



UPDATE ON RETINOPATHY OF PREMATURITY

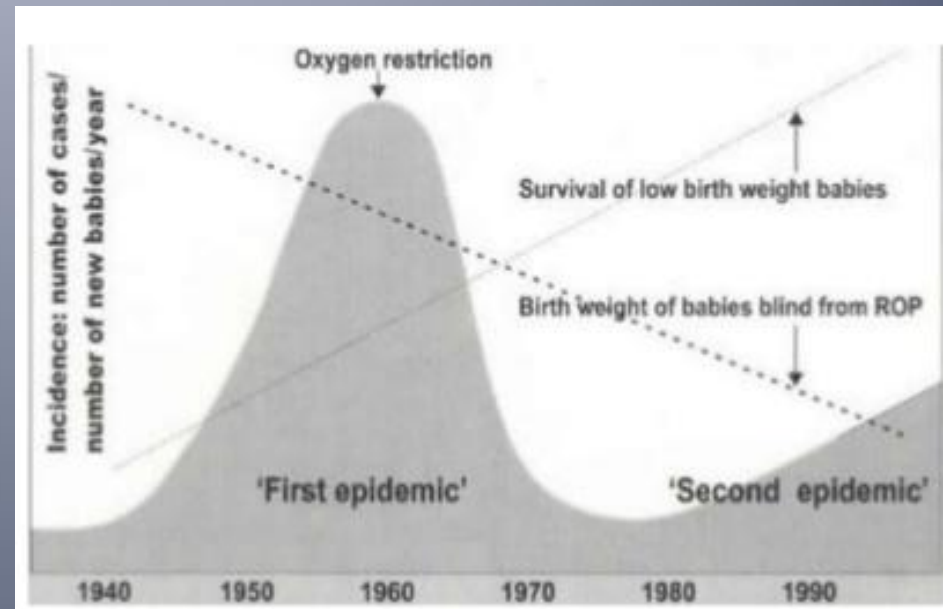
DR. RAJENDRA BISEN
VITREORETINA CONSULTANT
VASAN EYE CARE HOSPITAL
JABALPUR

Introduction

- ROP is one of the major emerging causes of avoidable childhood blindness globally, including in India
- 1942- Terry first identified ROP as ‘retrolental fibroplasia’ in 6 month premature infant
- 1951- Heath suggested term “Retinopathy of prematurity”

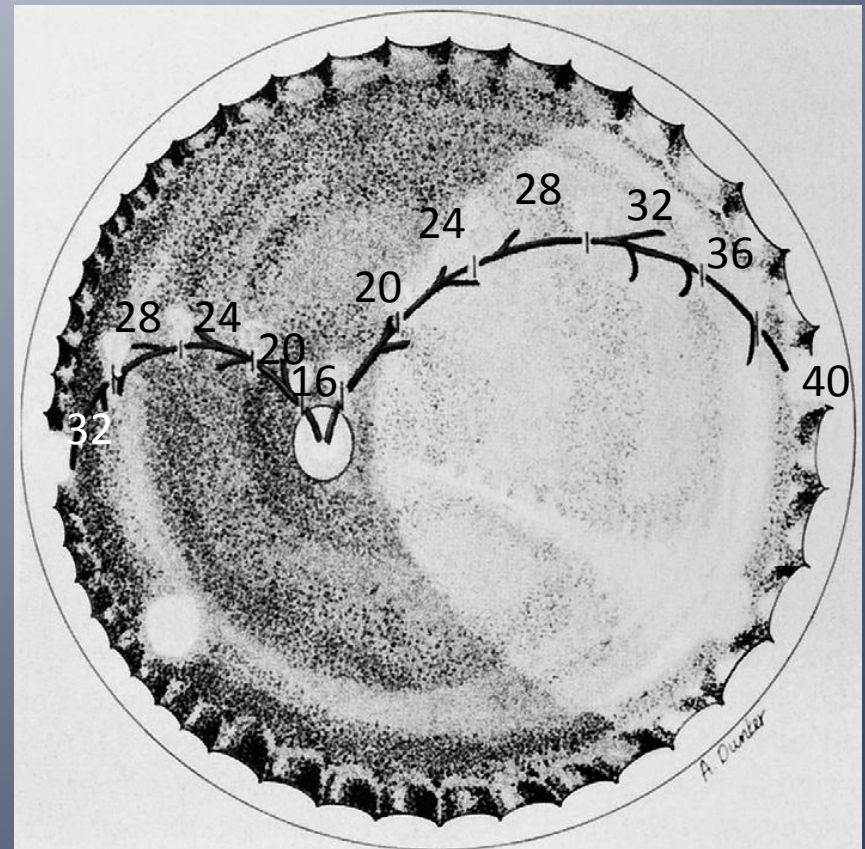
Introduction

- Nearly disappeared between 1954-1970, when oxygen use severely restricted.
- But now, has returned, secondary to improved neonatal practice of VLBW infants.
- Est. 400 infants blinded each yr; 4300 with serious retinal scars.



NORMAL RETINAL VASCULATURE

- Choroid vascularises at 6 week
- Retinal vascularization starts at optic nerve head at 16 weeks gestation
- Proceed outward to the periphery
- Vascularization is almost complete by term



ROP- Pathogenesis

- ROP can occur when the retinal vessels have not yet completed their centrifugal growth from the optic disc to the ora serrata.
- Primitive endothelial cells (“spindle cells”) form cords that canulize into capillaries and further differentiate into arterioles and venules.

ROP- Pathogenesis

Vasculogenesis

Insult ; hypoxia, ↑ o₂ supplementation
Shock, preterm delivery

Normal vasculogenesis interrupted

Sharp demarcation line

After injury recovery

Normal vessel growth
No ROP

Primitive vessels pileup within
The retina,
Growing without forward progress
Formation of ridge

ROP- Pathogenesis

Until completely vascularised, vasculogenesis is highly vulnerable to any sort of insult or stress, including medications, high level of oxygen, variations in light and temperature.

ROP- Risk Factors

- Gestational age and low birth weight
- Supplemental oxygen
- Vitamin E deficiency
- Race (increased in Caucasians)
- Surfactant
- Light levels
- Multiple births

Classification

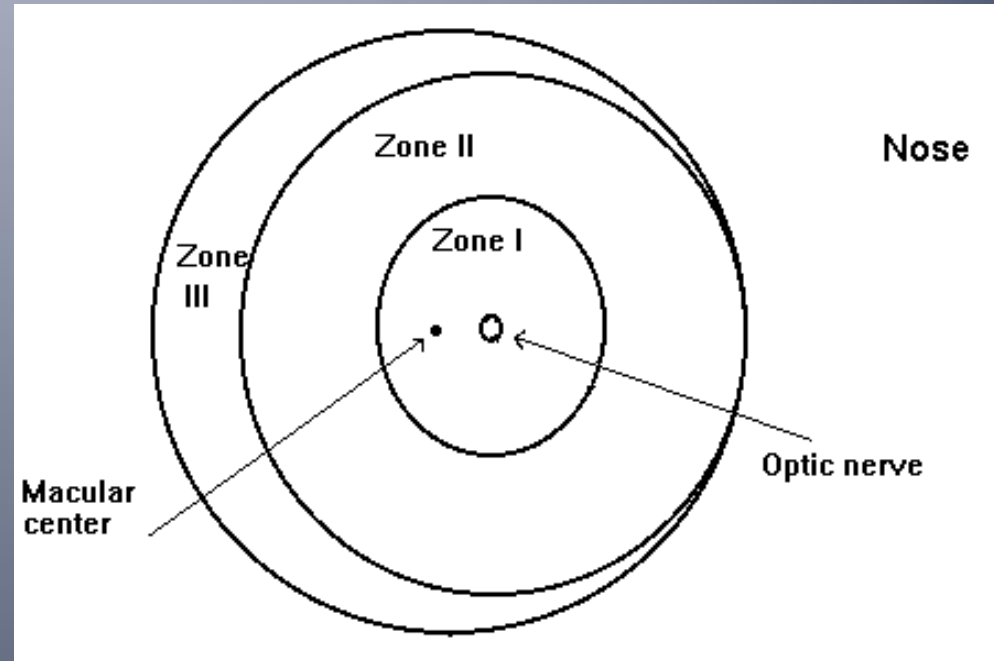
International classification for retinopathy of prematurity (ICROP) (1984 & 1987)

- Four features are evaluated:
 - Zone (1-3)
 - Stage
 - Extent
 - Presence or absence of plus disease
- ICROP revisited (2005)
 - APROP
 - Pre plus

*Committee for the classification of retinopathy of prematurity
An international classification of retinopathy of prematurity
Arch ophthalmology 1984 102: 1130-1134*

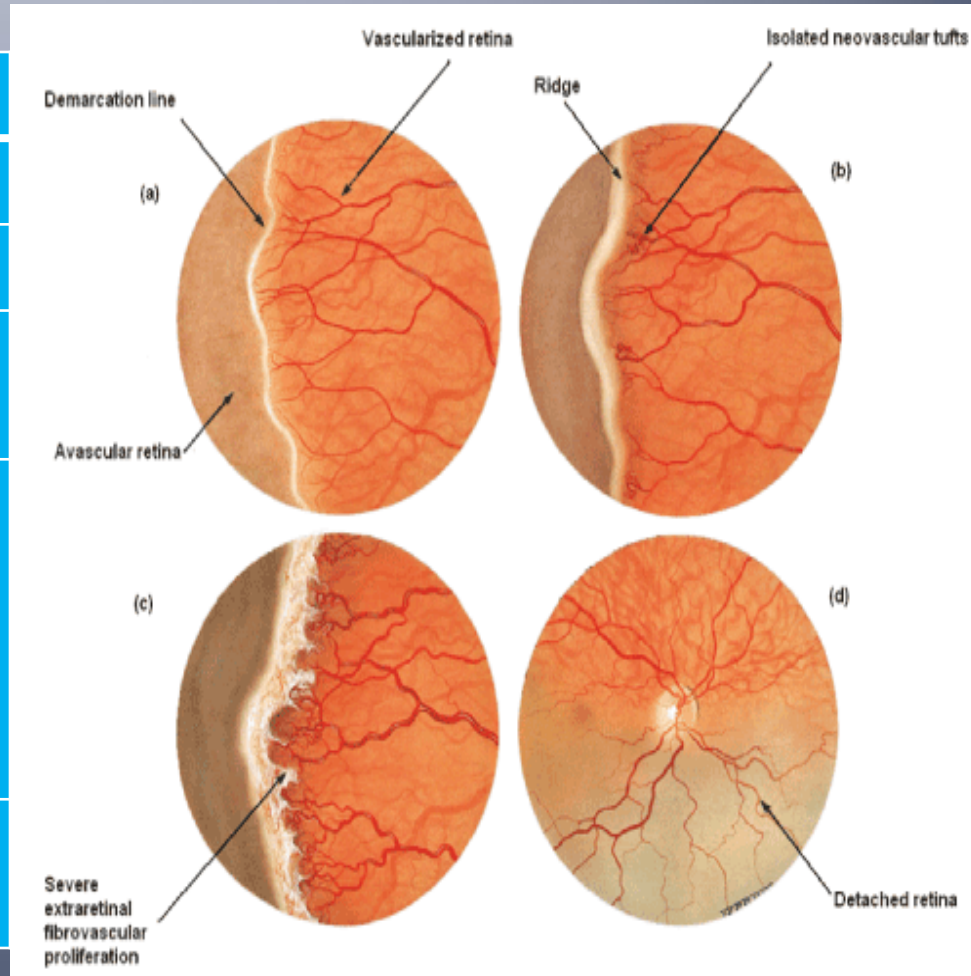
Zone

- Zone I: inner zone, radius is twice the distance from the disc to macula.
- Zone II: concentric circle tangential to the nasal ora serrata
- Zone III: remaining temporal crescent



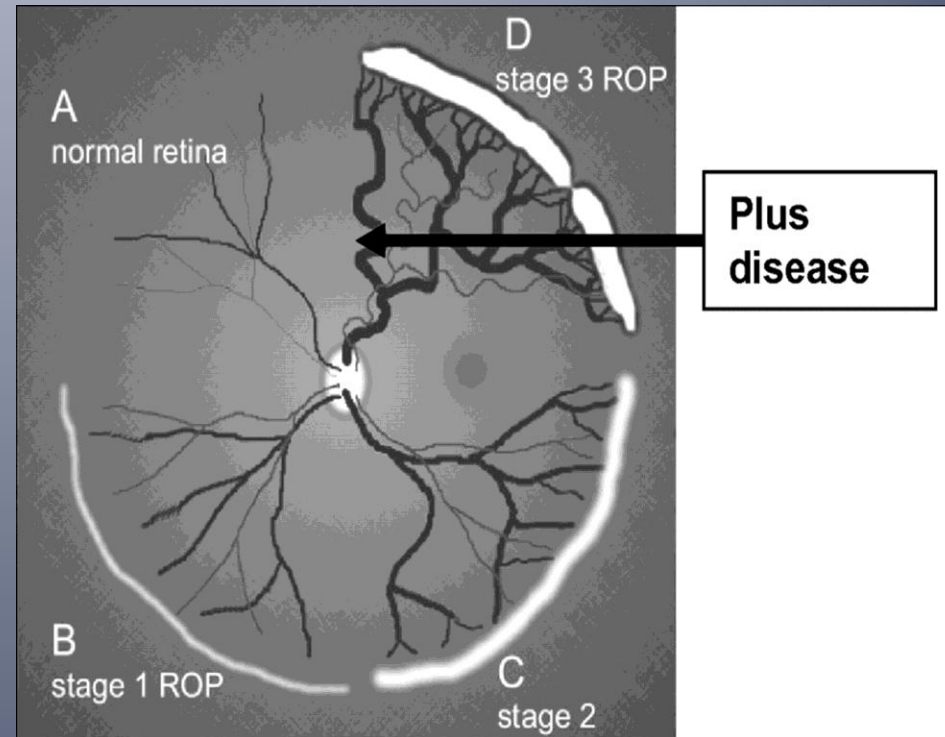
Stages

ROP stages	Description
Stage 1	Demarcation line
Stage 2	Ridge
Stage 3	Ridge with extra retinal proliferation
Stage 4	Subtotal retinal detachment
A.	A. Not involving macula
B.	B. Involving macula
Stage 5	Total retinal detachment



Posterior pole vascular abnormalities

- Plus disease:
Presence of dilated and tortuous vessels of the posterior pole present in two or more quadrants
- Preplus disease:
Abnormal vasculature dilation and tortuosity that is insufficient for diagnosis of plus disease present in two or more quadrants



AP-ROP (RUSH DISEASE)

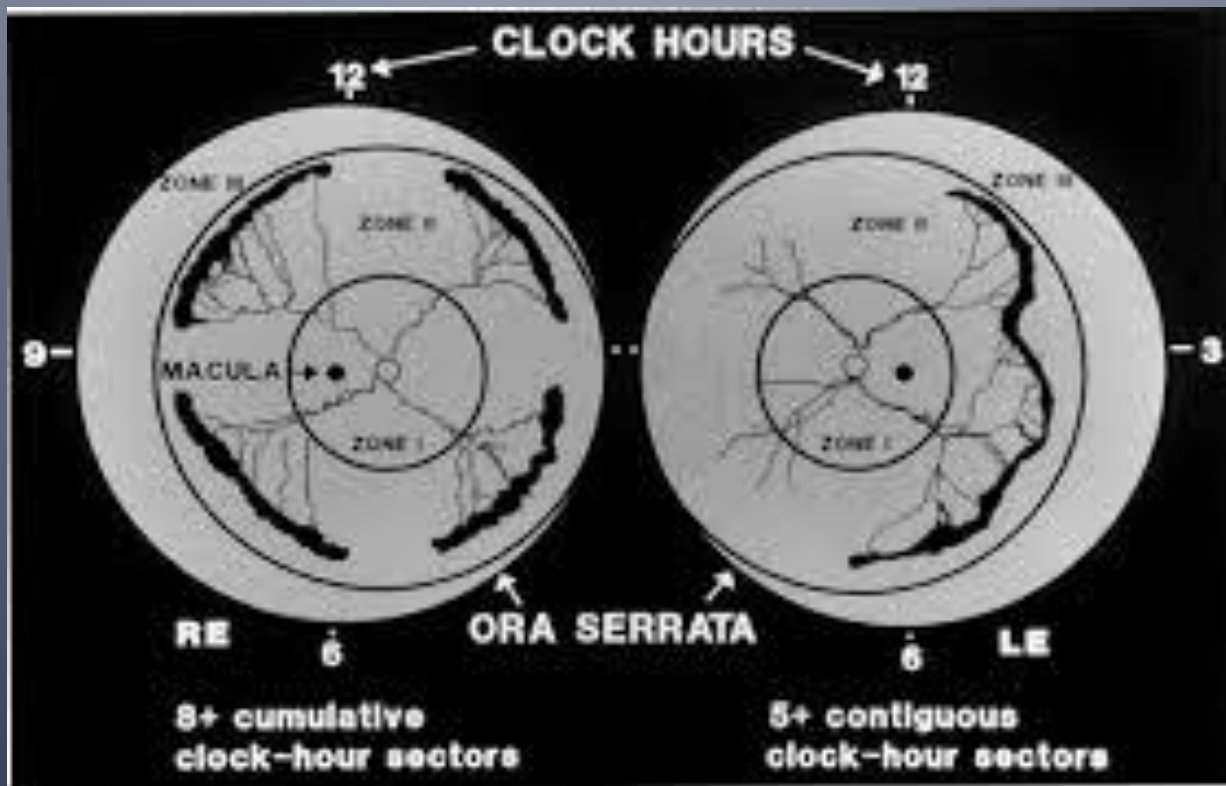
Aggressive posterior ROP
recognized by:

1. Marked dilation and tortuosity of posterior pole vessels
2. Difficulty in documenting the stage of ROP at junction between vascularised and avascular retina with Subtle neovascularization
3. Occurs in zone I or zone II



Threshold ROP

- ROP is defined as five contiguous clock hours or eight total clock hours of stage 3 and plus disease in zone 1 or 2.



Prethreshold ROP

- Defined as one of 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

Screening strategy

Why should we have screening program for ROP?

- The premature child is not born with ROP and retinal Disease is not present at birth
- The aim of screening is to identify those infants who have reached or have potential to reach vision threatening ROP

Whom should we screen?

- Gestational age at birth <34-35 weeks
- Birth weight < 1500gms
- Exposed to oxygen for >30days
- Infants <1200gm and born at 24-30 wks are at high risk of ROP at an early age and aggressive forms (RUSH Disease)

Other risk factors (<37wks and/or <2000gms)

- Respiratory distress syndrome
- Sepsis
- Multiple blood transfusions
- Multiple births(twins/triplets)
- Apnoeic episodes
- Intraventricular haemorrhage

When should we start screening?

20-30 day strategy

- Screening should not later than four weeks after birth
- For high risk infants (<30 wks at birth or <1200gms BW) earlier examination at 3 weeks
- Delaying the timing of first screening- ↑ seeing advanced disease, sp. APROP eyes

How to dilate ?

- Tropicamide 0.5% with phenylephrine 2.5%- 2-3 instillations, 5 minute apart (India 10% phenylephrine available, needs to dilute 1:4 ratio to make 2.5%)
- Cyclopentolate 0.5% to 1% can also be used
- 10% phenylephrine or atropine is inadvisable ✘
- One should always remember that errors in dilution of dilating drops can prove fatal for the baby

Where to examine ?

- The only pre-requisite for place is that it should be warm and clean enough
 - Nursery/clinic of neonatologist
 - Clinic of ophthalmologist
- Babies critically ill- NICU under guidance of neonatologist, monitored with pulse oxymeter

How to examine and classification of ROP

Examination for ROP does not require any sedation or general anesthesia

- Pediatric speculum
- Condensing lens 20D/28D
- Wire vectis/ pediatric depressor
- Irrigating fluid
- Cotton-buds



- Anterior segment first examine by condensing lens- Cornea, iris, pupil and lens to look for any media opacity, tunica vasculosa lentis, and iris new vessels

Posterior segment examination

- Evaluation of media clarity
- Posterior pole (zone I)- disc macula and retinal vessels
 - Any evidence of plus disease, vascular loop, retinal avascularity is ruled out
- Zone II- by using little movement of the head sideways
 - First nasal periphery should be examined till ora serrata
 - Any evidence of immaturity or ROP in nasal retina- qualify disease in zone II

- Complete vascularization of nasal periphery with avascular area in temporal periphery-qualify disease in zone III
- Findings must be well documented according to ICROP recommendations
 - Zone I-III, stage I-IV, extent of clock hours, with or without plus

How frequently to examined

1. Mature retina*	Follow-up 3month – 1 year
2. Immature retina#	Follow-up 2 weekly
3. Immature Zone I retina	Follow-up 1 weekly
4. AP-ROP	Treat urgently
5. Low risk Prethreshold ROP	Follow-up 3-7 days
6. Threshold ROP	Early treatment with in 48-72hrs
7. ROP stage 4 or 5 (retinal detachment)	surgical treatment

*Defined as retinal vessels seen up to nasal ora serrata. # retinal vessels are not seen upto Nasal ora serrata

- **In case of doubt about the retinal findings (especially beginners) it is good idea to see the baby again in 1-2 weeks, at least till child is 38-40 weeks old.**

ETROP Recommendations

Zone I	No plus	Stage 1	follow
		Stage 2	follow
		Stage 3	Treat
	plus	Stage 1	Treat
		Stage 2	Treat
		Stage 3	Treat
Zone II	No plus	Stage 1	follow
		Stage 2	follow
		Stage 3	follow
	plus	Stage 1	follow
		Stage 2	Treat
		Stage 3	Treat

Practical guide for treating

- Look out for plus and new vessels **TREAT**
- **Any ROP in zone I to be treated**
- **No treatment** for most ROP in zone III and those in Zone II with no new vessels and no plus follow closely
- Failures of treatment are highest in smallest baby group and hence such eyes need vigorous and early treatment

Laser Protocol

- Aim of the treatment is to ablate the entire avascular retina as rapidly and completely as possible with minimum side effects.
 - 810 Diode red
 - 532 green laser LIO
- Use of topical anesthetic agent
- NICU/OR- suction, resuscitation and intubation- rare event of apnoea/cardiac arrest
- Stand by neonatologist or anesthesiologist is desirable.



- Place test spots and adjust energy/time to get gray white spot
- Essential to treat the entire avascular retina from ridge to upto ora serrata for 360*
- Treat with confluent spots
- Do not leave any untreated 'skip' areas near posterior ridge of avascular retina

- Zone I disease/ APROP – 3000-4000 spots
- Prethreshold/threshold zone II with non APROP- 1000-2000 spots
- In case of inadequate treatment or poor response laser can be repeated safely at short intervals of 1-3 days



Landmark Studies

- Collaborative study for role of O₂ - 1950s
 - *Arch ophthalmol* 1950
- ICROP- 1984, 1987, 2005
 - *Arch ophthalmol* 1984; 102:1130-1134
- CRYO ROP (*Archives of Ophthalmology* 1988;106 :471-479)
 - Cryo group 21% adverse outcome
 - Control group 43% adverse out come
- ETROP (*Control Clin Trials* 2004 Jun;25(3):311-25)
- LIGHT ROP (*J Pediatr Ophthalmol Strabismus*. 1999 Sep-Oct;36(5):257-63.)
 - light reduction does not reduce the incidence of confirmed ROP in high risk infants.

Landmark Studies

- **STOP ROP** *Pediatrics. 2000 Feb;105(2):295-310*
 - Supplemental therapeutic oxygen
 - Conventional oxygen arm SpO₂ 84%-94%
 - Supplemental oxygen arm SpO₂ 96%-99%
 - Use of supplemental oxygen at pulse oximetry saturations of 96% to 99% did not cause additional progression of prethreshold ROP but also did not significantly reduce the number of infants requiring peripheral ablative surgery
- **HOPE ROP** *(Pediatrics. 2002 Sep;110(3):540-4)*
 - Spo₂ value as prognostic indicator
 - HOPE ROP group $\geq 94\%$ Spo₂
 - STOP ROP group $\leq 94\%$ Spo₂
 - Infant's SpO₂ value at the time of prethreshold diagnosis is a prognostic indicator for which infants may progress to severe ROP

Landmark Studies

- **PHOTO ROP** (*Retina. 2008 Mar;28(3 Suppl):S47-54.*)
 - Remote digital fundus imaging as compared to indirect ophthalmoscopy
 - Remote interpretation of digital fundus images is a useful adjunct to conventional bedside ROP screening by indirect ophthalmoscopy
- **BEAT ROP** (*N Engl J Med. 2011 Feb 17;364(7):603-15*)
 - Intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+
 - Showed a significant benefit for zone I but not zone II disease. Development of peripheral retinal vessels continued after treatment with intravitreal bevacizumab, but conventional laser therapy led to permanent destruction of the peripheral retina.

Conclusion

- Success of ROP program is largely dependent on team work
- Pediatrician/neonatologist should be trained to identify neonates at risk and refer to ophthalmologist
- Ophthalmologist should respond promptly to requests for screening, take responsibility of counseling, follow-up.
 - Keep primary physician updated about the case
- NICU Nurses should be educated about oxygen monitoring

Conclusion

- Awareness in the general public sp. Parents of newborn may be increased with posters and information pamphlets in and around the NICU
- Babies treated successfully for ROP need periodic refraction, extensive vision training and vision rehabilitation (low vision aids)
- Vision training is an essential part of any good ROP treatment program



THANK YOU