Retinopathy of Prematurity

INTRODUCTION
Retinopathy of prematurity or retrolental fibroplasia is a proliferative vitreoretinopathy affecting premature infants of very low birth weight that can cause retinal detachment. Retinal detachment occurs as a result of tractional forces caused by neovascular proliferation and its presentation can range from mild peripheral tractional retinal detachment to total retinal detachment. In retinopathy of prematurity patients, retinal detachment that develop shortly after birth are usually due to mechanical traction or exudation from retinal vessels in the active stage of proliferation. Those that develop later in life are usually of rhegmatogenous type and may or may not be associated with cicatricial ROP changes.

PATHOPHYSIOLOGY
Retinal receives its blood supply from both choroidal and retinal circulation. The choroidal circulation is complete prior to 20 weeks of gestational age, and therefore prior to survivable premature birth. But retinal circulation arising from optic nerve head is just beginning to develop a vascular bed at this time and thus is involved in ROP pathogenesis.

There are 2 theories in ROP –
A classic theory by Ashton and Patz and a gap junction theory by Kretzer and Hittner.
The “classical” theory proposed by Patz and Ashton describes an initial hyperoxic phase of the disease which causes arteriolar constriction with subsequent irreversible vasooobliteration. This is then followed by a second phase in which a vaso-proliferative response is induced by retinal ischemia as a result of retinal capillary closure. The “classical” theory has been followed by the “gap junction theory” of Kretzer and Hittner. Their theory of pathogenesis is based on the activity of mesenchymal spindle cell precursors of retinal capillaries. Accordingly, these cells migrate centrifugally from the optic disc toward the junction between vascular and nonvascularized retina, to form a new capillary network. Under hyperoxic conditions, abnormal gap junctions appear between adjacent spindle cells, and this interferes with normal cellular migration and vascular formation. The angiogenic factors secreted by these mesenchymal cells may in turn trigger a neovascular response.

RISK FACTORS
Systemic factors (1)
1) Younger gestational age
2) Multiple births
3) Out-of-nursery birth
4) Low birth weight
5) White race
6) More than 6 hours stage 3 labour

Ocular factors (1)
1) Lower PMA on ROP diagnosis
2) Zone 1 ROP in 1st exam
3) Rapid progression to prethreshold
4) Plus disease at 1st prethreshold exam
5) Iris vessel dilatation
6) Plus disease
7) Zone 1 ROP

Others (1)
1) Prematurity
2) High levels of supplemental oxygen
3) Mechanical ventilation
4) Multiple blood transfusion
5) Intraventricular hemorrhage
6) Concurrent illness
7) Anemia
8) Seizures and apnoea
9) Multiple prenatal maternal factors like diabetes, preeclampsia, smoking etc
10) Genetic polymorphism

SCREENING GUIDELINES AND PROCEDURES
According to American Academy Of Paediatrics the screening guidelines include:
1) Infants with birth weight ≤1500 g or gestational age of 30 weeks or less and selected infants with a birth weight between 1500 and 2000 g or gestational age of >30 weeks with an unstable clinical course, including those requiring cardiorespiratory support and who are believed by their attending pediatrician or neonatologist to be at high risk for ROP, should have retinal screening examinations performed after pupillary dilation by using binocular indirect ophthalmoscopy with a lid speculum and scleral depression (as needed) to detect ROP.

2) The initiation of acute-phase ROP screening should be based on the infant’s postmenstrual age. The onset of serious ROP correlates better with postmenstrual age (gestational age at birth plus chronologic age) than with postnatal age.
That is, the more preterm an infant is at birth, the longer the time to develop serious ROP.

### TABLE 1

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<tr>
<th>Gestational Age at Birth, wk</th>
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Older gestational age, high-risk factors 4

Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings classified according to the international classification (see Fig 1). The following schedule is suggested.

**FIGURE 1**

Scheme of retina of the right and left eyes showing zone borders and clock hours used to describe the location and extent of ROP. Diagrammatic representation of the potential total area of the premature retina, with zone I (the most posterior) symmetrically surrounding the optic nerve head (the earliest to develop). A larger retinal area is present temporally (laterally) rather than nasally (medially) (zone III). Only zones I and II are present nasally. The retinal changes discussed in recommendation 4 are usually recorded on a diagram such as this one.(2)

**1-Week or Less Follow-up**
- immature vascularization; zone I—no ROP
- immature retina extends into posterior zone II, near the boundary of zone I
- stage 1 or 2 ROP; zone I
- stage 3 ROP; zone II
- the presence or suspected presence of aggressive posterior ROP

**1- to 2-Week Follow-up**
- immature vascularization; posterior zone II
- stage 2 ROP; zone II
- unequivocally regressing ROP; zone I

**2-Week Follow-up**
- stage 1 ROP; zone II
- immature vascularization; zone II—no ROP
- unequivocally regressing ROP; zone II

**2- to 3-Week Follow-up**
- stage 1 or 2 ROP; zone III
- regressing ROP; zone III

Babies born with birth weight of less than or equal to 1500gm or gestational age of 31 weeks or less should be screened for retinopathy of prematurity. Screening should begin at 1-2 weekly intervals, depending on the severity of the disease and continue until retinal vasculature reaches zone 3. In the management of premature infants weighing less than 1200gm, the PaO2 level of blood from the umbilical artery should be monitored, levels of 50-100mmHg being regarded as unlikely to produce constriction of retinal vessels.

If minor signs of ROP are noticed, examination should be repeated at the ages of 1, 3 and 6 months and every 4 months up to the age of 4 years with the aim of diagnosing early retinal holes or localized detachment of the retina.

Screening conclusion done when
1) Zone 3 retinal vascularisation attained without previous zone 1 or 2 ROP, assuming no examiner error. If there is doubt about to the zone or if postmenstrual age is unexpectedly young, confirmatory exams may be warranted.
2) Full retinal vascularisation
3) Postmenstrual age of 45 weeks and no prethreshold ROP or worse presentation
4) Definite disease progression signs in compatibly aged infants.

According to Jalali et al (3), the screening criteria for ROP in the Indian scenario includes,

**Screening of all eligible babies to be started**
1. 31 weeks post conceptional age or 3-4 weeks after birth (whichever is earlier)
2. Infants weighing 1200gms at birth and those born at 24-30 weeks gestational age are screened early, usually not later than 2-3 weeks after birth
3. No examination needed in the first 2-3 weeks of life
4. Next examination date to be decided by ophthalmologist based on initial findings
5. Complete one screening session definitely before ‘Day 30’ of infants life

**Frequency of examination is**

1. Further evaluation for ROP is not needed if the retina is fully mature (defined as retinal vessels seen up to nasal ora serrata, in the context of ROP). This usually occurs by 40 weeks post-conceptional age. Babies, however, need to see an ophthalmologist for refraction, vision assessment, and ocular alignment (squint) at 3-12 months of age. Preterm babies are at higher risk for developing ametropia, delayed visual maturation and squint. If there is no apparent squint or vision problem, the child can be seen at one year of age. If there is an obvious squint, nystagmus, tearing, discharge, photophobia, leucocoria or vision loss, then early evaluation is needed. Usually the eyes are well aligned, and have good ability to fixate and follow an object by three months of age.

2. If the retina is immature (retinal vessels are not seen up to nasal ora serrata) then baby must be screened every two weeks till the retina is mature.

3. In eyes with retinal vessels seen only up to the Zone I area at initial visit, weekly evaluation is needed. These eyes can develop fulminate ROP or Rush disease very quickly, and not necessarily the classical stages 1-3 before reaching threshold ROP.

4. If there are early signs of ROP then the child must be examined every week for any progression or regression of the disease.

5. If child develops pre-threshold ROP, then the child should be seen every 3-7 days for progression.

6. In case of threshold ROP, urgent peripheral retinal laser/ cryo ablation should be done within 48-72 hours.

7. In eyes with ROP stage 4 or 5, early surgical treatment such as belt buckling or vitreous surgery can help save some vision, though the majority have a dismal prognosis.

8. In case of any doubt about the retinal findings (especially by beginners) it is a good practice to examine the baby again every 1-2 weeks, at least till the child is 38-40 weeks old.

**NATURAL HISTORY AND SEQUELAE**

ROP is divided into acute and cicatricial phase. The inherent activity in the retina determines the timing of the disease expression. Youngest infants at birth develop ROP at a later chronologic age and infants with the oldest gestational ages at birth develop ROP at an earlier gestational age.

ROP progression has natural breakpoints between disease without risk of unfavorable outcome and disease with this risk. Escalating disease with very low risk includes:

- Stage 1, zone 2 or 3, no plus
- Stage 2, zone 2 or 3, no plus
- Stage 3, zone 2 or 3, no plus

Constants above are not stage, but absence of Zone 1 or plus disease. All of them have a less than one percentage chance of poor outcome.

Maximal observed disease with significant and increasing risk includes:

- Stage 3 plus, 1-4 sectors, Zone 2
- Stage 1 & 2, Zone 1
- Stage 3 plus, 5-8 sectors, Zone 2
- Stage 3 plus, 9-12 sectors, Zone 2
- Stage 3, Zone 1

According to CRYO ROP, above risks of unfavourable outcome from 8-60%. The greatest risk of poor outcome was Zone 1 threshold ROP. The unfavourable visual outcome in those patients was close to 90% whether treatment was given or not.

Regression or cicatricial disease is less well understood and includes fibrovascular proliferation, contraction, scarring, pigmentary changes and permanent traction. CRYO-ROP study developed a macular scoring system as the degree of macular damage was the most clinically relevant cicatricial event. They classified tractions as:

- **MS 0**: Normal macula
- **MS 1**: Macular heterotopia
- **MS 2**: Macular fold
- **MS 3**: Macular retinal detachment
**INDICATIONS OF TREATMENT**

The presence of plus disease (defined as abnormal dilation and tortuosity of the posterior retinal blood vessels in 2 or more quadrants of the retina meeting) in zones 1 or II suggests that peripheral ablation, rather than observation, is appropriate.¹

Treatment should be initiated for the following retinal findings:

- zone I ROP: any stage with plus disease
- zone I ROP: stage 3—no plus disease
- zone II: stage 2 or 3 with plus disease

The revised International Classification of Retinopathy of Prematurity Revisited classification gives specific examples on how to identify zone I and zone II disease by using a 28-diopter lens with binocular indirect ophthalmoscopy. The presence of plus disease rather than the number of clock hours of disease may be the determining factor in recommending ablative treatment. Treatment should generally be accomplished, when possible, within 72 hours of determination of treatable disease to minimize the risk of retinal detachment. Follow-up is recommended in 3 to 7 days after treatment to ensure that there is no need for additional treatment in areas where ablative treatment was not complete.

According to ETROP study(4), early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcomes to a clinically important degree. Earlier treatment is defined as retinal ablation administered to the avascular retina when an eye reaches high risk prethreshold retinopathy of prematurity (ROP). Prethreshold indicates any Zone I ROP; or Zone II stage 2 with plus disease, or stage 3; or Zone II with less than 5 contiguous or 8 cumulative clock hours of stage 3 ROP with plus disease. High risk include birth weight, gestational age, ethnicity, singleton/multiple status, outborn status, Zone on first exam, severity of ROP and rate of progression of ROP.

**TREATMENT**

1] Laser photocoagulation-Recommended in infants with threshold disease. This is successful in 85% of cases, but the remainder progress to retinal detachment in spite of treatment. The visual and anatomical outcomes are better compared to cryotherapy as laser induces less myopia. The systemic adverse effects are significantly less, the ocular tissues are less traumatized, posterior zone 1 disease is treated easily, general anesthesia is not necessary, there is less incidence of late complications. Complications include corneal haze, burns of the iris, cataracts, and intraocular hemorrhages.

2] Intravitreal anti-VEGF agents- Bevacizumab has been used but the optimal timing, frequency and dose are yet to be established. According to BEAT ROP study(5) there was significant benefit with Intravitreal bevacizumab monotherapy, as compared with conventional laser therapy, in infants with stage 3+ retinopathy of prematurity for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, while conventional laser therapy led to permanent destruction of the peripheral retina. But safety issues of using Bevacizumab in ROP still persists as the study trial was too small.

3] Lens-sparing pars plana vitrectomy – For tractional retinal detachment not involving the macula(Stage 4a). It has better visual and anatomical outcome. The visual outcome in stages 4b and 5, in which the macula is involved, is disappointing despite successful reattachment.

**CONCLUSION**

Retinopathy of prematurity is a disease that affects immature vasculature in the eyes of premature babies. It can be mild with no visual defects, or it may become aggressive with new neovascularization and progress to retinal detachment and blindness. Increasing awareness among general public, neonatologists and ophthalmologists and a mandatory screening protocol for all NICUs can go a long way in preventing visual morbidity due to this condition.

**REFERENCES**


Dr Natasha Radhakrishnan et al - Retinopathy of Prematurity