Retinopathy of prematurity

Synonym: *retrolental fibroplasia*

Background

The retina is unique among developing fetal tissues in that it has no blood vessels until the 16th week of gestation. The vessels grow out from the optic disc, only fully reaching the periphery of the eye one month after birth. The incompletely vascularised retina is susceptible to oxygen damage, especially in the preterm infant.[1]

What is retinopathy of prematurity?

Retinopathy of prematurity (ROP) is a proliferative disorder of this immature retinal vasculature. It ranges from being mild with no visual sequelae to severe with marked or complete visual impairment. It is the leading cause of preventable childhood visual impairment in middle-income countries.

There are significant long-term ocular sequelae of ROP, underscoring the importance of lifelong follow-up of babies born prematurely.

How common is retinopathy of prematurity? (Epidemiology)

A study in 2010 estimated that, globally, 184,700 preterm infants developed any stage ROP, of whom 20,000 became blind or severely visually impaired from ROP and a further 12,300 developed mild/moderate visual impairment. Of those visually impaired from ROP, 65% were born in middle-income regions and 6.2% of all ROP visually impaired infants were born after 32 weeks' gestational age.

Many extremely preterm infants develop some degree of ROP and incidences of 66%–68% have been reported in infants of less than 1251g birthweight. In most of these cases the ROP never progresses beyond mild disease and resolves spontaneously without treatment.

Severe disease is relatively infrequent. A multicentre study found that only 18% of infants less than 1251g birthweight developed stage 3 ROP and only 6% reached threshold and required treatment.

In the UK, ROP-induced complete or partial blindness constituted 5%–8% of childhood vision impairment in 1985–1990 and was confined mainly to infants below 1000g birthweight. The incidence had decreased to 3% in 2000. In a 16-month UK-wide study, 13% of infants with stage 3 ROP had severe vision loss or blindness at one year of age.

Infants who develop ROP are also at increased risk of subsequent ophthalmic problems such as strabismus and myopia. In a study of infants with birthweight under 1701g, 29% with ROP stage 3 had strabismus at 6 months compared with 3% with no ROP.

Although some single-centre studies suggest the incidence of ROP is declining in the developed world, the latest Swedish national study shows a similar incidence of ROP over time and a significant increase in the frequency of treatment.

Improvement in survival rates of extremely preterm infants is leading to an increase in the number of infants who need screening.

Aetiology and pathogenesis[2] [3]

The pathogenesis of ROP is a two-phase process. Normally, the retinal vessels grow in an environment of relative hypoxia. In phase I, after premature birth, the retina is relatively hyperoxic (exposed to increased oxygen), resulting in reduced levels of vascular endothelial growth factor (VEGF).

This halts vascular growth: there is vasoconstriction then vaso-obliteration and involution. However, the eye continues to grow, resulting in a peripheral area of hypoxic retina. This ischaemia leads to increased levels of VEGF.[4]

This has three effects:

- Tortuosity of vessels (plus disease).

- Angiogenesis (pathological neovascularisation) - phase II. From late phase II onwards, this leads to fibrovascular proliferation. This causes intravitreal fibrosis with membrane formation and consequent retinal traction, leading in turn to retinal detachment.
- Iris vessel dilatation and rubeosis iridis

Other growth factors may play a role in ROP, including

- Insulin-like growth factor I (IGF-I).
- Growth hormone.
- Angiopoietin.
- Platelet-derived growth factor-β (PDGF-β)

Screening for retinopathy of prematurity

- All infants less than 31 weeks' gestational age (up to and including 30 weeks and 6 days) OR less than 1501g birth weight should be examined to screen for the presence of ROP (one criterion to be met for inclusion).
- For infants born before 31+0 weeks' gestational age, the first ROP examination should be performed between 31+0 and 31+6 weeks' postmenstrual age, or at 4 completed weeks' postnatal age (28–34 days), whichever is later.
- For infants born at and after 31+0 weeks' gestational age with birthweight less than 1501g, the first ROP examination should be performed at 36 weeks' postmenstrual age or 4 completed weeks' postnatal age (28–34 days), whichever is sooner.

The Royal College of Ophthalmologists' guideline provides details of referral criteria and subsequent examinations (see reference link).

Disease classification

There are a number of descriptors used to characterise the amount of ROP. Management and prognosis depend on the location, the extent, the staging and additional factors.

- **Location** - the retina is divided into concentric zones centred around the optic disc. There are three of these, zone 1 being the innermost and zone 3 the outermost.
- **Extent**: amount of disease - the retina is divided into clock hours and involvement is expressed in number of clock hours affected.
- **Staging**: what is occurring. There are several progressive stages, each describing increasing severity of the disease. They are:

    - **Stage 0** - no clear demarcation line between the developing but as yet non-vascularised area and the vascularised area.
    - **Stage 1** - a demarcation line appears between non-vascularised and vascularised areas.
    - **Stage 2** - the demarcation line becomes raised into a ridge.
    - **Stage 3** - abnormal neovascularisation now occurs.
    - **Stage 4** - partial retinal detachment.
    - **Stage 5** - total retinal detachment.
- **Plus and pre-plus disease**
    - '**Plus disease**' describes tortuosity and venular dilatation. It is the main factor determining the need for treatment at stage 3:

        - Plus disease is defined as increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least two quadrants of the eye.
        - It may progress to include iris vascular engorgement, poor pupillary dilation (rigid pupil) and vitreous haze.
    - '**Pre-plus disease**' describes vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease, but that cannot be considered normal.

- **Aggressive posterior ROP** - is an uncommon, rapidly progressing, severe form of ROP, usually in zone 1, with plus disease. Historically it was known as 'rush disease'. Its features are:

    - Posterior location with prominent plus disease.
    - Can progress rapidly without going through the classical stages 1-3.
    - The retinal changes are less obvious and more easily missed than in other forms of ROP.
    - Without treatment, it can rapidly progress to stage 5.

Retinopathy of prematurity treatment and management[5] [6]

The gold-standard treatment for ROP remains laser photocoagulation. It may be combined with intravitreal anti-VEGF administration, which is currently being evaluated, or surgery for advanced stages.

- Laser photocoagulation is the preferred treatment of choice. If laser is not available, cryotherapy may be performed. Laser photocoagulation is performed when ROP reaches **type 1 pre-threshold** disease.
- It is important to diagnose aggressive posterior ROP (AP-ROP) and treat it immediately, as this form of ROP can rapidly progress to retinal detachment.
- Anti-VEGF injections: intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) may cause rapid resolution of AP-ROP.[7]
- If laser or cryotherapy fails to prevent progression of ROP and the patient develops a retinal detachment, surgery (vitrectomy, scleral buckle) may be performed.
- Results are best when done before the fovea has detached.
- Stage 5 ROP has a poor visual prognosis.

Once the treatment threshold has been identified, treatment needs to be carried out within 48 hours for AP-ROP, and within 48-72 hours otherwise.

Treatment is usually given to both eyes as the severity and progression of ROP in the eyes of a given baby tend to be similar.

Follow-up

All babies with stage 3 ROP in which ROP resolved spontaneously, and babies requiring treatment of ROP, require ophthalmic review at least until 5 years of age.

Babies with only stage 1-2 ROP need only have the routine national vision screening, unless there is specific concern.

Complications

Complications of treatment [5]

- Progression of ROP despite treatment may occur despite well-applied laser, or as a consequence of incomplete peripheral retinal ablation.
- Treatment of ROP may cause intraocular haemorrhage, cataracts and aphakia (loss of the lens).
- There are various other reported ocular complications of treatment (detailed in current guidelines).
- Treatment of ROP can involve an extensive amount of peripheral retinal ablation, with the risk of visual field loss. The visual field results of the ETROP trial are awaited. [8]

Complications of ROP [9]

- There is an increased risk of less serious ophthalmic problems associated with prematurity - eg, strabismus and myopia.
- Patients with regressed ROP have a long-term risk of vitreoretinal diseases such as vitreous haemorrhage. [10]
- Severe or complete visual impairment may result from ROP, and are linked to ROP severity (see 'Prognosis', below).

- ROP can lead to cicatricial complications:
    - Myopia.
    - Very poor visual acuity.
    - Vitreoretinal fibrosis and abnormal retinal traction.
    - Peripheral retinal fibrosis.
    - Retinal detachment.
    - Secondary angle-closure glaucoma.
    - Early cataracts.
    - Band keratopathy and corneal opacity.

Prognosis[5]

Stage 1-2 ROP

- The outcomes are similar to those of preterm babies without ROP.

ROP stage 3 or more

- The prognosis varies according to the zone and severity of ROP. The outcomes (in terms of structural eye disease and visual acuity) are worse with more posterior location of ROP, increasing severity or the presence of plus disease. Severity of ROP may be linked to the degree of prematurity.[11]
- Without treatment, ROP leaves high rates of poor vision or severe sight impairment. For example, in the CRYO-ROP study, in the untreated group 64.3% had unfavourable visual acuity (severe sight impairment or a Snellen acuity score equal to, or worse than, 6/60).
- Treatment improves the prognosis. For example, in the ETROP trial, in the treated group, the rates of unfavourable visual acuity were 14.7%-30.8%, depending on the zone, stage and the presence of plus disease. In a UK study, 19% of babies with stage 3 ROP had severe or complete visual loss at one year of age.[11]

Retinopathy of prematurity prevention

The numerous factors involved in ROP development suggest that preventive strategies should be synergistic and complementary, including tight control of oxygen therapy, optimised nutritional intakes, breastfeeding, control of hyperglycaemic episodes associated with prematurity, normalisation of concentrations of essential factors such as insulin-like growth factor 1 and ω-3 polyunsaturated fatty acids, as well as curbing of the effects of infection and inflammation to promote normal growth and limit suppression of neurovascular development.[6] [12]

Dr Mary Lowth is an author or the original author of this leaflet.

Further reading

- Fu Z, Nilsson AK, Hellstrom A, et al; Retinopathy of prematurity: Metabolic risk factors. Elife. 2022 Nov 24;11:e80550. doi: 10.7554/eLife.80550.

Authored by:	Peer Reviewed by: Dr Toni Hazell	
Originally Published: 20/11/2023	Next review date: 22/09/2023	Document ID: doc_8672

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