The growth of blood vessels within the eye is essential for normal ocular development (Figure 1). During early fetal development, the retina lacks blood vessels and depends on the primary vitreous, or hyaloid system, for vascular support. Subsequent regression of this system coincides with the development of the mature retinal vasculature, consisting of two stages, vasculogenesis and angiogenesis. Vasculogenesis is the de novo formation of blood vessels from the differentiation of endothelial precursor cells, while angiogenesis is the formation of new vessels from existing vasculature. Vasculogenesis and physiologic angiogenesis are tightly orchestrated processes involving complex signaling cascades. Vasculogenesis continues from approximately 12 to 21 weeks of gestation and as the normally developing retina becomes more metabolically active, it uses more oxygen. In this relatively oxygen deprived environment, beginning about 17 weeks of gestation, vascular development transitions to physiologic angiogenesis through the recruitment of genes such as hypoxia-inducible factor (HIF)-1 and vascular endothelial growth factor (VEGF). Importantly, maternally derived factors such as insulin-like growth factor-1 and omega-3 and polyunsaturated fatty acids also influence fetal angiogenesis.

Fetal retinal development nears completion between 36 to 40 weeks of gestation, corresponding to delivery of a full-term infant. This development of normal retinal vasculature depends on precisely timed actions of specific growth factors fostered by the unique intrauterine environment. Alterations to this process can lead to abnormal retinal vascular development and retinopathy of prematurity (ROP).

Table 1: ROP Stages/Definitions

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Demarcation Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>Ridge</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Ridge with ERNV (extra retinal neovascularization)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Partial retinal detachment</td>
</tr>
<tr>
<td></td>
<td>4a – macula attached</td>
</tr>
<tr>
<td></td>
<td>4b – macula detached</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Total retinal detachment</td>
</tr>
<tr>
<td></td>
<td>5a – open funnel detachment</td>
</tr>
<tr>
<td></td>
<td>5b – closed funnel detachment</td>
</tr>
<tr>
<td>Plus Disease</td>
<td>Can be present at any stage. This stage describes a significant level of vascular dilation and tortuosity seen at the posterior retinal vessels.</td>
</tr>
<tr>
<td>Threshold Disease</td>
<td>Defined as disease that has a 50% likelihood of progressing to retinal detachment.</td>
</tr>
</tbody>
</table>
ROP definitions and clinical findings

ROP is a leading cause of blindness and visual impairment in infants and children worldwide. In the United States (US), ROP is the leading cause of blindness in children. A recent large study summarizing 9 years of data from the US reported the incidence to be 0.17%; therefore, it is estimated that ROP affects more than 1 of every 550 newborns. Many factors have been correlated with an increased risk of developing ROP including younger gestational age and lower birth weight. For example, the reported incidence of ROP in newborns weighing less than 1000 grams at birth is approximately 80% and in newborns less than 1251 grams is approximately 67%.

Upon premature delivery, the infant experiences a hyperoxic environment and an abrupt cessation of maternal growth factors and nutrients. This results in stage 1 ROP, characterized by obliteration of vessels and inhibition of physiologic retinal angiogenesis due in large part to degradation of HIF-1 and lack of its effect. As the developing retina continues to mature and increase its metabolic activity outside of the womb, areas of retina become hypoxic, transitioning to pathologic angiogenesis, again mediated at least partly by HIF-1 and VEGF. This disease process manifests itself at the boundary between vascular and avascular retina and is termed phase 2 ROP.

Classification of ROP employs several clinical factors to define the disease activity and aid the practitioner in determining which infants to treat. Clinical findings include the location of the disease, the extent, the stage, as well as other high-risk clinical features.

Location of disease describes the anterior-posterior localization and is defined by 3 concentric circles of increasing diameter with the optic disk at the center (Figure 2). The radius of zone 1 is twice the distance from the optic nerve to the fovea. Zone 2 extends from the border of zone 1 to the nasal ora serrata, and zone 3 includes the remaining temporal retina beyond zone 2. Extent of disease is described in clock hours.

Staging of ROP describes the abnormal response of the developing retina at the boundary of vascularized retina and avascular peripheral retina. In stage 1 a thin, flat, grayish-white demarcation line forms between vascularized and avascular retina (Figure 3). In stage 2, this boundary is an elevated ridge of mesenchymal tissue (Figure 4). In stage 3, extra-retinal fibrovascular proliferation extends above the ridge into the vitreous (Figure 5).
Stage 4 represents a partial retinal detachment; 4a, sparing the macula (Figure 6), and 4b, involving the macula (Figure 7). Stage 5 is a total retinal detachment, open or closed funnel detachment (Figure 8).

Plus disease is an important predictor of disease progression (Figure 9), often necessitating treatment. Plus disease represents an acute phase of ROP which is seen secondary to peripheral shunting of blood from the chronic ischemia of the avascular retina. The primary clinical findings are venous dilation and arteriole tortuosity of at least 2 quadrants of the posterior pole. Other clinical features can include limited pupillary dilation secondary to iris vessel engorgement, vitreous haze, and preretinal or vitreous hemorrhages.

An especially aggressive form of ROP is known as rush disease, or aggressive posterior-ROP (AP-ROP).

Figure 6: ROP stage 4a – temporal retina is detached.

Figure 7: ROP stage 4b – macula is detached.

Figure 8: (a) ROP stage 5 – total retinal detachment. (b) ROP stage 5 – total retinal detachment. (c) ROP stage 5 – total retinal detachment. (d) ROP stage 5 – External view of a closed funnel retinal detachment.

Figure 9: Plus disease – note the neovascularization at the ridge, the retinal and vitreous hemorrhage.
ROP – A Visual Experience

(Figure 10). AP-ROP is characterized by rapidly progressive disease primarily located in the posterior pole with substantial plus disease often affecting all 4 quadrants, as well as an ill-defined nature of the clinical findings (Figure 11). AP-ROP warrants aggressive treatment, as it can progress to stage 5 disease without following the classical course of stages 1 to 3.

**TREATMENT OF ROP**

Traditional treatment involves ablative therapy of ischemic retina when certain clinical criteria are met with cryotherapy or laser photocoagulation. In the 1980s, a multi-centered trial investigated the efficacy of cryotherapy for ROP (CRYO-ROP). Infants of less than 1251 grams underwent serial examinations until complete retinal vascularization. 66% developed ROP, with most disease regressing without treatment. However, 6% of infants progressed to threshold disease and were enrolled in the treatment arms of the trial. Threshold disease was defined as 5 continuous clock hours or 8 total clock hours of stage 3 disease in zone 1 or 2, with associated plus disease. Cryotherapy was compared with observation. At 15 years, the rate of unfavorable outcomes was significantly lowered by treatment: 51.9% for untreated eyes and 30% for treated eyes (Figure 12).

Despite the efficacy of cryotherapy, several drawbacks prompted investigators to pursue other treatment modalities. Laser photocoagulation allows more controlled, complete retinal ablation and many studies have demonstrated its safety, efficacy and superiority compared to cryotherapy.

Despite these efficacious treatments, a large percentage of infants continued to have poor visual and structural outcomes. As a result, investigators questioned whether the threshold level for treatment is too late in the disease course. To study the effects of earlier treatments, the Early Treatment of ROP (ETROP) study was initiated. Earlier treatment of eyes with high-risk, prethreshold disease significantly reduced unfavorable visual outcomes from 19.8% to 14.3%, and decreased unfavorable structural outcomes from 15.6% to 9.0%. As a result, earlier treatment is indicated for high-risk prethreshold disease (Figure 13), known as Type 1 ROP: any stage of disease in zone 1 with plus disease; stage 3 disease in zone 1 without plus disease; or stage 2 or 3 disease in zone 2 with plus disease.

Following adequate laser ablation (Figure 14), the rate of regression of disease is 76 – 100%. Guidelines recommend treating within 48 – 72 hours of diagnosis for any infant with Type 1 ROP. Laser choices include either diode (810nm) or the argon green (514nm).

**Figure 10:** (a) P-ROP (aggressive posterior ROP). (b) AP-ROP – by using a green filter there is a better view of the retinal vasculature in AP-ROP.

**Figure 11:** AP-ROP with a pre-retinal macular hemorrhage.

**Figure 12:** Cryo treatment in a 26 year old ex-premie – presenting now with a retinal detachment.
with the diode laser preferable due to its deeper penetration and a reduced risk of cataract formation. Treatment is aimed at avascular retina anterior to the developing ridge, but not including the ridge, and continues for 360 degrees extending to the ora serrata with a whitish-grey burn as the initial desired result.

The density of retinal laser ablation during ROP treatment has a significant impact on the ability to control disease progression and adequate laser treatment is imperative for appropriate treatment. Most studies recommend applying near-confluent burns with patterns placed one-half burn width or less apart, and no larger than one burn width apart. Complete 360 degree viewing of the retina is performed following laser treatment to ensure adequate treatment and to identify any skip areas (Figure 15). Infants are initially followed weekly, with re-treatment commencing for persistent plus disease or disease progression (Figure 16).

Eyes progressing to retinal detachment (Figure 17) may benefit from surgery, including a combination of scleral buckling and vitrectomy depending on the clinical situation. However, despite good anatomic results, visual results are guarded.

More recently, attention has been drawn to anti-VEGF-A (herein referred to as VEGF) treatments. VEGF is a key mediator of angiogenesis in the fetus as well as angiogenesis and vascular permeability in a multitude of ocular diseases. The signal transduction cascade associated

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**Figure 13:** Stage III ROP with plus disease.

**Figure 14:** Same patient as in Fig. 13, immediately following intermittent laser treatment (not dense pattern).

**Figure 15:** (a) Post laser treatment – note skip area (arrow) and the persistence of the ridge adjacent to skip area. (b) Skip area filled with supplemental laser. (c) 3 weeks later – ridge is gone and the retinal vasculature is normal.

**Figure 16:** (a) Skip area (arrow) in a patient with persistent plus disease. (b) Skip area filled with supplemental laser.
with VEGF can be inhibited at various stages. Ranibizumab (Lucentis, Genentech Inc., San Francisco, CA) was FDA approved in 2006 for the treatment of neovascular AMD\(^ {13} \) and is a monoclonal antibody fragment that binds to and inhibits VEGF. Bevacizumab (Avastin, Genentech Inc, San Francisco, CA) was FDA approved for intravenous use in metastatic colon cancer in 2004 and is a humanized monoclonal antibody that binds to and inhibits all VEGF. Bevacizumab was derived from the same murine antibody as ranibizumab and is currently used in a non-FDA approved fashion for treating a variety of ocular disorders.\(^ {14} \)

The introduction of anti-VEGF pharmaceuticals has revolutionized the management of many ocular diseases in a short time period. For example, ranibizumab was the first treatment for neovascular AMD to show an average improvement in visual acuity in multicenter, prospective, randomized trials, and therefore created a paradigm shift in our first-line approach to treatment from laser-based modalities to pharmacologic agents. Similar radical changes in treatment patterns for many other ocular diseases have followed.

While the use of anti-VEGF agents in ROP holds great promise, VEGF also plays multiple normal physiologic roles in the developing retina and brain. Therefore, while inhibition of VEGF may appear remarkably efficacious for the treatment of some forms of ROP, the normal physiologic role of VEGF in the developing child must be considered. Thus far, results have been encouraging with no reports of drug-related complications or any injection-related serious adverse events.\(^ {12} \)

As always, more data, especially prospective data, will be needed to optimize our long-term treatment outcomes.

### Complications

Laser ablative treatment for ROP can result in a variety of complications (Figure 18).\(^ {9} \)

Overtreatment can occur with high power settings or excessive laser application. Overtreatment can also occur when moving from posterior to anterior retina; with the decreased thickness of the anterior retina and less power needed for treatment, retinal breaks can complicate treatment. Overtreatment...
may also result in choroidal hemorrhage, exudative retinal detachment, and vitreous hemorrhage. Anterior segment complications can also develop following laser treatment. The cornea and iris may sustain laser burns and anterior segment hemorrhage may be seen. Mild to moderate inflammation may be seen, rarely resulting in posterior synechiae. Cataracts have been reported following laser application in up to 1% of treated infants, possibly secondary to absorption by a persistent tunica vasculosa lentis (Figure 19), most consisting of small transient lens opacities.

A potentially devastating complication is anterior segment ischemia which likely develops following ablation of the posterior ciliary arteries. Such affected eyes can develop corneal opacification, pupillary membranes, cataract and can progress to phthisis. Despite the goal of near-confluent treatment throughout the avascular retina, care must be taken along the horizontal meridians (3 and 9 o’clock) to avoid inadvertent destruction of the posterior ciliary arteries.

**CONCLUSION**

Premature infants who develop ROP require long term ophthalmic care, whether or not treatment is applied. These patients are at risk for a multitude of ophthalmic issues including myopia, amblyopia, strabismus and retinal detachment.

ROP is a leading cause of blindness and visual impairment in infants and children worldwide, and it will continue to increase. Although screening, treatment and follow up of these fragile babies can lead to excellent visual results (Figure 20), good ophthalmic photography is of the utmost importance and can play a crucial role in the diagnosis and treatment of this potential blinding disease.

**Figure 19:** Tunica vasculosa.

**Figure 20:** (a) Example of recommended dense laser pattern for AP-ROP. (b) same as Figure 20a.

**Figure 21:** Lid speculum.

**Figure 22:** Dark central circle secondary to poor dilation.
1. Documentation of disease.
2. Objective tool in the comparison of images as an aid in decision making.
3. Teaching tool for other ophthalmologists, neonatologists, nurses and parents.
4. As a telemedicine tool for places where there is a void of physicians who are willing or available to screen and/or treat.
5. For medicolegal documentation.

Table 2: The importance of digital RetCam photography for the physician.

| 1. Type of speculum (Figure 21): Gentle, less traumatic speculum for the use in babies that are awake. |
| 2. Dilation: Size of pupil will have an impact on the quality of the image. If the pupil is too small there will be a dark, central circle (Figure 22). |
| 3. Quadrants: For ROP screening there is a standard of necessary quadrants that need to be imaged. These are: a) posterior pole, b) temporal quadrant, including the macula, c) nasal quadrant, including the optic nerve, and d) superior and inferior quadrants, both including the optic nerve. |
| 4. Anterior structures: If the photographer notices abnormal anterior structures these should be photographed, such as: cataracts, persistent tunica vasculosa and iris neovascularization (Figures 19 and 23). |
| 5. Technique: When imaging such small and fragile sclera, great caution should be taken in the amount of pressure applied to the eyeball, as it can easily blanch the optic nerve from compression of the eye wall. |

Table 3: Important techniques/pearls for the photographer in obtaining good digital RetCam images in the neonate.

1. Type of speculum (Figure 21): Gentle, less traumatic speculum for the use in babies that are awake.
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REFERENCES