Development of incubators allowed salvaging of increasing numbers of premature neonates.

Apnea was notably reduced in the presence of supplemental O₂ among these early premies.

In the 1940s, the standard of care called for supplemental O₂ for preterm infants – the more the better!

Retrolental fibroplasia [RLF] became the leading cause of blindness among preterm neonates discharged from NBNs during the 40s and 50s.
Linkage between O₂ exposure and RLF resulted in more cautious O₂ Rx with resulting decrease in incidence and severity of "RLF"

Greatest risk occurs among infants ≤ 32 weeks gestation and/or < 1200 grams BW

These risk factors historically have included:
- Hyperoxia
- Hypoxia
- Hypercarbia
- Metabolic acidosis
- Metabolic alkalosis
- Assisted ventilation
- Blood transfusions
- Sepsis
- IVH
- Vitamin E deficiency
- Bright light exposure
- Prematurity

ROP is divided into acute and chronic phases

The acute phase occurs when there is interrupted vasculogenesis in response to retinal injury (i.e., relative HYPEROXIA associated with birth) among neonates at risk

Once injured, the immature retina arrests its development for a period of 3 – 8 weeks before the first visible signs of neovascularization begin to appear

The chronic phase occurs with proliferation of fibrous tissue growth into the vitreous which may result in retinal detachment from traction placed between the lens and the retinal surface

Blood supply to the retina is initiated adjacent to the optic nerve ~ 16 weeks gestation when the retina becomes too thick to be nourished by diffusion alone. Growth proceeds centrifugally from the optic disc to the ora serrata
The current concept of the pathogenesis of ROP suggests that preterm birth interrupts the normal process of retinal vessel development. The normal physiologic hypoxia “drive” of angiogenesis is reduced [down-regulated]. Local systemic concentrations of growth factors, notably IGF-1 & VEGF are low. Thus, the process of retinal vascularization is delayed, and the peripheral retina remains avascular.

VEGF [vascular endothelial growth factor] is a specific growth factor for endothelial cells induced by relative fetal hypoxia in retinal cells. Vascular endothelial growth factor/vascular permeability factor [VEGF/VPF] is an endothelial cell-specific mitogen recently identified whose origin appears to be within cell bodies within the inner nuclear layer of the retina. IGF-1 [insulin-like growth factor] is essential at critical threshold levels to stimulate VEGF-signaled angiogenesis during physiologic fetal hypoxia. Following birth, exposure of the retina to relative hyperoxia down regulates IGF-1, and inhibits VEGF activity leading to temporary cessation of normal retinal vessel growth [down regulation].

Preterm infants then have low tissue levels of IGF-1 which gradually rise with advancing postnatal age. When tissue levels of IGF-1 reach a critical threshold level, VEGF-signaled angiogenesis resumes [up regulation]. IGF-1 level increases are dependent on adequate nutrition. Resumption of vascular growth with resumed VEGF stimulation may progress normally or pathologically depending on gestation, ± risk factors, etc.
Although ROP affects the entire retina, abnormalities are particularly striking at the junction of the posterior vascularized retina and the anterior avascular retina.

- **Stage 1 ROP**: A flat line of demarcation occurs between the vascular and avascular retina.

- **Stage 2 ROP**: The line of demarcation acquires volume to become a ridge. Tufts of new vessels may appear on the posterior edge of the ridge, but these vessels still are within the retina.

- **Stage 3 ROP**: Neovascularization can be seen within the ridge, and extraretinal vascularization extends out of the retina.

- **Stage 3 ROP+ [threshold ROP]**: Increased dilation and tortuosity of the posterior retinal vessels noted; it is at this stage that intervention is recommended.
Aggressive Posterior ROP: previously described as “rush” disease; occurs typically in zone I and in posterior zone II
- It is deceptively featureless and may appear as a flat network of neovascularization within the retina.
- The most prominent feature is severe plus disease

ROP stage 4: Subtotal retinal detachment:
A. Extrafoveal
B. Retinal detachment including fovea

ROP stage 5: Total retinal detachment:

Normal premature infant fundus with complete retinal vascularization:
Classification of Clinical ROP Appearances

- Dilated, tortuous vessels typical of "plus disease" exiting the disc:

Research and Strategies to Decrease Risk of Progressive ROP among at-risk Prematures

Is assisted ventilation an independent risk factor favoring development of progressive ROP?

At JCMCH NICU, we reviewed retrospectively charts of infants admitted to the NICU who were < 1500 grams, and requiring mechanical ventilation to determine the incidence of and grading of ROP, and the need for laser surgery for threshold ROP. Infants < 1500 grams not requiring mechanical ventilation served as controls.

Data presented at the 2001 Southern Society for Pediatric Research Meeting.

Objective: To determine the efficacy and safety of supplemental therapeutic O2 for infants with prethreshold ROP to reduce the probability of progression to threshold ROP and the need for peripheral retinal ablation surgery.

Methods: Premature infants with confirmed pre-threshold ROP in at least one eye and median pulse oximetry < 95% were randomized to a conventional oxygen arm with pulse oximetry targeted at 89-94% SaO2 or a supplemental arm with pulse oximetry targeted at 96-99% SaO2, ≥ 2 weeks, and until both eyes were at study endpoints as determined by certified examiners.

A favorable ophthalmic endpoint was regression of ROP into zone III for at least 2 consecutive weekly exams or full vascularization.

At 3 months PCA, ophthalmic findings, pulmonary status, growth and interim illnesses were recorded.

~ 300 infants were studied in each arm of the study.

Findings
- The rate of progression to threshold in at least one eye was 48% in conventional arm, 41% in supplemental arm.
- Final structural status of all study eyes @ 3 months corrected age showed similar rates of severe sequelae in both treatment arms (~4% detachment or folds).
- Infants without + disease may be more responsive to supplemental therapy (48% progression in conventional arm vs 32% in supplemental arm but not statistically significant).
- Exacerbations of CLD occurred among more infants in the supplemental arm (8.5% conventional vs 13.2% supplemental).
- Growth and developmental milestones were compatible between arms.

Conclusions
- Use of supplemental O2 at SaO2 96-99% did not cause additional progression of prethreshold ROP but also did not significantly reduce the # of infants requiring laser ablative surgery.
- Supplemental O2 increased the risk of adverse pulmonary events including pneumonia and/or exacerbations of CLD and the need for O2, diuretics and hospitalization at 3 months corrected age.

On the basis of these studies and other confirmatory studies, we have adopted a conservative O2 approach attempting to keep oxygen within limits.

These tags are placed at the bedside of all premature infants receiving supplemental O2 either while on assisted ventilation, SiPAP, HFNC or nO2.

Despite these measures, we noted a worrisome trend in incidence of threshold ROP among at-risk premature infants during 2006 when compared to Vermont Oxford Multi-institutional data.
Should be noted that during this period (2005-2007), epogen dosing was being started < initial 2 weeks of life and therapeutic iron was being added to TPN fluids in an effort to reduce the need for PRBC IV replacement Rx. During this time, hematocrit levels prompting transfusions among infants requiring assisted ventilation were ≤ 40%. Dr. Mike DeVoe, Renee Lowe, RN and Lisa Carter RN established a ROP Prevention Project Flow Diagram aimed at reviewing literature concerning ROP risk factors, reviewing practices from among VON participants to determine if additional preventive strategies could be applied.

A web of causation became clear during this intensive investigation and literature research:

**Why the concern about iron therapy?**

Dani C, Reali MF, et al. published an article entitled: The role of blood transfusions and iron intake on retinopathy of prematurity. Early Human Devel. 62(2001); 57-63

Aim of Study: to evaluate the influence of PRBC transfusions and iron intake on ROP incidence

Study Design: 45 preterm infants < 1250 grams studied; following ROP exams, infants divided into 2 groups: group A (n=24) no ROP; group B (n=21)

Iron Rx added @ 2 mg/kg/d when infant ≥ 100 ml/kg/d formula intake, then to 6 mg/kg/d FV feeds Epogen Rx generally added starting @ 3 weeks age

**Results:**

A significant increase in PRBC transfusion volumes and iron intake statistically significant between groups during the first week of life and during the first 2 months following birth; i.e.: infants who developed ROP were exposed to greater total iron intake than among infants with no ROP.
The reported mechanisms by which blood transfusions could contribute to the development of ROP are:

(a) increase of oxygen to the retina (increased delivery of oxygen from adult Hgb A vs fetal Hgb)

(b) secondary iron overload

Protection against free iron is via binding by ceruloplasmin and transferrin, but in preterm infants < 33 weeks GA, occurs → ↑ free iron concentrations

Increased amounts of free iron may catalyze Fenton reactions which produce free radicals. Iron-bound oxygen is capable of producing free radical damage to the retina.

On September 8th, 2007 based on aforementioned research, a new policy was instituted to address these additional risk factors:

**Purpose of Study:** Comparison of 2 equivalent groups of VLBW premature infants < 28 weeks gestation regarding incidence of threshold ROP before and after initiating a ROP risk reduction strategy [RRS] in September, 2007

**Methods Used:** Preterm infants < 28 weeks gestation born between 1/2005 through 8/2007 [group 1] and preterm infants < 28 weeks gestation born between 9/2007 through 7/2010 [group 2] of equivalent number were compared for threshold ROP requiring ROP laser surgery. The risk reduction strategy [RRS] consisted of minimizing need for packed red cell transfusions; keeping SaO2 levels between 82-95% [O.W.L. strategy] when possible; delaying erythropoietin dosing until > 14 days age; measuring serum ferritin levels starting at 3 weeks age with followup levels at 2 weeks intervals; avoiding exogenous administration of intravenous iron therapy until ferritin levels decreased < 100 mcg/ml (usually not given until infant > 6 weeks chronologic age).
**A Risk Reduction Strategy Reduces Incidence of Threshold Retinopathy of Prematurity in Neonates < 28 Weeks Gestation**

**Summary of Results:**

- Pre-RRS infants (group 1; n=69) noted to develop threshold ROP statistically significantly more often than infants treated with the RRS (group 2; n=63): 20/69 (29%) vs 5/63 (7.9%); p < .05
- Additionally, no threshold ROP was noted among infants 26 or 27 weeks gestation in the RRS group suggesting a complementary role for RRS and advancing gestational age

**Conclusions:**

- Strict attention to oxygen therapy (O.W.L. approach); minimizing PRBC transfusions; restricting iron therapy while monitoring serum ferritin levels and initiating erythropoietin > 14 days of age appear beneficial in this limited retrospective study

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**Clinical Data Table 2:**

<table>
<thead>
<tr>
<th>GA</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 weeks</td>
<td>3/3 (100%)</td>
<td>1/2 (50%)</td>
<td>NS</td>
</tr>
<tr>
<td>24 weeks</td>
<td>5/9 (55%)</td>
<td>2/12 (17%)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>25 weeks</td>
<td>7/16 (44%)</td>
<td>2/11 (18%)</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>26 weeks</td>
<td>2/19 (11%)</td>
<td>0/22 (0%)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>27 weeks</td>
<td>3/22 (14%)</td>
<td>0/16 (0%)</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

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**Screening Examination of the Retina**

- Most infants < 28 weeks gestation will develop some degree of ROP. A small proportion, even up to 32 weeks gestation (and if SGA, even greater gestations) develop potentially severe retinopathy, with the danger of visual impairment or even total blindness

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**Table 1. Division of Responsibilities**

<table>
<thead>
<tr>
<th>Responsibilities</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsibilities of the Hospital Physician</td>
<td>- Infants' parents/guardians are informed about the risk of ROP and the need for screening.</td>
</tr>
<tr>
<td>Responsibilities of the Screening Ophthalmologist</td>
<td>- Perform the screening examination following the hospital's guidelines.</td>
</tr>
<tr>
<td>Responsibilities of the Screening Retinalist</td>
<td>- Interpret the examination results and report any signs of ROP.</td>
</tr>
</tbody>
</table>

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**Table 2. Timing of Follow-up Screening Examinations**

<table>
<thead>
<tr>
<th>Time of Follow-up</th>
<th>Date of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week or sooner</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>2-3 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>4-5 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>6-7 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>8-9 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>10-11 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>12-13 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>14-15 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>16-17 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>18-19 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>20-21 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
<tr>
<td>22-23 weeks</td>
<td>Directly after the initial examination.</td>
</tr>
</tbody>
</table>

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**Infants whose birthweights are < 1500 grams or GA ≤ 30 weeks should be screened, or 1500-2000 gms, with unstable courses**
Treatment Criteria

The threshold degree of severity defined by the ETROP study that requires early treatment is classified as Type 1 ROP:

- Type 1 ROP consists of:
  - Zone I, any stage of ROP with + disease
  - Zone I, stage 3 ROP without + disease
  - Zone II, stage 2 or 3 ROP with + disease
- The extent of clock hours of ROP no longer is used as a criterion for treatment

Severity Level

<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Visual Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Myopia</td>
</tr>
<tr>
<td>Grade II</td>
<td>Severe myopia and astigmatism</td>
</tr>
<tr>
<td>Grade III</td>
<td>Able to see only hand motions</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Light perception or total blindness</td>
</tr>
</tbody>
</table>

Amended List of Risk Factors for ROP

- Hyperoxia
- Hypoxia
- Hypertension
- Metabolic acidosis
- Metabolic alkalosis
- Assisted ventilation
- Blood transfusions
- Sepsis
- IVH
- Vitamin E deficiency
- Bright light exposure
- Prematurity
- Excessive iron load from PRBC transfusions
- Exogenous iron therapy

A Capsule of the Economy

Good Prospects for a Happy Holiday

- Late economic recovery
- Weak growth through first quarter
- Continued improvement in the second quarter
- Sustained growth in the third and fourth quarters
- High likelihood of policy changes
- Strong economic growth
- Continued improvement in the second quarter
- Sustained growth in the third and fourth quarters
- High likelihood of policy changes
- Strong economic growth
And Finally →

For those worried about what may happen on 12/21/12

As quoted from THE WEEK, vol.10; issue 488; p. 8:

“It was a bad week for everyone who bought one of those 2012 books, after new research found an error in the conversion of the Mayan to modern calendars, and that the “end of days” predicted by the Mayan calendar is NOT December 21, 2012, but may be 50 to 100 years later” ☺

References

Alini S & A Clausen: Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of systematic Reviews, issue 3 (2007)