

## Bevacizumab; Moving away from destructive treatments for Retinopathy of Prematurity

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## Review of ROP

- Retinal Vasculature:
  - At what point in gestation do you see retinal vasculature?
  - Nasal retina is vascularized by 32 weeks GA and temporal retina by just after term

## Current Recommendations for Screening

- Infants with a birth weight of  $\leq 1500$  g or gestational age of 30 weeks or less
- Selected infants with a birth weight between 1500 and 2000 g or gestational age of  $>30$  weeks with an unstable clinical course

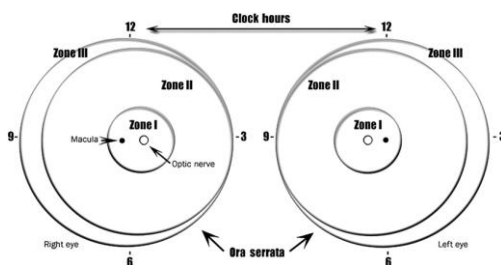
## EPIDEMIOLOGY

- Occurs in 16% of all premature births.
- Frequency:
  - the incidence of ROP in preterm babies is inversely proportional to their birth-weight.
  - $<1500$  g 65.8%
  - $<1000$  g 81.6%
  - 500 -700 children become blind due to ROP in the U.S annually
- M=F in distribution
- Black and African-Caribbean infants appear less susceptible.



Stage 2 ROP

## Zones of Vascularization



## Stages of ROP

- Stage 1: demarcation line
- Stage 2: ridge
- Stage 3: ridge with extraretinal vascular proliferation
- Stage 4: subtotal retinal detachment
  - 4A: extrafoveal detachment
  - 4B: foveal detachment
- Stage 5: total retinal detachment

## Severity of the disease

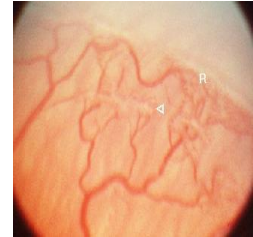
### Stage 1

#### Demarcation Line

- A line that is seen at the edge of vessels, dividing the vascular from the avascular retina.
- Retinal blood vessels fail to reach the retinal periphery and multiply abnormally where they end.

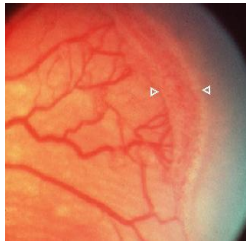
## ROP - Classification

- **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

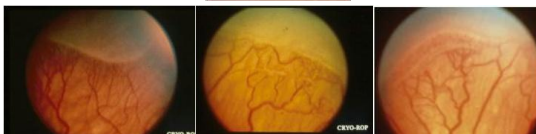
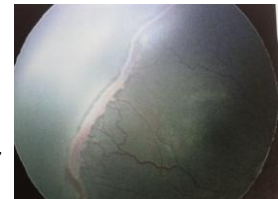
- **Stage 3** - Increased size of the vascular ridge (between the arrowheads), with growth of fibrovascular tissue on the ridge and extending out into the vitreous.
- Fibrous scar tissue is beginning to form in this stage, with attachments between the vitreous gel and the ridge.



## Stage 3

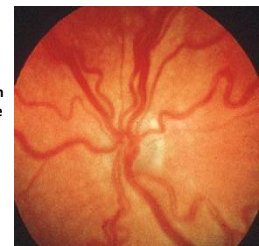
#### Ridge with extra-retinal fibrovascular proliferation

- The ridge of stage 2 develops more volume and there is fibrovascular proliferation into the vitreous.
- This stage is further subdivided into mild, moderate and severe, depending on the amount of fibrovascular proliferation



## 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).



## Plus Disease

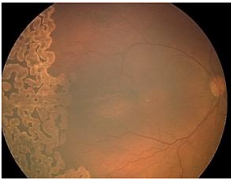


## Treatment

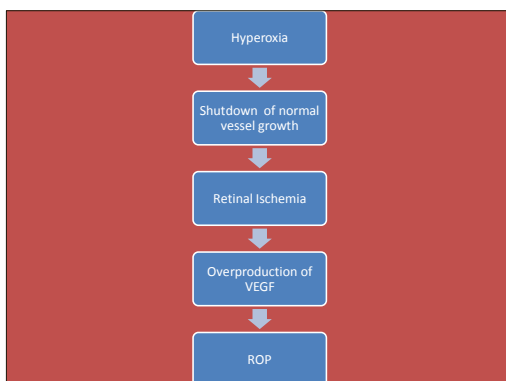
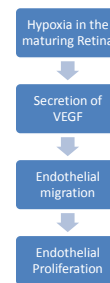
- zone I ROP: any stage with plus disease
- zone I ROP: stage 3—no plus disease
- zone II: stage 2 or 3 with plus disease

## Use of Conventional Laser

Use of laser especially zone 1 is associated with significant visual field loss

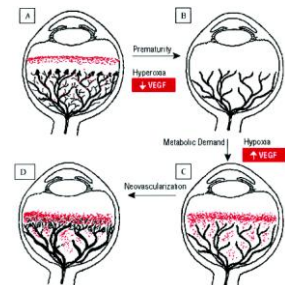


## WHY DOES ROP DEVELOP Normal vs Abnormal Retinal Vasculature



## Role of VEGF in ROP

- 1 - Cessation of the normal retinal vascularization.
- 2 - Avascular retina is hypoxic and metabolically active.
- 3 - Hypoxia causes VEGF induced neovascularization.
- 4 - New vessels bleed into eye.
- 5 - Blood causes fibroproliferation and traction retinal detachment (RD).
- 6 - RD loss of photoreceptors.
- 7 - BLINDNESS.



- So what if we can produce a medication that can down regulate this excessive VEGF?

## Bevacizumab



## BEAT-ROP

- Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity
  - Prospective, randomized, stratified, controlled, multicenter clinical trial
- Compared intravitreal avastin and conventional laser therapy
- Recruited 150 infants from 2008 to 2010.

## Results- BEAT-ROP

- The rate of recurrence for zone 1 was significantly higher in the conventional laser group.
- The rate of recurrence with Zone 2 did not differ significantly from the conventional laser

## ? Side effects

- 7 infants ( 5 who underwent avastin and 2 laser died)
  - OF the 5, 2 passed away at home with cause of death “low oxygen” and 3 as inpatients from respiratory failure

## Conclusions

- This study was large enough to show significant efficacy of bevacizumab for zone 1 disease and equal efficacy for zone 2 .
  - Inexpensive drug, can be rapidly administered
  - No requirements of intubation, expense of the OR
- An assessment of local or systemic toxicity would require a sample size of around 3,000

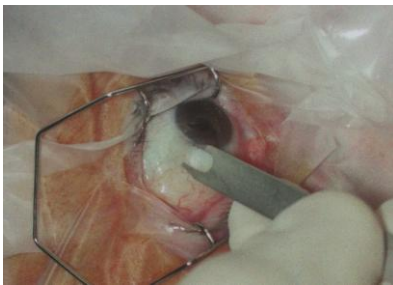
## Other notes of caution

- Recurrence with avastin was found to occur 16 weeks  $\pm$  4.6 vs 6.2 weeks  $\pm$  5.7 weeks after conventional laser
- Careful follow up of these pts until complete vascularization occurs with no active disease

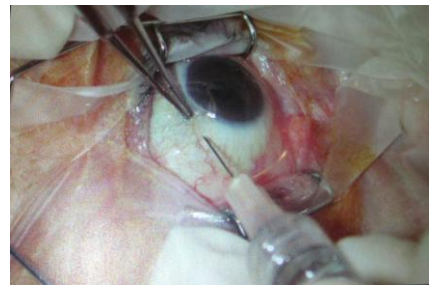
## Intravitreal Injections

- Anesthesia
- Ideal Drug:
  - Ocular safety, systemic safety, infrequent administration and therapeutic efficacy with low volumes

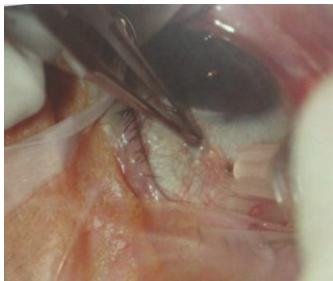
## Injection Site



## Needle Introduction and Injection



**The most effective prevention of retinopathy of prematurity is prevention of premature birth**



## References