

**IN THE NAME
OF GOD**

Retinopathy of Prematurity

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ROP
?!



B



Definition

- Retinopathy of prematurity (ROP) was formerly known as retrolental fibroplasia.
- It is a developmental vascular proliferative disorder that occurs in the incompletely vascularized retina of primarily premature infants.
- ROP is one of the most common causes of blindness in children.

Retinopathy of Prematurity

History

- 1941-First described by Terry (retrolental fibroplasia)
- 1952-'retinopathy of prematurity' was first suggested by Heath
- **1984**-The International *Classification of Retinopathy of Prematurity (ICROP)*

Epidemiology

- Incidence of prematurity (**2010 US census**)
 - the preterm birth rate (<37 weeks) -12% of all births
 - the low birth weight rate (<2500 g) - 8% of all births
 - VLBW (<1500 g) birth rate was 1 %

Incidence of ROP-**rising** world wide (American Association for Pediatric Ophthalmology and Strabismus)

- 3.9 million infants born in the U.S. each year
- 14,000 are affected by ROP (0.4%)
- 400-600 infants each year in the U.S. become legally blind from ROP.

ROP

- Originally described as “retrolental fibroplasia” in the early 1940s, owing to (overly?) aggressive oxygen use.
- Nearly disappeared between 1954-1970, when oxygen use severely restricted.
- But now, has returned, secondary to improved neonatal practice of VLBW infants.

Incidence of ROP

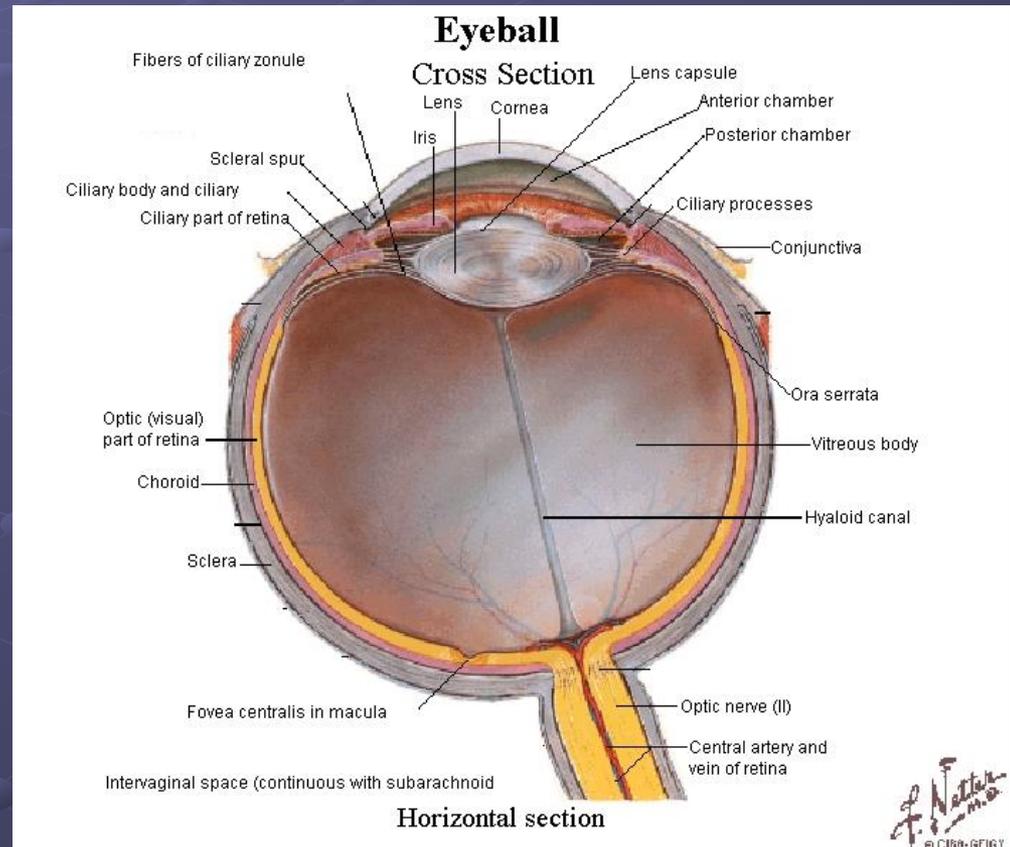
- Hussain et al. (Pediatrics 1999; 104:e26): 950 infants born between 1989 and 1997 had serial eye exams if they were less than 30 wks GA, less than 1300g BW, or required O₂ supplementation.
- Incidence of ROP increased with decreasing GA or decreasing BW.

Pathogenesis

- Not well understood but thought to involve two stages:
 - Stage I: an initial injury (such as hypotension, hypoxia, or hyperoxia) causes vasoconstriction and reduced blood flow to the retina, disrupting the normal process of vascularization.
 - Stage II: Vessels then either resume normal growth or new vessels grow abnormally out from the retina into the vitreous. The abnormal vessels have increased permeability which can result in edema and hemorrhage. Inflammation → fibrous tissue → traction on the retina and detachment. Alternatively, the abnormal vascularization may regress with little residual effect.
- Recently, the interaction between insulin-like growth factor-1 (IGF-1) and VEGF has been studied and proposed to play a role in the pathogenesis of ROP (Hellstrom et al. PNAS 2001; 98:5804).

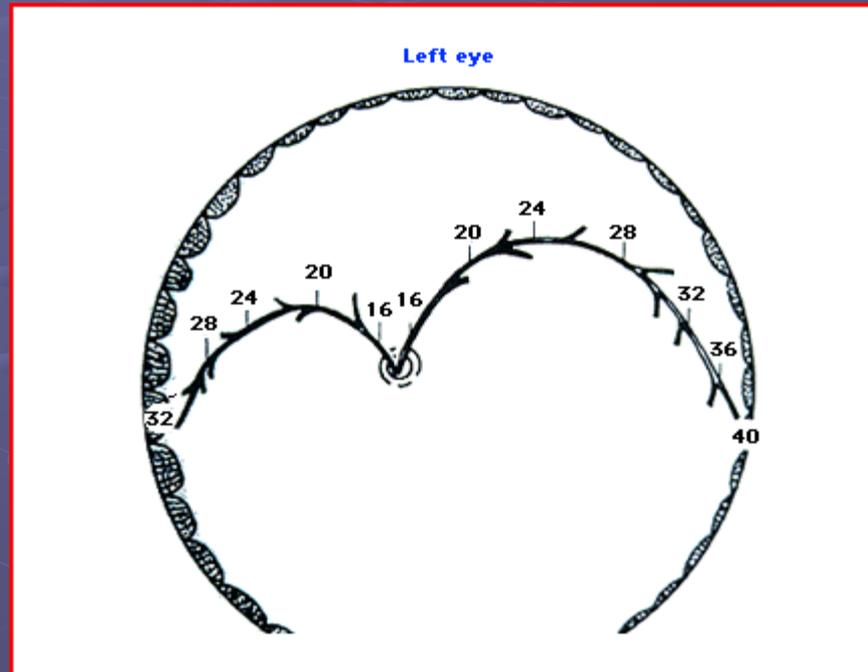
ROP - Pathogenesis

- **16 weeks of gestation - primitive spindle cells gradually grow out over the surface of the retina.**
- **29 weeks -reached ora serrata. At this time these spindle cells start to form blood vessels.**
- **The vessels reach the anterior edge of the retina and stop their progression at about the time of birth.**



Vascular Development of the Eye

Nasal side



Temporal side

Retinal vascularization. Vascularization of the retina begins at approximately 16 weeks gestation at the optic nerve and proceeds peripherally. Retinal vessels reach the ora serrata (the periphery of the eye) on the nasal side at 32 weeks gestation and on the temporal side at 36 to 40 weeks gestation. The numbers in the figure are weeks of gestation.

ROP - Pathogenesis

- **The retina anterior to this line does not have an adequate oxygen supply, and probably exudes chemical signals that stimulate new vessel growth. As more new vessels grow in response to the chemical signals, they form arterio-venous shunts at the location of the barrier on the surface of the retina. This shunt gradually enlarges, becoming thicker and more elevated. The new vessels are accompanied by fibroblasts, which produce fibrous scar tissue.**
- **When this scar tissue contracts, it pulls on the retina and produces a traction retinal detachment.**

Role of IGF-1 and VEGF in the pathogenesis of ROP

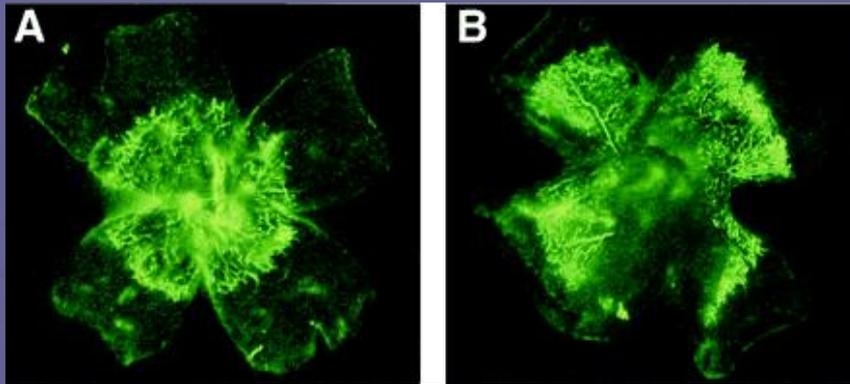


Fig. 1. Effect of IGF-1 inhibition on vascular growth. Flat-mounted whole retina shows that, in IGF-1^{-/-} mice (A), there is less progression of vascular development (bright area) compared with IGF-1^{+/+} littermate controls (B).

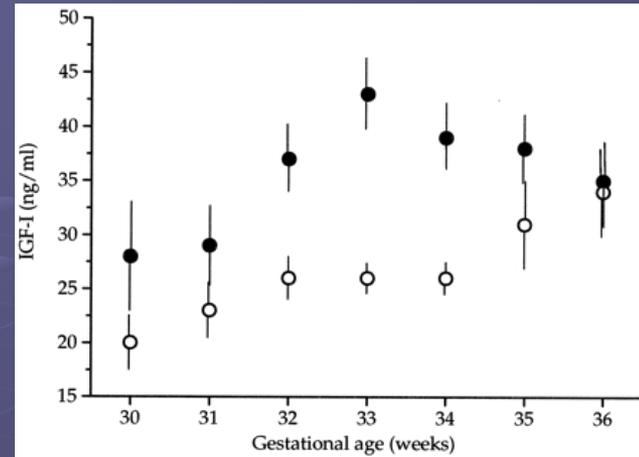


Fig. 3. Mean serum IGF-1 at matched gestational ages in infants with and without ROP. The mean IGF-1 level for infants with ROP (○) and without ROP (●) is shown vs. gestational age. (Bars = SEM.)

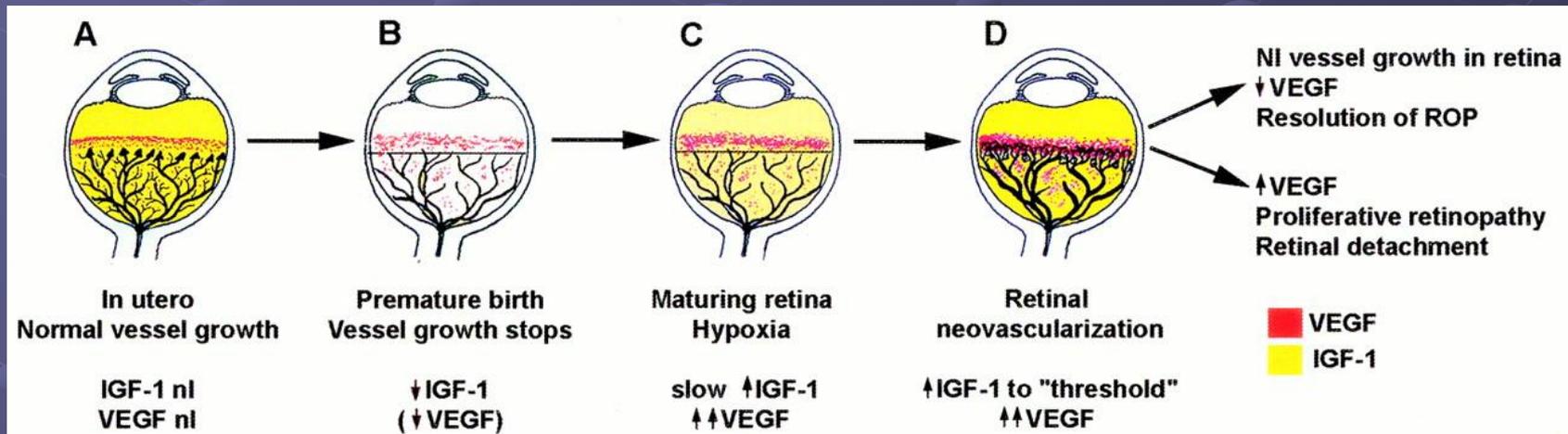


Fig. 5. Schematic representation of IGF-1/VEGF control of blood vessel development in ROP.

ROP - Risk Factors

● OTHER

Indomethacin

Elevated blood carbon dioxide levels

Anemia

Blood transfusions

IVH

RDS

Chronic hypoxia in utero

Multiple spells of apnea or bradycardia

Mechanical ventilation

Seizures

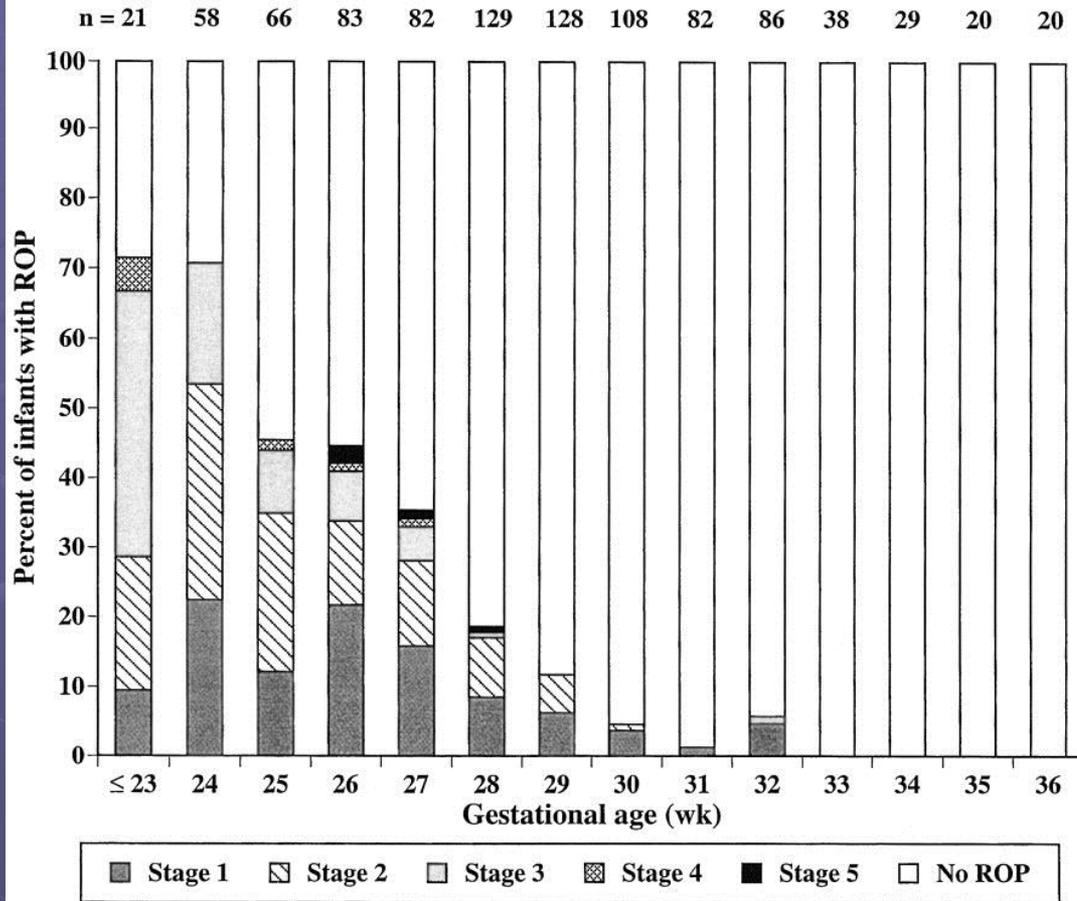
RISK FACTORS

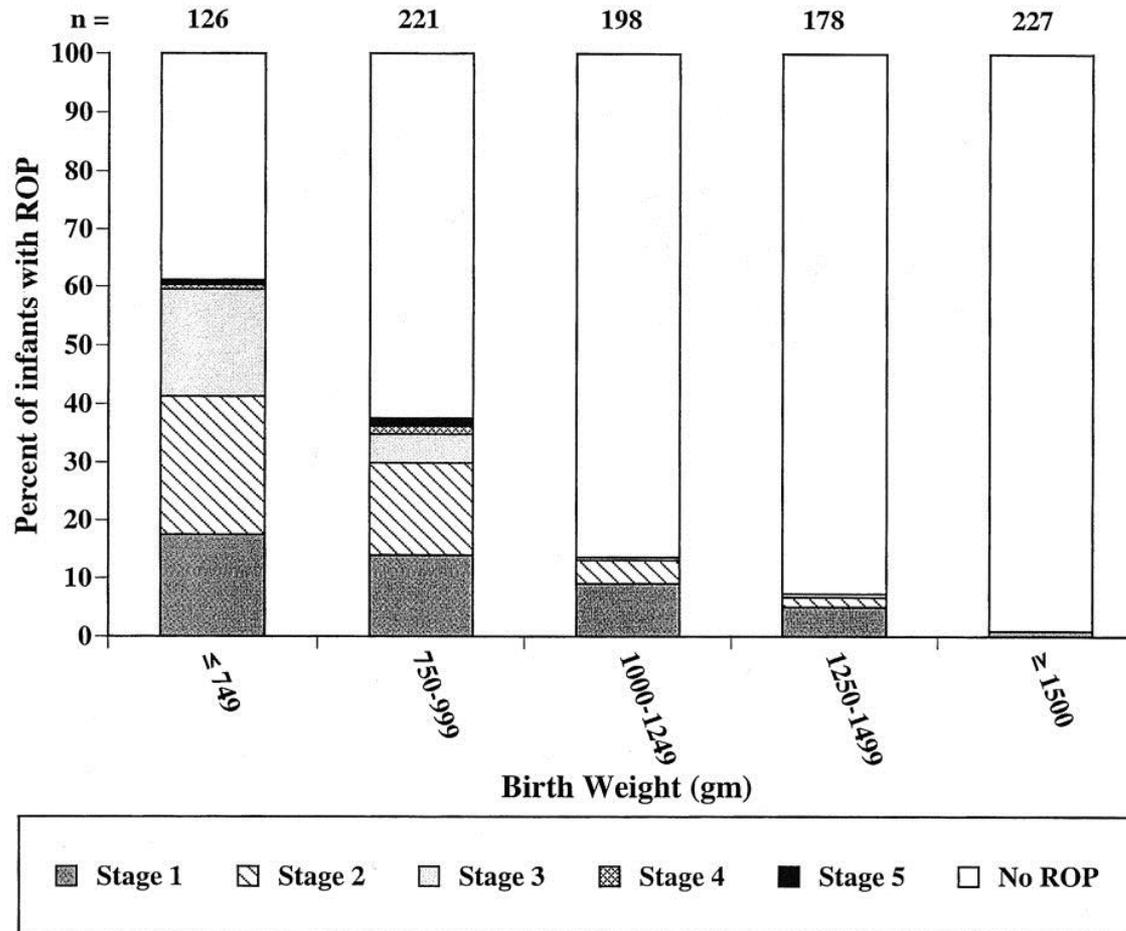
| | |
|---|---|
| | |
| Low gestational age – single most important risk factor | |
| Low birth weight Poor postnatal weight gain/delay in return to B.wt in 14 days | Mechanical ventilation Lability in oxygen requirement(hypoxia-hyperoxia) Prolonged oxygen exposure Hypercarbia |
| Males>Females | IVH |
| Anemia Blood transfusion(HbA-> more oxygen delivery) | Exposure to light |
| | |

Known or Suspected Risk Factors

- Prematurity (most significant)
- LBW
- Assisted ventilation longer than one week
- Surfactant therapy
- High blood transfusion volume
- Sepsis
- IVH
- Bronchopulmonary dysplasia
- Elevated arterial oxygen tension

INCIDENCE OF ROP BY GESTATIONAL AGE AT BIRTH



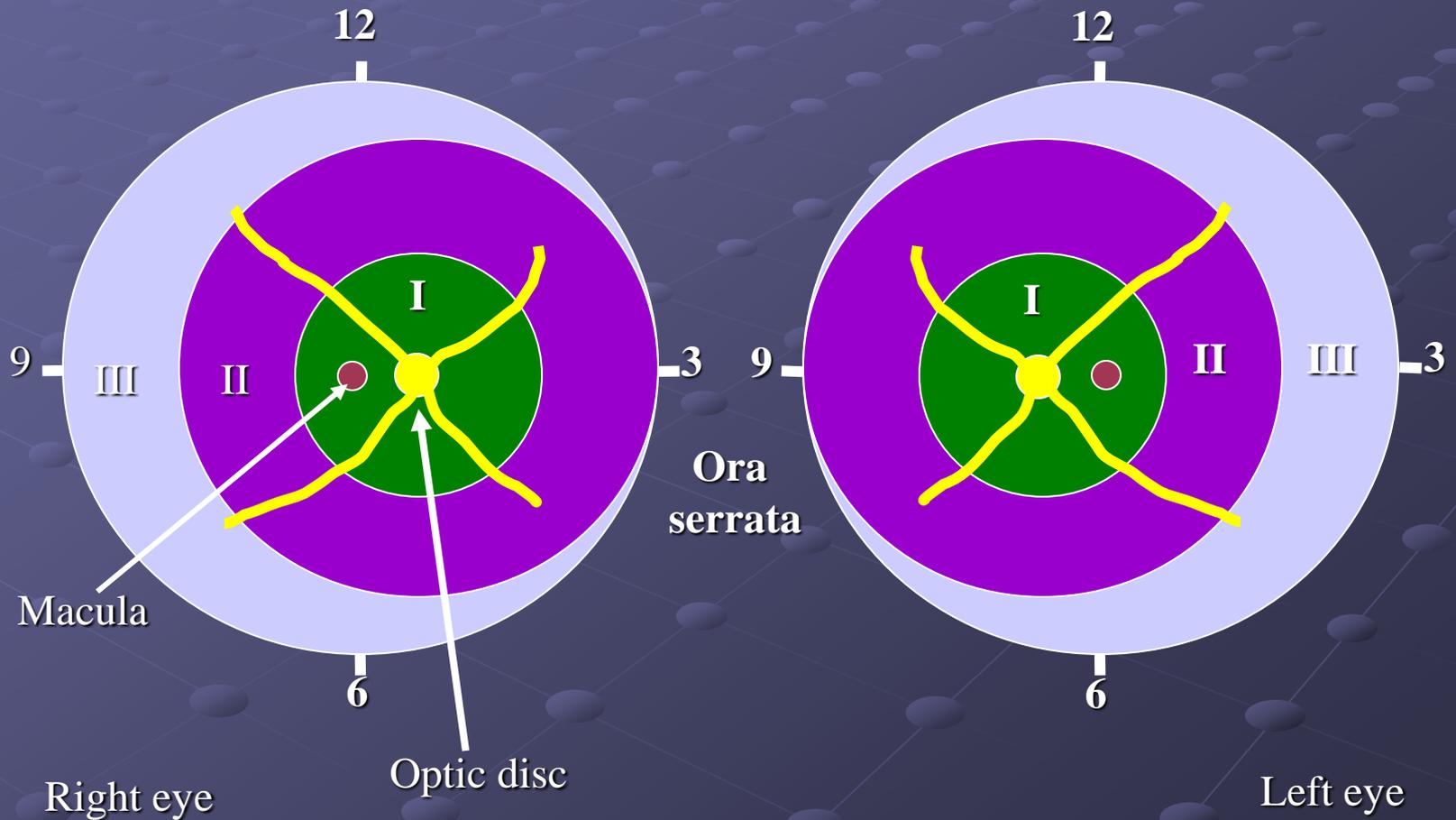
A**INCIDENCE OF ROP BY BIRTH WEIGHT**

ROP - Classification

1984 and 1987 International Classification of ROP:

- **3 Zones (location)**
- **Clock hours (extent)**
- **Stages 1 through 5**
- **Plus Disease**

ROP - Classification



Extent

- Described by dividing the retinal surface into 12 segments (clock hours). The stage of retinopathy can vary among segments.

ROP - Classification

- Stage 1. Demarcation line between the normal retina (left) and the non-vascularized retina (right).
- Multiple small abnormally braching vessels can sometimes be seen leading into the demarcation line.

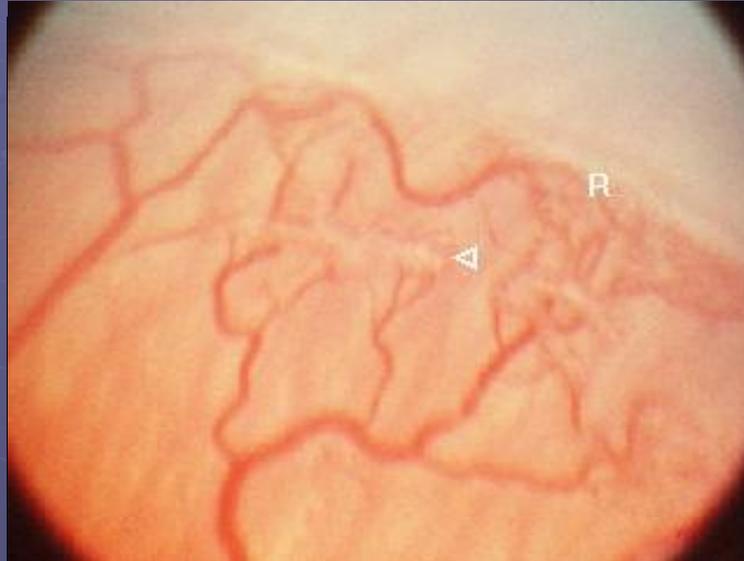


Stage 1



Stage 1 retinopathy of prematurity In stage 1 ROP, a flat white demarcation line separates the vascular and avascular retina.

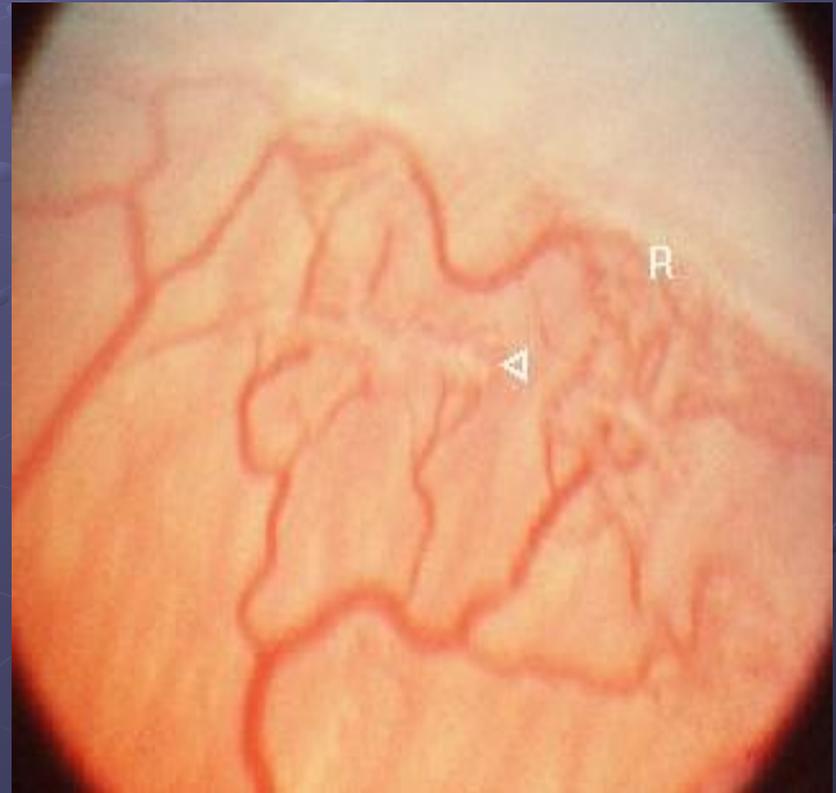
Stage 2



Stage 2 retinopathy of prematurity In stage 2 ROP, a ridge of fibrous tissue protrudes anteriorly in the region between the vascular and avascular retina.

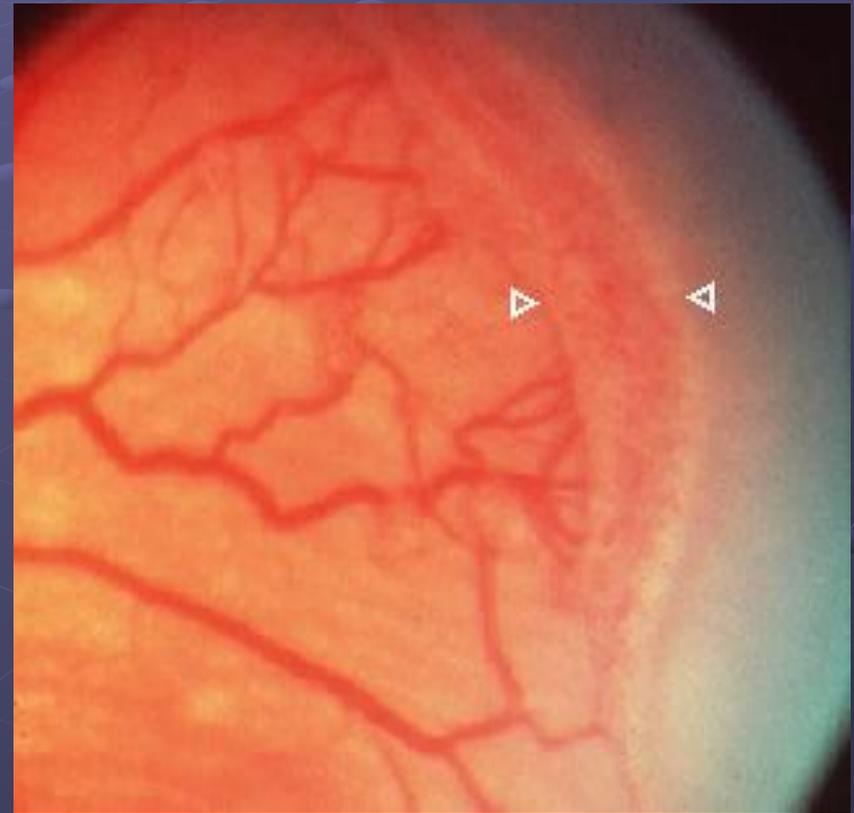
ROP - Classification

- Stage 2 - ridge (R) of scar tissue and new vessels in place of the demarcation line. The white line now has width and height, and occupies some volume.
- Small tufts of new vessels ("popcorn vessels") may appear posterior to the ridge (arrowhead).



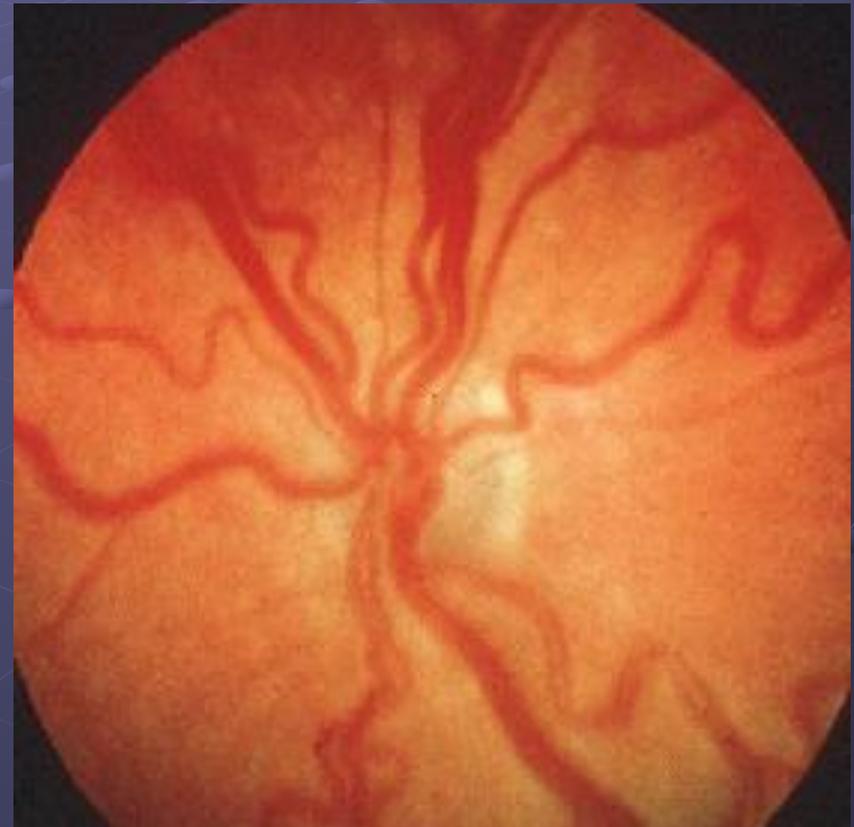
ROP - Classification

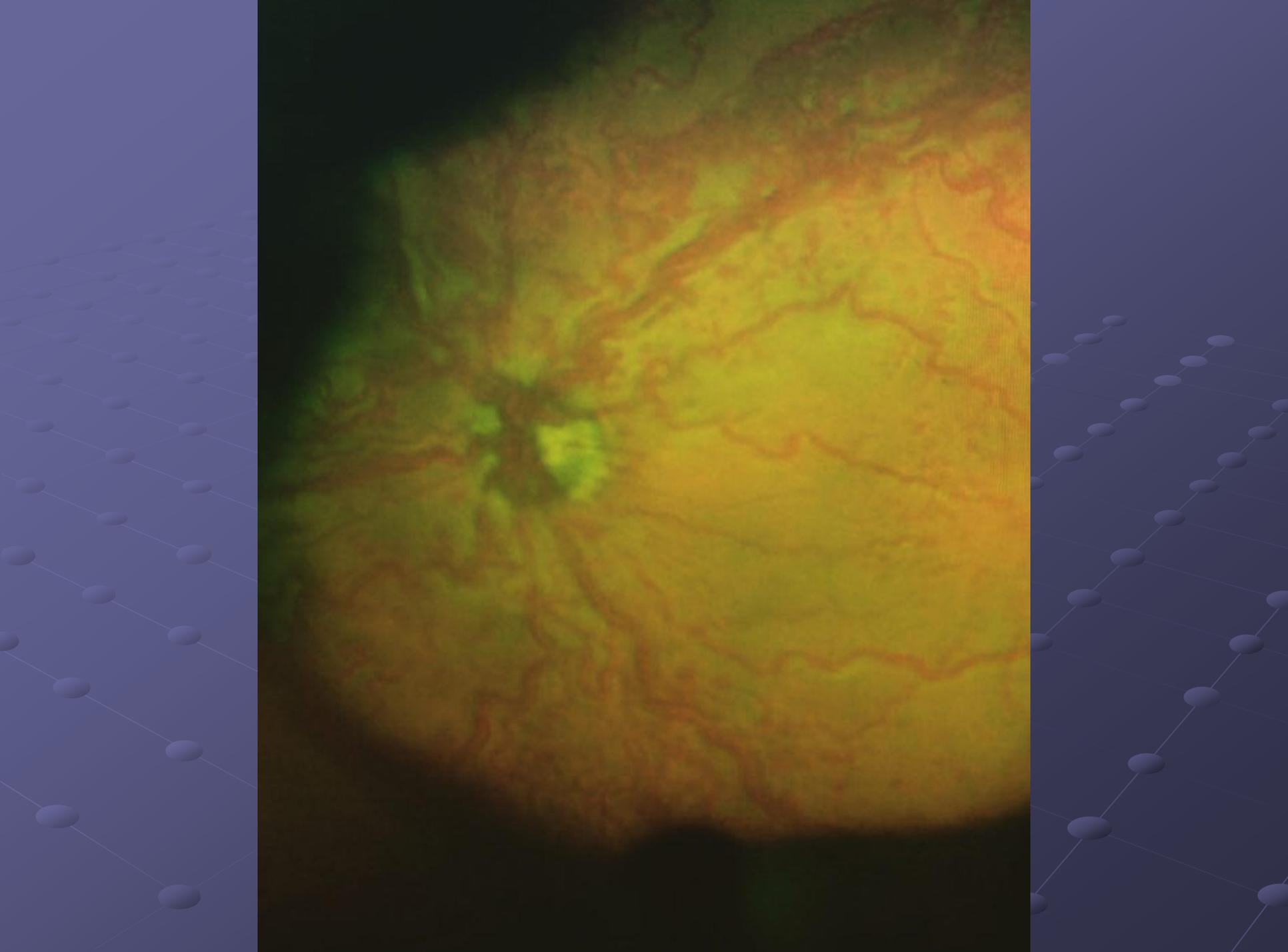
- Stage 3 - Increased size of the vascular ridge (between the arrowheads), with growth of fibrovascular tissue on the ridge and extending out into the vitreous.
- Fibrous scar tissue is beginning to form in this stage, with attachments between the vitreous gel and the ridge.



ROP - Classification

- Plus disease - engorgement and tortuosity of the blood vessels near the optic nerve.
- Also includes growth and dilation of abnormal blood vessels on the surface of the iris, rigidity of the iris, and vitreous haze (exudate along the retinal vessels).
- Can accompany any stage, but indicates greater likelihood of progression to Stage 3 (or greater).





ROP - Classification

Rush Disease:

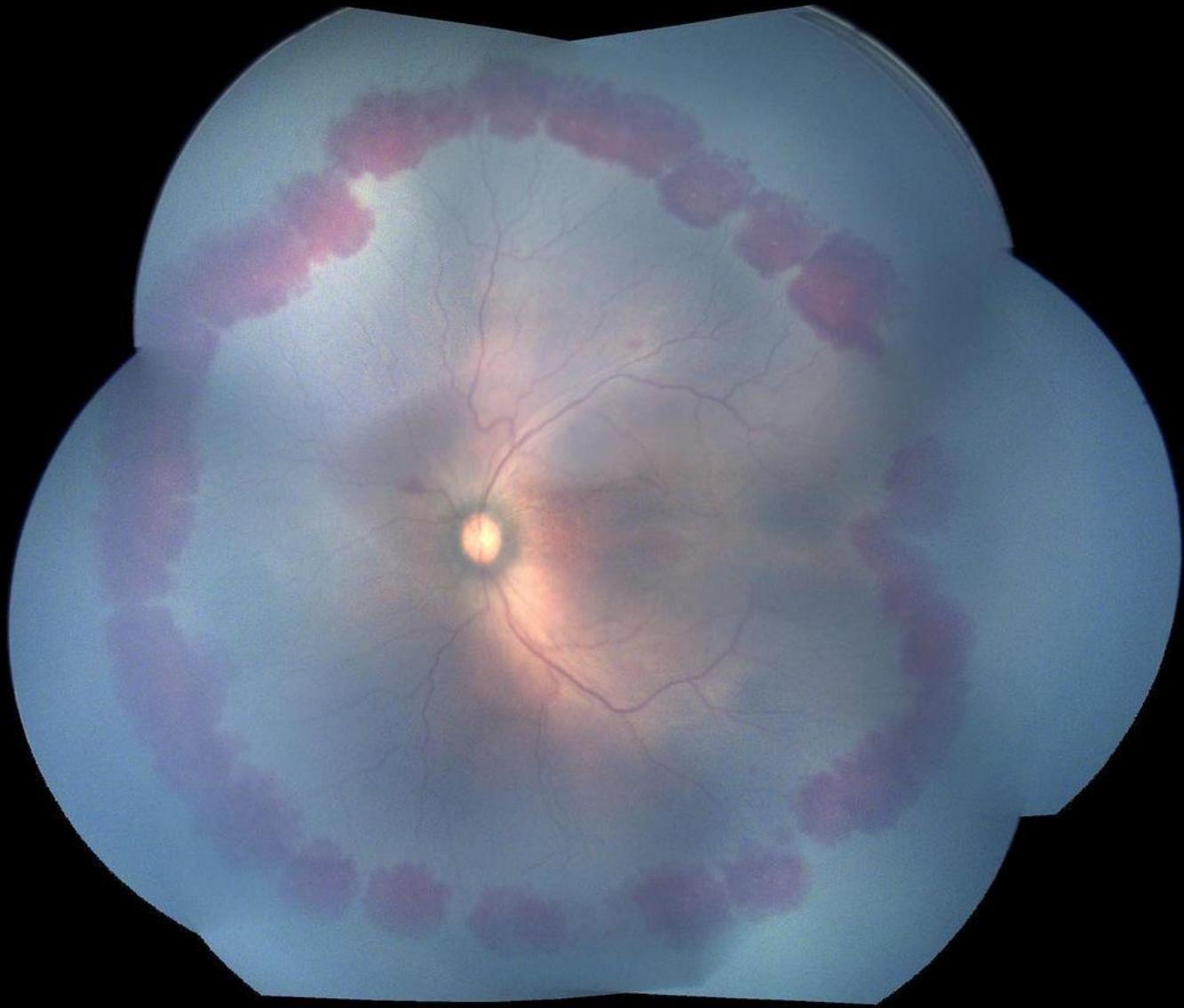
Plus disease + Zone I ROP

Progression occurring in days, rather than weeks.

Pre-threshold ROP

Increased likelihood of progression to retinal detachment if left untreated>

- Zone I, any stage
- Zone II, “plus disease” with stage 1, 2



Threshold ROP

ROP with 50% likelihood of progression to retinal detachment if left untreated>

- Stage 3 with 5 continuous clock hours or 8 cumulative clock hours with plus disease**

ROP - Classification

- Stage 4 - Partial retinal detachment.
 - Stage 4A - detachment does not include the macula, and the vision may be good.
 - In Stage 4B - macula is detached, and the visual potential is markedly decreased.
- Stage 5 - Complete retinal detachment.

Plus disease



Plus disease in retinopathy of prematurity In plus disease, the blood vessels in the posterior pole of the retina appear dilated and tortuous.

Presence indicates severe ROP and is often followed by rapid progression to retinal detachment. May be accompanied by vitreous haze, engorgement of the iris vessels, and poor dilation of the pupil.

Rush disease: ROP in zone 1 with plus disease.

PREVENTION OF ROP

- Attach pulse-oximeter preferably to RUL after birth
- Remember SpO₂ takes 3-5 minutes to increase after birth. Avoid oxygen administration if baby has good respiratory efforts
- FiO₂ recommendation for resuscitation of preterm infants: 30-90% only
- If using BMV for PPV remove reservoir and ventilate. This will ensure FiO₂ < 40%
- If using Neopuff for PPV use oxygen-air blender and start with 30% FiO₂. Adjust based on SPO₂ readings

PREVENTION OF ROP

- Target SPO₂ of 88-92%
always(resuscitation/NICU/transport)
- Avoid large changes in FiO₂ during desaturation episodes n NICU. Increase or decrease by 5% at a time and evaluate each time
- Have a display of Oxygen saturation recommendation on a wall in NICU
- Remember: Sicker the baby, higher is the risk of developing ROP

PREVENTION OF ROP

- Aggressive Nutrition
 - Poor postnatal weight gain is a risk factor for ROP
 - Use TPN for all babies <31 weeks / <1250gm
 - Start enteral feeds early or as soon as baby is hemodynamically stable
- Avoid Hypotension
 - Target Mean BP as per norms for GA

PREVENTION OF ROP - STUDIES

- **Lower or more tightly controlled oxygen saturation limits** early in the neonatal course reduce severity of ROP without any adverse effects on mortality, BPD & neurological sequelae.
- **Antenatal Steroids & Surfactant:** Decrease RDS and hence may decrease serious ROP
- **Prophylactic Vitamin E:** Till now no benefit was shown in the trials but further research is warranted
- **Reduction in light exposure:** No clear benefit
- **Administration of penicillamine:** No clear benefit

PREVENTION OF ROP - STUDIES

- In some studies **Insulin-like growth factor-1 (IGF-1) was deficient** in premature infants almost immediately after birth, and they observed that children who were **slow to recover to normal serum levels of IGF-1 were more likely to develop ROP** (Hellstrom et al, 2001).
- In several careful follow-up studies, these investigators demonstrated that **determining the rate of weight gain**, essentially a noninvasive surrogate for growth hormone level, was effective in stratifying the risk of developing serious ROP even before the retinopathy is manifest

Timing of Eye Exam

TABLE 1 Timing of First Eye Examination Based on Gestational Age at Birth

| Gestational Age at Birth, wk | Age at Initial Examination, wk | |
|------------------------------|--------------------------------|-------------|
| | Postmenstrual | 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 |
| 31 ^b | 35 | 4 |
| 32 ^b | 36 | 4 |

Shown is a schedule for detecting prethreshold ROP with 99% confidence, usually well before any required treatment.

SCREENING OF ROP (KIDROP)

- **WHOM TO SCREEN?**
 - All preterm infants with B.Wt <1750 gm (mandatory) or <2000gm(preferred)
 - GA <34 weeks
 - Up to 36 weeks with risk factors
 - Do not exclude any baby based on the absence of risk factors if they are eligible by weight or prematurity
 - Remember even if you don't give an ounce of oxygen, ROP can still develop
 - Screening to continue till 44 weeks of GA

SCREENING OF ROP (KIDROP)

- **PRECAUTIONS AND PROCEDURE FOR SCREENING**
 - Best performed in the presence of neonatologist
 - Step-down room of NICU is ideal
 - Last feed approximately 1 hour prior to examination
 - Pupillary dilatation: Phenylephrine 2.5% and Cyclopentolate 0.5% (Auropent plus eye drops)
 - One drop in each eye, 2-3 times, 15 min apart
 - Wipe off excess drops from the cheeks, blocking punctum also advisable
 - Poor dilatation may be an indicator of severe disease
 - **DONOT** over administer eye drops, wait for ophthalmologist to opine

SCREENING OF ROP (KIDROP)

PRECAUTIONS AND PROCEDURE FOR SCREENING

- Swaddle the baby with warm linen wraps
- Procedure: Indirect ophthalmoscopy using a 20 D or 28 D lens or with RETCAM imaging
- Peripheral scleral depression with an infant depressor and a infant wire speculum are required
- Failure to depress may risk missing peripheral disease
- Monitor for apnea and bradycardia
- For analgesia 10%Dextrose/24% sucrose can be used
- A resuscitation kit must be accessible and functional

International Classification for Retinopathy of Prematurity (ICROP)

● Four features are evaluated:

- Zone (1-3)
- Stage (1-5)
- Extent
- Presence or absence of plus disease

SCREENING GUIDELINES

Recommendations based on review of data from the CRYO-ROP and LIGHT-ROP studies

Table 4. Timing of the Initial Eye Examination Designed to Detect at Least 99% of Serious ROP*

| Gestational Age at Birth, wk | Age at Initial Examination, wk | |
|------------------------------|--------------------------------|-------------|
| | Postmenstrual | Chronologic |
| 22† | 31 | 9 |
| 23† | 31 | 8 |
| 24 | 31 | 7 |
| 25 | 31 | 6 |
| 26 | 31 | 5 |
| 27 | 31 | 4 |
| 28 | 32 | 4 |
| 29 | 33 | 4 |
| 30 | 34 | 4 |
| 31 | 35 | 4 |
| 32 | 36 | 4 |

*ROP indicates retinopathy of prematurity.

†This guideline should be considered tentative rather than evidence based for 22- to 23-week infants owing to the small number of survivors in these gestational age categories.

- Initial screening should be performed by 31 wks PMA or 4 wks CA, whichever is later.
- Screening can be discontinued when any of the following three signs are identified:
 - Lack of development of prethreshold or worse ROP by 45 wks PMA.
 - Progression of retinal vascularization into zone 3 without previous ROP in zone 2.
 - Full vascularization

International Classification for Retinopathy of Prematurity (ICROP)

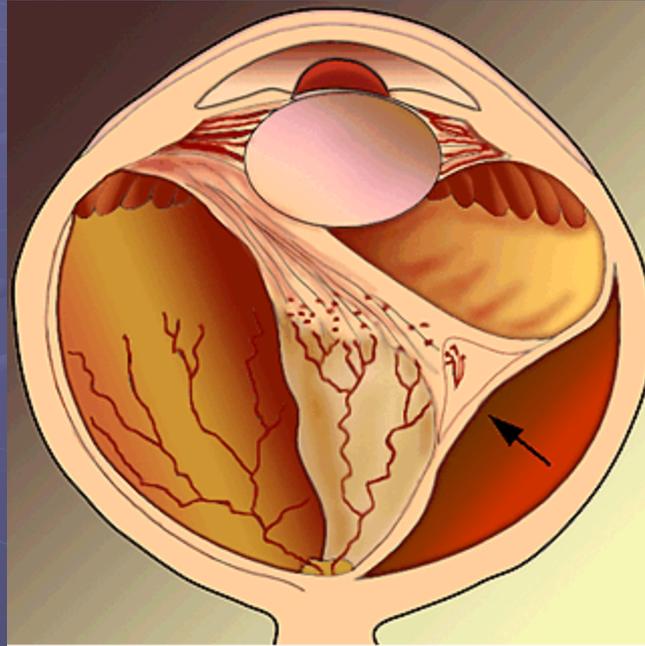
● Four features are evaluated:

- Zone (1-3)
- Stage (1-5)
- **Extent**
- Presence or absence of plus disease

ROP - screening Management

- **Screening: according to our protocols , all infants <35 wks gestational age AND <2000 g birthweight are screened between 4-6 weeks of age.**

Stage 4

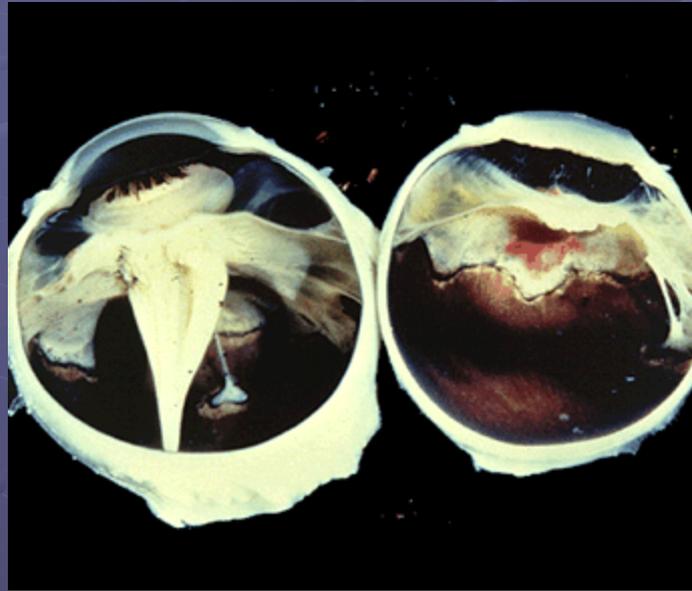


Stage 4 retinopathy of prematurity Stage 4 ROP signifies a partial retinal detachment indicated by the arrow. In this example, the detachment excludes the macula, and is therefore stage 4A.

Stage 4A: excludes the macula

Stage 4B: includes the macula

Stage 5



Stage 5 retinopathy of prematurity Stage 5 ROP indicates total retinal detachment.

HOW TO EXAM?

- -ADMISSION TO ROP ROOM N P O FOR ONE TO TWO HOURS
- ATTENDANCE OF PARENTS & NURSE
- TROPICAMID AND PHENYLEPHRINE DROPS FOR PUPILS DILATION
- INDIRECT OPHTHALMOSCOPE AND RETCAM CAMERA









Retinopathy of prematurity, or ROP, is a form of blindness caused by abnormal blood vessel growth in the eyes of premature infants. Images of the retina taken with a special eye camera indicate which premature infants may have signs of the condition and require treatment to prevent it. Here, an infant's eyes are scanned in the Neonatal unit of Children's Hospital in Philadelphia, Penn.

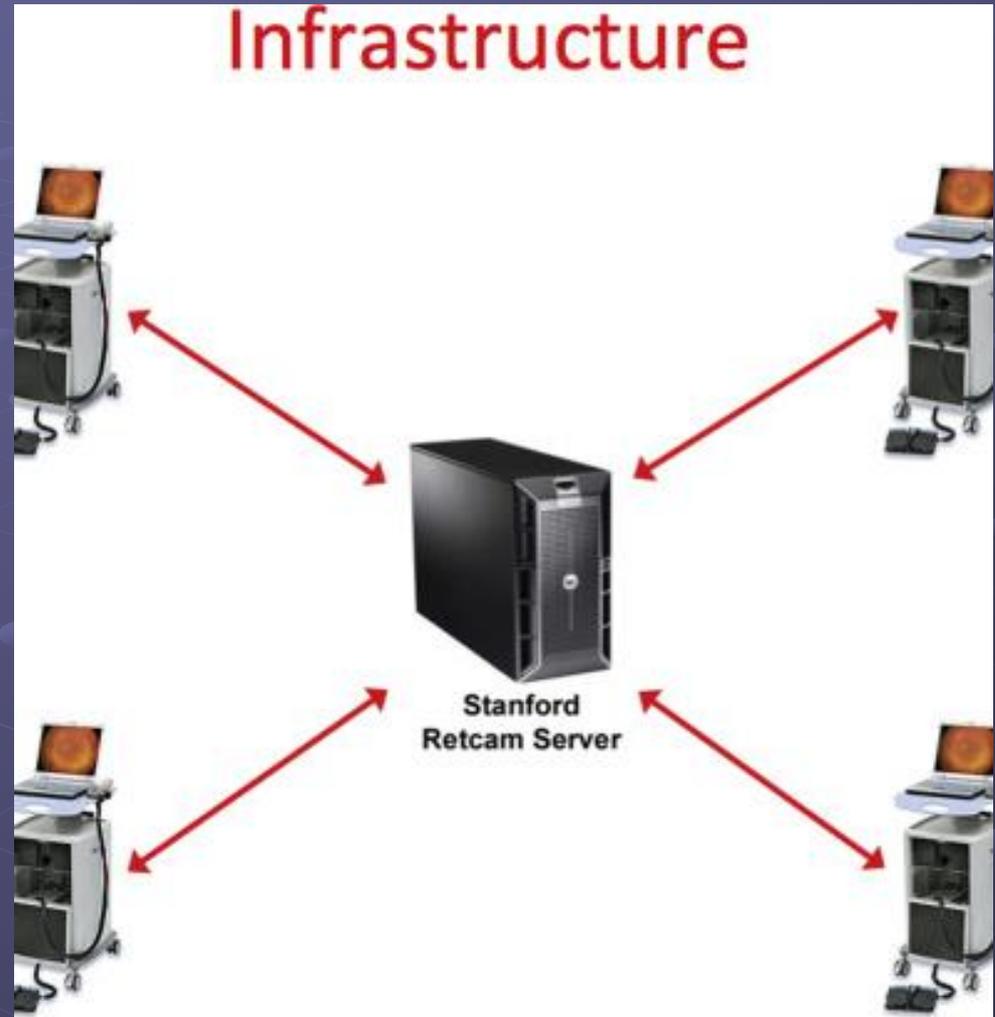
The LDI Health Economist
Photography: Hoag Levins

Leonard Davis Institute of Health Economics © 2012

<http://LDIHealthEconomist.com>

TELE MEDICINE AND

ROP





Treatment Criteria

● Treat when threshold ROP is reached. **Threshold**

ROP:

- 5 contiguous clock hours or 8 total clock hours of stage 3 and plus disease in zone 1 or 2.
- **Prethreshold ROP** – one of the following:
 - ROP at any stage less than threshold in zone 1
 - Stage 2 and plus disease in zone 2
 - Stage 3 without plus disease in zone 2
 - Stage 3 with plus disease in zone 2 but with fewer clock hours of stage 3 than required to meet threshold.

Approx. 1/3 of infants with prethreshold ROP progress to threshold disease and can do so rapidly. Therefore repeat exams are usually needed every 2-4 days.

ROP - Management

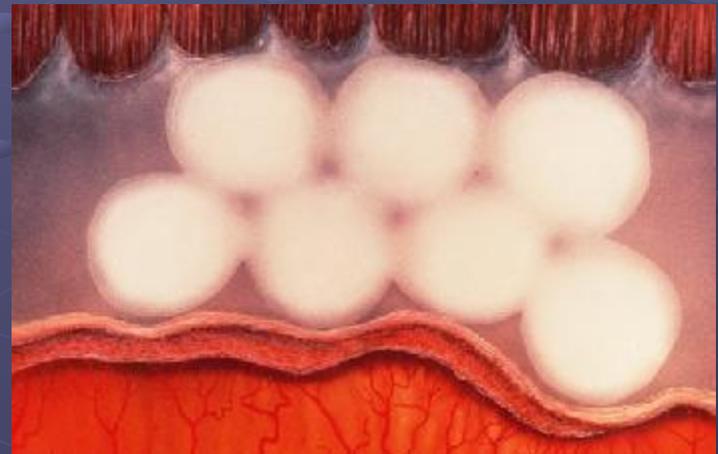
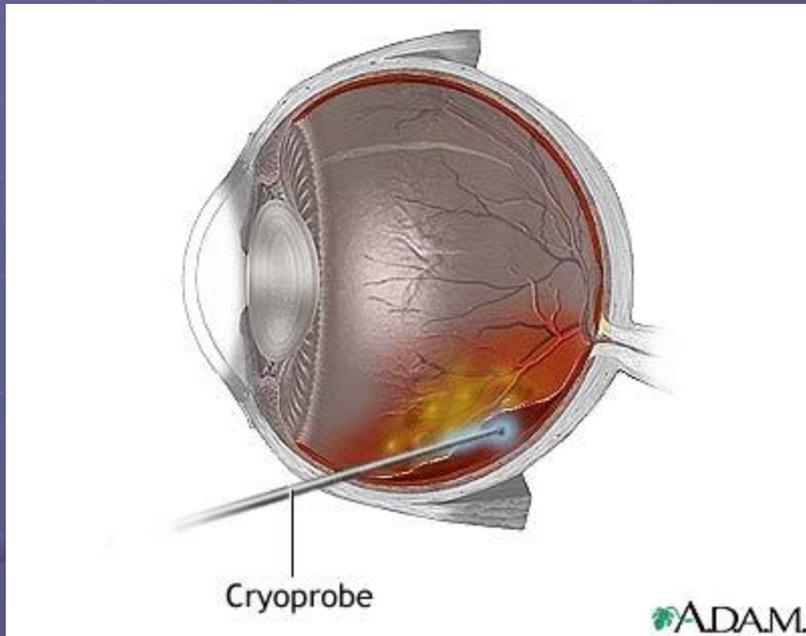
● PREVENTION -

- Prevent preterm labor.
- (Optimal) minimum use of oxygen.
- Prevention of complications.

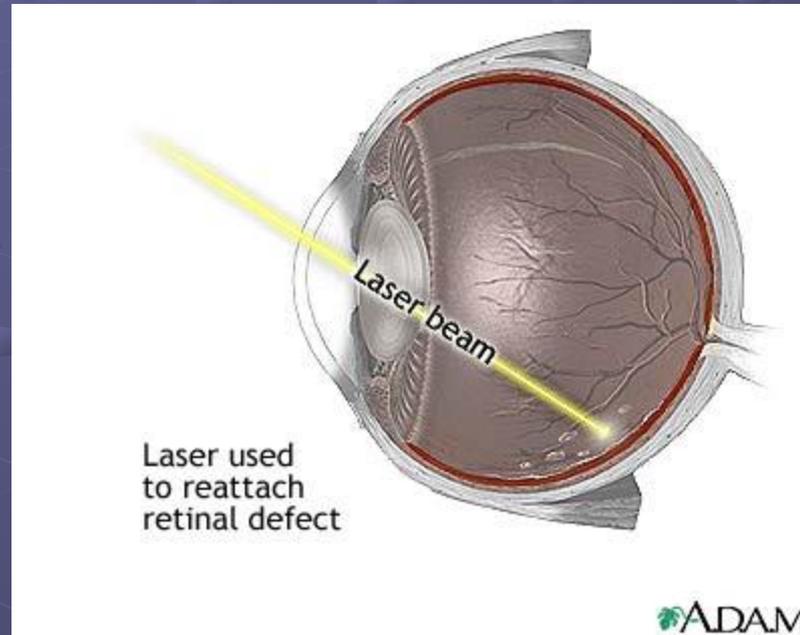
Treatment Options

- Cryotherapy
- Laser photocoagulation – standard treatment
- Surgical interventions
 - Scleral buckling
 - Vitrectomy

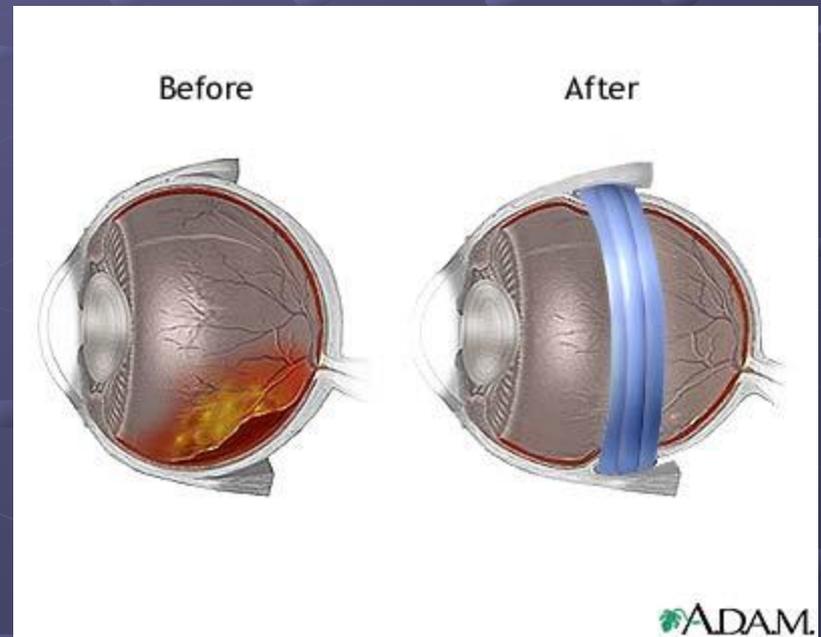
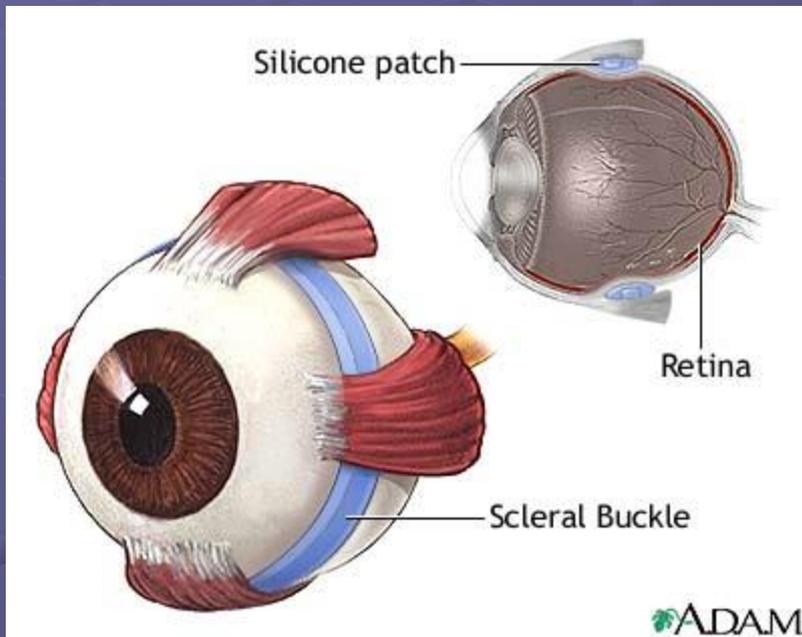
Cryotherapy



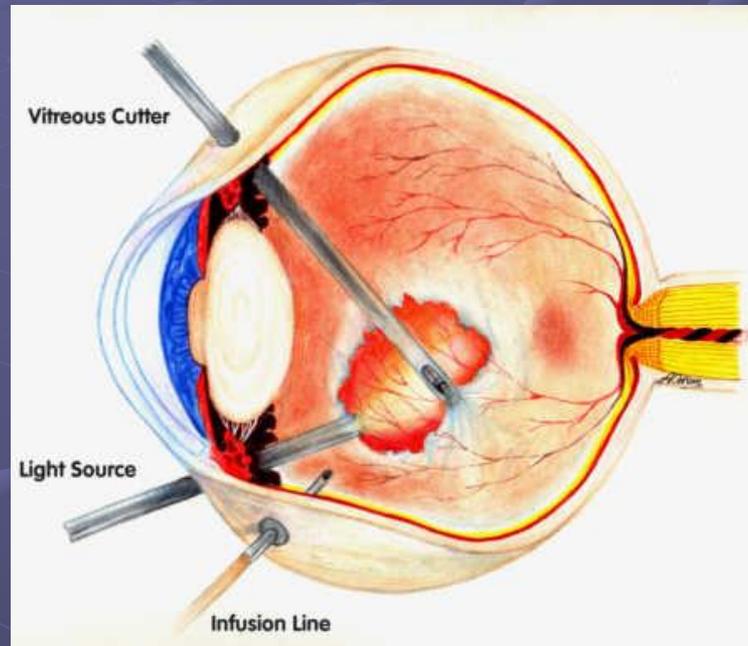
Laser photocoagulation



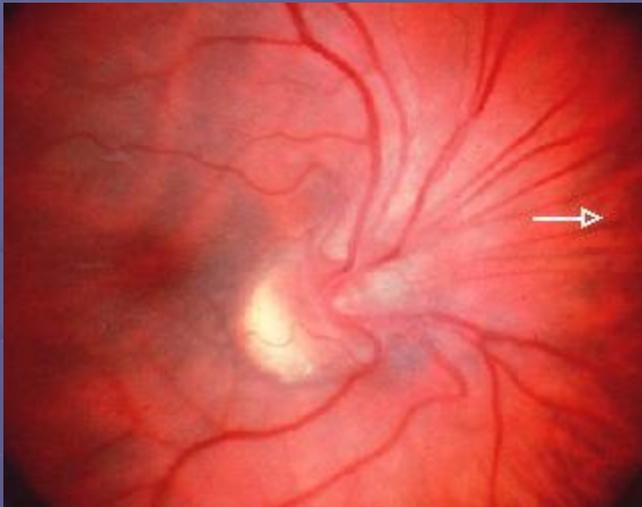
Scleral Buckling



Vitreotomy



Long Term Complications of ROP



Retinal Dragging
and Folds



Strabismus

Others:

Glaucoma

Late onset Retinal Detachment

Significant myopia

Anisometropia

Amblyopia

Importance of Follow-Up

- Prematurity (even in the absence of ROP) puts infants at increased risk of ophthalmologic complications.
- Therefore, all premature infants should undergo examination by an ophthalmologist at 9-12 mos. of age and be followed more frequently in the first few years of life than term infants.

Thank you for
attention to webinar

