Retinopathy of Prematurity

What is Retinopathy of Prematurity?

Retinopathy of prematurity (ROP) is one of the most common avoidable causes of blindness in children.[1] It is estimated that, out of 15 million babies born preterm (born before 37 completed weeks of gestation) every year[2], about 15 to 20% are affected by ROP.[3]

ROP is a retinal[a] disease that primarily affects very preterm babies born before 31 weeks of gestation.[4] Incidence of ROP has increased in recent years in countries where there is an advancement in neonatal care.[3] In middle- and low- income countries with less advanced neonatal care, ROP also occurs in more mature babies.[5]

During development in the womb, neurons and vessels in the eye grow outwards from the optic nerve head[b] and fully cover the retina by full-term.[5] When a baby is born preterm, the normal development is interrupted. As the retina develops late in pregnancy, this leads to a partly avascular retina. At room air, or in an incubator, the preterm baby is exposed to a much higher oxygen concentration than in the womb. As a consequence, developing vessels in the retina stop growing resulting in peripheral avascular area. The tissue and the neurons in the avascular retina are subsequently not provided with enough nutrients and oxygen, which over the course of time leads to an increased expression of vascular endothelial growth factor (VEGF), and other factors. Unfortunately, these factors subsequently trigger an abnormal growth of vessels. The vessels grow into the vitreous (the gelatinous mass between the retina and the lens) which can even pull off the retina, referred to as retinal detachment. This ultimately leads to vision loss or blindness in the baby.[6]

In the majority of babies born before 31 weeks gestational age, some stage of ROP develops, but it often disappears without need for intervention.[7] It is, however, very important to identify those infants where this spontaneous resolution of ROP does not occur and who need treatment.

What are the risk factors for developing ROP?

The more preterm a baby is born, the sooner the growth of vessels into the retina is interrupted and the larger the area that remains without vessels.

These are the risk factors for developing ROP that requires treatment:[5,8]

- Low gestational age and birth weight
- Postnatal oxygen supplementation
- Anaemia
- Thrombocytopenia
- Infections
- Long-term parenteral nutrition
- A complicated clinical course

What can you as a healthcare professional do to help prevent a baby from developing ROP needing treatment?

As described above, mainly very small and sick preterm babies, and babies with an unstable clinical course develop ROP that requires treatment. Certain measures can be taken to help prevent severe ROP stages:[9,10]

- Manage oxygen carefully, avoid hyperoxia through implementation of appropriate alarm levels, education of healthcare professionals, oxygen titration guidelines and sufficient number of skilled attendants
- Minimise rates of infections
- Minimise blood sampling and minimise transfusions
- Provide mother's own milk
- Provide optimised nutrition to improve postnatal growth
- Provide supportive individual developmental care
- Support skin-to-skin care

[a] The retina is the light-sensitive layer in the back of the eye that sends visual signals to the brain.
[b] Optic nerve head is the location where the neurons of the retina exit the eye

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How is ROP diagnosed?

In order to identify whether a baby has ROP, a specialised ophthalmologist screens the eyes of the baby regularly. Neonatologists, nurses and parents need to be informed when scheduling these appointments. It is recommended that parents/care takers are present during the screening and diagnosis. Before these exams, the pupils of the baby are dilated so that the doctor can see the back part of the eye using a specialised lens or camera. In some cases, the doctor uses an instrument to turn the eye in different directions to examine it from every angle. This may be uncomfortable for the baby, and topical pain relief (eye drops) should therefore be used during these exams.

Before, during and after the assessment, please consider the following measures to reduce stress as much as possible to the baby:

- Prepare the baby's position with the feet able to brace on a nest or the end of the bed
- Tuck a blanket around the baby or swaddle with hands free nearby the baby's mouth
- Encircle the head with a roll of soft blanket and put your hand on this roll to keep the head in midline
- Encourage the baby to grasp your (or the parents') fingers with their hand
- Work at the pace of the baby
- Comfort and reassure the baby after the exam
- If possible, reposition on side after the exam
- Avoid other procedures for at least one hour or longer
- Be extra alert for light. Protect the baby from direct light for several hours after the procedure

Options for non-pharmacological pain relief during ROP screening: use of mothers' own milk or glucose on a pacifier, presence and support of the baby by parents during the assessment (e.g. skin-to-skin care or holding by parents).[11]

The ophthalmologist examines the growth and development of vessels in the retina (vascularised area), the area with no vessels (avascular area), and the border between these two areas. Then, the doctor decides when the eyes need to be re-checked. The doctor also decides if a treatment is necessary, or if no further screening needs to be done, in case both eyes are fully vascularised. Parents need to be personally informed about the findings and the next steps.

The first screening usually takes place at about 6 weeks after birth, but not before 31 weeks postmenstrual age (calculated since the first day of the last period of the mother).

The exact timing of the first and the following screening visits depends on the gestational age at birth, the current status of the eye, and the national/local guidelines on screening for ROP. These guidelines are adapted to the characteristics of ROP that are most prevalent in the respective country.

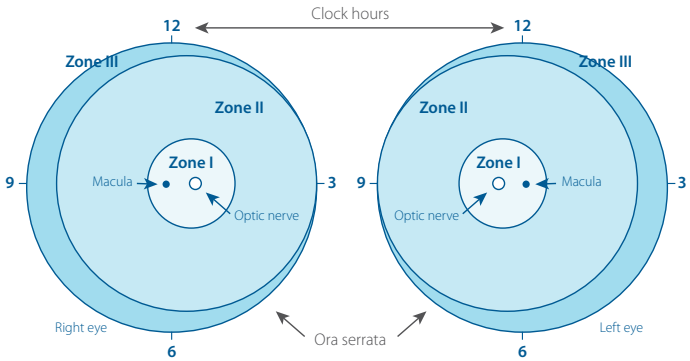
Does every form of ROP need treatment?

ROP can be categorised into several zones (I to III) and stages (1 to 5). While only certain zones and stages require treatment, about 32% of babies born before 31 weeks of pregnancy develop some stage of ROP.[12]

Zones:[13]

The zone describes the localisation of the border between the vascularised and the avascular area in the retina, with zone I being the most central zone[a].

Zone I is a circle around the optic disc with a radius of twice the distance between optic disc and macula. ROP in zone I is most likely to progress and become severe. Zone II is a circle around the optic disc where the radius is the distance between optic disc and the ora serrata[b] on the nasal side. Zone III is the remaining part of the retina which rarely shows aggressive disease.



Scheme of retina showing zone borders and clock hours to describe the location and extent of ROP.[13]

[a] The macula is the part of the eye where the highest density of neurons is located. Thus, the macula is also known as the area of the best vision.
[b] The ora serrata marks the peripheral end of the retina.

Stages:[13]

Stages of ROP describe the disease progression ranging from mild to severe where stage 1 is considered as mild (least severe), stage 5 as the most severe stage of ROP.

1 In stage 1 ROP, there is a white line between the vascularised and the avascular area that can be seen during the eye exam by the ophthalmologist, also called a demarcation line.

2 In stage 2, the border is not flat any longer and becomes wider and is now called a ridge.

3 Stage 3 is characterised by abnormal growth of blood vessels and some tissue on the ridge and into the vitreous.

4 In stage 4, misguided fibrovascular tissue growing into the vitreous pulls at a part of the retina causing a partial retinal detachment.

5 Stage 5 is a complete retinal detachment.

In some cases, the vessels at the back part of the eye get dilated and tortuous. This is called "plus disease" and is a sign of a progressing disease that needs treatment.

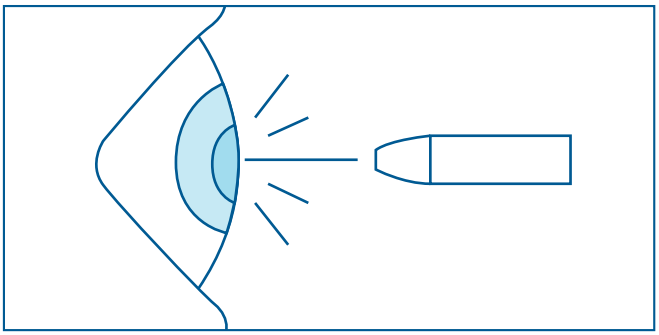
A subtype of ROP called aggressive-posterior ROP (AP-ROP) is characterised by plus disease and an aggressive progression of the disease. AP-ROP is a very dangerous form of the disease and usually occurs in zone 1 and can progress quickly to retinal detachment.

The treatment of ROP based on the zones and stages of ROP is to be carried out as per the local country guidelines.

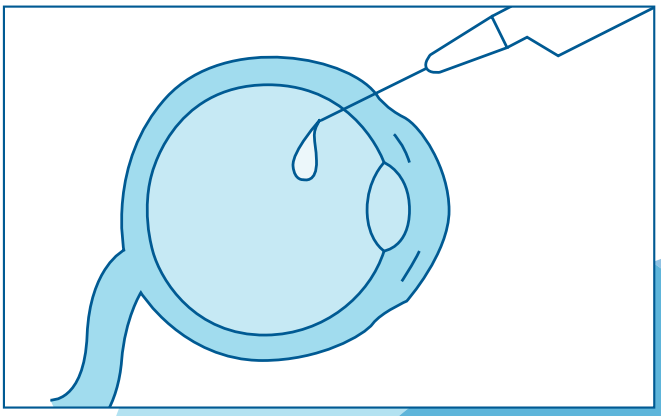
→ It is very important to ensure appropriate and regular screening by a skilled ophthalmologist to identify the babies who need treatment according to your national guidelines.

How can ROP be treated?

During the past years, ROP was mainly treated by **laser coagulation**. The retina in the avascular part of the eye is destroyed with a high number of laser spots and can thus no longer produce VEGF. This treatment is time consuming and therefore general anesthesia is required. The part of the retina that is destroyed by laser loses its function as viable neuronal tissue, while the central part of the retina which is not affected by laser can still provide useful vision.[14]



In September 2019, ranibizumab, an **anti-VEGF drug** was approved in Europe for the treatment of ROP in preterm babies with zone I (stages 1+, 2+, 3 or 3+), zone II (stage 3+) or aggressive posterior ROP (AP-ROP) disease. This treatment takes less time to administer compared to laser and some hospitals inject the drug under local anesthesia only. Myopia and negative structural changes of the retina are less common with anti-VEGFs, but the rate of re-treatment is higher than with laser. As the use of anti-VEGFs is still new in the treatment of ROP, the long-term effects on different organ systems are yet to be explored.



Parents need to be well informed about the different treatment options and their risk-benefit ratios. The decision on a treatment option should take into account the clinical and family situation and should be communicated by ophthalmologists to parents and neonatologists.

ROP treatment must be performed by a trained ophthalmologist at a centre where all treatment options and facilities are available.

Is follow-up after the treatment necessary?

Laser treatment destroys the area of the retina that produces VEGF, while an anti-VEGF drug like ranibizumab binds the existing VEGF in the eye. The effect of the therapy can thus be seen within a few hours after anti-VEGF treatment, and within a few days after laser treatment. In both cases, the ophthalmologist needs to examine the retina at regular intervals after treatment. In some cases, a re-treatment can become essential.

→ There might be a greater need for re-treatment after an anti-VEGF drug compared to laser treatment. Therefore, follow-up exams must be conducted regularly over a period of months after anti-VEGF treatment.[15]

→ It is very important that all follow-up exams are scheduled and are not ignored/missed. It is best to note the need for regular follow-up visits in the discharge summary. In addition, the parents need to be thoroughly educated about the importance of follow-up exams.

References:

1. Solebo AL. Arch. Dis. Child 102, 853-867 (2017)
2. WHO Factsheet: Preterm birth.
3. Ludwig CA. Ophthalmic Surg. Lasers Imaging Retina 48, 553-562 (2017)
4. Walz JM. Acta Ophthalmol. 94, e744-e752 (2016)
5. Hellström A. The Lancet 382, 1445–1457 (2013)
6. Chan-Ling T. Prog Retin Eye Res. 62, 77-119 (2018)
7. Holmström GE. Arch. Opthalmol 130, 1418-1424 (2012)
8. Fierson W. M. Pediatrics 142, e20183061 (2018)
9. Darlow BA. Semin. Perinatol. 43, 333–340 (2019)
10. EFCNI ESCNH: Prevention, detection, documentation, and treatment of retinopathy of prematurity (ROP). (2018)
11. EFCNI ESCNH: Support during painful procedures and pain assessment. (2018)
12. Holmström G. Br. J. Ophthamol. 104, 943-949 (2020)
13. The ICROP Revisited. Arch. Ophthalmol. 123, 991 (2005)
14. Yang CS. Eye Lond. Engl. 24, 14–20 (2010)
15. Walz JM. Ophthalmologe 115, 476–488 (2018)

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Special thanks to Professor Ann Hellström, Professor Andreas Stahl and Monique Oude-Reimer for their support and advice in the preparation of this factsheet.

Independently developed by EFCNI, with support from Novartis Pharma AG.

GLOPH/LUC/0826

About EFCNI

The European Foundation for the Care of Newborn Infants (EFCNI) is the first pan-European organisation and network to represent the interests of preterm and newborn infants and their families. It brings together parents, healthcare experts from different disciplines, and scientists with the common goal of improving long-term health of preterm and newborn children. EFCNI's vision is to ensure the best start in life for every baby.

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