# Chapter 19: Retinopathy of Prematurity

*Nina Menda, MD*

- ROP is a multi-factorial condition of abnormal vascularization of developing retinal vessels occurring in premature infants due to incomplete vasculogenesis of the retina at the time of birth.
- Leads to retinal detachment and blindness if severe and untreated.

**etinal Vasculature Embryology**

- Retinal vasculature begins to develop at 14-15 weeks gestation
- Growth of the vessels begins centrally at the optic disc and grows out peripherally to the ora serrata
- Retinal vessels develop initially by the process of vasculogenesis and later angiogenesis
- 70% of retinal vasculature present at 27 weeks
- Reaches nasal ora serrata by 36 weeks and the temporal ora serrata by 39-41 weeks
- Preterm birth leads to an avascular zone in the peripheral retina

**pidemiology**

- Global health epidemic
- Leading cause of childhood blindness worldwide
- Overall prevalence is between 10-25% in premature infants, while incidence is about 50-70% in infants weighing ≤ 1500 grams at the time of birth. [Incidence of 18-40% in premature infants in developed countries]

**athogenesis of ROP**

- Phase 1 (Vaso-obliteration)
  - Characterized by cessation of normal new retinal vessel growth
  - Occurs shortly after birth, following hyperoxia exposure
  - Hyperoxia downregulates vascular endoethelial growth factor (VEGF) secretion
- Phase 2 (Vaso-proliferation)
  - Characterized by retinal neovascularization, fibrosis and detachment
  - Four to six weeks after birth, the retina becomes hypoxic due to inadequate vasculature to nourish it
  - Hypoxia upregulates VEGF secretion, and excess VEGF leads to dysregulated angiogenesis
  - Vessels leave the retinal plane and grow into the vitreous leading to cicatrization, tugging of fibrous scars on the retina and eventual detachment

**isk Factors**

- Prematurity (ROP incidence is inversely proportional to gestational age at birth)
- Prolonged hyperoxia or supplemental oxygen use
- Low birth weight
- Post-natal growth restriction
- Inadequate post-natal nutrition
- Sepsis
- RDS/BPD
- Shock
- Asphyxia
- Hypothermia
- Acidosis
- Vitamin E deficiency

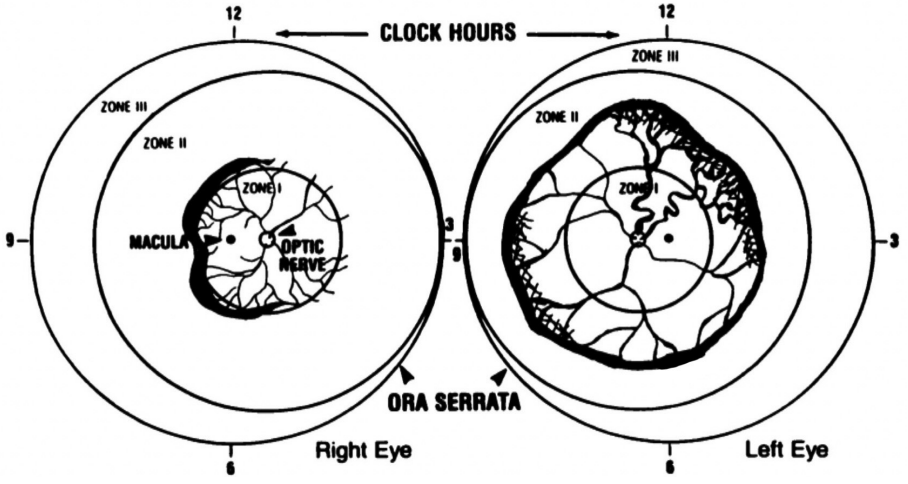
**lassification**

- Zone = Location of abnormal vascularization
- Clock Hour = Extent
- Stage = Severity

| Stage | Features of Disease |
|---|---|
| 1 | Demarcation line between the vascular and avascular portions of the retina |
| 2 | Ridge-like structure between avascular and vascular retina |
| 3 | Fragile new vessel proliferation from the ridge into the vitreous gel |
| 4A | Partial retinal detachment not involving the macula |
| 4B | Partial retinal detachment involving the macula |
| 5 | Total retinal detachment |

- Plus Disease is defined as a significant retinal vein dilation and arterial tortuosity
- Pre-threshold disease is defined as stage 3 ROP in Zone II or any ROP in Zone I

xample of what ophthalmologists document in chart




ight Eye = Stage 2 Zone I/II, 6 clock hours without plus disease

eft Eye = Stage 2/3 Zone II, 12 clock hours with plus disease in one quadrant

**reatment**

*lost treatments for ROP are targeted for Phase 2 ROP*

A. Monitoring of pulse oximetry and judicious use of oxygen
   - Monitoring oxygenation using pulse oximetry has become the mainstay of ROP prevention.
   - Controversies surround target $SpO_2$ levels due to concerns of multi-centered randomized clinical trial (SUPPORT trial) showing increased mortality in low oxygen saturation target group (85-89%) compared to high (91-95%), despite reduction in severe ROP.
   - Oxygen saturation goals from birth to <37 weeks corrected age (90-94%), while infants >37 weeks corrected age (>95%)

B. Serial Monitoring : Dilated retinal exams using a binocular indirect ophthalmoloscope by an ophthalmologist to determine retinal maturity and early detection of ROP to facilitate early treatment.

C. Laser photocoagulation or cryosurgery
   - Current standard therapy for ROP
   - Ablates the avascular portion of the retina to reduce hypoxic stimulus from VEGF production, stopping abnormal vessel growth
   - Goal is to prevent retinal detachment
   - Patients will still lose some peripheral vision after treatment
   - Who should be treated?
     - Zone I any stage with Plus disease
     - Zone I Stage 3 without Plus disease
     - Zone II stage 2-3 with Plus disease

D. Intravitreal bevacizumab (avastin) monotherapy has shown significant benefit for Zone I stage 3 disease in a RCT. Bevacizumab is a monoclonal antibody against VEGF. It is an intravitreal injection, used in premature infants with severe ROP and has shown significant promise in the treatment of ROP.
   - There is concern for systemic absorption of Avastin, which may result in pan-VEGF blockade which may interfere with angiogenesis in other developing organs. There is insufficient long term data on efficacy and safety.

**rognosis**

- Up to 80% of ROP will resolve spontaneously or regress
- Less than 6% require any treatment
- 3% or less will become blind from ROP

# Screening Eye Exams

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AP/Meriter Guidelines

- All infants with a birth weight ≤ 1500 grams, or gestational age at birth of ≤ 30 weeks
- Select infants with birth weight 1500-2000 grams or gestational age at birth of
- 30 weeks with an unstable clinical course and at higher risk for ROP as determined by attending neonatologist
- In most cases, ROP exams will begin at a PMA of 31 weeks or a chronological age of 4 weeks, whichever is longer.
- **As an exception, infants born at < 25 weeks gestation should be considered for earlier initiation of ROP screening at 6 weeks chronological age based on severity of comorbidities to identify and treat posterior ROP (severe form that is aggressive with rapid progression)

**iming of Initial ROP Exam**

| Gestational Age at Birth, Completed Weeks | Age at Initial Exam in Weeks | |
|---|---|---|
| | Postmenstrual | Chronological |
| 22** | 31 (28**) | 9 (6**) |
| 23** | 31 (29**) | 8 (6**) |
| 24** | 31 (30**) | 7 (6**) |
| 25 | 31 | 6 |
| 26 | 31 | 5 |
| 27 | 31 | 4 |
| 28 | 32 | 4 |
| 29 | 33 | 4 |
| 30 | 34 | 4 |
| Older gestational age, high-risk factors | | 4 |

Discontinuation of examinations

- PMA 45 weeks with no Pre-threshold disease
- Progression of vascularization in zone III without previous ROP in zone I or II
- Mild and regressing of ROP in zone III
- Full retinal vascularization

**References:**


1. AAP Policy Statement. Screening Examination of Premature Infants for Retinopathy of Prematurity. *Pediatrics* 2013;131:189-195. doi: 10.1542/peds. 2012-2996.
2. Smith, L.E., Pathogenesis of retinopathy of prematurity. *Semin Neonatol*, 2003. 8(6): p. 469-73.
3. Mezu-Ndubuisi, O.J., In Vivo Angiography Quantifies Oxygen-Induced Retinopathy Vascular Recovery. *Optometry and Vision Science*, 2016. 93(10): p. 1268.
4. Silva RA and. Moshfeghi DM. Interventions in Retinopathy of Prematurity. *Neoreviews* 2012;13;e476. DOI: 10.1542/neo.13-8-e476.
5. Phelps DL. Retinopathy of Prematurity. *Pediatrics in Review.* 1995; 16: 50-56.
6. Gilbert, C., Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. *Early Human Development*, 2008. 84: p. 77-82.
7. Good, W.V., Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc*, 2004. 102: p. 233-48; discussion 248-50.
8. SUPPORT Network, S.S.G.o.t.E.K.S.N.N.R., et al., Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*, 2010. 362(21): p. 1959-69.
9. Owen LA, Morrison MA, Hoffman RO, Yoder BA, DeAngelis MM. Retinopathy of prematurity: A comprehensive risk analysis for prevention and prediction of disease. Vavvas DG, ed. *PLoS ONE*. 2017;12(2):e0171467. doi:10.1371/journal.pone.0171467.
10. Helen a. Mintz-Hittner, Kathleen Kennedy. Efficacy of Intravitreal Bevacizumab for stage 3+ retinopathy of prematurity. *NEJM* 2011; 364:603-15.