Congenital Vascular Vitreoretinopathies

III.A.

Ronald Paul Hobbs and Mary Elizabeth Hartnett

Outline

Keywords

Retinopathy of prematurity (ROP) • Neovascularization • Angiogenesis • Vasculogenesis • Bevacizumab • Pharmacologic vitreolysis • Persistent fetal vasculature (PFV) • Hyaloid vessels • Familial exudative vitreoretinopathy (FEVR) • Retinal detachment

Key Concepts

1. Retinopathy of prematurity (ROP) continues to cause serious problems in developed countries and has seen a recent dramatic increase in developing countries. Our improved understanding of its pathogenesis has led to a useful classification system of ROP and reasonably effective therapies being utilized today with potential new therapies on the horizon.
2. Persistent fetal vasculature results from failure(s) of regression of the fetal vitreous circulations including the vasa hyaloidea propria. Resulting pathologies have variable clinical presentations, genetic associations, and treatment options.
3. Familial exudative vitreoretinopathy was first described in 1969 and since been identified to have tremendous variability in the clinical presentation, course, and even inheritance patterns. When severe, FEVR can be a lifelong retinal vascular disease with variable periods of quiescence.

R.P. Hobbs, MD
Vitreoretinal Fellow, University of Utah, John A Moran Eye Center, 65 Mario Capecchi Drive, Salt Lake City, UT 84132, USA
e-mail: ronald.hobbs@hsc.utah.edu

M.E. Hartnett, MD (✉)
Director of Pediatric Retina, Vitreoretinal Service and Surgery, Retinal Angiogenesis Laboratory, University of Utah, John A. Moran Eye Center, 65 Mario Capecchi Drive, Salt Lake City, UT 84132, USA
e-mail: me.hartnett@hsc.utah.edu

J. Sebag (ed.), *Vitreous: in Health and Disease*,
DOI 10.1007/978-1-4939-1086-1_13,

I. Introduction

Congenital vitreoretinopathies manifest in the pediatric or adult population in a variety of ways and cause varying levels of vision loss. These conditions can also be influenced by environmental factors, as in retinopathy of prematurity (ROP), or be associated with inheritance involving autosomal dominant, autosomal recessive, or X-linked patterns or be sporadic, as with familial exudative vitreoretinopathy (FEVR). As more is learned regarding gene associations, it is anticipated that complex genetic interactions may also play a role in the pathophysiology. Given the rarity of the diseases and their variable manifestations, along with the difficulty of obtaining longitudinal clinical information in the pediatric population, correct diagnosis and treatment can be quite challenging.

The goal of this chapter is to describe the presentations and classifications of ROP, persistent fetal vasculature (PFV), and FEVR that will be helpful to the caregiver to identify these diseases. In order to accomplish this goal, ancillary tests that are helpful in distinguishing different vitreoretinopathies will also be reviewed. In addition, up-to-date treatment options will be discussed. A history of past treatment options and studies that have led to current treatment recommendations for ROP will be included. Whereas fewer analogous studies exist for PFV and FEVR, the current literature and treatment recommendations will also be reviewed. Finally, the expanding knowledge of the genetic components of these diseases will be reviewed as well as systemic associations.

II. Retinopathy of Prematurity

Retinopathy of prematurity (ROP) was first described by Terry in 1942 as the most advanced stage, stage 5 ROP, then described as retrolental fibroplasia. ROP involves aberrant developmental angiogenesis in preterm infants associated with first a delay in physiologic retinal vascular development and later vasoproliferation into the vitreous, which can lead to complete retinal detachment and blindness. In the United States alone, it is estimated that 14,000–16,000 infants are affected by some degree of ROP annually with 1,100–1,500 requiring treatment and 400–600 becoming legally blind [1].

Studies by Patz [2] in 1952 and Kinsey [3] in 1956 demonstrated a link between high oxygen concentrations at birth and the development of ROP. A 40 % limit of oxygen delivered was recommended and was associated with decreased blindness from ROP. However, the reduction in oxygen delivered to the preterm infant was associated with increased mortality and a greater prevalence of cerebral palsy among survivors [4]. Today it is understood that low birth weight and young gestational age are highly associated with increased risk of developing ROP [5]. However, ROP remains the second most common cause of childhood blindness in the United States and other developed countries, next to cortical blindness [6]. More recent data from middle-income and low-income countries have shown an explosive increase in severe ROP worldwide. Indeed, it is thought that two-thirds of the 50,000 children who are blind from ROP worldwide live in Latin America [5]. This is largely believed to be due to increased survival in premature babies; however, oxygen regulation, screening programs, prenatal care, and therapies may be limited due to reduced financial and personnel resources. This section will review current classifications of ROP, our changing understanding of its pathogenesis, and current and potential therapies utilized in its treatment.

A. Classification

The International Classification of Retinopathy of Prematurity (ICROP) provides standards for documenting the extent and severity of ROP. Four parameters are used: zone, stage, extent of stage, and presence or absence of plus disease. Since physiologic retinal vascular development proceeds peripherally to the ora serrata from the optic nerve, the optic nerve is considered the center of the diagram that divides the retina into zones. The zone is indicated as the highest zone into which vascularization in any clock hour occurs.

- *Zone I* corresponds to a circle, the center of which is the optic disk, with a radius of twice the distance from the optic disk to the center of the fovea.
- *Zone II* forms a circle peripheral to zone I with a radius from the optic nerve to the nasal ora serrata.
- *Zone III* is made up of the remaining temporal crescent of retina outside zones I and II.

The vascular stages of ROP (stages 1–3) are defined according to the appearance of the junction between vascularized and avascular retina. Staging is based on the most severe stage present in any location within the eye.

- *Stage 1* is characterized by a flat white line that separates vascularized from avascular retina.
- *Stage 2* is a ridge with volume in the region between the vascularized and avascular retina. Small tufts of new vessels may be seen in the vascularized retina posterior to the ridge (Figure III.A-1).
- *Stage 3* is characterized by neovascularization growing along the ridge and into the vitreous and may cause vitreous hemorrhage (Figure III.A-2).
- In *stage 4*, with advancing fibrovascular proliferation, traction is exerted on the retina, and progressive stage 4 ROP develops with a partial retinal detachment as a result. Stage 4 ROP is divided into stages 4A and 4B. In 4A, the detachment does not involve the macula, whereas in 4B, it does (Figure III.A-3).
- *Stage 5* denotes a total retinal detachment, sometimes with a peripheral attached trough anteriorly. These are almost always funnel shaped and further classified as "open" or "closed" anteriorly or posteriorly depending on the shape of the funnel.

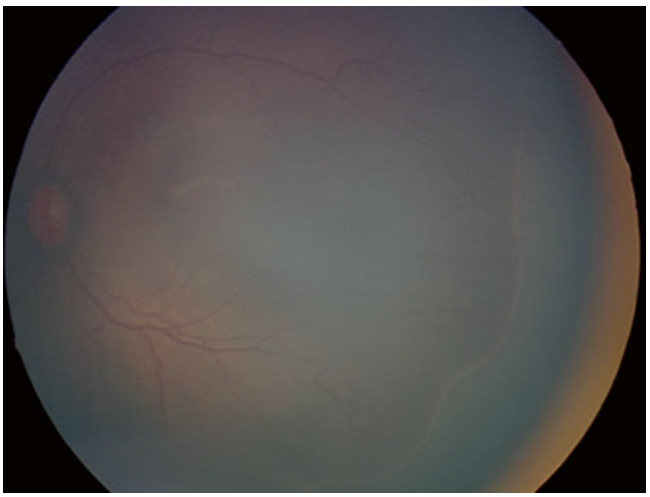

Figure III.A-1 Left eye of premature infant demonstrating Stage 2 ROP (RetCam image, Clarity)

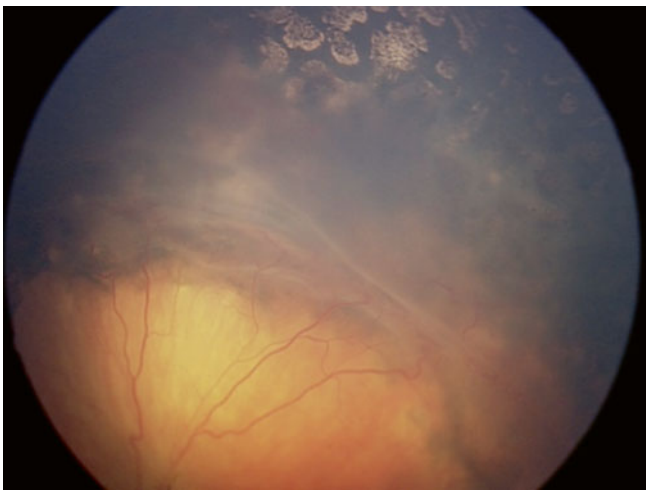

Figure III.A-3 Left eye of premature infant with stage 4A ROP demonstrating peripheral retinal detachment not involving the macula. Note the previous laser therapy to the surrounding avascular retina (RetCam image, Clarity)

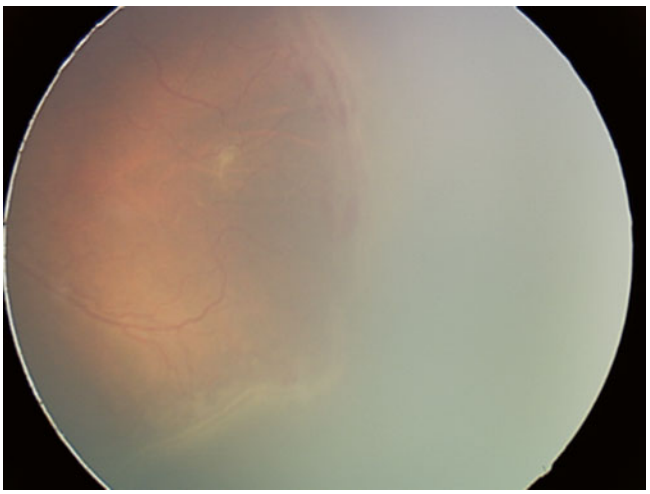

Figure III.A-2 Left eye of a premature infant with stage 3 ROP with small hemorrhages and prominent neovascular vessels along the ridge (RetCam image, Clarity)

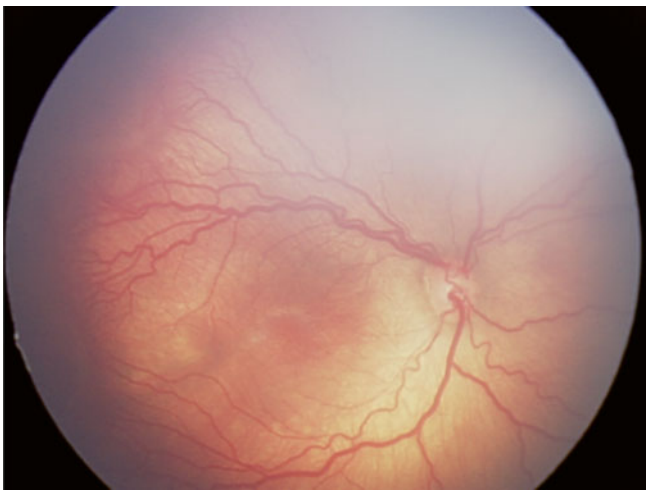

Figure III.A-4 Infant with ROP demonstrating plus disease (RetCam image, Clarity)

Plus disease refers to dilation and tortuosity of the retinal arterioles and veins and is defined by a standard photograph published in the CRYO-ROP study [6] (Figure III.A-4). Recently, "pre-plus disease" and "aggressive posterior ROP" (APROP) were added as categories. Pre-plus disease is defined as abnormal dilation and tortuosity of the posterior pole arterioles and veins that are insufficient for the diagnosis of plus disease. APROP is a severe plus disease in posterior zone II or zone I, which behaves in an aggressive manner with rapid progression often not adhering to the progression of stage of severity and with a higher likelihood of complete retinal detachment.

"*Threshold ROP*" was defined in the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study as 5 contiguous clock hours or 8 total clock hours of stage 3 ROP and plus disease in zone I or zone II. A "prethreshold ROP" classification defined eyes at risk of developing threshold ROP and was further subdivided into high-risk (type 1) and low-risk (type 2) prethreshold disease in the Early Treatment for Retinopathy of Prematurity (ETROP) study. High-risk (type I) eyes were estimated to have a ≥15 % chance of an unfavorable outcome, whereas low-risk (type II) eyes had <15 % chance.

Type 1 ROP – (high-risk) prethreshold ROP – was defined as:

- Zone I, any stage with plus disease
- Zone I, stage 3 with or without plus disease
- Zone II, stage 2 or 3 with plus disease

Type 2 ROP – (low-risk) prethreshold ROP – was defined as:

- Zone I, stage 1 or 2 without plus disease
- Zone II, stage 3 without plus disease

Results from the ETROP study recommended peripheral laser ablation to the entire avascular retina for type 1 ROP and weekly or twice weekly observation of type 2 ROP. Early treatment of infants resulted in fewer unfavorable structural outcomes and significantly reduced unfavorable visual acuity at 6 years' follow-up compared with conventional treatment [7, 8].

B. Pathophysiology

In utero, retinal development takes place in a relatively hypoxic environment with an arterial oxygen level (PaO_2) of approximately 30 mmHg and a saturation level of approximately 70 % [9]. This physiologic hypoxia is believed to induce growth factors that promote blood vessel development [10]. The hyaloid artery is the first vessel within the eye, appearing at approximately 6 weeks' gestation. The retina begins undergoing vascularization at approximately 16 weeks' gestation with vessels extending from the posterior pole toward the ora serrata and completes its extent by 40 weeks or term birth [11]. Initially, the retinal vascularization is believed to occur by vasculogenesis from endothelial precursor cells or angioblasts that arise from the deeper layers of the retina [12]. Angioblasts cover the posterior pole of the retina through at least 22 weeks' gestation. Following that, less is known about what happens in humans and, therefore, studies are based on other species. Retinal vascularization is believed to progress by angiogenesis, i.e., proliferation of endothelial cells from existing blood vessels that then migrate toward a gradient of vascular endothelial growth factor (VEGF) [13]. Other cells and growth factors, such as insulin-like growth factor-1 (IGF-1) and erythropoietin, can interact with VEGF and play a role [13–15].

From human observation and animal studies, ROP has been characterized as having two phases. In the first phase, a delay in physiologic retinal vascular development occurs. Premature infants have retinas that are not yet fully vascularized, and, therefore, there are areas of peripheral avascular retina when a preterm infant is born. The premature infant experiences fluctuations in blood oxygen levels that likely alter the oxygen status of the retinal tissue and the concentration of hypoxia-inducible factor-regulated growth factors, including vascular endothelial growth factor (VEGF). In addition, other angiostatic factors, such as pigment epithelium-derived factor, are upregulated during hyperoxia and downregulated during hypoxia. Oxygen fluctuations increase the expression of VEGF and also trigger signaling pathways related to reactive oxygen species from oxidative signaling that slows vascular development [16–18]. As the infant matures, supplementation of oxygen is reduced and the hyaloid vasculature regresses, contributing to hypoxia in the avascular retina. VEGF signaling through VEGF receptor 2 (KDR or Flk-1) increases and affects downstream pathways to delay physiologic retinal vascular development [19] and cause disordered growth of vessels into the vitreous rather than into the retina during the second phase of ROP at around 32–37 weeks' gestation. The abnormal vessels and later fibrovascular scarring can place traction on the retina and thus cause subsequent retinal detachment.

1. Mechanism of Retinal Detachment

Retinal detachments associated with ROP are divided into stages 4A, 4B, and 5. Others use the terms "predominantly effusive" or "predominantly tractional" to further classify these detachments [20]. The retina in a *predominantly effusive* detachment is convex toward the lens with fluid extending posterior to the ridge and toward the macula. This detachment is believed to result as vascular structures leak fluid into the subretinal space. It is seen less frequently after laser treatment than following cryotherapy. In a *predominantly tractional* detachment, peaked retinal folds pull the retina toward the center of the eye. Often, a central stalk and spokes of traction extend posteriorly when associated with regression of posterior hyaloid vessels and extend anteriorly when predominantly associated with delayed regression of the tunica vasculosa lentis. Both components can be seen (Figure III.A-5). Additionally, excessive growth factors in the eyes with ROP are associated with upregulation of hyaluronan and disproportionately liquefied vitreous that then provides reduced internal tamponade allowing the retina to be pushed (*effusive*) or pulled (*tractional*) away from the underlying choroid. A retrospective analysis by Hartnett et al. [21] reported that ridge elevation, recurrent or persistent plus disease, or vitreous haze and the appearance of vitreous organization in front of the lens in eyes treated for threshold ROP predicted progressive stage 4 ROP. In addition, Coats reported that vitreous organization and vitreous hemorrhage were associated with progressive stage 4 ROP [22].

Vitreous liquefaction is often unidentified [23] in stages 1 and 2 ROP and likely occurs as a result of both reactive oxygen species [24] and inadequate synthesis by the underlying peripheral retina where immature Müller cells do not support typical gel vitreous synthesis and may account for the vitreous trough apparent during surgery for stage 4 ROP. The disrupted molecular composition may limit the inherent vitreous ability to inhibit cell invasion [25–27], thereby permitting neovascularization in stage 3 ROP to grow [28, 29] between posterior gel and peripheral liquid vitreous anteriorly [29] (Figure III.A-6). Instability at the interface between gel and

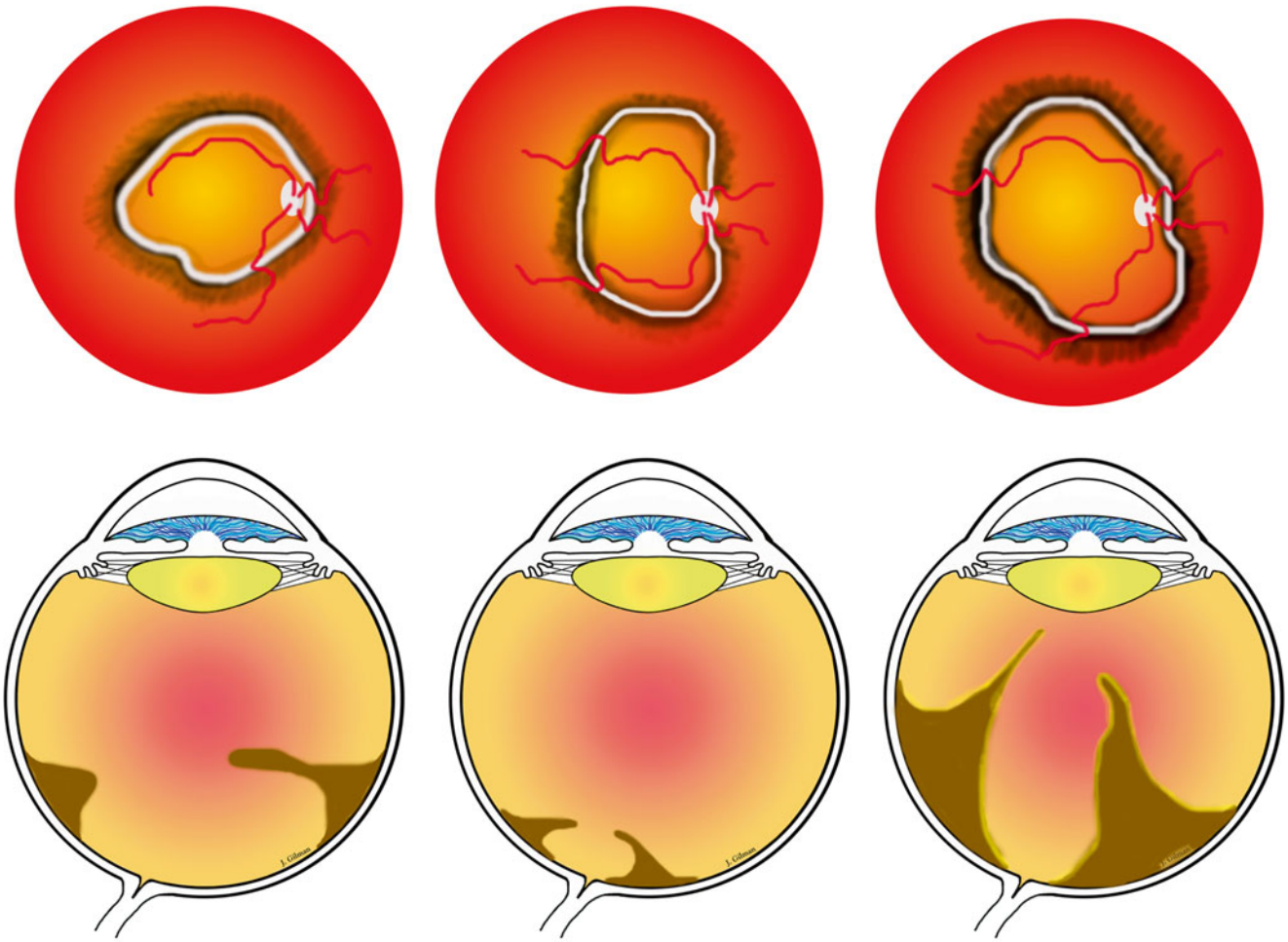

Figure III.A-5 Artist's rendition of a traction retinal detachment due to retinopathy of prematurity. *Left*: Asymmetrical traction associated with posterior elements of hyaloid vasculature. *Center*: Symmetrical traction of the posterior hyaloid vasculature. *Right*: Traction secondary to anterior hyaloid, i.e., tunica vasculosa lentis. *Top row* corresponds with view through indirect ophthalmoscope (adapted from [20])

liquid vitreous causes localized collapse of the peripheral vitreous at the ridge exerting traction on the underlying ridge, contributing to tractional retinal detachment.

C. Risk Factors

Prior to the ability to regulate oxygen to preterm infants, high oxygen at birth was recognized as a cause of ROP [2], Now, other oxygen conditions including fluctuations in oxygenation [30], hypoxia, hyperoxia (see below), and other stresses have been associated with ROP. The most important risk factors for developing ROP are young gestational age and low birth weight. However, more than 50 separate risk factors have been identified. Multivariate analyses demonstrate that low birth weight, young gestational age, poor postnatal weight gain, low IGF-1 levels, hyperglycemia, artificial ventilation more than 7 days, need for blood transfusions, surfactant therapy, and systemic infections are all independently associated with higher rates of ROP [31].

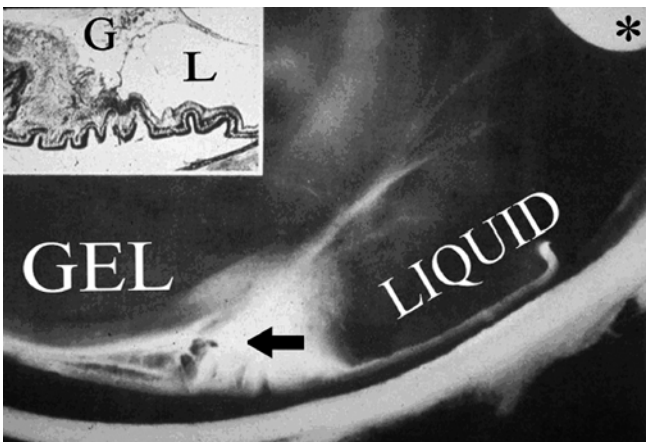

Figure III.A-6 Photomicrograph of the peripheral fundus in retinopathy of prematurity. The lens (*) is in the upper right-hand corner. Below, a fibrovascular membrane is present at the interface between the posterior gel vitreous and the peripheral liquid vitreous. Ridge elevation is seen (*arrow*). The inset (*upper left*) shows the histopathology that clearly distinguishes between gel (*G*) and liquid (*L*) vitreous (Courtesy of Maurice Landers, MD; reprinted with permission from: Sebag and Nguyen [132])

D. Prevention

Many interventions have been studied in an effort to limit the development or progression of ROP. Identifying strategies to prolong gestation through good prenatal care [32], reduced teenage pregnancies [33], and avoidance of illegal drugs [34] may reduce the morbidity experienced in association with premature birth.

In the 1990s interest in treating the hypoxic stimulus for neovascularization developed, and the Supplemental Therapeutic Oxygen for Prethreshold ROP (STOP-ROP), a multicenter trial to study the efficacy of supplemental oxygen in reducing the progression of ROP to threshold, was undertaken [35]. Six hundred and forty-nine patients with prethreshold ROP were randomly assigned to maintain oxygen saturation at 96–99 % (supplemented group) vs. 89–94 % (conventional group). Progression to threshold was not statistically significant between the two groups (41 vs. 48 %), but adverse pulmonary effects occurred more frequently in the oxygen-supplemented group. On the other hand, several studies in recent years have shown a benefit to carefully regulating oxygen saturation levels. One such study by Chow et al. [36] utilized strict oxygen management with saturation limits of 85–93 % SaO_2 for infants younger than 32 weeks' gestation. They demonstrated a reduction in incidence of stages 3 and 4 ROP from 12.5–2.5 % and decreased need for laser treatment from 4.5–0 %. In 2006, VanderVeen et al. [37] reported a dramatic reduction in the incidence of prethreshold disease in at least one eye of infants weighing less than 1,250 g from 17.5 to 5.6 % after lowering oxygen alarm levels from 87 to 97 % to 85–93 %. Britt and Sandoval [38] also instituted a policy to maintain oxygen saturation at 85–93 % for infants younger than 30 weeks' gestation and found that the incidence of stage 3 or more advanced ROP decreased from 49 to 15 % and the need for laser decreased from 38 to 15 %.

Recent clinical trials [39], the Surfactant Positive Airway Pressure Pulse Oximetry Randomized Trial (SUPPORT), in the US, Benefits of Oxygen Saturation Targeting Study II (BOOST II) in Australia, UK, and New Zealand and the Canadian Oxygen Trial (COT) in Canada, US, Argentina, Finland, Germany and Israel tested the role of oxygen saturation targets (85–89 % SaO_2) compared to infants with high oxygen saturation targets (91–95 % SaO_2) and the association with ROP. In SUPPORT and BOOST II, there was increased death in the infants with low oxygen saturation targets (85–89 % SaO_2) compared to infants with high oxygen saturation targets (91–95 % SaO_2), but in survivors, ROP was reduced in infants with low oxygen saturation targets. In the COT, neither ROP nor survival was affected.

Currently, the recommendation for oxygen level is still unclear. Generally, low-birth-weight infants are maintained at oxygen saturation levels in the high 80s or low 90s with ventilators set to avoid frequent changes in oxygen in response to variation in saturation levels [39]. Research is needed to determine the best appropriate oxygen levels to reduce the risk of severe ROP and optimize development of other organs. In addition, studies in relevant animal models can provide knowledge of signaling pathways that have been altered by stresses associated with prematurity and lead to targeted treatment to reduce specifically the risk of ROP.

Antioxidant therapies such as vitamin E and D-penicillamine have been studied; however, results are controversial to this point [40–45]. Early promising results have been demonstrated in murine models involving triamcinolone [46] and 17-alpha-estradiol [47], a 5-alpha-reductase inhibitor. However, further studies are required.

1. Screening

Successful preventative treatment of ROP is predicated on timely screening. Evaluation consists of pupil dilation and a comprehensive fundus examination with scleral depression. Monitoring the infant throughout the exam is essential as both manipulation of the eye and the use of dilating drops can produce apnea or bradycardia. The American Academy of Pediatrics (AAP) and the American Academy of Ophthalmology (AAO) have joint recommendations for ROP screening [48]. They recommend screening for all infants with a birth weight ≤1,500 g or a gestational age (GA) of ≤ 30 weeks and infants with a birth weight between 1,500 g and 2,000 g or a GA of more than 30 weeks whose clinical course places them at increased risk for ROP. Since it is estimated that less than 10 % of infants screened will require treatment [49], models using various combinations of GA, birth weight, postnatal weight gain, and serum IGF-1 levels to predict ROP risk have been developed [50–55]. Validation studies show that these models have potential but further validation is needed prior to changes in screening recommendations.

The first examination should be performed prior to hospital discharge at 4–6 weeks after birth or 31 weeks' postmenstrual age (PMA), whichever is later. Routine screening before 30 weeks' PMA is difficult as the cornea is hazy [56]. The AAP/AAO recommend follow-up examinations at intervals of 1–3 weeks depending on the severity of disease evident. Exams are continued until criteria for discontinuation are reached.

E. Treatment

The current recommendation is treatment be initiated for ROP for those with type I ROP [48]. This recommendation is based on the ETROP study [57], which reported that unfavorable visual outcomes can be reduced from 19.5 to 14.5 % and unfavorable structural outcomes from 15.6 to 9.1 % at 9 months' corrected age with early treatment. However, infants in the early treatment group experienced more apnea and bradycardia and required re-intubation more frequently. At 6 years of age, early treated eyes continued to have fewer

unfavorable structural outcomes (8.9 % vs. 15.2 %) and relatively preserved peripheral vision [58]. At 6 years, visual acuity outcomes were no longer statistically superior in the early treatment group (24.6 % vs. 29.0 % unfavorable); however, subgroup analysis showed improved visual acuity for "higher-risk" zone I prethreshold eyes in the early treatment group. Additionally, a large retrospective review performed by Alme et al. [59] in 2008 found a decrease in the incidence of retinal detachment from 10.3 to 1.9 % with the change in guidelines. This occurred even though this later study group had lower birth weights and younger gestational ages, on average.

Current treatment options which are discussed in detail below consist of ablation of avascular retina by laser photocoagulation, cryotherapy, or potentially the use of intravitreal anti-vascular endothelial growth factor (VEGF) for some zone I eyes. In general, laser therapy remains the treatment of choice by ophthalmologists throughout the world.

1. Cryotherapy

Cryotherapy was the primary treatment of ROP for many years but has now been largely replaced by laser photocoagulation [60]. The benefit of cryotherapy was demonstrated in the large multicenter trial CRYO-ROP. In this study, 291 infants with birth weights of less than 1,251 g who developed threshold ROP were randomized to observation or treated with cryotherapy within 72 h of diagnosis. Cryotherapy was found to significantly decrease unfavorable outcomes (31 % in treated vs. 51 % in observed), defined as posterior retinal detachment, posterior retinal fold, or retrolental tissue that obscured visualization of the posterior pole at 3 months. At the 15-year follow-up, 254 survivors of the original study [61] continued to have benefit with significantly fewer eyes in the treated group having poor ocular structure, new retinal folds, retinal detachments, and obstruction of the view of the posterior pole (30 % treated vs. 52 % observed). Treated eyes also demonstrated a lower incidence of poor visual acuity, defined as 20/200 or worse (45 % treated vs. 64 % observed). Cryotherapy is not as common now that laser delivery with the indirect ophthalmoscope is possible.

2. Laser Photocoagulation

In the past 20 years, laser photocoagulation using the diode or green laser on an indirect ophthalmoscope has almost completely replaced cryotherapy in the treatment for ROP. Generally, laser is better tolerated than cryotherapy with less conjunctival chemosis, inflammation, pain, or apnea and bradycardia. Laser is applied to peripheral avascular retina with gray to gray-white burns spaced one-half width apart, completely filling the avascular retina from the ora serrata, up to 360° [62]. Care should be taken to avoid "skip areas." Structural and visual outcomes suggest that laser photocoagulation is superior to cryotherapy. Paysse et al. [63] retrospectively compared 70 infants receiving laser treatment with 63 infants treated with cryotherapy at a single institution and found that 88 % of the laser-treated group vs. 56 % of the cryotherapy-treated group had resolution of ROP. There was not a statistically significant difference in cycloplegic refraction at 1 year. Visual acuity was better in the laser-treated group vs. the cryotherapy-treated group (20/49 vs. 20/103). A 10-year follow-up study of 44 eyes from 25 patients by Ng and associates [64, 65] demonstrated that when compared to cryotherapy, laser resulted in a better mean best-corrected visual acuity (20/66 vs. 20/182), and these eyes were seven times less likely to develop retinal dragging and developed less myopia (−4.48 vs. −7.65 diopters). These findings have been verified by other studies including a Cochrane systematic review [66].

3. Pharmacotherapy

a. Bevacizumab

Recent studies have tested bevacizumab, an anti-VEGF monoclonal antibody utilized in the treatment of many neovascular eye conditions. Potential advantages to its use in ROP include the ease of administration, rapidity of response, and ability to use this treatment when corneal, lens, or vitreous opacities preclude treatment with laser. Concerns exist because dose and safety studies have not yet been performed and intravitreally administered bevacizumab can enter the systemic circulation and has also been shown to suppress systemic VEGF levels for more than 2 weeks after a single intraocular injection [67]. The potential effects on the development of the kidneys, lungs, and brain remain unknown, but it is possible that anti-VEGF may further compromise organs that have reduced function because of the premature state.

A multicenter randomized trial by Mintz-Hittner and associates [68] compared bevacizumab (0.625 mg in .025 mL of solution) to conventional laser therapy in 150 infants with stage 3+ ROP in zone I or posterior zone II. In this study, bevacizumab was associated with decreased rates of recurrence (4 % vs. 22 %) and fewer structural abnormalities (macular dragging and retinal detachment) at 1 year. Specifically, among infants with zone I disease (with the highest rate of treatment failure after conventional laser therapy), the recurrence rate was 6 % in the intravitreal bevacizumab subgroup vs. 42 % in the laser-treated group. The differences in outcomes were not significant in infants with posterior zone II disease. No systemic or local toxic effects were observed; however, the study was too small to adequately assess ocular and systemic safety, and the follow-up period was only 54 weeks. A recent single institution study by Hu and associates [69] demonstrated a later recurrence of severe ROP on average than that seen with laser therapy, and in one case recurrence occurred over 1 year later. The authors of this study concluded that although intravitreal bevacizumab treatment is effective in inducing regression of ROP, the effect may be transient. In addition, the use of anti-VEGF in an experimental model led to reduced body weight gain and recurrent intravitreal neovascularization and activation of angiogenic pathways that not only included VEGF but

also erythropoietin, which is independent of VEGF signaling, suggesting that treatment for recurrent neovascularization with anti-VEGF may not be effective [70].

The AAP/AAO guidelines [48] currently state that consideration may be given to treatment of infants with zone I, stage 3+ ROP with an intravitreal injection of bevacizumab—however, only after a thorough discussion for informed consent, since there remain unanswered questions involving dosage, timing, safety, visual outcomes, and other long-term effects. Bevacizumab is not FDA approved for the treatment of ROP. The guidelines also advise weekly monitoring of infants after injection until retinal vascularization is completed. The antibody fragment ranibizumab has a shorter serum half-life in monkeys [71] (3.5 days vs. 12.3 days for bevacizumab [72]) and may be an alternative for use in preterm infants, since bevacizumab reduced VEGF levels in preterm infants for at least 2 weeks following a single intravitreal dose [73]. A study in adults showed that ranibizumab did not reduce serum VEGF levels, whereas intravitreal bevacizumab lowered serum levels [74]. However, in preterm infants who have smaller blood volumes, a case report found that VEGF levels were significantly reduced following intravitreal ranibizumab; [75] thus, more study is needed.

b. Pharmacologic Vitreolysis

Pharmacologic vitreolysis [76, 77] is a new therapeutic paradigm to alter the vitreous on a macromolecular level to induce gel liquefaction and vitreoretinal dehiscence to detach vitreous from the retina [see chapter VI.A. pharmacologic vitreolysis]. Some have suggested using forms of plasmin (e.g., ocriplasmin) to cleave fibronectin and reduce intravitreal neovascularization in stage 3 ROP or vasoproliferation in stage 4 ROP. However, using forms of plasmin in stage 3 may not safely reduce intravitreal neovascularization without affecting physiologic retinal vascular development, because fibronectin and other components of the extracellular matrix that are cleaved by plasmin, such as laminin, are important in normal retinal vascular development [78]. Inhibition of plasmin activity reduces intravitreal neovascularization without adversely affecting physiologic retinal vascular development in the oxygen-induced retinopathy model in rats [79]. Therefore, using plasmin to cleave the vitreoretinal interface may be counterproductive in reducing intravitreal neovascularization and may adversely affect retinal vascular development. Using ocriplasmin in infant vitrectomy for stage 4 or 5 ROP may hold promise by facilitating retinal reattachment in the eyes that develop retinal breaks and recurrent retinal detachments after ROP surgery [80]. Ocriplasmin is therefore being considered in pediatric retinal conditions that are associated with retinal detachments [81] [see chapters VI.E.1. Pharmacologic vitreolysis with ocriplasmin: basic science studies and VI.E.2. Pharmacologic vitreolysis with plasmin: clinical studies.].

4. Treatment of Retinal Detachment

Laser treatment of avascular retina is effective in reducing vascular activity and subsequent retinal detachment in a majority of cases; however, one large study reported retinal detachment in 14 % of the eyes 6–12 weeks after laser treatment [82]. When ROP progresses to partial or total retinal detachment, surgical intervention is undertaken to promote retinal reattachment in the posterior pole, minimize distortion, and preserve vision.

Scleral buckling (SB) and vitrectomy have been used with some success to manage retinal detachments with ROP. One study utilizing these methods demonstrated light perception or better vision in 72 % of eyes with a visual acuity of 20/300 or better in 15 % [83]. Poor outcomes for all surgical interventions are predicted by the presence of plus disease, vitreous haze, and continued neovascularization; [84] therefore, treatment to reduce vascular activity is recommended before proceeding with vitreous surgery. Scleral buckling involves the placement of a silicone band around the eye, sometimes with drainage of subretinal fluid. High degrees of myopia, anisometropia, and amblyopia are associated with scleral buckles [85]. Scleral buckles are the initial treatment for rhegmatogenous detachments and can be used in cases with limited tractional components located near or anterior to the equator. Placement of a scleral buckle almost always necessitates a second procedure 6–9 months later to remove the band and allow the eye to grow.

Vitrectomy with or without a scleral buckle is considered especially for posterior disease and many forms of tractional detachments. A lens-sparing vitrectomy (LSV) allows for the removal of the vitreous and any tractional membranes present, thus enabling the retina to be reattached to the wall of the eye. It also allows better visual development by retaining the lens (Figure III.A-7). A direct comparison of stage 4 detachments repaired by vitrectomy vs. scleral buckle demonstrated a 73 % reattachment rate for eyes treated with a primary LSV vs. 31 % in eyes with a primary scleral buckle [86]. Complications associated with LSV include retinal tears, cataracts, and glaucoma. The incidence of cataract following an LSV varies between 5 and 15 % [87, 88].

III. Persistent Fetal Vasculature

The hyaloid vasculature consists of the vasa hyaloidea propria, tunica vasculosa lentis, and pupillary membrane. Hyaloid vessel development and regression are complex [see chapter II.A. Development and developmental disorders of vitreous failure can result in several ocular pathologies, which are part of a spectrum known as persistent fetal vasculature (PFV). The vasa hyaloidea propria is made up of the hyaloid artery that enters the eye through the optic stalk and its anterior branches that extend through the vitreous toward the lens. The tunica vasculosa lentis is a capillary network

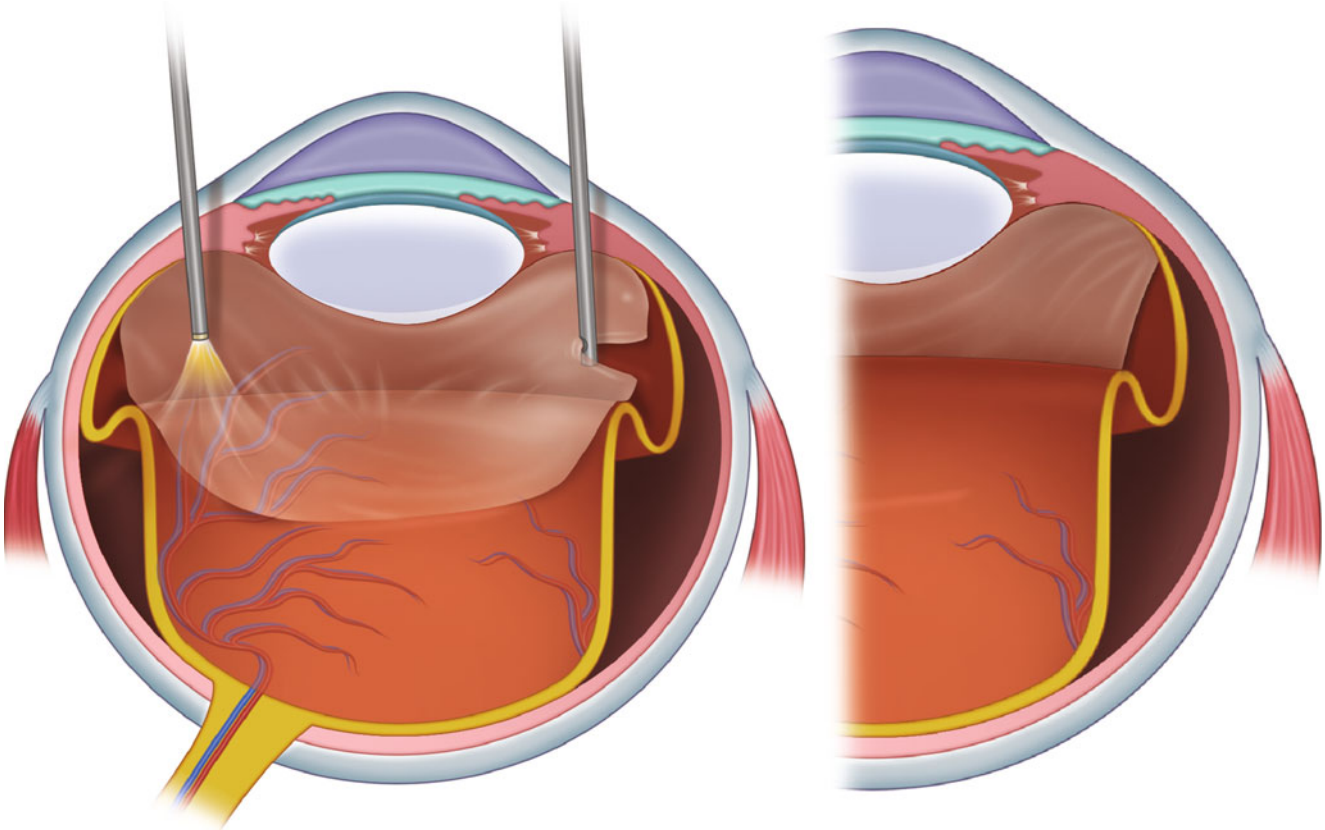

Figure III.A-7 Left rendering demonstrates location of ports in lens-sparing vitrectomy. Right rendering more clearly shows traction component to retinal detachment. Removing this traction is key to successfully reattaching the retina

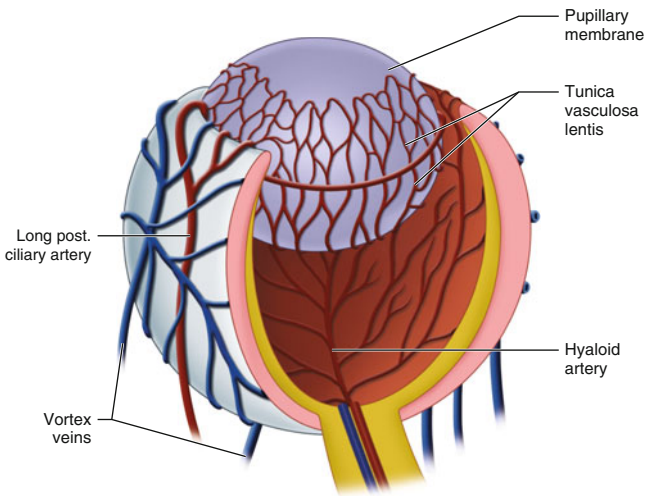

Figure III.A-8 Extensive anastomoses of fetal vasculature (Redrawn based on Goldberg MF. Persistent fetal vasculature [PFV]: an integrated interpretation of signs and symptoms associated with persistent primary vitreous [PHPV]. LIV Edward Jackson Memorial Lecture [107]

that encompasses the posterior developing lens and connects to the lens equator with the pupillary membrane, which covers the anterior lens capsule (Figure III.A-8). The hyaloid artery first appears in humans during the fourth week of gestation and peaks in prominence during approximately the ninth week of gestation [89]. In early stages of development, the retina and optic nerve lack blood vessel support and are oxygenated by the choroidal and hyaloidal vessels [90–92].

As the eye enlarges and retinal angiogenesis ensues, hyaloid vasculature regression occurs [93, 94]. The first elements to undergo regression are the vasa hyaloidea propria, followed by the tunica vasculosa lentis and pupillary membrane, and lastly the main hyaloid artery trunk. Cessation of blood flow in the hyaloid artery is seen at roughly 7 months and culminates with the involution of the entire hyaloid vessel complex by approximately 36 weeks' gestation [89, 95]. As the vascular structures regress, the primary vitreous retracts, and collagen fibers with a ground substance of collagen, fibronectin, laminin, and other extracellular matrix components (but not hyaluronan) are produced to form the secondary vitreous [see chapter II.A. Vitreous embryology]. By the sixth month of gestation, the posterior segment is largely composed of the secondary vitreous, and the primary vitreous is reduced to a small central portion of the posterior segment that extends from the optic disk to the posterior lens surface and is referred to as Cloquet's canal (Figure III.A-9).

PFV is the term used to describe the array of pathology that results from failed involution of the primary vitreous and

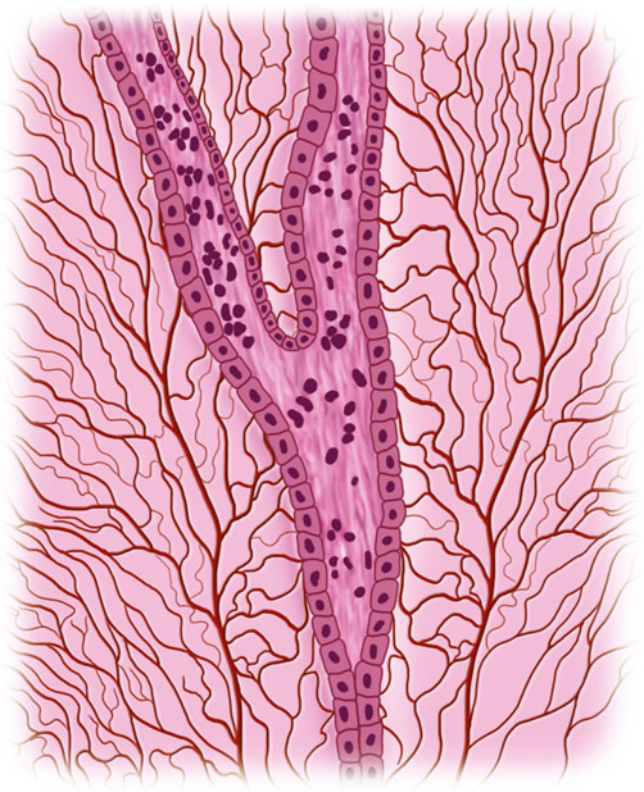

Figure III.A-9 Artist's rendering of longitudinal section of Cloquet's canal and the contained hyaloid artery. The condensation between primary and secondary vitreous is seen forming the wall of Cloquet's canal. (adapted from Ida Mann [89], p. 174 – Figure 147)

regression of the fetal hyaloid vasculature [see chapters I.D. Proteomics of fetal hyaloid vasculature regression and II.A. Vitreous embryology] involving the anterior or posterior compartments of the eye. Mild changes from PFV commonly affect the eye; however, functional complications are rare. Prior studies have estimated that 3 % of full-term infants display some degree of PFV [96] and more than 90 % of those born earlier than 36 weeks of gestation demonstrate incomplete regression of the embryonic hyaloid vessel system [97]. A recent review of individuals at one US institution for the visually impaired found that 4.8 % of blind patients had PFV [98]. Individual components of the fetal vasculature often persist in combination with others; however, any anatomically identifiable vascular remnant may present individually as well. When present in full-term infants, persistent fetal intraocular vessels frequently are compatible with normal ocular and visual functions. However, more severe manifestations of PFV can cause secondary abnormalities resulting in defective physiology and decreased visual acuity. Ancillary tests consisting of ultrasonography, fluorescein angiography (FA), OCT, computed tomography (CT), magnetic resonance imaging (MRI), electroretinography (ERG), and visual evoked potential (VEP) can all be helpful in evaluating PFV.

PFV can be classified as anterior or posterior depending on the intraocular structures involved. The most common complications are seen anteriorly and are frequently associated with abnormal regression of the tunica vasculosa lentis. Common manifestations include cataract formation with associated lens swelling and risk of induced angle closure glaucoma. Frequently, engorgement of iris vessels, pain, and microphthalmia are also present. Posterior PFV, most commonly associated with abnormal regression of the vasa hyaloidea propria, is much less common. It presents with a tractional retinal detachment and adherent preretinal membranes emanating from a persistent stalk, which places traction on the retina. Accompanying retinal dysplasia and optic nerve abnormalities can be seen. As with anterior PFV, microphthalmia and leukokoria may be present.

A. Anterior Persistent Fetal Vasculature

1. Persistent Pupillary Membrane

Noted in approximately 95 % of healthy newborns, a persistent pupillary membrane consists of fine vessels along the pupillary margin. They are non-pathologic and almost always disappear shortly after birth [99]. When associated with cataract or retrolental membranes, they should clue the diagnostician to the possibility of other manifestations of PFV.

2. Iridohyaloid Blood Vessels

Iridohyaloid blood vessels connect the posterior tunica vasculosa lentis to the pupillary membrane vessels. Normal regression of these vessels is required for the development of the zonule at the equator of the lens [100]. The presence of iridohyaloid vessels often manifests as a subtle pupillary sphincter notch [101] or a prominent superficial iris vessel. A severe manifestation would be ectopia lentis et pupillae [102].

3. Mittendorf's Dot

Mittendorf's dot is a remnant of the primary vitreous that corresponds to the location of previous junction of the hyaloid artery to the tunica vasculosa lentis and is almost always on the inferior and nasal posterior lens capsule. It is usually asymptomatic and can be seen in 0.7–2 % of the population [103] (Figure III.A-10).

4. Muscae Volitantes

Latin for "flying flies," muscae volitantes are vitreous remnants of the regressed vasa hyaloidea propria [see chapter I.D. Proteomics of fetal hyaloid vasculature regression]. They are usually found floating in the anterior vitreous. Sometimes, small corkscrew remnants are seen attached to the posterior capsule. Associated visual symptoms are rare, but floaters would be the only clinical manifestations [see chapter V.B.8.

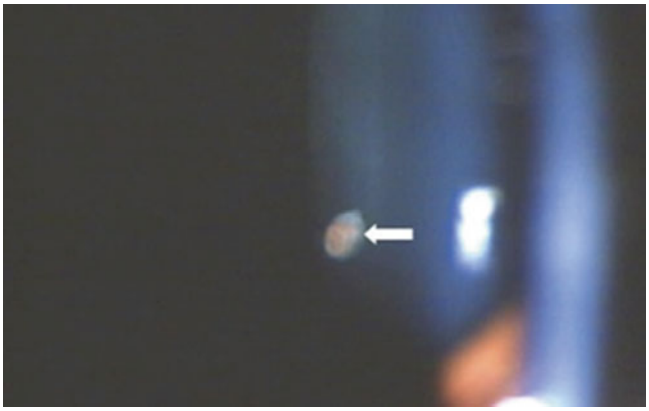

Figure III.A-10 Mittendorf's dot – Mittendorf's dot located on posterior lens capsule at the site of the former anastomosis of the tunica vasculosa lentis to the hyaloid vasculature. It is almost always located inferonasally without associated visual dysfunction (Courtesy of Dr Parag Shah)

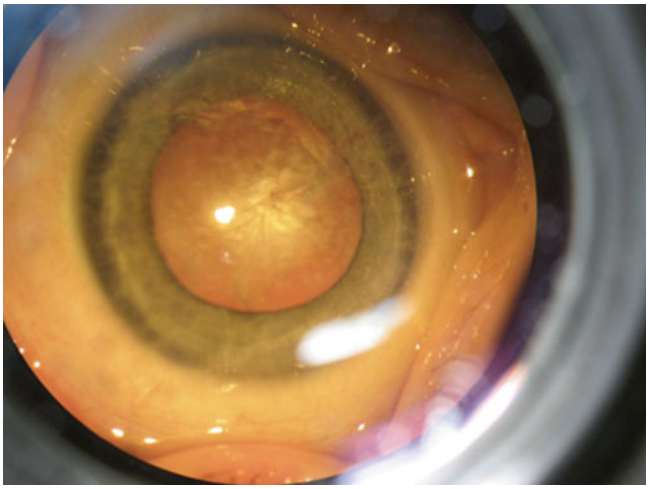

Figure III.A-11 Prominent retrolental membrane obscuring the entire visualized posterior lens capsule with associated iridohyaloid vessel (Courtesy of Dr David Dries, Moran Eye Center)

Floaters and vision – current concepts and management paradigms].

5. Retrolental Membrane

Associated with persistence of the posterior tunica vasculosa lentis, these membranes are variable in presentation, ranging from 1.0 mm to more extensive, covering the entire posterior surface of the lens [104]. They result from fibrovascular tissue that attaches to the ciliary processes and draws them to the center of the pupil. They are most commonly seen with corresponding radially oriented blood vessels that are seen clearly on fluorescein angiography and distinguish PFV from Coats disease, retinoblastoma, or stage 5 ROP. Frequently, abnormalities in lens development are also present (Figure III.A-11).

B. Posterior Persistent Fetal Vasculature

1. Bergmeister's Papilla

First described by Austrian Ophthalmologist O. Bergmeister, Bergmeister's papilla arises from the center of the optic disk and consists of a small tuft of fibrous tissue that at one time ensheathed the hyaloid artery.

2. Persistent Hyaloid Artery

Most commonly seen as a flaccid vascular remnant attached to the posterior pole of the lens, this occurs when the hyaloid artery fails to involute completely. Normally, the hyaloid artery cleaves near its center, with both ends retracting and regressing completely [105] [see chapter II.A. Development and Developmental Disorders of Vitreous]. Very rarely, the entire hyaloid artery may persist from the optic nerve head and extend to the posterior lens capsule or into the anterior vitreous with branches of the vasa hyaloidea propria present. Rarely, a persistent hyaloid artery is associated with vitreous hemorrhage.

3. Congenital Nonattachment of the Retina and Retinal Detachment

Retinal detachments have been noted in 56 % of patients with PFV [106]. Two different mechanisms are believed to contribute to retinal detachment. In the first, adhesion of the primary vitreous and its blood vessels from one portion of the optic cup prevents the secondary vitreous from forming between the primary vitreous and the retina [107]. This causes traction and detachment of the retina as the eye enlarges. Later, a continuous stalk of hyaloidal tissue can be seen to extend from the optic disk to the posterior lens or ciliary body. Contraction of the stalk or growth of the eye results in tractional retinal detachment. In these cases the retina may be adherent to the ciliary body, dragged centrally, or drawn anteriorly and elevated around the optic nerve.

4. Globe Malformations

Microphthalmos and microcornea are two common malformations associated with PFV. However, variations in the size and shape of the globe, cornea, or lens can be seen. In the presence of leukokoria, corresponding microphthalmos or microcornea can be helpful in diagnosing PFV.

5. Macular Abnormalities

Often subtle macular changes can be associated with posterior PFV. Most commonly the result of traction, there is failure of the foveal pit to develop and irregularities in retinal layers can occur. Often these changes are noted on optical coherence tomography (OCT).

6. Optic Nerve Head Abnormalities

Optic nerve head hypoplasia and dysplasia are believed to result from abnormal traction associated with PFV.

C. Genetics

Most cases of PFV are sporadic, but autosomal recessive and autosomal dominant patterns of familial transmission have been documented. Defects in the *NDP* and *FZD4* genes have been identified in cases of unilateral and bilateral PFV. These genes are also associated with familial exudative vitreoretinopathy (see below) and Norrie disease. These genes are associated with the Wnt signaling pathway, and experimental evidence exists to support Wnt signaling in the development of PFV [108]. In addition, mice with defects in genes, *Atoh7* and *Lama1*, responsible for the genesis of retinal ganglion cells, have a high incidence of phenotypes similar to PFV [109, 110]. Also, transgenic mice lacking tumor suppressor genes *arf* [111], *p53* [112], and *frizzled-5* [113] or overexpressing *vegf-a188* [114] have also been shown to develop a PFV phenotype similar to human PFV. Finally, PFV has also been reported in association with trisomies 13, 15, and 18. If bilateral disease is suspected, Norrie disease and trisomy 13 should be ruled out. In general, infants presenting with unilateral PFV and no other developmental anomalies are not subjected to testing for other conditions unless other symptoms are present.

D. Treatment of Persistent Fetal Vasculature

Surgical intervention to clear media opacities, to relieve tractional forces, or simply to preserve the globe from the natural course of PFV can be helpful. In eyes with visual potential, visual rehabilitation is important, and the need for careful follow-up must be conveyed to parents. Studies have demonstrated that the eyes with anterior disease have a greater chance of achieving form vision than eyes with posterior malformations. Posterior PFV, microphthalmia, glaucoma, and amblyopia are known to limit visual acuity outcomes even after aggressive intervention. In our experience, tractional effects on the lens or retina due to a stalk can often be relieved with surgical division of the stalk. This can release traction and allow subsequent flattening of the retina, which is particularly important as the eye lengthens during development. In cases of cataract, a limbal-based surgical approach is preferred to removal of the lens during vitrectomy, because the pars plicata/pars plana area can be abnormal, and there is risk of creating a tear in the peripheral retina when the media are too cloudy for direct visualization. Also, the peripheral retina can be drawn anteriorly into the retrolental membrane. In cases with clear lenses, a pars plana/pars plicata approach can be performed with careful examination of the ora serrata to avoid injury to the retina. Relieving the traction on the stalk is usually sufficient, and complete amputation of the stalk is neither necessary to allow the retina to reattach nor safe, since the peripapillary retina can also be drawn into the stalk and tissue. Complete removal of the stalk may then lead to retinal injury and inoperable retinal detachment. These cases are complicated and often require expertise and training in the procedure.

IV. Familial Exudative Vitreoretinopathy

Familial exudative vitreoretinopathy (FEVR) is a vitreoretinal dystrophy that was first described in 1969 by Criswick and Schepens [115] when they noted retinal changes similar to retinopathy of prematurity (ROP) in children and adolescents who had no risk factors for ROP. They described bilateral involvement, although often asymmetric, of peripheral neovascularization with thick fibrovascular membranes causing traction on the retina and distorting the macula and optic disk. Some eyes were noted to develop peripheral subretinal exudates with associated exudative and traction retinal detachments. Since that time, many studies have identified tremendous variability in the presentation, course, and even inheritance pattern of FEVR. When severe, FEVR can be a lifelong retinal vascular disease with variable periods of quiescence.

A. Clinical Presentation

Due to its rarity and many variable manifestations, the diagnosis of FEVR can be challenging and is likely underdiagnosed. FEVR has been described in all ethnic groups. In a recent review by Ranchodetal [116], only 41/145 or 28 % of patients referred to their practice with FEVR had been correctly diagnosed prior to referral. Many were misdiagnosed as having unspecified retinal detachment, persistent fetal vasculature syndrome (PFV), ROP, retinal folds, or Coats disease. Of note, the average age at presentation for patients in this study was 6 years. Young patients with FEVR can also be referred with a diagnosis of leukokoria, poor vision, retrolental plaque, strabismus associated with a positive angle Kappa, cataract, or even premacular membrane with pucker. Other diseases not already mentioned that should be considered in the differential diagnosis of FEVR include the Norrie disease, retinoblastoma, incontinentia pigmenti, sickle cell disease, and toxocariasis.

FEVR can present with various combinations of macular dragging, radial retinal folds, retinal neovascularization, pre-

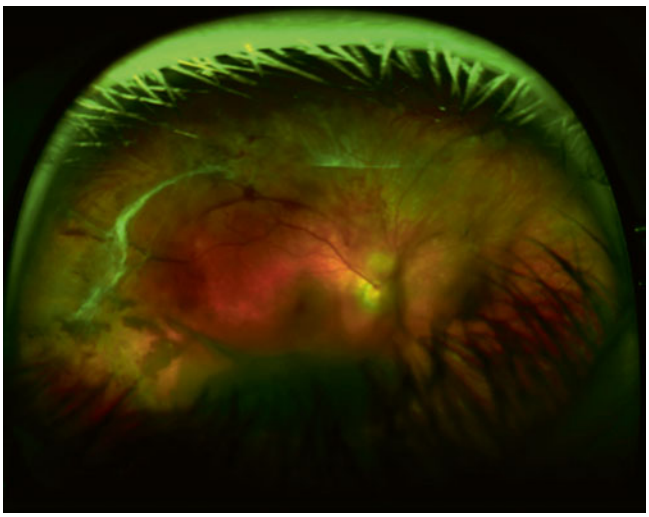

Figure III.A-12 A 10-year-old female presented with vitreous hemorrhage. Following clearing of the hemorrhage, fibrovascular changes were noted with traction on the retina and preretinal hemorrhages (Optos)

retinal vitreous organization, vitreous hemorrhage, tractional retinal detachment, and subretinal exudation [117] (Figure III.A-12). The most prominent feature is the abrupt cessation of peripheral retinal vessels, commonly at the temporal equator; however, they can extend 360° [118]. These vessels take on a scalloped pattern that is often referred to as a "brush border" when seen on fluorescein angiography and frequently demonstrate vascular buds at the junction of avascular and vascularized retina. Subretinal exudates are often present and can be massive resembling the Coats disease. Partial or total retinal detachment due to exudative and fibrovascular proliferative tractional forces can be seen. Miyakubo et al. [119] and van Nouhuys [120] noted that approximately 20 % of patients with FEVR developed retinal detachments and almost all within the first decade of life. Benson [117] noted that children presenting in the first 3 years of life had a worse prognosis than those presenting later in life. In his review of FEVR, Trese [121] also noted a poor prognosis in infants presenting in the first year of life. The presence of bilateral findings can also be helpful in the diagnosis of FEVR. Pendergast [122] reported that 85 % of eyes had bilateral involvement in FEVR and only 15 % had unilateral involvement.

B. Clinical Classification

Different systems have been used to classify FEVR. The most recently recommended system parallels the International Classification of Retinopathy of Prematurity (ICROP) guidelines with five stages ranging from avascular retina to total retinal detachment [121]. They are defined as:

Stage 1: Avascular periphery
Stage 2: Retinal neovascularization
  2A Without exudates
  2B With exudates
Stage 3: Extramacular retinal detachment
  3A Without exudates
  3B With exudates
Stage 4: Macula-involving retinal detachment, subtotal
  4A Without exudates
  4B With exudates
Stage 5: Total retinal detachment

C. Genetics

The most common mode of inheritance of FEVR is autosomal dominant (AD); however, many individuals with autosomal dominant FEVR are asymptomatic due to reduced penetrance. In addition, there are known lines of X-linked and autosomal recessive inheritance, as well. In the review by Ranchod et al. [116], 18 % of patients had a diagnosed family history of FEVR upon referral and 37 % had histories consistent with FEVR but had not been diagnosed. Mutations in one of three genes are known to be responsible for the autosomal dominant FEVR. *FZD4* encoding the protein frizzled-4, *LRP5* encoding low-density lipoprotein receptor-related protein 5, and *TSPAN12* encoding tetraspanin-12 are responsible for fewer than 50 % of autosomal dominant FEVR cases. Another locus, EVR3, has been mapped, but the gene is unknown at this time. Molecular genetic testing for mutations in *FZD4*, *LRP5*, and *TSPAN12* is available at this writing. However, more than 50 % of the time, a known genetic mutation will not be detected in patients presenting with clinical features of FEVR. *NDP* encoding the Norrie disease protein is associated with X-linked inheritance, and *LRP5* is also associated with autosomal recessive inheritance [123]. Genetic counseling can be very helpful as offspring of a patient with autosomal dominant FEVR will have a 50 % risk of inheriting the mutation, and prenatal testing is currently available. Molecular genetic testing should begin with the sequence analysis of *FZD4*; if the pathologic mutation is not identified, then sequence analysis of *LRP5* and then *TSPAN12* should be performed in that order. All genes associated with AD FEVR have not been identified, so failure to identify a mutation in the above genes does not rule out the diagnosis.

1. Ancillary Testing

The diagnosis of FEVR is based on typical clinical findings in the absence of prematurity or other risks of ROP. A positive family history is helpful. In suspicious cases of asymptomatic stage 1 or 2 FEVR, examination of parents, siblings, and children can help in the diagnosis. Shukla et al. [124] noted in a review that 41 % of patients with FEVR were in

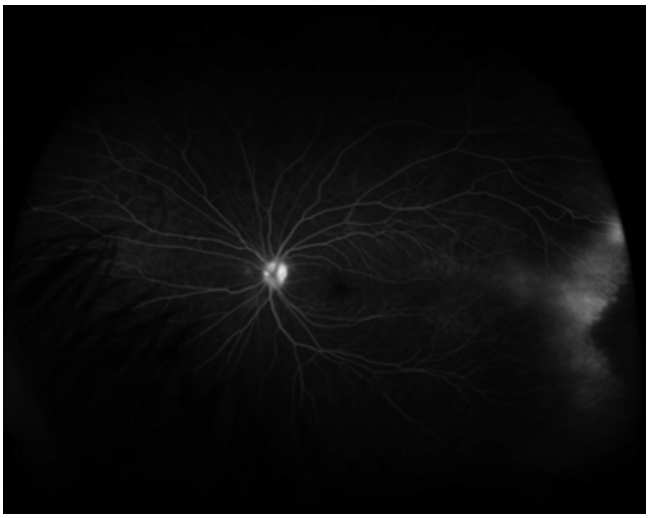

Figure III.A-13 Left eye of patient in Figure III.A-12. Note the leakage of capillaries at the junction of vascular and avascular retina (Optos)

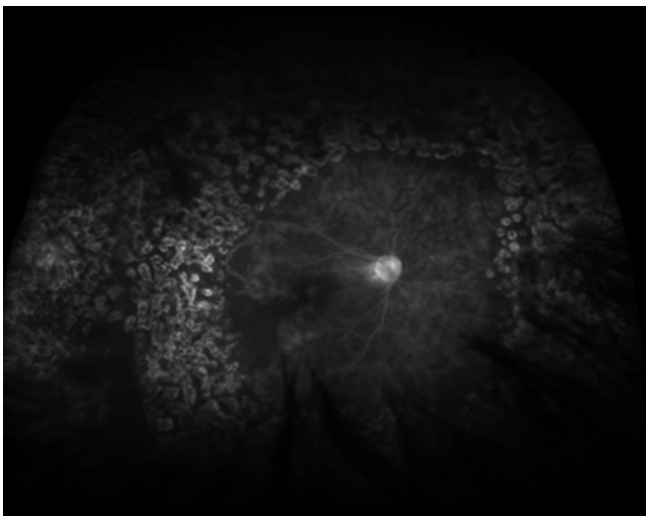

Figure III.A-14 Fluorescein angiogram of same eye as Figure III.A-12 after vitrectomy and extensive laser applied over multiple sessions to treat recurring vitreous hemorrhages (RetCam Image, Clarity). Persistent avascular retina extends to fovea

the mild end of the spectrum with normal vision and only a sector of peripheral retinal avascularity noted. Wide-angle fluorescein angiography is helpful to identify avascular retina and vascular abnormalities that may be otherwise missed. Depending on patient cooperation, this can be performed in clinic or while under anesthesia for an examination. Contrasts between peripheral avascular and vascularized retinas are clearly highlighted with fluorescein angiography, and characteristic straightening of peripheral vessels in a "brush border" pattern can be identified. Fluorescein angiography is very useful to detect the vascular/avascular junction and identify leakage of capillaries (Figure III.A-13). ERG changes other than possible mild reductions in b-wave amplitude are not seen with FEVR.

2. Systemic Associations

Individuals with AD FEVR and mutations in *LRP5* have been noted to have reduced bone mass [125]. This does not appear with other forms of FEVR. Reduced bone mass is often only evident upon examination with dual x-ray absorptiometry and leaves affected patients predisposed to fractures.

D. Treatment

As noted with many vitreoretinopathies, early intervention often results in better vision for patients. Screening with wide angle fluorescein angiography of family members of patients with known disease is important as is the need to emphasize that the course of FEVR can wax and wane, and lifelong follow-up is pivotal. Currently, we recommend treating the peripheral avascular retina of stage 2 or greater FEVR with near-confluent laser to the avascular retina, regardless of whether exudates are present (Figure III.A-14). In addition, FEVR may progress with new capillary involvement resulting in avascular retina later in life. Therefore, until more is known about this condition, patients should be examined regularly throughout their lives.

Vitreous plays a major role in the pathogenesis of FEVR and, specifically, often leads to formation of retinal folds or traction retinal detachment through firm attachment of the posterior vitreous cortex to the retina. With this in mind, vitrectomy might be useful in the eyes with severe FEVR [118, 122, 126, 127]. Ikeda et al. [126] noted in their case series that peripheral vitreoretinal adhesions overlying avascular retina caused iatrogenic breaks during surgery in 22 of 28 eyes. In all their cases, bimanual technique with vitreous scissors and forceps was required to dissect the posterior vitreous cortex from the retinal surface. Vitrectomy was then combined with a lensectomy and scleral buckle placement to help relieve residual vitreoretinal traction. Utilizing these techniques, they successfully reattached the retina in 86 % of cases and improved visual acuity in 71 %. Others report success using similar bimanual techniques for vitrectomy, but reserving the scleral buckle for eyes with a rhegmatogenous component to their retinal detachment [122, 128]. However, vitreous is very adherent to the retina in youth, and care must be exercised to avoid creating retinal breaks.

Recent reports advocate using autologous plasmin to assist with pharmacologic vitreolysis [129, 130] [see chapters VI.D.1. Pharmacologic vitreolysis with plasmin: basic science studies and VI.D.2. Pharmacologic vitreolysis with plasmin: clinical studies. Pharmacologic vitreolysis with plasmin]. Wu et al. [130] noted that a combination of reduced suction and a high cutting rate made it possible to remove sheets of vitreous off the retina but that a clean retinal surface was almost impossible to

Figure III.A-15 Demonstration of new-onset iris neovascularization which occurred ~6 weeks following intravitreal anti-VEGF injection in a child with FEVR who had previously been treated with lens-sparing vitrectomy and extensive ablation of peripheral avascular retina

achieve by mechanical dissection only. They propose that plasmin can remove vitreous from the retinal surface and silicone oil can then be used to stabilize the eye by providing long-term tamponade and reducing the stimulus for vascular leakage. As described above, promising results have been seen recently in the treatment of some forms of ROP with injection of forms of anti-vascular endothelial growth factor (anti-VEGF) agents to reduce abnormal neovascularization. Anti-VEGF agents have been reported for a patient with vitreous hemorrhage and neovascularization attributed to FEVR [131]. However, in our experience, new-onset iris neovascularization can occur in eyes treated with intravitreal anti-VEGF (personal observation, MEH 01/13) (Figure III.A-15). Therefore, much further study is needed before recommending anti-VEGF at this point.

1. FEVR Treatment Outcomes

It can be difficult to accurately quantify successful surgical outcomes in FEVR due to its progressive nature and associated periods of waxing and waning. Success rates of retinal reattachment range from 96 to 63 % [118, 122, 126–128]. Some authors feel that silicone oil decreases the frequency of recurrence and may be considered in eyes that have previously undergone vitrectomy and still show signs of activity [121].

Abbreviations

AAO	American Academy of Ophthalmology
AAP	American Academy of Pediatrics
AD	Autosomal dominant
APROP	Aggressive posterior retinopathy of prematurity
CRYO-ROP	Cryotherapy for Retinopathy of Prematurity
CT	Computed tomography
ERG	Electroretinography
ETROP	Early Treatment for Retinopathy of Prematurity
FA	Fluorescein angiography
FEVR	Familial exudative vitreoretinopathy
GA	Gestational age
ICROP	International classification for retinopathy of prematurity
IGF-1	Insulin-like growth factor-1
LSV	Lens-sparing vitrectomy
MRI	Magnetic resonance imaging
OCT	Optical coherence tomography
PFV	Persistent fetal vasculature
PMA	Postmenstrual age
ROP	Retinopathy of prematurity
SB	Scleral buckling
STOP-ROP	Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity
VEGF	Vascular endothelial growth factor
VEP	Visual evoked potential

References

1. NEI press release. http://www.nei.nih.gov/health/rop/rop.asp. October 2009.
2. Patz A, Hoeck LE, DeLaCruz E. Studies on the effect of high oxygen administration in retrolental fibroplasias. I. Nursery observations. Am J Ophthalmol. 1952;35:1248–53.
3. Kinsey VE. Cooperative study of retrolental fibroplasia and the use of oxygen. Arch Ophthalmol. 1956;56:481–543.
4. Crosse VM, Evans PJ. Prevention of retrolental fibroplasias. AMA Arch Ophthalmol. 1952;48(1):83–7.
5. Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P, et al. Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: implication for screening programs. Pediatrics. 2005;115:e510–25.
6. Schaffer DB, Palmer EA, Plotsky DF, Metz HS, Flynn JT, Tung B, et al. Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology. 1993;100:230–7.
7. Early Treatment for Retinopathy of Prematurity Cooperative Group, Good WV, Hardy RJ, et al. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2010;128:663–71.
8. Early Treatment for Retinopathy of Prematurity Cooperative Group, Dobson V, Quinn GE, et al. Grating visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2011;129:840–6.
9. Chen J, Smith LE. Retinopathy of prematurity. Angiogenesis. 2007;10(2):133–40.
10. Chan-Ling T, Gock B, Stone J. Supplemental oxygen therapy: basis for noninvasive treatment of retinopathy of prematurity. Invest Ophthalmol Vis Sci. 1995;36:1215–30.
11. Ashton N. Retinal angiogenesis in the human embryo. Br Med Bull. 1970;26:103–6.

12. Hasegawa T, McLeod DS, Prow T, Merges C, Grebe R, Lutty GA. Vascular precursors in developing human retina. Invest Ophthalmol Vis Sci. 2008;49:2178–92.
13. Chan-Ling T, Gock B, Stone J. The effect of oxygen on vasoformative cell division: evidence that 'physiological hypoxia' is the stimulus for normal retinal vasculogenesis. Invest Ophthalmol Vis Sci. 1995;36:1201–14.
14. Hellstrom A, Carlsson B, Niklassen A, et al. IGF-1 is critical for normal vascularization of the human retina. J Clin Endocrinol Metab. 2002;87:3413–6.
15. Smith LE. IGF-1 and retinopathy of prematurity in the preterm infant. Biol Neonate. 2005;88:237–44.
16. Hartmann JS, Thompson H, Wang H, Kanekar S, Huang W, Budd SJ, Hartnett ME. Expression of vascular endothelial growth factor and pigment epithelial-derived factor in a rat model of retinopathy of prematurity. Mol Vis. 2011;17:1577–87.
17. Hartnett ME. Studies on the pathogenesis of avascular retina and neovascularization into the vitreous in peripheral severe retinopathy of prematurity (an american ophthalmological society thesis). Trans Am Ophthalmol Soc. 2010;108:96–119.
18. Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. N Engl J Med. 2012;367(26):2515–26.
19. Wang H, Byfield G, Jiang Y, Smith GW, McCloskey M, Hartnett ME. VEGF-mediated STAT3 activation inhibits retinal vascularization by down-regulating local erythropoietin expression. Am J Pathol. 2012;180(3):1243–53.
20. Evolution of Stage 4 Retinopathy of Prematuirty Capone A and Trese MT in Pediatric Retina, volume 2 Lippincott Wolters Kluwer. Chapter 44, 2013;568–573.
21. Hartnett ME, McColm JR. Retinal features predictive of progression to stage 4 ROP. Retina. 2004;24:237–41.
22. Coats DK. Retinopathy of prematurity: involution, factors predisposing to retinal detachment, and expected utility of preemptive surgical reintervention. Trans Am Ophthalmol Soc. 2005; 103:281–312.
23. Sebag J. Imaging vitreous. Eye. 2002;16(4):429–39.
24. Ueno N, Sebag J, Hirokawa H, Chakrabarti B. Effects of visible-light irradiation on vitreous structure in the presence of a photosensitizer. Exp Eye Res. 1987;44(6):863–70.
25. Raymond L, Jacobson B. Isolation and identification of stimulatory and inhibitory cell growth factors in bovine vitreous. Exp Eye Res. 1982;34(2):267.
26. Lutty GA, Mello RJ, Chandler C, Fait C, Bennett A, Patz A. Regulation of cell growth by vitreous humour. J Cell Sci. 1985;76(1):53–65.
27. Jacobson B, Dorfman T, Basu P, Hasany S. Inhibition of vascular endothelial cell growth and trypsin activity by vitreous. Exp Eye Res. 1985;41(5):581–95.
28. Machemer R. Description and pathogenesis of late stages of retinopathy of prematurity. Ophthalmology. 1985;92(8):1000.
29. Foos R. Chronic retinopathy of prematurity. Ophthalmology. 1985;92(4):563–74.
30. Cunningham S, Fleck BW, Elton RA, et al. Transcutaneous oxygen levels in retinopathy of prematurity. Lancet. 1995;346: 1464–5.
31. Seiberth V, Linderkamp O. Risk factors in retinopathy of prematurity. A multivariate statistical analysis. Ophthalmologica. 2000;214:131–5.
32. Vintzileos AM, Ananth CV, Smulian JC, et al. The impact of prenatal care in the United States on preterm births in the presence and absence of antenatal high-risk conditions. Am J Obstet Gynecol. 2002;187:1254–7.
33. Akinbami LJ, Schoendorf KC, Kiely JL. Risk of preterm birth in multiparous teenagers. Arch Pediatr Adolesc Med. 2000;154: 1101–7.
34. Datta-Bhutada S, Johnson HL, Rosen TS. Intrauterine cocaine and crack exposure: neonatal outcome. J Perinatol. 1998;18:183–8.
35. The STOP-ROP Multicenter Study Group. Supplemental therapeutic oxygen for prethreshold retinopathy of prematurity (STOP-ROP), a randomized, controlled trial. I: Primary outcomes. Pediatrics. 2000;105:295–310.
36. Chow LC, Wright KW, CSMC Oxygen Administration Study Group. Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003;111(2):339–45.
37. VanderVeen DK, Mansfield TA, Eichenwald EC. Lower oxygen saturation alarm limits decrease the severity of retinopathy of prematurity. J AAPOS. 2006;10(5):445–8.
38. Britt MT, Sandoval M, Siegel LM. Decreased incidence of laser surgery for severe retinopathy of prematurity with supplemental oxygen protocol. J AAPOS. 2005;9(1):89.
39. Lane RH, Hartnett ME. Effects of oxygen on the development and severity of retinopathy of prematurity. J AAPOS. 2013;17(3): 229–34.
40. Raju TNK, Langenberg P, Bhutani V, et al. Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials. J Pediatr. 1997;131:844–50.
41. Johnson L, Bowen Jr FW, Abbasi S, et al. Relationship of prolonged pharmacologic serum levels of Vitamin E to incidence of sepsis and incidence of necrotizing enterocolitis in infants with birth weight 1500 grams or less. Pediatrics. 1985;75:619–38.
42. Phelps DL, Lakatos L, Watts JL. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Cochrane Database Syst Rev. 2001;(1):CD001073.
43. Christensen RD, Alder SC, Richard SC, et al. D-Penicillamine administration and the incidence of retinopathy of prematurity. J Perinatol. 2007;27(2):103–11.
44. Tandon M, Dutta S, Dogra MR, Gupta A. Oral D-Penicillamine for the prevention of retinopathy of prematurity in very low birth weight infants: a randomized, placebo controlled trial. Acta Paediatr. 2010;99(9):1324–8.
45. Siatkowksi RM, Yanovitch TL, Ash JD, Moreau A. The effects of D-penicillamine on a murine model of oxygen-induced retinopathy. J AAPOS. 2001;15(4):370–3.
46. May CA. The influence of triamcinolone on endostatin-like proteins in oxygen-induced retinopathy of prematurity. Exp Eye Res. 2012;100:86–7.
47. Zhang HB, Sun NX, Liang HC, et al. 17-Alpha-estradiol ameliorating oxygen induced retinopathy in a murine model. Jpn J Ophthalmol. 2012;56(4):407–15.
48. American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2013;131: 189–95.
49. Early Treatment For Retinopathy Of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results for the early treatment of retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684–94.
50. Lofqvist C, Hansen-Pupp I, Anderssen E, et al. Validation of a new retinopathy of prematurity screening method monitoring longitudinal postnatal weight and insulin-like growth factor I. Arch Ophthalmol. 2009;127:622–7.
51. Hellstrom A, Hard AL, Engstrom E, et al. Early weight gain predicts retinopathy in preterm infants: new, simple, efficient approach to screening. Pediatrics. 2009;123:e638–45.
52. Wu C, Lofqvist C, Smith LE, et al. Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants: a multicenter study analyzing weight velocity deviations

for the prediction of retinopathy of prematurity. Arch Ophthalmol. 2012;130:992–9.
53. Wu C, Vanderveen DK, Hellstrom A, et al. Longitudinal postnatal weight gain measurements for the prediction of retinopathy of prematurity. Arch Ophthalmol. 2010;128:443–7.
54. Binenbaum G, Ying GS, Quinn GE, et al. The CHOP postnatal weight gain, birth weight, and gestational age retinopathy of prematurity risk model. Arch Ophthalmol. 2012;130:1560–5.
55. Binenbaum G, Ying GS, Quinn GE, et al. A clinical prediction model to stratify retinopathy of prematurity using postnatal weight gain. Pediatrics. 2011;127:e607–14.
56. O'Keefe M, Kirwan C. Screening for retinopathy of prematurity. Early Hum Dev. 2008;84:89–94.
57. Good WV, Hardy RJ, Dobson V, et al. Early Treatment for Retinopathy of Prematurity Cooperative Group. Final visual acuity results in the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2010;128(6):663–71.
58. Quinn GE, Dobson V, Hardy R, et al. Visual field extent at 6 years of age in children who had high-risk prethreshold retinopathy of prematurity. Arch Ophthalmol. 2011;129:127–32.
59. Alme AM, Mulhern ML, Hejkal TW, et al. Outcome of retinopathy of prematurity patients following adoption of revised indications for treatment. BMC Ophthalmol. 2008;8(1):23.
60. Simpson JL, Melia M, Yang MB, et al. Current role of cryotherapy in retinopathy of prematurity: a report by the American Academy of Ophthalmology. Ophthalmology. 2012;119:873–7.
61. Palmer EA, Hardy RJ, Dobson V, et al. 15 year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. Arch Ophthalmol. 2005;123:311–8.
62. Banach MJ, Ferrone PJ, Trese MT. A comparison of dense versus less dense diode laser photocoagulation patterns for threshold retinopathy of prematurity. Ophthalmology. 2000;107:324–8.
63. Paysse EA, Lindsey JL, Coats DK, et al. Therapeutic outcomes of cryotherapy versus transpupillary diode laser photocoagulation for threshold retinopathy of prematurity. J AAPOS. 1999;3(4):234–40.
64. Ng EY, Connolly BP, McNamara JA, et al. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: part 1. Visual function and structural outcome. Ophthalmology. 2002;109(5):928–34.
65. Connolly BP, Ng EY, McNamara JA, et al. A comparison of laser photocoagulation with cryotherapy for threshold retinopathy of prematurity at 10 years: part 2. Refractive outcome. Ophthalmology. 2002;109(5):936–41.
66. Andersen CC, Phelps DL. Peripheral retinal ablation for threshold retinopathy of prematurity in preterm infants. Cochrane Database Syst Rev. 2000;(2): CD001693.
67. Matsuyama K, Ogata N, Matsuoka M, Wada M, Takahashi K, Nishimura T. Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. Br J Ophthalmol. 2010;94:1215–8.
68. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603–15.
69. Hu J, Blair MP, Shapiro MJ, et al. Reactivation of retinopathy of prematurity after bevacizumab injection. Arch Ophthalmol. 2012;130:1000–6.
70. McCloskey M, Wang H, Jiang Y, Smith GW, Strange J, Hartnett ME. Anti-VEGF antibody leads to later atypical intravitreous neovascularization and activation of angiogenic pathways in a rat model of retinopathy of prematurity. Invest Ophthalmol Vis Sci. 2013;54(3):2020–6.
71. Gaudreault J, Fei D, Rusit J, Suboc P, Shiu V. Preclinical pharmacokinetics of ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Opthalmol Vis Sci. 2005;46:726–33.
72. Miyake T, Sawada O, Kakinoki M, Sawada T, Kawamura H, Ogasawara K, et al. Pharmacokinetics of bevacizumab and its effect on vascular endothelial growth factor after intravitreal injection of bevacizumab in macaque eyes. Invest Ophthalmol Vis Sci. 2010;51:1606–8.
73. Sato T, Wada K, Arahori H, et al. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol. 2012;153(2):327–33.
74. Zehetner C, Kirchmair R, Huber S, et al. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. Br J Ophthalmol. 2013;97(4):454–9.
75. Hoerster R, Muether P, Dahlke C, et al. Serum concentrations of vascular endothelial growth factor in an infant treated with ranibizumab for retinopathy of prematurity. Acta Ophthalmol. 2013;91(1):e74–5.
76. Sebag J. Pharmacologic vitreolysis. Retina. 1998;18(1):1–3.
77. Sebag J. Pharmacologic vitreolysis – premise and promise of the first decade. Retina. 2009;29(7):871–4.
78. Stenzel D, Lundkvist A, Sauvaget D, et al. Integrin-dependent and -independent functions of astrocytic fibronectin in retinal angiogenesis. Development. 2011;138:4451–63.
79. Pepper MS. Role of the matrix metalloproteinase and plasminogen activator-plasmin systems in angiogenesis. Arterioscler Thromb Vasc Biol. 2001;21:1104–17.
80. Wu W-C, Drenser KA, Lai M, Capone A, Trese MT. Plasmin enzyme-assisted vitrectomy for primary and reoperated eyes with stage 5 retinopathy of prematurity. Retina. 2008;28:S75–80. doi:10.1097/IAE.0b013e318158ea0e.
81. Wong SCC, Jr A. Microplasmin (ocriplasmin) in pediatric vitreoretinal surgery: update and review. Retina. 2013;33:339–48.
82. Coats DK, Miller AM, Hussein MA, et al. Involution of retinopathy of prematurity after laser treatment: factors associated with development of retinal detachment. Am J Ophthalmol. 2005;140:214–22.
83. Trese MT, Droste PJ. Long-term postoperative results of a consecutive series of stages 4 and 5 retinopathy of prematurity. Ophthalmology. 1998;105:992–7.
84. Hartnett ME. Features associated with surgical outcome in patients with stages 4 and 5 retinopathy of prematurity. Retina. 2003;23(3):322–9.
85. Clark D, Mandal K. Treatment of retinopathy of prematurity. Early Hum Dev. 2008;84:95–9.
86. Hartnett ME, Maguluri S, Thompson HW, McColm JR. Comparison of retinal outcomes after scleral buckle or lens-sparing vitrectomy for stage 4 retinopathy of prematurity. Retina. 2004;24:753–7.
87. Ferrone PJ, Harrison C, Trese MT. Lens clarity after lens-sparing vitrectomy in a pediatric population. Ophthalmology. 1997; 104:273–8.
88. Lakhanpal RR, Davis GH, Sun RL, et al. Lens clarity after three port lens-sparing vitrectomy in stage 4A and 4B retinal detachments secondary to retinopathy of prematurity. Arch Ophthalmol. 2006;124(1):20–3.
89. Mann I. The development of the human eye. New York: Grune& Stratton Inc.; 1950.
90. Hamming NA, et al. Ultrastructure of the hyaloid vasculature in primates. Invest Ophthalmol Vis Sci. 1977;16:408–15.
91. Gergely K, Gerinec A. A consonant construction of the hyaloids and retinal vascular systems by the angiogenic process. Bratisl Lek Listy. 2011;112(3):143–51.
92. Alvarez Y, et al. Genetic determinants of hyaloid and retinal vasculature in zebrafish. BMC Dev Biol. 2007;7:114.

93. Jack RL. Regression of the hyaloid artery system: an ultrastructural analysis. Am J Ophthalmol. 1972;74:261–72.
94. Latker CH, Kuwabara T. Regression of the tunica vasculosalentis in the postnatal rat. Invest Ophthalmol Vis Sci. 1981;21:689–99.
95. Duke-Elder S. System of ophthalmology. Vol. 3. Normal and abnormal development. Part 1: embryology. St. Louis: The C.V. Mosby Company, 1964. In: Hamming NA, Apple DJ, Gieser DK, Vygantas CM. Ultrastructure of the hyaloid vasculature in primates. Invest Ophthalmol Vis Sci. 1977;16:408–15.
96. Delaney WV. Prepapillary hemorrhage and persistent hyaloid artery. Am J Ophthalmol. 1980;90:419–21.
97. Renz B, Vygantas C. Hyaloid vascular remnants in human neonates. Ann Ophthalmol. 1977;9:179–84.
98. Mets MB. Childhood blindness and visual loss: an assessment at two institutions including a "new" cause. Trans Am Ophthalmol Soc. 1999;97:653–96.
99. Gans B. The pupillary membrane in premature infants. Arch Dis Child. 1959;34:292–7.
100. Hollenberg MJ, Dickson DH. Scanning electron microscopy of the tunica vasculosa lentis of the rat. Can J Ophthalmol. 1971;6:301–10.
101. Meisels H, Goldberg MF. Vascular anastomoses between the iris and persistent hyperplastic primary vitreous. Am J Ophthalmol. 1979;88:179–85.
102. Goldberg MF. Clinical manifestations of ectopia lentis et pupillae in 16 patients. Ophthalmology. 1988;95:1080–7.
103. Gifford SR, Latta JS. Pseudoglioma and remains of the tunica vasculosalentis. Am J Ophthalmol. 1923;6:565–71.
104. Sellheyer K, Spitznas M. Ultrastructure of the human posterior tunica vasculosalentis during early gestation. Graefes Arch Clin Exp Ophthalmol. 1987;225:377–83.
105. Hittner HM, Hirsch NJ, Rudolph HJ. Assessment of gestational age by examination of the anterior vascular capsule of the lens. J Pediatr. 1977;91:455–8.
106. Pollard ZF. Persistent hyperplastic primary vitreous, diagnosis, treatment, and results. Am Ophthalmol Soc. 1997;95:487–549.
107. Goldberg MF. Persistent fetal vasculature (PFV): an integrated interpretation of signs and symptoms associated with persistent hyperplastic primary vitreous (PHPV) LIV Edward Jackson Memorial Lecture. Am J Ophthalmol. 1997;124:587–626.
108. Xu O, Wang YS, Dabdoub A, et al. Vascular development in the retina and inner ear: control by norrin and frizzled 4, a high affinity ligand receptor pair. Cell. 2004;116:883–95.
109. Prasov L, et al. ATOH7 mutations cause autosomal recessive persistent hyperplasia of the primary vitreous. Hum Mol Genet. 2012;21(16):3681–94.
110. Edward MM, Mcleon DS, Grebe R, Heng C, Lefebvre O, Lutty GA. Lama1 mutations lead to vitreoretinal blood vessel formation, persistence of fetal vasculature, and epiretinal membrane formation in mice. BMC Dev Biol. 2011;11:60.
111. Martin AC, Thornton JD, Liu J, et al. Pathogenesis of persistent hyperplastic primary vitreous in mice lacking the arf tumor suppressor gene. Invest Ophathlmol Vis Sci. 2004;45:3387–96.
112. Reichel MB, Ali RR, D'Esposito F, et al. High frequency of persistent hyperplastic primary vitreous and cataracts in p-53 deficient mice. Cell Death Differ. 1998;5:156–62.
113. Zhang J, Fuhrmann S, Vetter ML. A nonautonomous role for retinal frizzled-5 in regulating hyaloids vitreous vasculature development. Invest Ophathlmol Vis Sci. 2008;49:5561–7.
114. Rutland CS, Mitchell CA, Nasir M, Konerding MA, Drexler HC. Microphthalmia, persistent hyperplastic hyaloid vasculature and lens anomalies following overexpression of VEGF-A188 from the alpha A-crystallin promoter. Mol Vis. 2007;13:47–56.
115. Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. Am J Ophthalmol. 1969;68:578–94.
116. Ranchod TM, Ho LY, Drenser KA, Capone Jr A, Trese MT. Clinical presentation of familial exudative vitreoretinopathy. Ophathalmology. 2011;118:2070–5.
117. Benson WE. Familial exudative vitreoretinopathy. Trans Am Ophthalmol Soc. 1995;93:473–521.
118. Tasman W, Augsburger JJ, Shields JA, et al. Familial exudative vitreoretinopathy. Trans Am Ophthalmol Soc. 1981;79:211–26.
119. Miyakubo H, Inohara N, Hashimot K. Retinal involvement in familial exudative vitreoretinopathy. Ophthalmologica. 1982;185:125–35.
120. Van Nouhuys CE. Dominant exudative vitreoretinopathy and other vascular developmental disorders of the peripheral retina [thesis]. Doc Opahthalol. 1982;54:1–415.
121. Trese MT, Capone Jr A. Familial exudative vitreoretinopathy. In: Pediatric retina. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 425–8.
122. Pendergast SD, Trese MT. Familial exudative vitreoretinopathy: results of surgical management. Ophathalmology. 1998;105:1015–23.
123. Toomes C, Downey L. Familial exudative vitreoretinopathy: autosomal dominant. GeneReviews. Available at www.genetests.org. Accessed Mar 2013.
124. Shukla D, Singh J, Sudheer G, et al. Familial exudative vitreoretinopathy (FEVR). Clinical profile and management. Indian J Ophthalmol. 2003;51:323–8.
125. Toomes C, Bottomley HM, Jackson RM, et al. Mutations in LRP5 or FZD4 underlie the common familial exudative vitreoretinopathy locus on chromosome 11q. Am J Hum Genet. 2004;74:721–30.
126. Ikeda T, Tano Y, Tsujikawa K, et al. Vitrectomy for rhegmatogenous or tractional retinal detachment with familial exudative vitreoretinopathy. Ophthalmology. 1999;106:1081–5.
127. Glazer LC, Maguir A, Blumenkranz MS, et al. Improved surgical treatment of familial exudative vitreoretinopathy in children. Am J Ophthalmol. 1995;120:471–9.
128. Chen SN, Hwang JF, Lin CJ. Clinical characteristics and surgical management of familial exudative vitreoretinopathy-associated rhegmatogenous retinal detachment. Retina. 2012;32(2):220–5.
129. Williams JG, Trese MT, Williams GA, et al. Autologous plasmin enzyme in the surgical management of diabetic retinopathy. Ophthalmology. 2001;108:1902–5.
130. Wu WC, Drenser KA, Trese MT, et al. Pediatric traumatic macular hole: results of autologous plasmin enzyme-assisted vitrectomy. Am J Ophthalmol. 2007;144(5):668–72.
131. Tagami M, Kusuhara S, Honda S, et al. Rapid regression of retinal hemorrhage and neovascularization in a case of familial exudative vitreoretinopathy treated with intravitreal bevacizumab. Graefes Arch Clin Exp Ophthalmol. 2008;246(12):1787–9.
132. Sebag J, Nguyen N. Vitreous embryology and vitreo-retinal developmental disorders. In: Hartnett ME et al., editors. Pediatric retina. Philadelphia: Lippincott; 2005. p. 13–28.