RETINOPATHY OF PREMATURITY

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All about the Eye

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Retinopathy of prematurity

1. "**Plus disease**" in retinopathy of prematurity. 2000
2. What are the **screening guidelines and methodology of examination** of retinopathy of prematurity? 2006
3. **Screening** of a case of retinopathy of prematurity J2009
4. **Management** of retinopathy of prematurity.D2009, 2005
5. Retinopathy of prematurity 1999, 2000, 2006, J2010
6. How is retinopathy of prematurity **classified indicating the indications & principles for therapy**? 10 J2011
7. Describe **staging, risk factors and outline management** principles of retinopathy of prematurity. (4+2+4) D2011
8. Describe the **clinical characteristics and staging of retinopathy of prematurity** (ROP). Write the criteria for its **screening with management** principles. J2012
9. **Risk factors, classification and management** of retinopathy of prematurity. (2+4+4) D2016
10. **Etiology, evaluation, classification and management** of retinopathy of prematurity. (2+2+3+3) D2017

1. Introduction 2. Epidemiology 3. Etiopathogenesis 4. Risk factors 5. ICROP- zones, stage, extent, type	6. Sequelae 7. Differential diagnosis 8. Screening , Diagnosis and examination 9. Management 10. Rehabilitation and counseling

1. Introduction

- Retinopathy of Prematurity (ROP) is a vasoproliferative retinopathy seen in premature infants with low birth weight, additional systemic illness and early exposure to high ambient oxygen concentrations is also a risk factor.
- The underlying pathological change is retinal neovascularization in response to retinal ischemia
- The estimated risk of blindness without treatment in threshold ROP is 50%.
- First described by Terry in 1942 as retrolental fibroplasia, ROP is unique in that it affects an immature, incompletely vascularized retina.
- The spectrum of outcome varies from minimal sequelae in mild cases to bilateral, irreversible, total blindness in advanced cases.

2. Epidemiology

In the United States, ROP that is severe enough to require treatment occurs in approximately 1100– 1500 infants annually. Among these infants, 400–600 will never achieve vision better than 20/200.

I. Early history:

- The first epidemic of retinopathy of prematurity was first identified by Terry in 1942.
- Terry's original report designated the condition as retrolental fibroplasia (RLF) on the basis of the impression that primary change involved a proliferation of the embryonic hyaloid system that incorporated the retina.
- Owens and Owens subsequently showed that the hyaloid system was normal at birth and disease developed in the postnatal period.
- As the pathogenesis and the clinical spectrum of the disease became clear it came to be known as retinopathy of prematurity.
- Within a decade of the original description, retinopathy of prematurity became the main cause of childhood blindness in United States and in the technologically developed world.
- This is what we now recognize as the first epidemic of ROP.
- In 1950s, the discovery of the relationship between supplemental oxygen therapy and ROP led to the rigid curtailment of oxygen therapy to premature infants.
- This led to a decrease in the incidence of ROP.
- Arterial blood gas analysis was not available at that time and restricted oxygen therapy had a significant adverse effect on premature infant morbidity and mortality.

II. The first lull and the second epidemic.

- In the 1960s and 1970s, a significant advance was the availability of arterial blood gas analysis which allowed neonatologists to titrate the incubator oxygen concentration to meet the premature infant's oxygen needs to a more physiological extent.
- This minimized the morbidity associated with rigid oxygen curtailment and at the same time optimized oxygen concentrations to prevent ROP.
- ROP screening programs were generally not in place as the first epidemic had got over.

- Interestingly by the early 1980s, incidence of ROP began to rise again.
- This new epidemic of ROP was attributed to increased survival of very low birth weight babies (<1000 gm) due to advances in neonatal care.
- It is these infants with the greatest immaturity of retinal vasculature, who have the highest risk of ROP.
- This second epidemic of ROP led to a renewed interest in the disease.

III. Modern epidemic

- Modern epidemic of ROP in middle income group countries and the decreasing incidence in the western world:
- In the 1940s and 1950s, retinopathy of prematurity (ROP) was the single most common cause of blindness in children in many industrialized countries.
- However, at present, it accounts for only 6 to 18 percent of blindness registrations in these countries.
- Currently, there is an increasing body of evidence that suggests that the incidence and severity of ROP in babies <1250 gm is decreasing in industrialized countries and is attributable to improvements in neonatal care.
- A blind school survey reveals that the proportion of severe visual impairment or blindness due to ROP ranged from 0% in most African countries to 38.6 percent in Cuba.
- In most African countries (low income group countries),the neonatal services are poor and babies do not survive to develop ROP.
- The current epidemic of ROP concerns the middle income group countries.
- Firstly, more premature babies are surviving with the setting up of more neonatal intensive care units (NICU).
- Secondly, neonatal services are in a stage of infancy and have not reached an adequate level of care as yet leading to most babies receiving unmonitored supplement of oxygen.
- Wagner in his editorial noted that oxygen monitoring requires sophisticated pulse oximeters and other equipment not readily available in developing countries.
- Not surprisingly, heavier and more mature babies are also developing ROP in developing countries.

Early history	The first lull and the second epidemic	Modern epidemic
1st epidemic of ROP was first identified by Terry in 1942 designated the condition as retrolental fibroplasia	1960s and 1970s, a significant advance was the availability of arterial blood gas analysis	The current epidemic of ROP concerns the middle income group countries
Owens and Owens showed that the hyaloid system was normal at birth and disease developed in the postnatal period	By the early 1980s, incidence of ROP began to rise again	More premature babies are surviving with the setting up of more neonatal intensive care units (NICU)
In 1950s, the relationship between supplemental oxygen therapy and ROP discovered	This new epidemic of ROP was attributed to increased survival of VLBW babies (<1000 gm) due to advances in neonatal care.	Neonatal services are in a stage of infancy and have not reached an adequate level of care as yet leading to most babies receiving unmonitored supplement of oxygen
This is what we now recognize as the first epidemic of ROP	These infants have immaturity of retinal vasculature, & highest risk of ROP	Not surprisingly, heavier and more mature babies are also developing ROP in developing countries
Arterial blood gas analysis was not available at that time	This second epidemic of ROP led to a renewed interest in the disease	This is the modern epidemic

3. Etiopathogenesis

I. Retinal vascular development

- The retinal vessels begin to grow from the disk at 4(16wk)months of gestation and reach the nasal ora serrata at 8(36wk) months of gestation.
- Vessels reach temporal ora serrata only shortly after term (40wk)
- In a premature infant, there is peripheral avascular retina.
- Recent studies by Flynn et al demonstrate two phases in retinal vascular development.
  - i. **Vasculogenesis** results in formation of four major arcades of posterior retina from the mesenchymal vascular precursor cells which exit from the optic disk. This first phase begins before 14 weeks of gestation and completes by 21 weeks.
  - ii. **Angiogenesis -** results in the formation of remaining retinal vessels by budding of endothelial cells from vessels formed in the first phase.

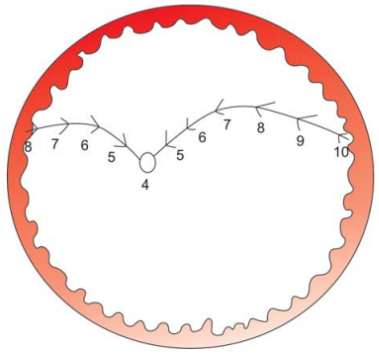


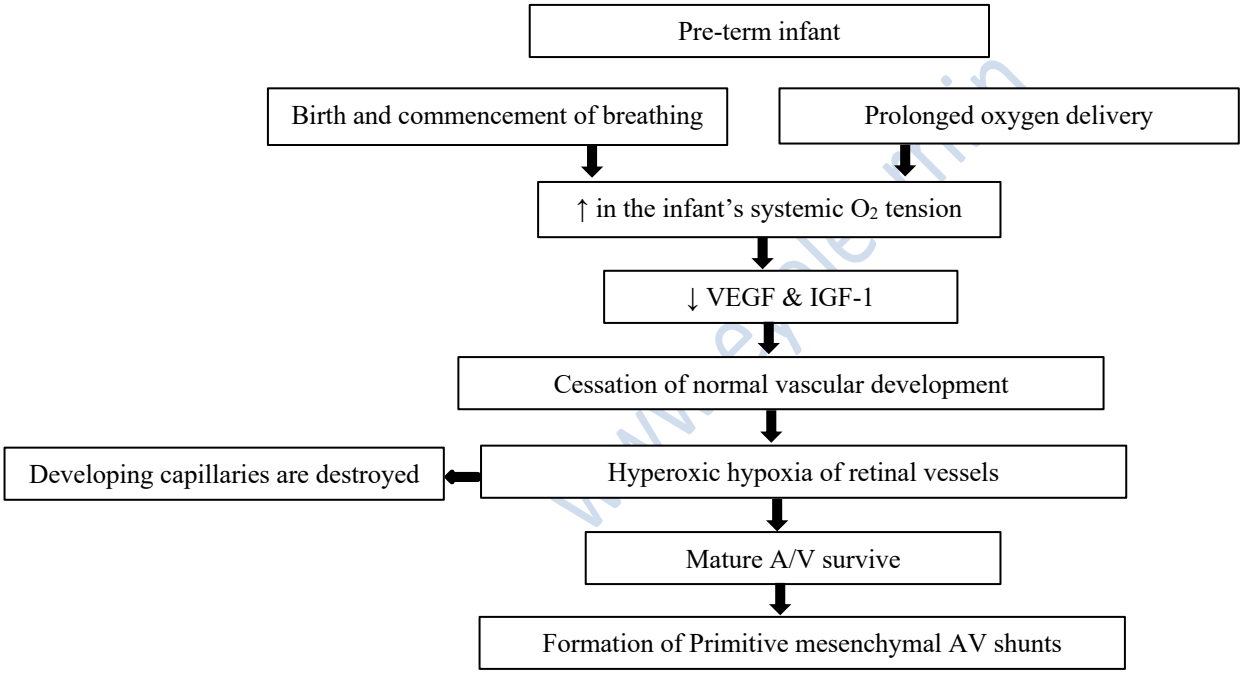
Fig. 18.8.1: Schematic diagram showing retinal vascular development. Vessels arise from optic disk at 4 months of gestation and reach nasal ora at 8 months of gestation and temporal ora at 10 months (after birth)

II. Pathogenesis of ROP

- Much has been learnt about the pathogenesis of ROP from experimental studies and has been supported by clinical data.
- A simplified view of events described by Flynn and coworkers is presented here.
- Although the current understanding of the pathophysiology of ROP is incomplete, it is thought of as a 2-phase process.

- **The first phase**

i. It is characterized by the cessation of normal vascular development.
ii. Cessation occurs largely as the result of a decrease in the level of hormones and growth factors governing normal vascular development in the eye, such as VEGF & IGF-1.
iii. The cause for the drop in expression and levels of these growth factors is thought to be an increase in the infant's systemic oxygen tension that occurs following birth and commencement of breathing by the infant or if subjected to continuous and prolonged oxygen, the developing retinal vessels undergo hyperoxic reflex vasoconstriction.
iv. This is also referred to as hyperoxic hypoxia.
v. The mature retinal arteries and veins developed till now survive this insult.
vi. However, the developing capillaries at junction of vascular and avascular retina get destroyed. Injury to the endothelium of the developing capillary meshwork is the primary event
vii. In place of developing capillaries, the remaining vascular channels (A+V) form a primitive mesenchymal arteriovenous shunt at the junction of vascular and avascular retina and represents the pathognomomic lesion of acute ROP



- **The second phase**

i. It begins at approximately 31–34 weeks' postconceptional age.
ii. It is characterized by an abundance of growth factors secreted by the ischemic retina-particularly VEGF and IGF-1, among others-as well as by oxidative damage to endothelial cells, which leads to disorganized vascular growth.
iii. During this acute phase of ROP, the hypoxic peripheral retina releases angiogenic factors that have potential to derive both normal and abnormal neovascularization.
iv. 90 % of times, the mesenchymal shunt regresses with normal vascular channels forming inside the retina and reaching the temporal ora serrata.
v. In progressive ROP, primitive endothelial cells in the mesenchymal shunt proliferate and erupt through internal limiting membrane, growing on surface of retina and ultimately into the vitreous.
vi. Hence, we see various stages of ROP depending on the extent of abnormal angiogenesis.
vii. Initially, this process causes the formation of a visible tissue ridge (ROP stages 1, 2).
viii. As the disease progresses, vascular growth proliferates into the vitreous cavity (ROP stage 3).
ix. Eventually, growth factor and hormone shifts cause involution of the blood vessels with cicatricial contraction, which can lead to tractional retinal detachment (ROP stages 4, 5).

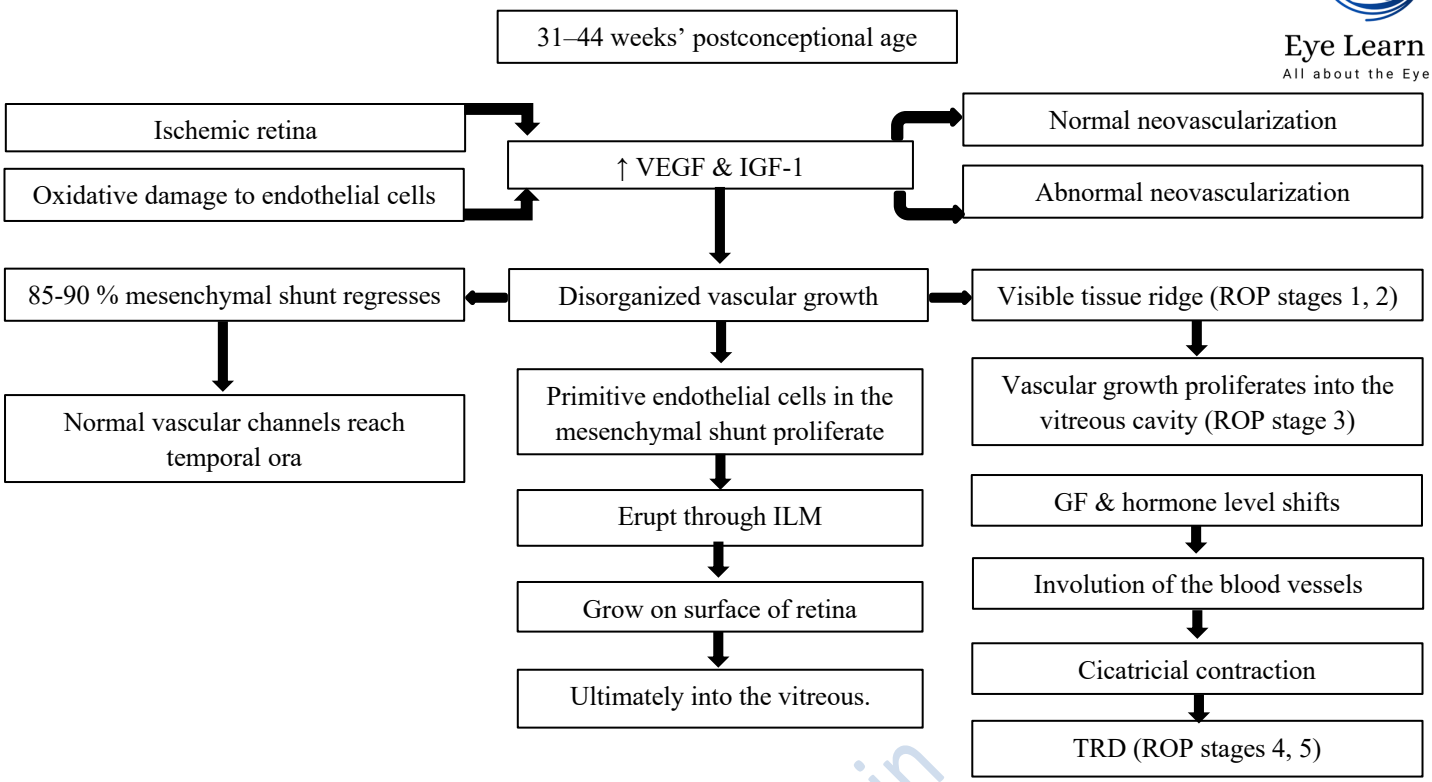


Table 25-1 Interaction Between VEGF and IGF-I in Development of ROP

Phase I
- Occurs at 22–30 weeks' gestational age
- Retina is hyperoxic (relative to intrauterine oxygen levels)
- VEGF levels are low
- Retinal blood vessels stop growing; this arrested growth is
  - worsened by high oxygen levels
  - worsened by low levels of IGF-I
  - correlated with poor weight gain

Phase II
- Occurs at 31–44 weeks' gestational age
- Avascular retina is hypoxic
- VEGF levels rise (due to the hypoxic avascular retina)
- Neovascularization occurs

Treatment of ROP
- Laser therapy destroys hypoxic avascular retina, so VEGF levels fall
- Bevacizumab inhibits VEGF

- **TRD**
  i. Active neovascularization with shunting of blood flow is associated with dilation and increased tortuosity of the retinal vessels posteriorly.
  ii. A notable finding in active disease is increased and abnormal terminal arborization of retinal vessels as they approach the shunt or ridge.
  iii. In addition, microvascular abnormalities (eg, microaneurysms, areas of capillary nonperfusion, and dilated vessels) may be visible posterior to the ridge.
  iv. In the vasoproliferative phase, new vessels varying widely in size and extent arise from retinal vessels just posterior to the shunt.
  v. These new vessels can induce contracture of the firmly attached vitreous gel, which results in progressive tractional retinal detachment.
  vi. Vitreous hemorrhage can occur in stages 3–5, as can exudative retinal detachment.

- **Natural Course**
  i. Although the systemic and/or local tissue factors that influence regression and progression of ROP are not known, the time course is predictable.
  ii. ROP is a transient disease in the majority of infants, and spontaneous regression occurs in 85% of eyes.

iii. The more peripheral the neovascularization and the smaller its size and extent on the retina, the better is the outlook for spontaneous regression with minimal scarring.
iv. The initial clinical sign of regression is the development of a clear zone of retina beyond the shunt, followed by the development of straight vessels crossing the shunt and an arteriovenous feeder extending into the avascular retina.

- **Foos Concept**

i. Foos has given the concept of vanguard and rearguard to describe the cellular components of the developing retina and suggested a pathogenetic mechanism of ROP based on it.
ii. According to him, the vanguard or the anterior component contains spindle cells which play a role in nourishing the immature retina.
iii. The rearguard contains primitive endothelial cells.
iv. As the retina matures, the endothelial cells form cords which later lumenize and form primordial capillaries of the retina.
v. It is from the rearguard that the neovascularization of ROP develops

4. **Risk factors**

- Gestational age and weight at birth, 2 of the strongest risk factors for ROP, are inversely correlated with the development of ROP

i. Prematurity

- Greatest risk factor for ROP is prematurity itself.
- Prematurity in terms of both gestational age (<32 wks) and birth weight (<1250 gms) is the biggest risk factor for ROP.
- Risk of ROP is the inversely related to gestational age and birth weight.25
- The "smallest and sickest" infants are at greatest risk. However, prematurity is not the only factor as more mature infants (>1250 gm) are developing severe ROP in developing countries.

ii. Oxygen Therapy

- ROP has been correlated with duration of oxygen exposure but not with arterial oxygen levels.
- Prolonged oxygenation has been reported as risk factor for ROP.
- Different modes of oxygen delivery including mechanical ventilation and continuous positive airway pressure (CPAP) have been reported as risk factor.
- Use of supplemental oxygen is a risk factor, as shown in the 1960s when ROP markedly decreased (and death and cerebral palsy markedly increased) with the severe limitation of oxygen for premature infants.
- However, the exact role that oxygen plays is still not well understood.
- Despite many studies, the optimal amount of supplemental oxygen to give to premature infants to promote normal development and limit ROP remains elusive.
- Even though some studies have shown that maintaining oxygen saturation levels at a lower level than was customary prior to 34 weeks' corrected age can lower the incidence of ROP, it is unclear whether the benefit is significant enough to warrant the systemic risks to the infant.

iii. Low early levels of IGF-I

- Low early levels of IGF-I are associated with slower-than-expected weight gain and more severe ROP.
- The weight, IGF-I, neonatal ROP (WINROP) algorithm (Premacure AB, Uppsala, Sweden) is a surveillance system that identifies babies at high risk for development of type 1 ROP.
- This algorithm—which uses the gestational age, serum IGF-I levels, and tracking of the infant's weight gain—may allow for targeted, cost-effective screening of infants at high risk for severe ROP.

iv. Other Reported Neonatal Risk Factors

- These associations require further investigations to identify causal relationships.

1. Cyanosis 2. Apnea 3. Intraventicular hemorrhage 4. Hyaline membrane disease 5. Neonatal hyperbilirubinemia 6. Exchange transfusion	**7. Anemia** **8. Blood transfusion** **9. Sepsis** 10. Patent ductus arteriosus 11. Parenteral antibiotic administration.

- It may be stressed however that the combination of one or more of the above reported factors may be important, which need to be identified by prospective studies.
- This may help in identifying infants at risk for disease.
- Risk factors reported in Indian setting include oxygen therapy, anemia, blood transfusion and sepsis.
- Infusion of blood products has been reported as risk factor for threshold ROP

iv. Maternal Risk Factors

- Maternal factors reported as risk factors for ROP include. All these factors require further studies

1. Preeclampsia	2. Maternal essential hypertension	3. Diabetes	4. Antihistaminic drug use

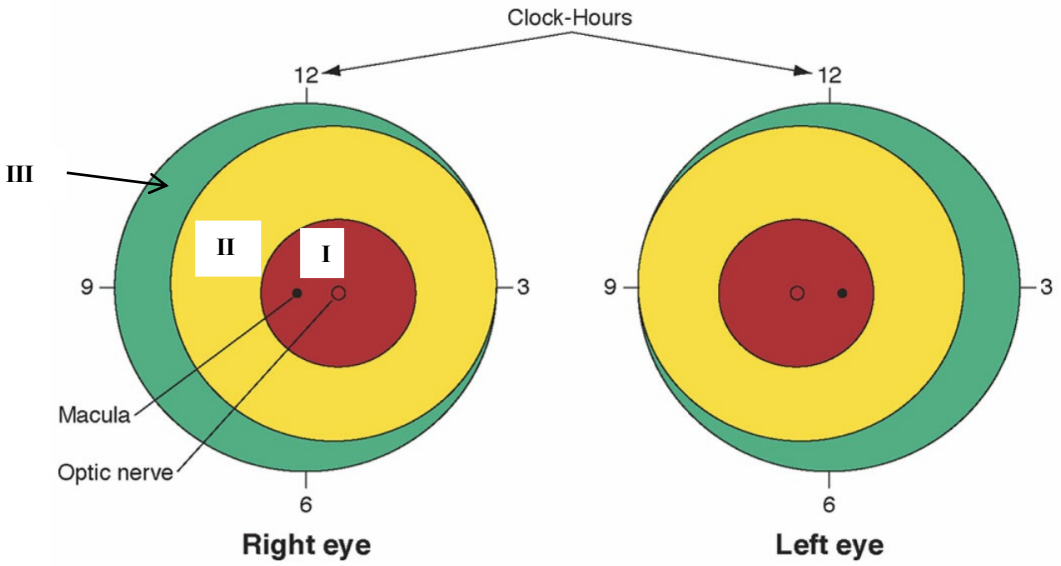
5. Classification of ROP

- International Classification of ROP (ICROP) should be followed universally to document and treat ROP.
- It is a consensus statement of an international group of retinopathy of prematurity experts originally introduced in 1984 and expanded in 1987 and 2005.
- It is based on

Original ICROP	ICROP Revisited in 2005
1. Location of retinal involvement by zone 2. Extent of retinal involvement by clock hour 3. Stage or severity of retinopathy at the junction of the vascularize and avascular retina 4. The presence or absence of dilated and tortuous posterior pole vessels (plus disease)	1. The concept of a more virulent form of retinopathy observed in the tiniest babies (aggressive, posterior ROP), 2. A description of an intermediate level of plus disease (pre-plus) between normal posterior pole vessels and frank plus disease, and 3. A practical clinical tool for estimating the extent of zone- I.

A. Zones

- The anteroposterior location of the retinopathy has been divided into 3 concentric zones of retinal involvement.
- Each zone is centered on the optic disc.
- Zone I- As a practical approach, the approximate temporal extent of zone I can be determined by using a 25- or 28 diopter (D)–condensing lens. By placing the nasal edge of the optic disc at one edge of the field of view, the limit of zone I is at the temporal field of view.
- Any ROP that is continuous and circumferential must by definition fall into 1 of these 2 posterior zones.
- By convention, zones II and III are considered to be mutually exclusive.
- Retinopathy of prematurity should be considered to be in zone II until it can be determined with confidence that the nasal-most 2 clock hours are vascularized to the ora serrata.
    - The more posterior the zone at the time of recognition of the disease, the more non perfused retina there is and thus the moreworrisome the prognosis.



Zone I (Posterior pole)	Is a circle centered on the disk whose radius is twice the distance from the disk to the center of the macula It subtends an arc of about 60
Zone II	Is a circle which extends from the edge of Zone I to the nasal ora serrata (At the 3- O'clock position in the right eye and the 9- O'clock position in the left eye).
Zone III	Is the residual temporal crescent of retina anterior to Zone II

B. Extent of Disease

- The extent of disease is recorded as hours of the clock or as 30° sectors.

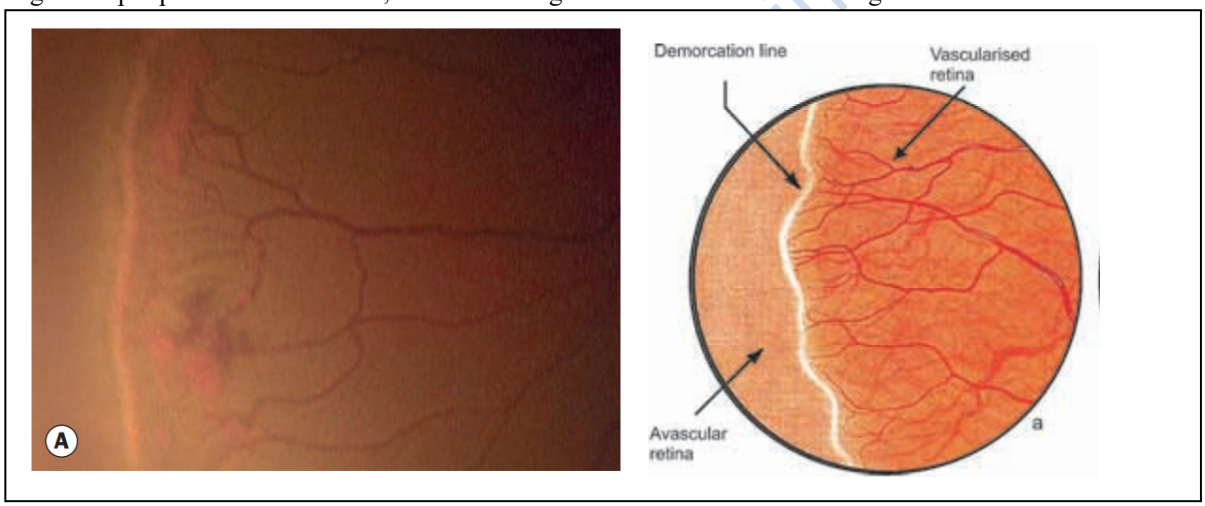
- As the observer looks at each eye, the 3-o'clockposition is to the right and nasal in the right eye and temporal in the left eye, and the 9-o'clock position is to the left and temporal in the right eye and nasal in the left eye.
- The boundaries between sectors lie on the clock hour positions; that is, the 12-o'clock sector extends from 12 o'clock to 1 o'clock.

C. Stage of ROP

Stage 0	**Immature retinal vasculature without pathologic changes**
Stage 1	**Demarcation Line**
Stage 2	**Ridge**
Stage 3	**Extraretinal Fibrovascular Proliferation**
Stage 4A	**Extrafoveal Partial Retinal Detachment**
Stage 4B	**Foveal Partial Retinal Detachment**
Stage 5	**Total Retinal Detachment**

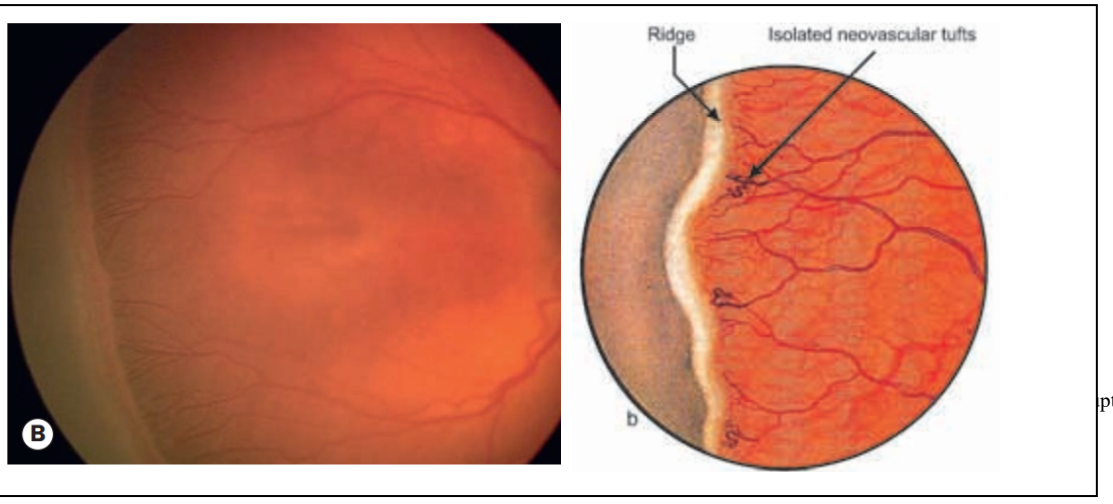
Stage 1: Demarcation Line

- It is a thin but definite flat, tortuous, grey-white line running roughly parallel with the ora serrata.
- It is more prominent in the temporal periphery.
- The demarcation line separates the avascular retina anteriorly from the vascularized retina posteriorly.
- It lies in the plane of the retina and has no volume.
- There is abnormal branching or arcading of vessels leading up to the demarcation line
- Vascular changes can be apparent prior to the development of the demarcation line, such as dilatation rather than
- tapering of the peripheral retinal vessels, but these changes are insufficient for the diagnosis of ROP



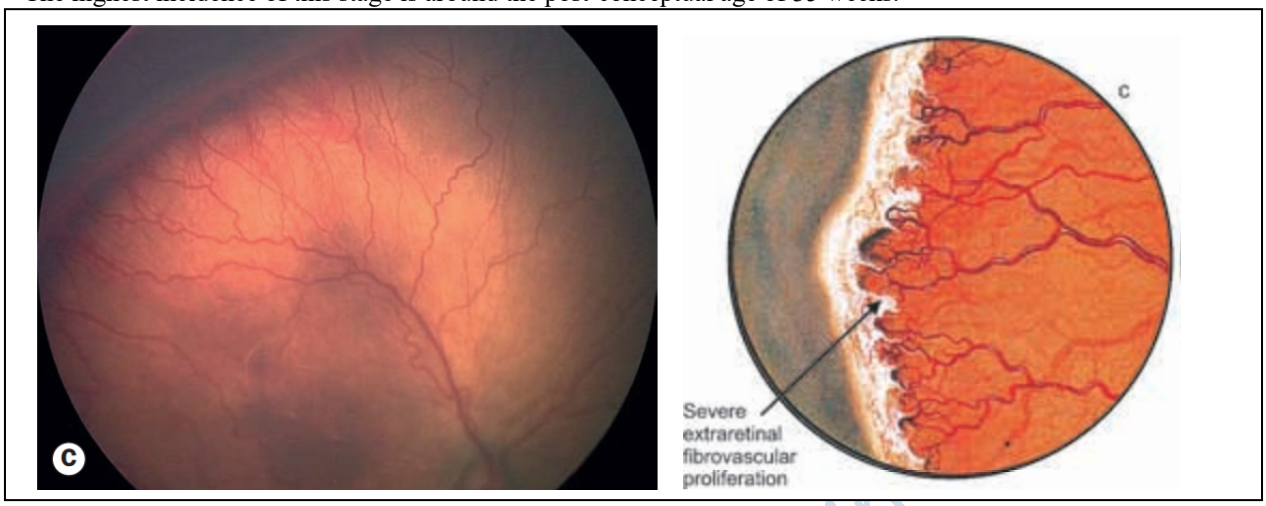
Stage 2: Ridge

- The ridge is the hallmark of stage 2 ROP.
- It arises in the region of the demarcation line, has height and width, and extends above the plane of the retina.
- The ridge may change from white to pink
- Blood vessels may leave the plane of the retina posterior to the ridge to enter it.
- Small isolated tufts of neovascular tissue lying on the surface of the retina, commonly called "popcorn" may be seen posterior to this ridge structure but are not attached to the ridge



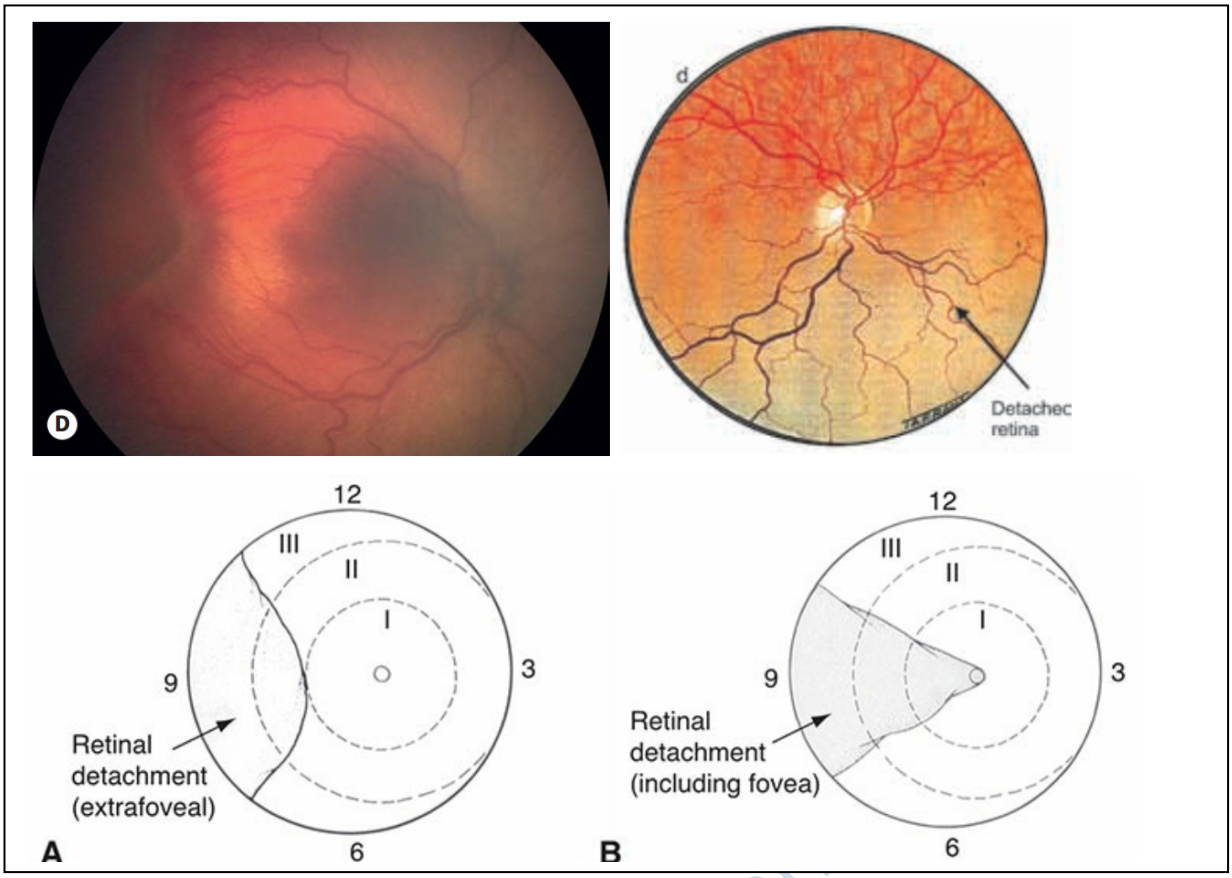
Stage 3: Extraretinal Fibrovascular Proliferation

- In stage 3, extraretinal fibrovascular proliferation or neovascularization extends from the ridge into the vitreous.
- This extraretinal proliferating tissue is continuous with the posterior aspect of the ridge, causing a ragged appearance as the proliferation becomes more extensive.
- The severity of a stage 3 lesion can be subdivided into mild, moderate, or severe depending on the extent of extraretinal fibrovascular tissue infiltrating the vitreous.
- The highest incidence of this stage is around the post-conceptual age of 35 weeks.



Stage 4: Partial Retinal Detachment

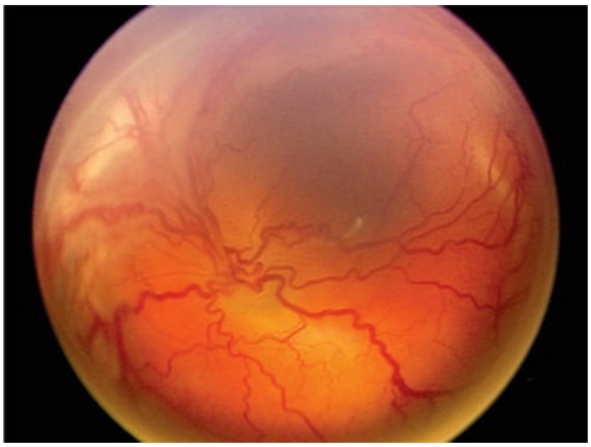
- Stage 4 is divided into extrafoveal (4A) and foveal (4B) partial retinal detachments.
- Stage 4 retinal detachments are generally concave and most are circumferentially oriented.
- Retinal detachments are generally tractional and may occasionally be exudative or combined (tractional and exudative).
- The extent of retinal detachment depends on the number of clock hours of fibrovascular traction and their degree of contraction.
- Typically, retinal detachments begin at the point of fibrovascular attachment to the vascularized retina.
- In progressive cases, the fibrous tissue continues to contract and the tractional retinal detachment increases in height, extending both anteriorly and posteriorly.
- **Stage IVa**:
  i. It is an extrafoveal tractional detachment which is usually present in anterior zone II or zone III
  ii. It has a concave configuration and may be segmental or extend circumferentially for 360 degree, but without involvement of the macula.
  iii. The prognosis is generally good in the absence of posterior extension.
  iv. Less than three clock hours of stage IV, a detachment can be observed because often the fibrovascular membrane separates into the vitreous spontaneously with release of traction.
- **Stage IVb:**
  i. It is partial retinal detachment involving the fovea.
  ii. It extends from the disk and involves zone I extending up to zone II or III.
  iii. Visual prognosis becomes poor once fovea gets involved



Stage 5: Total Retinal Detachment

- Retinal detachments are generally tractional and may occasionally be exudative. They are usually funnel shaped.
- The funnel is divided into anterior and posterior parts.
- Various configurations of funnel in order of frequency are:

Anterior	Posterior	Remark
Open	Open	The detachment has a concave configuration and extends to the optic disc. Most common
Narrow	Narrow	The detached retina is located just behind the lens
Open	Narrow	-
Narrow	Open	Least common



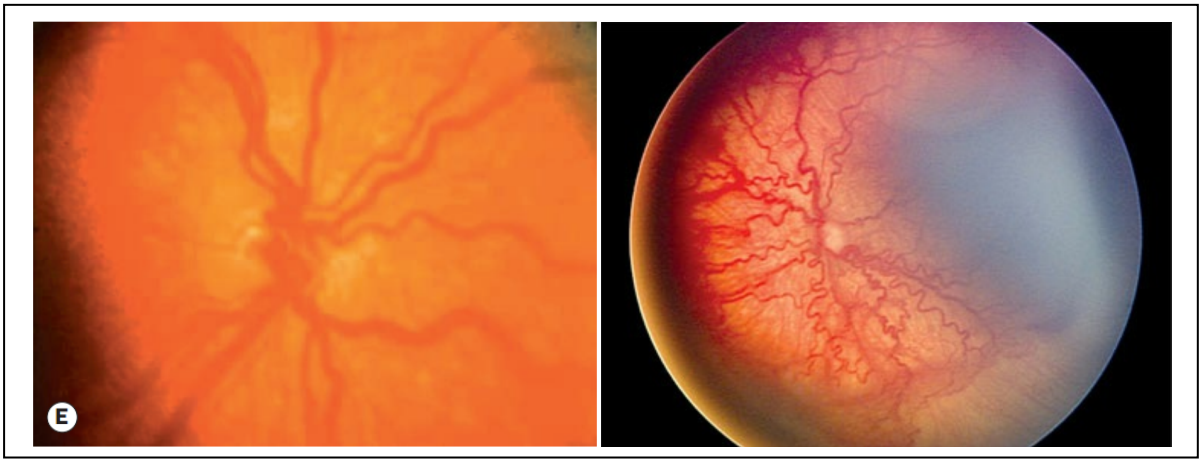
- Additional features seen in stage V ROP are

1. Retrolental fibrovascular tissue 2. Adherence of detached retina to posterior lens capsule.	**Anterior segment changes** 1. Acute angle closure, 2. Corneal edema,	3. Iris atrophy, 4. Posterior synechiae Ectropion

Plus disease

- It refers to increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels in at least two quadrants.
- It may increase in severity to include
  - i. Iris vascular engorgement
  - ii. With extension onto anterior lens surface (tunica vasculosa lentis)
  - iii. Poor pupillary dilatation (rigid pupil),
  - iv. Vitreous haze.
- All these signs together in the original classification were referred to as plus disease.
- Subsequent multicentered clinical trials have used a "standard" photograph to define the minimum amount of vascular dilatation and tortuosity required to make the diagnosis of plus disease.

- This definition has been further refined in the later clinical trials in which the and tortuosity are present in at least 2 quadrants of the eye. A + symbol is added to the ROP stage number to designate the presence of plus disease.



Preplus disease

- Pre-plus disease is defined as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal.
- Over time, the vessel abnormalities of pre-plus may progress to frank plus disease as the vessels dilate and become more tortuous.
- The presence of pre-plus disease can be noted beside the stage, for example, stage 2 with pre-plus. disease

Aggressive posterior ROP (APROP)

- An uncommon, rapidly progressing, severe form of ROP is designated APROP by the revisited ICROP classification in 2005.
- Previously referred as "Type II ROP" and "Rush disease" "fulminate ROP" but was not included in ICROP.
- This is a fulminant type of ROP characterized by severe plus disease with a flat brush like proliferation with vascular loops and hemorrhages.
- If untreated, it rapidly progresses to stage 5 ROP without passing through intermediate stages sometimes within a few days
- The characteristic features are
  i. Its posterior location (most commonly in zone I/ posterior zone II),
  ii. Prominence of plus disease (dilatation and tortuosity in all 4 quadrants),
  iii. And ill-defined nature of retinopathy.
- Because of shunting of vessels in vascularized retina and resultant tortuosity of vessels, it is difficult to distinguish between arterioles and venules.
- Hemorrhages at the junction of vascularized and avascular retina may be present.
- It may appear as a flat network of brush like neovascularization at the deceptively featureless junction between vascular and avascular retina.
- APROP typically extends circumferentially and is often accompanied by a circumferential vessel.
- This ROP occurs in smallest of infants born <30 wks of gestation and requires immediate and aggressive treatment.

Regression of ROP

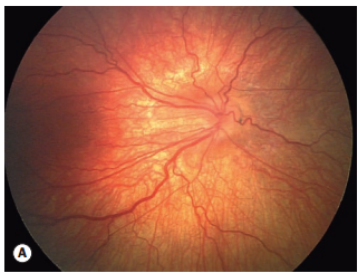
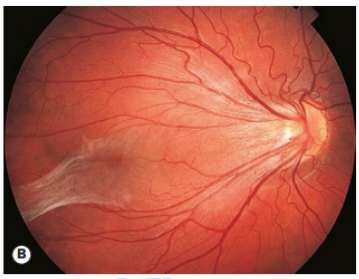
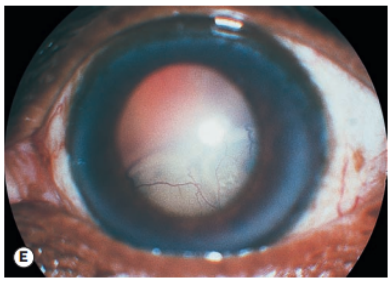
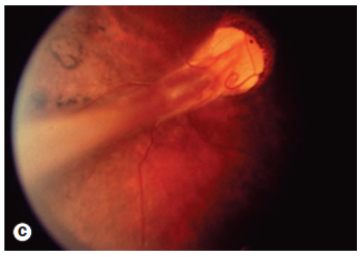
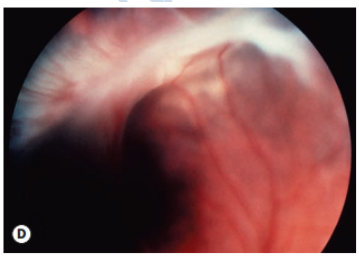
- In most of the cases, ROP regresses spontaneously by a process of involution or evolution from a vasoproliferative phase to a fibrotic phase.
- One of the first signs of stabilization of the acute phase of ROP is failure of the retinopathy to progress to the next stage.15
- The process of regression occurs largely at the junction of vascular and avascular retina as retinal vascularization advances peripherally.
- On serial examinations, the anteroposterior location of retinopathy may change from zone I to zone II or from zone II to zone III.
- The ridge may change in color from salmon pink to white
- Variable changes can be seen in spontaneously involuted ROP depending on severity of initial disease.
- Peripheral changes include abnormally branching or telangiectatic retinal vessels, pigmentary changes, lattice like degeneration, vitreous membranes, localized tractional detachments and even retinal breaks.
- Posterior pole changes include tortuous vessels, narrow temporal arcade, disk drag, macular heterotopia and falciform fold

- Infants with spontaneously regressed ROP may develop myopia, the exact mechanism of which is obscure. It has however been correlated to the initial stage of ROP.
- A pseudoexotropia may develop due to temporal dragging of macula

Myopia, Astigmatism Amblyopia	Strabismus Nystagmus Cataract	Glaucoma Macular pigment epitheliopathy	Tractional retinal detachment Anomalous foveal anatomy Vitreoretinal scarring

Cicatricial disease

- About 20% of infants with active ROP develop cicatricial complications, which range from innocuous to extremely severe.
- The more severe the acute phase of the retinopathy, the more likely involutional changes will be severe as the disease enters the "cicatricial" phase.
- In general, the more advanced or the more posterior the proliferative disease at the time of involution, the worse the cicatricial sequelae.
- Findings range from
  i. Moderate temporal vitreoretinal fibrosis and straightening of vascular arcades
  ii. With 'dragging' of the macula and disc
  iii. Progressing to retrolental fibrovascular tissue
  iv. That can lead to falciform retinal fold formation
  v. And to retinal detachment , sometimes total and known as 'retrolental fibroplasia';
- The latter term has been used synonymously with ROP in the past.
- Secondary angle-closure glaucoma may develop due to progressive shallowing of the anterior chamber caused by forward displacement of the iris–lens diaphragm with anterior synechiae formation.
- Lensectomy and anterior vitrectomy may be tried, but the results are generally poor

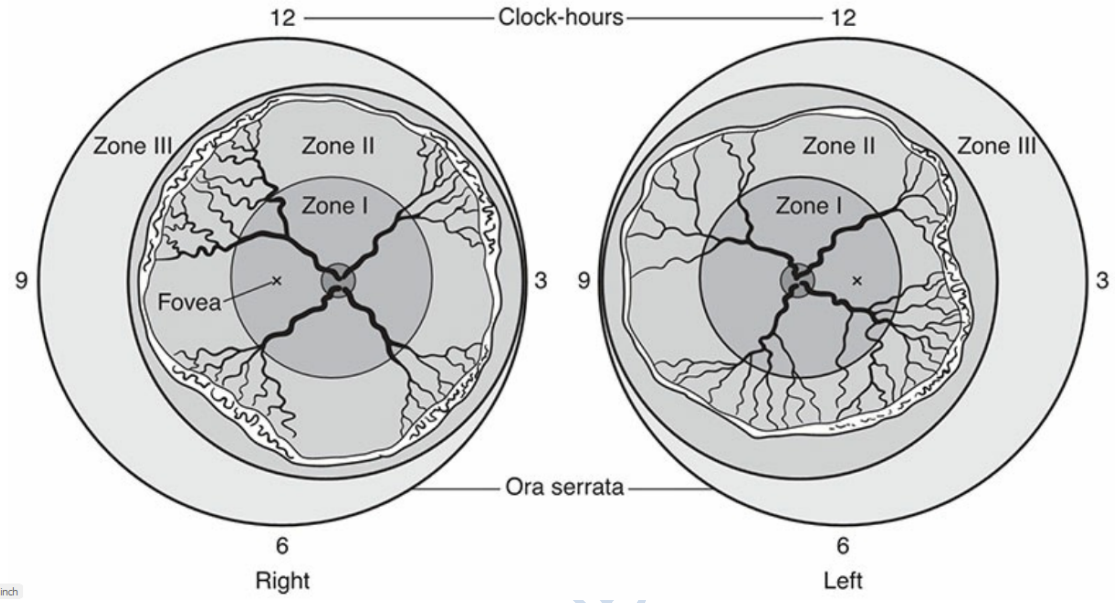






(A) Straightening of vascular arcades; (B) 'dragging' of the disc and macula; (C) falciform retinal fold; (D) retrolental fbrovascular tissue and partial retinal detachment; (E) total retinal detachment

6. Involution Sequelae of Retinopathy of Prematurity	
Peripheral changes	**Posterior changes**
Vascular	**Vascular**
1. Failure of peripheral retinal vascularization 2. Abnormal nondichotomous branching of retinal vessels 3. Vascular arcades with circumferential interconnection 4. Telengiectatic vessels	1. Vascular tortuosity 2. Straightening of blood vessels in temporal arcades 3. Decrease in angle of insertion of major temporal arcade
Retinal	**Retinal**
1. Pigmentary changes 2. Vitreoretinal interface changes 3. Thin retina 4. Peripheral folds 5. Vitreous membranes with or without attachment to the retina 6. Lattice like degeneration 7. Retinal breaks 8. Traction-rhegmatogenous retinal detachment	1. Pigmentary changes 2. Distortion and ectopia of macula 3. Stretching and folding of retina in macular region leading to periphery 4. Vitreoretinal interface changes 5. Vitreous membrane 6. Dragging of retina over optic disc 7. Traction-rhegmatogenous retinal detachment

Threshold disease

- Threshold disease, as characterized in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity.
  i. 5 contiguous clock hours of Extraretinal neovascularization or
  ii. 8 cumulative clock hours of Extraretinal neovascularization in association with plus disease and location of retinal vessels within zone I or II
- Threshold ROP eventually develops in approximately 7% of infants with a birth weight of 1250 g or less.
- Eyes that demonstrate progression undergo a gradual transition from the active to the cicatricial stage of ROP
- Right, 8 cumulative, noncontiguous clock-hours of stage 3 disease. Left, 5 contiguous clock hours of proliferation



Pre-threshold disease

- Prethreshold disease is a term coined by the Early Treatment for Retinopathy of Prematurity (ETROP) study
- It encompasses all zone I and zone II ROP changes, except zone II stage 1 and zone II stage 2 without plus disease, that do not meet threshold treatment criteria.
- It is further divided into high-risk pre-threshold ROP, or type 1 ROP, and lower-risk pre-threshold ROP, or type 2 ROP

Type 1	**Type 2**
Zone I , any stage ROP with plus disease Zone I, stage 3 ROP without plus disease Zone II stage 2or 3 ROP with plus disease	Zone I stage 1 or 2 without plus disease Zone II stage 3 ROP without plus dease
Treat within 72 hours	**observe**

Table 8-1 Descriptive Terminology for Acute Retinopathy of Prematurity

Location

Zone I: posterior retina within a 60° circle centered on the optic nerve

Zone II: from the posterior circle (zone I) to the nasal ora serrata anteriorly

Zone III: remaining temporal peripheral retina

Extent: number of clock-hours involved

Severity

Stage 0: immature retinal vasculature without pathologic changes

Stage 1: presence of a demarcation line between vascularized and nonvascularized retina (Fig 8-1)

Stage 2: presence of a demarcation line that has height, width, and volume (ridge); small, isolated tufts of neovascular tissue lying on the surface of the retina, commonly called "popcorn," may be present (Fig 8-2)

Stage 3: a ridge with extraretinal fibrovascular proliferation that may be mild, moderate, or severe, as judged by the amount of proliferative tissue present (Fig 8-3)

Stage 4: partial retinal detachment
A. extrafoveal
B. retinal detachment including fovea (Fig 8-4)

Stage 5: total retinal detachment with funnel configuration; combinations are listed in order of frequency: top row is the most common and bottom row the least common configuration (Fig 8-5)

Anterior	*Posterior*
Open	Open
Narrow	Narrow
Open	Narrow
Narrow	Open

Plus disease: vascular dilatation (venous) and tortuosity (arteriolar) of posterior retinal vessels in at least 2 quadrants of the eye; iris vascular dilatation and vitreous haze may be present (Fig 8-6)

Table 8-2 Classification of Acute Retinopathy of Prematurity (ROP)

Aggressive posterior ROP (rush disease)

Vascularization ends in zone I or very posterior zone II and is accompanied by plus disease; may progress rapidly

Threshold disease

5 contiguous clock-hours of extraretinal neovascularization
or
8 cumulative clock-hours of extraretinal neovascularization in association with plus disease and location of the retinal vessels within zone I or II

Prethreshold disease

All zone I and zone II changes, except zone II stage 1, and zone II stage 2 without plus disease, that do not meet threshold treatment criteria, and subdivided into type 1 and type 2 disease:

Type 1
zone I, any stage ROP with plus disease, or
zone I, stage 3 ROP without plus disease, or
zone II, stage 2 or 3 ROP with plus disease

Type 2
zone I, stage 1 or 2 ROP without plus disease, or
zone II, stage 3 ROP without plus disease

8. Differential Diagnosis

1. Familial exudative vitreoretinopathy (FEVR)	I –III, FH+ AD, asymmetric in both eyes, temporal retina is avascular in asymptomatic family members, fever- birth-10 yrs., NV changes progress over several years
2. Persistent hyperplastic Primary vitreous (PHPV)	U/L, Microcornea, USG attached retina with stalk extending from optic disc to posterior lens surface
3. Norrie disease	X- linked, deaf, MR, Leukocoria in 4-5 weeks ROP V
4. Retinoblastoma	V, asymmetric, FH+ 1/3rd -1/4th , USG- calcification USG- ROP- multiple echoes depending on type of RD
5. Congenital cataract	It must be noted that even in stage V ROP lens is clear
6. Incontinentia pigmenti	dermatological, dental, neurological and ocular abnormalities Post seg – NV and pre-retinal /VH vesicobullous skin
7. Retinoschisis	**8 . Atypical coats**

i. **Familial exudative vitreoretinopathy (FEVR)**:

- FEVR is associated with neovascular disease which may be indistinguishable from acute ROP.
- It may resemble changes seen in stage I to stage III ROP.
- In contrast to ROP in FEVR, there is generally no history of prematurity, a positive family history (autosomal dominant), and is usually asymmetric in both eyes.
- The temporal retina is avascular in older asymptomatic affected family members.
- FEVR changes may be detected anytime from birth to ten years.
- In contrast to ROP, neovascular changes in FEVR may progress over several years.

ii. Retinoblastoma:

- It forms differential diagnosis of stage V ROP.
- The main differentiating feature of retinoblastoma are generally absent history of prematurity, asymmetry with one eye having more advanced retinoblastoma and other with minimal changes and positive family history in one-third to one-fourth of cases.
- Ultrasonography is confirmatory. On ultrasonography, retinoblastoma exhibit posterior mass lesions with calcification.
- In ROP, ultrasonography exhibits complex patterns with multiple echoes behind lens or in the retinal periphery depending on configuration of the retinal detachment.

iii. Persistent hyperplastic primary vitreous (PHPV):

- It is a congenital anomaly which is usually unilateral and occurs in a term infant.
- It is associated with microcornea, dragging of ciliary processes towards the pupil and a grayish white membrane behind the lens.
- In contrast, in retinal detachment of ROP, the vessels are often seen behind the lens.
- On ultrasonography, the retina is usually attached and there is a stalk extending from the optic disk to the posterior lens surface.

iv. Congenital cataract:

- Diagnosis of congenital cataract is usually straightforward and should not be confused with ROP.
- It must be noted that even in stage V ROP lens is clear. Hence, surgeons can perform lens sparing vitrectomy for ROP.

v. **Norrie disease**:

- It is a rare X-Linked disorder presenting in males with Leukocoria, deafness and mental retardation.
- An examination at four to six weeks of age reveals Leukocoria in Norrie disease in contrast to ROP in which leucocoria presents much later due to stage V ROP.

vi. Incontinentia pigmenti:

- It is a multisystem disorder with dermatological, dental, neurological and ocular abnormalities.
- It affects females as males die in utero.

- Most characteristic are posterior segment findings which include peripheral retinal vascular nonperfusion, preretinal neovascularization, preretinal or vitreous hemorrhage and infantile tractional retinal detachment.
- Birth at term and characteristic vesicobullous skin lesions help in differentiating it from ROP

vii. **Atypical coats and retinoschisis**. Prematurity is absent in these cases

9. Screening and examination

- Screening consists of performing dilated funduscopic examinations using binocular indirect ophthalmoscopy
- Screening criterion: Every country has its own criterion for ROP screening.
- The American screening guidelines for ROP 2013

i. Infants with a birth weight of =1500 g or gestational age of 30 weeks or less (as defined by the attending neonatologist)
ii. 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

- However, heavier and older infants need screening in India and other developing countries as they are likely to develop ROP.
- Screening guidelines followed in India are:

i. Infants weighing <2000 gm at birth and/or
ii. Infants <34 wks of gestation
iii. Heavier or older babies may be included depending on the attending risk factors, like prolonged ventilation or oxygen administration, prolonged hospitalization or an adverse respiratory or cardiac disease profile.

Screening Protocol: First Screening

- The first screening examination for ROP should be done after three to four weeks of birth irrespective of gestational age.
- As a simple rule, each premature eligible for screening should receive one examination by day 30 of life.

Procedure for examination

- The examination can be performed in the neonatal intensive care unit, the nursery or in eye OPD.

Pretreatment

- Effort should be made to minimize the discomfort and systemic effect of this examination by pretreatment of the eyes with a topical anesthetic agent such as proparacaine;
- Consideration also may be given to the use of pacifiers, oral sucrose, etc.

Pupillary dilation

- Cyclomydril (0.2% cyclopentolate and 1.0% phenylephrine) is recommended for the examination of premature infants.
- Alternatively, tropicamide 0.5% or 1.0% and phenylephrine 2.5% can be used(AAO)
- Excess drops should be wiped from the medial canthus to avoid absorption and systemic toxicity.
- Dilating drops should be sufficient to allow adequate examination of the fundi,
- But care should be used in using multiple drops if the pupil fails to dilate,
- Because poor pupillary dilation can occur in advanced ROP, tunica vasculosa lentis and plus disease should be suspected.
- And administering multiple doses of dilating drops can adversely affect the systemic status of the infant.
- Overdosage of the drops in such cases should be avoided to prevent toxicity.

IDO

- Retinal screening examinations performed after pupillary dilation by using binocular indirect ophthalmoscopy with a lid speculum and scleral depression (as needed) to detect ROP
- Sterile instruments should be used to examine each infant to avoid possible cross-contamination of infectious agents.
- A binocular indirect ophthalmoscope with a small pupil device and +20 or +28 D lens is used.
- The anterior segment is viewed first with the 20 D magnification for the presence of tunica vasculosa lentis.
- The oculocephalic reflex is used by rotating the infants' head to view the required periphery of the retina.
- A pediatric eye speculum may be used with infant scleral depressor or a simple wire vectis to rotate the globe and view the retinal periphery
- One examination is sufficient only if it unequivocally shows the retina to be fully vascularized in both eyes.
- A nurse should be present for examinations in the neonatal intensive care unit because the infant may experience apnea and bradycardia during examination.
- If an examination must be postponed, the postponement and medical reason should be documented in the patient's medical record.

- Retinal examinations in preterm infants should be performed by an ophthalmologist who has sufficient knowledge and experience to identify accurately the location and sequential retinal changes of ROP.
- The International Classification of Retinopathy of Prematurity Revisited should be used to classify, diagram, and record these retinal findings at the time of examination.

The initiation of acute-phase ROP screening

- 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.
- This knowledge has been used previously in developing a screening schedule.
- Table 1 was developed from an evidence-based analysis of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity natural history data and confirmed by the Light Reduction in ROP Study, which was conducted a decade later.
- It represents a suggested schedule for the timing of the initial eye examinations based on postmenstrual age and chronologic (postnatal) age to detect ROP before it becomes severe enough to result in retinal detachment while minimizing the number of potentially traumatic examinations.
- Although Table 1 provides a schedule for detecting ROP potentially damaging to the retina with 99% confidence, it should be appreciated that infants born before 25 weeks' gestational age should be considered for earlier screening on the basis of severity of comorbidities
- (6 weeks' chronologic age, even if before 31 weeks' postmenstrual age to enable earlier identification and treatment of aggressive posterior ROP [a severe form of ROP that is characterized by rapid progression to advanced stages in posterior ROP] that is more likely to occur in this extremely high-risk population).

Timing of First Eye Examination Based on Gestational Age of Birth		
Gestational Age at Birth, wk	**Age at Initial Examination, wk (Postmenstrual)**	**Age at Initial Examination, wk (Chronologic)**
22[a]	31	9
23[a]	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
Older gestational age, high-risk factors[b]		4
Shown is a schedule for detecting prethreshold ROP with 99% confidence, usually before any required treatment. [a] This guideline should be considered tentative rather than evidence-based for infants with a gestational age of 22 to 23 wk because of the small number of survivors in these postmenstrual-age categories. [b] Consider timing based on severity of comorbidities.		

Follow-up

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

Recommended intervals of follow-up eye examinations for ROP without plus disease	
1-Week or Less Follow-up	**2 Week 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	• Stage 1 ROP: zone II • Immature vascularization: zone II—no ROP • Unequivocally regressing ROP: zone II
1-2 Week Follow- up	**2- 3 Week Follow- up**
• Immature vascularization; posterior zone II • Stage 2 ROP: zone II • Unequivocally regressing ROP: zone I	• Stage 1 or 2 ROP: zone III • Regressing ROP: zone III

The conclusion of acute retinal screening examinations

- It should be based on age and retinal ophthalmoscopic findings.
- Findings that suggest that examinations can be terminated include the following:
  i. Zone III retinal vascularization attained without previous zone I or II ROP (if there is examiner doubt about the zone or if the postmenstrual age is less than 35 weeks, confirmatory examinations may be warranted);
  ii. Full retinal vascularization in close proximity to the ora serrate for 360°-that is, the normal distance found in mature retina between the end of vascularization and the ora serrata. This criterion should be used for all cases treated for ROP solely with bevacizumab;
  iii. Postmenstrual age of 50 weeks and no prethreshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present; or
  iv. Regression of ROP (care must be taken to be sure that there is no abnormal vascular tissue present that is capable of reactivation and progression in zone II or III).

Fundus Photographic Screening of ROP

- Ultra-wide-angle (120°) fundus photography of premature infant eyes is very useful, both to document the findings and to use in fundus photographic screening.
- Remote screening of photographic fundus images has established itself as an efficient and cost-effective method for screening premature infants for ROP.
- A significant advance in screening for ROP is the introduction of wide field digital fundus photography using the Ret-Cam.
- The image capture unit is a palm-sized digital color fundus camera, using fiber optics specifically designed for the visualization of the retina of premature infants.
- The camera system provides an immediate wide-angle view of 130° and also produces real-time images on a computer monitor.
- This video capture technique provides the operator a “dynamic image” of the premature retina and facilitates capturing only those images which are desired.
- Pilot studies have shown that remote interpretation of wide-angle digital retinal images obtained by Ret-Cam may have adequate sensitivity and specificity to identify cases of severe ROP that warrant ophthalmologic referral for treatment.
- Indirect ophthalmoscopy still remains the gold standard examination for screening of ROP.
- However, Ret-Cam has two important implications. First, photodocumentation of ROP and monitoring the response to laser treatment and second, it has opened the gateway for mass tele screening at a remote location by a technician or nurse in developing countries where trained manpower is a constraint.
- The images can be immediately sent to an ophthalmologist trained, in ROP, available at a distant location, for interpretation and advice regarding treatment
- A study by the Photographic Screening for Retinopathy of Prematurity (Photo-ROP) Cooperative Group concluded that remote interpretation of weekly digital fundus images was a useful adjunct to conventional bedside ROP screening by indirect ophthalmoscopy.
- The study also concluded that because of limitations of image quality in some cases, there continued to be a need for the availability of an ophthalmologist skilled at examining premature infant eyes.
- In addition, the study established a definition of clinically significant ROP, the presence of which warrants evaluation by an ophthalmologist for assessment and possible treatment

10. Management

The Era of Cryotherapy

- Prior to introduction of laser for ROP, cryotherapy was being used to ablate the peripheral avascular retina.
- Such a treatment was based on the multicentric trial CRYO-ROP study which introduced the concept of threshold ROP.51
- Threshold ROP meant a 50 percent risk of developing retinal detachment.
- Cryotherapy used to be applied to avascular retina when disease reached threshold stage.
- Use of retinal cryoablation is now rare (in the United States), but the technique may still have a role in the treatment of eyes with media opacities or persistent tunica vasculosa lentis, or when a laser is not available.
- Treatment should be performed in conjunction with pediatric consultation and with systemic monitoring because respiratory or cardiorespiratory arrest can occur in up to 5% of treated infants.
- Use of systemic analgesia is also advisable to minimize stress and risk to the infant.
- Some neonatologists prefer that infants undergo treatment with general anesthesia in an operating room.
- With introduction of laser treatment of ROP, both Cryotherapy and CRYO-ROP guidelines are no longer used

- In 1988, **the Cryotherapy for ROP study**
- The largest prospective randomized control trial of retinal ablative therapy for ROP was designed in 1985 to evaluate the safety and efficacy of cryotherapy.
- Results of this study at a follow-up of 5.5 years demonstrated that ablation of avascular anterior retina in ROP eyes with threshold disease reduced by approximately half the incidence of an unfavorable outcome such as macular dragging, retinal detachment, or retrolental cicatrix formation.
- Treatment reduced these sequelae from 47% to 25% at 1 year follow-up, and visual results were shown to parallel anatomical results.
- At 10 years, eyes that received cryotherapy were still much less likely to be blind than untreated control eyes.

Laser Treatment for ROP: Indications, Procedure and Follow-up

- Laser treatment has certain advantages over cryotherapy like
  i. More complete treatment of posteriorly located disease where cryo probe is not accessible,
  ii. No need for general anesthesia
  iii. And an overall good structural and functional outcome.

ETROP

- The current indications for laser are based on multicentric ETROP randomized trial.
- The early treatment for retinopathy of prematurity (ETROP) study was a multicentric randomized trial which showed that early treatment of high-risk prethreshold ROP significantly reduced unfavorable outcome.
- The concept of threshold ROP is no longer used.
- The ETROP trial randomly assigned 1 eye of infants with bilateral, high-risk, prethreshold ROP to receive early ablation of the avascular retina and the fellow eye to receive conventional management according to Cryotherapy for ROP study methods.
- High risk was determined using a computational model based on the natural history cohort of the Cryotherapy for ROP study; this model used demographic characteristics of the infants and clinical features of ROP to classify eyes with prethreshold ROP as high risk or low risk.
- Results- In infants with high-risk prethreshold ROP, earlier treatment was associated with a reduction in unfavorable grating visual acuity outcomes (from 19.5% to 14.5%; P = .01) and a reduction in unfavorable structural outcomes (from 15.6% to 9.1%; P <.001) at 9 months when diode laser was done in high risk prethreshold stage as compared to treatment at threshold.
- The study determined that the clinical categorization of prethreshold eyes into type 1 or type 2 ROP achieved very similar results to the computational model for risk assessment to prethreshold eyes.
- Any eyes meeting the criteria for type 1 ROP should be considered for peripheral retinal ablative treatment, whereas type 2 ROP eyes can be monitored in short intervals and laser ablative treatment considered if they progress to type 1 ROP or threshold ROP.
- The authors of the ETROP study pointed out that the prethreshold treatment algorithm did not take into account all other known risk factors for progression, such as systemic disease, and that clinical judgment is still required for optimal management

Indications

- According to the study, the indications for laser treatment of ROP are high risk ROP (a disease with high risk of progression)

1. Zone I, stage 1-3 ROP with plus disease	3. Zone II, stage 2 or 3 ROP with plus disease
2. Zone I, stage 3 ROP without plus disease	4. Aggressive Posterior ROP

- The number of clock hours of disease may no longer be the determining factor in recommending ablative treatment.
- Treatment should generally be accomplished, when possible, within72 hours of determination of treatable disease to minimize the risk of retinal detachment
- Done using the indirect ophthalmoscope in a confluent or subconfluent scatter fashion to the avascular retina anterior to the ridge

Laser Treatment: Procedure and its Complications

- A written informed consent from parents or legal guardian should always be obtained before treatment.
- Essential to be explained in the consent is the nature of disease, necessity and nature of treatment, chances of disease regression, complications and long-term sequelae.
- The possibility of retreatment, further surgical intervention, need for glasses and long-term follow-up should also be explained.
- Pupillary dilation is achieved in the same manner as for examination.

- Feeds to the infant should be withheld for at least half an hour prior to treatment to avoid regurgitation during the procedure.
- Most preferred mode is to treat the infant under topical anesthesia under monitoring by neonatologist or anesthesiologist.
- General anesthesia is seldom necessary.
- If an infant is incubator dependent, the authors reported that it can be screened and lasered inside the incubator through the sloping walls.
- Laser parameters used through the transparent wall of incubator are similar to conventional treatment.
- A portable infrared diode laser, frequency doubled Nd: YAG laser or an argon green laser can be used for treatment.
- The laser is delivered through laser indirect ophthalmoscope (LIO) delivery system.
- Diode LIO system is most commonly used and preferred worldwide for treatment due to better penetration in eyes with tunica vasculosa lentis (TVL) and vitreous hemorrhage.
- An infant lid speculum, a wire vectis or infant scleral depressor for scleral indentation, and a 20 or 28-diopter aspheric lens for visualization are used during the treatment.
- The power setting of diode laser varies from 300 to 400 mw and duration of 300 to 400 ms.
- The power settings of laser should be kept to a minimum to produce light gray burn.
- The aim of treatment is to ablate the entire avascular retina from the ridge up to the ora serrata in a near confluent burn pattern (less than half burn width apart) getting as close to the edge of the ridge as possible.
- In recent years, there is a trend towards confluent laser treatment.
- A near confluent treatment decreases the rate of progression as compared to less dense laser treatment.
- In cases of APROP (which is characterized by severe plus disease and flat neovascularization in the absence of definite demarcation line or ridge) the peripheral avascular retina is ablated, getting as close as possible to the edge of vascularization.
- While treating these cases, laser spots are delivered in areas enclosed by the flat neovascular loops as these areas appear avascular on examination.
- In cases where pupillary dilation is poor due to severe plus disease or tunica vasculosa lentis (TVL), a sufficient dilation is usually achieved by mechanical pupillary stretching due to scleral indentation during the course of the laser treatment.
- Frequent instillation of topical carboxymethylcellulose eyedrops over cornea provides a clear view for the duration of the procedure.
- After the laser treatment steroid–antibiotic drops are instilled for a week or two to minimize inflammation.

Complications

- Laser photocoagulation for ROP is a safe and effective procedure.
- However, a premature infant is prone to develop apnea during treatment which may require resuscitation and ventilatory support by an attending neonatologist or anesthesiologist.
- Some infants may develop media haze and corneal edema during laser photocoagulation especially in the presence of tunica vasculosa lentis.
- In some cases, it may clear after waiting for some time and keeping the cornea moist with topical carboxymethylcellulose drops.
- In case where it does not clear, laser may be completed the next day.
- Conjunctival chemosis and subconjunctival hemorrhage can develop if excessive scleral indentation is done.
- Preretinal hemorrhage or vitreous hemorrhage may rarely occur during laser treatment.
- Cataract formation is uncommon with diode laser.
- In the horizontal meridia, laser treatment should be applied in a lighter pattern to avoid damage to the long ciliary vessels and nerves.
- Damage to these structures due to intense laser photocoagulation of the avascular retina can uncommonly lead to severe anterior segment ischemia and necrosis. This can result in hypotony and phthisis bulbi.
- Other rarely reported anterior segment complications of laser treatment include hyphema, acute angle closure glaucoma and posterior synechiae

Follow-up after Laser

- The first follow-up is done at 3 days to one week after treatment to ensure that there is no need for additional treatment in areas where ablative treatment was not complete.The clinical response is assessed by:

1. Extent of plus disease (This is first to show regression after a week)	4. Tunica vasculosa lentis
2. Presence of skip areas (i.e. areas missed during first treatment)	5. Any vitreous organization
3. Status of ridge or presence of fibrovascular proliferation	6. Presence or absence of vitreous hemorrhage.

- At one week, if significant plus disease is still present, additional laser may be done if there are skip areas.
- Plus disease without skip areas, prominent ridge or area of fibrovascular proliferation needs to be followed at weekly interval.
- However, if there is significant regression of the plus disease and the ridge, follow-up can be done at two weeks.
- We follow till regression of the disease occurs as defined by complete disappearance of the plus disease and any active neovascular tissue (i.e. ridge or fibrovascular proliferation).
- This usually completes within 6 to 12 weeks following laser.
- At this time, if there is no fibrovascular organization in the vitreous, the infant can be next seen at six months of age.
- However, if there is significant fibrovascular organization in the vitreous, the infant is followed up closely at weekly intervals for development of tractional retinal detachment.
- Less than three clock hours of extramacular detachment (stage IVa) may be observed. Often, the fibrovascular membrane separates into the vitreous cavity, relieving the traction and leading to spontaneous regression of detachment.
- However, if retinal detachment progresses to four or more clock hours of stage IVa or stage IVb (macular detachment) lens sparing vitrectomy is indicated.
- An infant with regression of ROP can be next seen at six months of age for squeal of ROP.
- CRYO-ROP study defines unfavorable outcome at six months as follows:
  1. a posterior retinal fold involving the macula,
  2. a retinal detachment involving the macula, or
  3. Retrolental tissue or mass obscuring the view of the posterior pole.
- Major sequelae include disk drag, narrowing of the temporal arcade and peripheral tractional detachment were significantly correlated with the presence of severe ROP with more clock hours of involvement
- Infants should be also examined for development of myopia, strabismus, anisometropia, amblyopia or nystagmus and should undergo atropine retinoscopy at one year of age.

Outcome after Laser Treatment

Short term outcomes:

- The rate of favorable structural outcomes varies with the stage, zone of disease, pattern of treatment and whether the treatment is done at threshold or before threshold.
- Overall, recent series report 86 to 93 percent favorable outcome for threshold ROP treated with diode.
- The severest of disease is zone I threshold ROP.
- The rate of unfavorable outcome varies from 18 to 44.8 percent for zone I threshold ROP.
- Better results have been reported for prethreshold ROP.
- Studies report 100 percent favorable outcome for prethreshold ROP with diode laser.

Long term visual outcome and sequelae:

- Recent studies report long term visual outcome of eyes treated with diode laser compared with eyes treated with cryotherapy, eyes treated with laser photocoagulation at threshold are 5.2 times more likely to have a 20/50 or better best corrected visual acuity (BCVA) at ten years.
- Another study showed that laser treated eyes with favorable structural outcome have a good long term visual outcome.
- Mcloone et al, reported Goldman perimetry results 11 years after laser and showed a slight constriction of peripheral visual fields compared with untreated subthreshold eyes. This field loss is of little functional significance.
- As regards, the refractive outcome myopia has been reported with variable incidence in infants treated for ROP. 55.2 percent of eyes had myopia of -5 diopter (31.3%) or greater (23.9%) in a recently published series.
- Connolly et al, in a ten year assessment of refractive outcome showed that, the mean spherical equivalent (SE) of eyes treated with laser was –4.48 diopter (D) compared with a mean SE of –7.65 D for eyes treated with cryotherapy.

Surgical Techniques for ROP: Scleral Buckling and Lens Sparing Vitrectomy

- Surgery is indicated for stage IVa detachments greater than three clock hours, stage IVb and stage V ROP
- Eyes undergoing surgical intervention at stage 4A—rather than at later stages 4B or 5—have more favorable outcomes.

Scleral Buckling for ROP

- Scleral buckling has been described for both stage IVa and IVb detachments.
- It involves placement of a single encircling band of 2 mm width for 360°.
- The procedure is done with or without external drainage of subretinal fluid.

- The success rate of scleral buckles is 60 to 75 percent
- Scleral buckling for ROP has certain drawbacks. Scleral buckling procedures may not adequately address vitreous traction.
- Placement of a scleral buckle requires removal of the encircling band to allow normal growth of the eye.
- The division of scleral band is done after reattachment of retina, usually after three months of surgery.
- Unilateral scleral buckling would induce severe myopia, anisometropia (up to 5–9 D), and may lead to amblyopia.
- This may lead to poor functional outcome despite anatomical reattachment.
- Scleral buckling at best is reserved for eyes with predominant peripheral traction.

Lens Sparing Vitrectomy for ROP

- Lens sparing vitrectomy is now preferred over scleral buckling.
- Lens sparing vitrectomy for ROP may be done using two or three ports 20 G, 23 G and 25 G pars plana vitrectomy.
- The most important point is to make sclerotomies 1 mm posterior to the limbus through the pars plicata epithelium.
- The entry should be vertical to avoid hitting the lens.
- Aim of surgery is removal of as much of proliferation as possible.
- In a stage V ROP, layers of proliferation, fibrovascular membranes and adherent vitreous are dissected sequentially with vitrectomy probe and intraocular scissors approaching the retina in the following order:
  i. Ridge/retina to lens/anterior hyaloid face
  ii. Ridge to ridge
  iii. Ridge to optic nerve
  iv. Ridge to vitreous base, and
  v. Circumferential along the ridge.
- It has been successful in fully or partially reattaching the retina in approximately 30% of eyes. Nevertheless, only 25% of retinas in eyes with initial partial or total reattachment after surgery remained fully attached a median of 5 years later.
- Among the patients whose retinas were initially reattached, only 10% eventually have ambulatory vision.
- If a drainage retinotomy is performed or an iatrogenic retinal break occurs during a vitrectomy for ROP, the prognosis for that eye becomes uniformly poor
- The posterior hyaloid often cannot be removed due to firm attachment.
- Peripheral vitreous attachments of the ridge require careful segmentation to prevent iatrogenic retinal breaks. Thus, the ridge is freed of all traction.
- A thorough indirect ophthalmoscopy examination with scleral depression is performed to note any breaks in retinal periphery.
- If no retinal breaks are noted during the procedure, only balanced salt solution is infused.
- If retinal breaks are noted during the procedure fluid gas exchange is done.
- While infusing gas, intraocular pressures should not exceed 20 mm Hg, as higher pressures can close the central retinal artery.
- Breaks should be treated with laser or cryotherapy.
- Perfluoropropane (C3F8) or silicone oil is used as a long-acting tamponade after treatment of the breaks.
- Postoperatively, specific positioning is required after tamponade.
- The development of retinal tears intraoperatively portends a poor prognosis for reattachment.
- In the ETROP study, where both scleral buckling and vitrectomy was used, the structural and functional outcome of retinal detachment owing to ROP was generally poor. Anatomical macular attachment could be achieved in only 33 percent eyes.
- With advances in surgical techniques, surgeons performing LSV have reported higher anatomic success rates in recent series.
- Their results (i.e. a 90% success during the mean follow-up of 1 year) are better than what have been achieved by scleral buckling (60–75%).
- Late identification of disease, lack of prior treatment such as laser or cryo, and higher incidence of narrow funnel configuration portend a poor surgical prognosis.

Anti-VEGF Drugs

- The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) Cooperative Group conducted a prospective, randomized, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3 ROP with plus disease.
- Compared with conventional laser therapy, a statistically significant treatment benefit for bevacizumab was demonstrated for zone I ROP, whereas zone II disease had similar outcomes with either treatment.
- Thus, this study showed a significant structural outcome benefit for zone I eyes compared with laser treatment
- Normal peripheral retinal vascularization continued after treatment with intravitreal bevacizumab, whereas laser therapy led to permanent destruction of the peripheral retina.

- However, recurrence of ROP requiring retreatment occurred a mean of 16 weeks after initial treatment with bevacizumab, which was significantly later than recurrence of ROP in laser-treated eyes (mean of 6 weeks), and late-onset retinal detachments have been reported. Recurrences occurred significantly later with bevacizumab than with laser therapy.
- Therefore, prolonged, close follow-up is essential.
- The study was too small and the follow-up too short to allow proper evaluation of the safety of intravitreal bevacizumab for the treatment of ROP. The use of bevacizumab in eyes previously treated with laser is not recommended.
- There is also concern about the effects of antiangiogenic drugs on the developing vasculature in other areas of the body.
- A reduction in serum VEGF has been demonstrated in infants after intravitreal injections.

11. Counseling and rehabilitation

- Parents should be aware of ROP examinations and should be informed if their child has ROP, with subsequent updates on ROP progression.
- The possible consequences of serious ROP should be discussed when there is a significant risk of poor visual outcome.
- Responsibility for examination and follow-up of infants at risk of ROP must be carefully defined by each NICU.
- If hospital discharge or transfer to another neonatal unit or hospital is contemplated before retinal maturation into zone III has taken place or if the infant has been treated by ablation for ROP and is not yet fully healed, the availability of appropriate follow-up ophthalmologic examination must be ensured, and specific arrangement for that examination must be made before such discharge or transfer occurs.
- If responsibility for arranging follow-up ophthalmologic care after discharge is delegated to the parents, they should be made to understand the potential for severe visual loss, including blindness; that there is a critical time window to be met if treatment is to be successful; and that timely follow-up examination is essential to successful treatment.
- Pediatricians and other practitioners who care for infants who have had ROP, regardless of whether they require treatment, should be aware that these infants may be at risk of other seemingly unrelated visual disorders such as strabismus, amblyopia, cataract, etc.
- Ophthalmologic follow-up for these potential problems after discharge from the NICU is necessary