Retinopathy of Prematurity: A Comprehensive Review of Risk Factors, Screening, and Management

Islam Elsayed Mohamed Elsayed Hussien[1], Salah M Elmosalamy[2], Ehab Albanna[3], Esaam M Gomaa[4], Hesham A Enani[5]

1. Resident of Ophthalmology, Faculty of Medicine, Zagazig university,
2. Professor of Ophthalmology, Faculty of Medicine, Zagazig university,
3. Professor of Pediatrics and Neonatology, Faculty of Medicine, Zagazig university,
4. Lecturer of Ophthalmology, Faculty of Medicine, Zagazig university,
5. Assistant Professor of Ophthalmology, Faculty of Medicine, Zagazig university,

Corresponding author: Islam Elsayed Mohamed Elsayed Hussien

Abstract

Retinopathy of Prematurity (ROP) is a leading cause of childhood blindness, particularly in preterm infants with low birth weight and prolonged oxygen therapy. The epidemiology of ROP varies globally, with higher incidences in low- and middle-income countries due to increasing neonatal survival rates and inconsistent screening programs. In developed countries, advances in neonatal care have reduced the severity of ROP but have not eliminated its occurrence. The condition primarily affects infants born before 32 weeks of gestation or with a birth weight below 1500 grams. Risk factors include oxygen supplementation, sepsis, intraventricular hemorrhage, and poor postnatal weight gain. Diagnosis of ROP relies on screening protocols based on gestational age and birth weight, with examinations performed by indirect ophthalmoscopy or wide-field retinal imaging. Screening typically begins at 4-6 weeks postnatally and continues until vascularization is complete or regression occurs. The International Classification of ROP (ICROP) is used to stage the disease based on the severity of vascular abnormalities and retinal involvement. Investigations for ROP include retinal imaging techniques such as fluorescein angiography, which can identify avascular zones, neovascularization, and vascular leakage. Optical coherence tomography (OCT) is also utilized to detect structural changes in the retina that may precede clinical manifestations of ROP. Laboratory tests, such as blood gas analysis, may help monitor oxygen therapy, as excessive oxygen exposure is a major contributing factor. Treatment of ROP is stage-dependent, with mild cases often regressing spontaneously. However, severe ROP (Stage 3 or higher) requires intervention to prevent retinal detachment and blindness. Laser photocoagulation is the gold standard for treating threshold ROP, effectively ablating avascular retina and reducing the risk of progression. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections, such as bevacizumab and ranibizumab, have emerged as alternatives or adjuncts to laser therapy, particularly in aggressive posterior ROP (AP-ROP). However, long-term systemic effects remain a concern. In advanced cases, surgical interventions like vitrectomy or scleral buckling may be necessary to address retinal detachment. Despite advancements in neonatal care and ROP management, prevention through optimal oxygen delivery, nutritional support, and timely screening remains crucial. Strengthening screening programs and increasing awareness among healthcare professionals can significantly reduce the burden of ROP-related blindness worldwide.

Keywords: *Retinopathy of prematurity, diagnosis, treatment*

1. Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina primarily affecting preterm infants. It is a significant cause of childhood blindness worldwide, with its incidence correlating strongly with decreasing gestational age and birth weight [1]. The condition was first identified in the 1940s when it was linked to high supplemental oxygen therapy used in neonatal care. Advances in neonatal intensive care have increased the survival rates of very preterm infants, thereby also increasing the population at risk for ROP [2].

The epidemiology of ROP varies globally, with higher incidences reported in low- and middle-income countries due to disparities in neonatal care. In high-income countries, improved oxygen monitoring and neonatal care have reduced the incidence of severe ROP, whereas in developing nations, inadequate neonatal care leads to higher rates of blindness from ROP [3]. Studies indicate that in regions with suboptimal neonatal care, the threshold for ROP development occurs at higher gestational ages compared to more developed settings [4].

Oxygen therapy plays a pivotal role in the pathogenesis of ROP. Hyperoxia in premature infants leads to retinal vascular arrest, followed by hypoxia-induced neovascularization when oxygen levels are reduced. This biphasic pathophysiological mechanism underlies the disease progression and severity [5]. Excessive oxygen suppresses vascular endothelial growth factor (VEGF), causing delayed retinal vessel growth. Upon the return to normoxia, a rebound increase in VEGF triggers abnormal vessel proliferation, predisposing to retinal detachment [6].

Gestational age and birth weight are primary risk factors for ROP. Infants born before 30 weeks or weighing less than 1500 grams are at the highest risk. The immaturity of their retinal vasculature predisposes them to the effects of oxidative stress and VEGF dysregulation, making them particularly vulnerable to severe ROP [7]. Other risk factors include prolonged mechanical ventilation, blood transfusions, sepsis, and fluctuations in oxygen saturation [8].

Screening for ROP is crucial in early detection and management. Guidelines for screening are based on gestational age and birth weight criteria, with examinations starting at 4–6 weeks postnatal age. The International Classification of ROP (ICROP) categorizes the disease based on severity, location, and presence of plus disease, aiding in standardized diagnosis and treatment decisions [9].

The pathophysiology of ROP is closely linked to oxidative stress and inflammatory responses. Premature birth exposes the retina to postnatal metabolic stress, leading to reactive oxygen species (ROS) accumulation. This oxidative stress damages developing retinal vessels, contributing to the characteristic avascular and neovascular phases of ROP [10]. Inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha exacerbate this process, promoting further retinal damage [11].

Vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) are critical mediators in ROP development. While VEGF is essential for normal vascular development, its dysregulation leads to pathological neovascularization. IGF-1 deficiency in preterm infants impairs normal vessel growth, exacerbating the avascular retina's susceptibility to subsequent VEGF-induced abnormal vessel proliferation [12].

Treatment strategies for ROP focus on inhibiting pathological angiogenesis while preserving normal retinal vascular development. Laser photocoagulation remains the standard treatment for

severe ROP, particularly for threshold disease. This method reduces VEGF levels by ablating the avascular retina, preventing disease progression [13]. However, laser therapy can lead to peripheral vision loss, necessitating careful patient selection and follow-up [14].

Anti-VEGF therapy has emerged as a promising alternative, particularly for posterior ROP. Intravitreal injections of anti-VEGF agents like bevacizumab and ranibizumab effectively suppress neovascularization while allowing continued retinal vascularization. However, concerns remain regarding systemic absorption and potential adverse effects on neurodevelopment [15]. Studies have demonstrated that anti-VEGF therapy may be superior to laser treatment in certain cases, especially in aggressive posterior ROP [16].

Long-term outcomes of ROP vary based on disease severity and treatment modalities. While many infants experience regression without significant visual impairment, severe cases may result in retinal detachment and blindness. Even in treated cases, long-term complications such as high myopia, strabismus, and retinal scarring are common, necessitating ongoing ophthalmologic follow-up [17].

Neurodevelopmental outcomes in infants with ROP are also a growing concern. Studies have shown an association between severe ROP and neurodevelopmental impairments, likely due to shared risk factors such as prematurity, hypoxia, and systemic inflammation. Cognitive, motor, and behavioral delays have been reported in preterm infants with severe ROP [18].

Preventive strategies for ROP focus on optimizing neonatal care. Oxygen therapy must be carefully titrated to maintain saturation within safe limits (90–95%). Avoiding fluctuations in oxygenation and implementing strict oxygen monitoring protocols significantly reduce ROP incidence and severity [19]. Nutritional interventions, including omega-3 fatty acid supplementation and adequate IGF-1 levels, have been explored as potential preventive strategies [20].

Multidisciplinary care involving neonatologists, ophthalmologists, and pediatricians is essential for optimal ROP management. Early screening, timely intervention, and post-treatment monitoring improve visual outcomes and reduce blindness rates [21]. Future research continues to explore novel therapeutic approaches, including gene therapy and neuroprotective agents, to mitigate ROP-related complications [22].

Current Diagnosis and Investigations of Retinopathy of Prematurity

The diagnosis of retinopathy of prematurity (ROP) relies on comprehensive ophthalmologic examinations performed in preterm infants at risk. These examinations are critical for early detection and timely intervention. The screening process is primarily guided by gestational age and birth weight criteria, with most guidelines recommending initial examination at 4 to 6 weeks postnatal age [23]. Ophthalmologists use indirect ophthalmoscopy to assess retinal vascular development and detect signs of ROP progression [24].

Retinal imaging has significantly enhanced the diagnosis and monitoring of ROP. Digital fundus photography, using devices such as the RetCam, enables high-resolution imaging of the retina. These images can be stored and reviewed remotely, allowing for telemedicine-based screening programs that improve access to specialized care, particularly in resource-limited settings [25]. Automated image analysis systems are also being developed to assist in early detection and classification of ROP severity [26].

The International Classification of ROP (ICROP) provides a standardized framework for grading the severity of the disease. This classification is based on zone (location of disease in the retina), stage (extent of vascular abnormality), and the presence of plus disease, which indicates

significant vascular dilation and tortuosity [27]. Plus disease is a critical indicator of disease progression and often necessitates immediate intervention [28].

Fluorescein angiography (FA) has been increasingly utilized to gain deeper insights into the vascular abnormalities in ROP. This imaging technique provides detailed visualization of retinal vasculature and areas of non-perfusion. FA can identify subtle vascular leakage and abnormal shunting, which may not be evident through standard ophthalmoscopic examination [29]. However, its routine use remains limited due to concerns about the invasiveness of the procedure in fragile preterm infants [30].

Optical coherence tomography (OCT) and OCT angiography (OCTA) are emerging as valuable tools for assessing retinal structure and vascular integrity in ROP. These imaging modalities provide cross-sectional and en face views of the retina, revealing microstructural abnormalities such as retinal thinning, cystoid changes, and foveal immaturity. These insights contribute to a better understanding of the long-term visual implications of ROP [31].

Biochemical and molecular markers are being explored as potential diagnostic adjuncts in ROP. Elevated levels of vascular endothelial growth factor (VEGF) in the vitreous and serum correlate with disease severity. Similarly, inflammatory markers such as interleukin-6 and C-reactive protein have been associated with an increased risk of ROP progression. These biomarkers could aid in identifying infants at higher risk for severe disease [32].

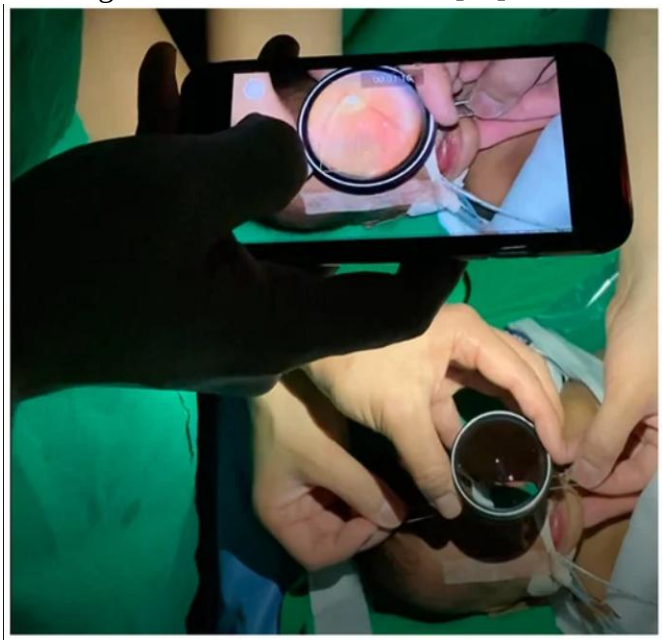

Figure (1): Technique of smartphone fundus imaging for the evaluation of the retinopathy of prematurity

Figure (2): Paxos Scope smartphone adapter

Figure (3): Wide-field digital ROP screening by Retcam imaging

Figure (4): 3nethra neo during examination of Retinopathy of Prematurity case

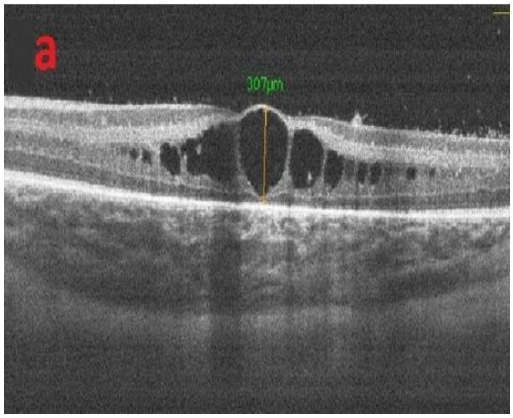

Figure (4): OCT image of a premature infant with type 1 ROP (zone 2 stage 3 with plus disease) before intravitreal ranibizumab treatment

Genetic studies have highlighted the role of genetic predisposition in ROP susceptibility. Variations in genes related to angiogenesis, oxidative stress, and inflammation may contribute to disease risk and severity. Identifying genetic markers could facilitate risk stratification and individualized screening strategies in the future [33].

The role of systemic factors in ROP development underscores the need for multidisciplinary assessment. Blood gas analysis, monitoring of oxygen saturation, and evaluation of systemic inflammation provide additional insights into disease pathogenesis. Studies suggest that fluctuations in oxygen levels and prolonged mechanical ventilation are key contributors to disease progression [35].

Neonatal intensive care units (NICUs) have implemented stringent oxygen therapy protocols to mitigate ROP risk. Targeting oxygen saturation levels between 90% and 95% has been shown to reduce the incidence of severe ROP. However, maintaining this delicate balance remains challenging, as lower oxygen levels can increase the risk of other complications such as neurodevelopmental impairment [36].

Electrophysiological tests, including electroretinography (ERG), offer functional assessment of retinal activity in preterm infants. ERG can detect early retinal dysfunction before clinical signs of ROP appear. Reduced amplitudes in scotopic and photopic responses have been associated with more severe disease and poor visual outcomes [37].

Systemic comorbidities such as sepsis, intraventricular hemorrhage, and necrotizing enterocolitis have been linked to increased ROP severity. Close monitoring and aggressive management of these conditions in preterm infants can reduce the overall disease burden and improve outcomes [38].

Advanced screening techniques continue to evolve, integrating multi-modal imaging and AI-assisted diagnostics. Future developments in ROP diagnosis may include non-invasive molecular imaging and personalized risk prediction models based on genetic and clinical parameters [39].

Longitudinal studies assessing the correlation between early diagnostic markers and long-term visual outcomes are essential. Such studies can refine screening guidelines and improve prognostic accuracy, ensuring better visual function preservation in affected infants [40].

Treatment of Retinopathy of Prematurity

The treatment of retinopathy of prematurity (ROP) aims to prevent retinal detachment and

preserve vision in affected infants. Management strategies depend on disease severity, with interventions guided by established treatment criteria. The mainstay treatments include laser photocoagulation, anti-vascular endothelial growth factor (anti-VEGF) therapy, and surgical approaches for advanced cases [41]. Early detection through regular screening is crucial to initiating timely treatment and optimizing visual outcomes [42].

Laser photocoagulation remains the gold standard treatment for severe ROP, particularly for threshold disease. This procedure involves ablating the avascular retina to reduce VEGF production and prevent abnormal neovascularization. While effective in halting disease progression, laser therapy may cause peripheral vision loss due to the destruction of retinal tissue [43]. Advances in laser technology have improved precision and minimized collateral damage, enhancing visual prognosis [44].

Anti-VEGF therapy has emerged as an alternative or adjunctive treatment for ROP. Intravitreal injections of agents such as bevacizumab and ranibizumab inhibit VEGF activity, suppressing neovascularization while allowing continued vascular development. This approach is particularly beneficial for aggressive posterior ROP, where laser therapy may be less effective [45]. However, concerns remain regarding potential systemic absorption and long-term neurodevelopmental effects [46].

Combination therapy involving both laser photocoagulation and anti-VEGF injections is increasingly being utilized to optimize treatment outcomes. This approach balances the benefits of VEGF inhibition with the long-term stability provided by laser ablation. Studies suggest that combination therapy reduces recurrence rates and preserves retinal integrity more effectively than monotherapy [47].

Surgical intervention is necessary in advanced cases of ROP where retinal detachment has occurred. Procedures such as scleral buckling and vitrectomy aim to reattach the retina and prevent further deterioration. While surgical outcomes have improved, visual prognosis remains guarded in severe cases, emphasizing the importance of early-stage interventions [48]. Advances in microsurgical techniques continue to enhance the success rates of ROP-related retinal surgeries [49].

Cryotherapy, once a standard treatment for ROP, has largely been replaced by laser therapy due to its lower precision and higher complication rates. However, in settings where laser equipment is unavailable, cryotherapy remains a viable alternative. This technique involves freezing the avascular retina to achieve similar effects as laser ablation in reducing VEGF-driven neovascularization [50].

Ongoing clinical trials are exploring newer therapeutic options, including novel anti-angiogenic agents and neuroprotective treatments. Emerging research suggests that targeting additional angiogenic pathways may offer enhanced efficacy in preventing disease progression. Gene therapy and regenerative medicine approaches are also being investigated as potential future treatments [51].

Oxygen therapy optimization plays a critical role in preventing severe ROP and reducing the need for aggressive interventions. Maintaining optimal oxygen saturation levels (90-95%) in preterm infants minimizes oxidative stress and excessive VEGF stimulation. Implementing strict oxygen monitoring protocols in neonatal intensive care units has significantly reduced the incidence of severe ROP [52].

Systemic factors such as sepsis, intraventricular hemorrhage, and poor postnatal growth influence ROP severity and treatment response. Optimizing neonatal nutrition, minimizing inflammatory insults, and ensuring adequate weight gain can improve treatment outcomes and reduce disease

progression [53]. Multidisciplinary care involving neonatologists, ophthalmologists, and pediatricians is crucial for comprehensive ROP management [54].

Long-term follow-up is essential for infants treated for ROP, as they remain at risk for visual impairments such as high myopia, strabismus, and retinal detachment later in life. Regular ophthalmologic assessments and early interventions for refractive errors can improve functional vision and quality of life [55].

Parental education plays a key role in ROP management. Providing caregivers with information on the importance of follow-up examinations, potential visual complications, and early signs of recurrent disease empowers them to actively participate in their child's visual health [56]. Community-based screening and telemedicine initiatives further enhance accessibility to timely diagnosis and treatment [57].

Despite advances in treatment, ROP remains a leading cause of childhood blindness worldwide. Disparities in neonatal care and access to specialized interventions contribute to varying disease outcomes. Strengthening healthcare infrastructure and expanding training programs for neonatal ophthalmologists are essential steps toward improving global ROP management [58].

Future research aims to refine current treatment protocols and develop personalized approaches based on genetic and clinical risk factors. Predictive models integrating artificial intelligence and big data analytics may enable earlier identification of high-risk infants and individualized treatment strategies [59].

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