROP in zone II
- Regressing ROP in zone I

Follow-up within two weeks is recommended for infants with any of the following:

- Stage 1 ROP in zone II
- Immature vascularization in zone II, without ROP
- Regressing ROP in zone II

Follow-up within two to three weeks is recommended for infants with either/both of the following:

- Stage 1 or 2 ROP in zone III
- Regressing ROP in zone III

When an infant is discharged home before the retinal vasculature is mature, parents/caregivers must understand the importance of timely follow-up [51,71].

Discontinuation — Screening examinations continue until the risk of serious disease has passed, ROP regresses and the vasculature matures, or treatment is needed. Screening examinations can be discontinued when any of the following conditions occurs (usually not before 35 weeks PMA):

- Lack of development of type 1 or worse ROP by 45 weeks PMA [51]; some experts suggest extending screening to 50 weeks PMA
- Zone III retinal vascularization attained without previous ROP in zone I or zone II
- Regression of ROP with no abnormal vascular tissue capable of reactivation and progression in zone II or III
- Full retinal vascularization

In large randomized trials, these signs indicated that the risk of visual loss from ROP was minimal or had passed [49,66,67].

Telemedicine screening — Telemedicine systems can be used to identify infants with potentially severe ROP [72-74]. The process involves using wide-angle ocular digital fundus

photography to create digital retinal images. Up to six standard images may be taken. The images are then transmitted to a remote location for interpretation. Initially, telemedicine was used to provide screening for remote locations without access to an ophthalmologist skilled in ROP screening; however, telemedicine is increasingly used as the primary mode of screening even in locations with access to an ophthalmologist skilled in ROP screening [51]. When a telemedicine screening approach is used, the AAP/AAO/AAPOS/AACO joint statement suggests that it follow the same schedule as ophthalmoscopic screening (as described above) and that infants at risk undergo indirect ophthalmoscopy by a qualified ophthalmologist at least once before initiating treatment or terminating screening [51].

Digital retinal photography has high accuracy for the detection of clinically significant ROP. In the Telemedicine Approaches to Evaluating Acute-phase ROP (e-ROP) study, in which 1257 infants with BW <1251 g underwent regularly scheduled evaluations, both by an ophthalmologist and by nonphysician staff using wide-field digital camera, remote grading of the images of both eyes had high sensitivity (90 percent) and specificity (87 percent) for detecting referral-warranted ROP (defined as zone I ROP, stage 3 ROP or worse, or plus disease) [74]. The accuracy of wide-angle photography for detection of mild levels of ROP is less clear [72]. However, strategies designed to identify referral-warranted ROP do not rely on identification of mild disease for success.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient education" and the keyword[s] of interest.)

- Basics topic (see "Patient education: Retinopathy of prematurity (ROP) (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definition and importance** – Retinopathy of prematurity (ROP) is a developmental proliferative vascular disorder that occurs in the retina of preterm infants with incomplete retinal vascularization. It is an important cause of severe visual impairment in childhood. (See 'Introduction' above.)

- **Incidence** – The incidence and severity of ROP increase with decreasing gestational age (GA) and birth weight (BW). Severe ROP develops in approximately 40 percent of infants born at 22 to 25 weeks GA, 20 percent of those born at 25 to <27 weeks GA, and <5 percent of those born at 27 to 30 weeks GA. (See 'Incidence' above.)

- **Risk factors** – In addition to GA and BW, other important risk factors for ROP include prolonged mechanical ventilation, hyperoxemia, high severity of illness, and other comorbid neonatal conditions (eg, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, intraventricular hemorrhage). (See 'Risk factors' above.)

- **Classification** – The International Classification for ROP provides a uniform approach to documenting the extent and severity of disease (figure 2). It is based upon four features: zone, stage, extent, and presence or absence of plus disease. (See 'Classification' above.)

- **Natural history** – ROP typically begins at approximately 34 weeks postmenstrual age (PMA), but may be seen as early as 30 to 32 weeks. It advances irregularly until 40 to 45 weeks PMA, but resolves spontaneously in most affected infants. (See 'Natural history' above.)

- **Screening** – We suggest screening for ROP in all infants with BW ≤1500 g or GA of ≤30 weeks (**Grade 2C**). In addition, screening is warranted in select infants with BW between 1500 g and 2000 g or GA of >30 weeks whose clinical course places them at increased risk for ROP (as determined by the neonatologist). (See 'Screening' above.)

  The screening evaluation consists of a comprehensive eye examination performed by an ophthalmologist with expertise in neonatal disorders. (See 'Screening examination' above.)

  Alternatively, telemedicine systems can be used to identify infants with potentially severe ROP. (See 'Telemedicine screening' above.)

- **Examination schedule** – We initiate retinal examinations as follows (table 1):

- For infants born at 22 to 27 weeks GA, the first examination is performed at 31 weeks PMA
- For infants born at ≥28 weeks GA, the first examination is performed at four weeks of chronologic age

Subsequent examinations are performed at intervals of one to three weeks, depending on the severity of ROP and the health of the infant. Retinal examinations continue until the risk of serious disease has passed, ROP regresses and the vasculature matures, or treatment is needed. (See 'Examination schedule' above and 'Discontinuation' above.)

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