Retinopathy of Prematurity (ROP): A Review of Potential Demographic and Clinical Risk Factors

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Abstract

In this literature review, we will be discussing potential risk factors contributing to the development of retinopathy of prematurity (ROP), a significant cause of childhood blindness worldwide. While the majority of current guidelines focus on gestational age and birth weight, more recent literature has suggested other factors, including demographic and clinical risk factors might be at play. Studies have revealed sex, sepsis, blood transfusion, oxygen supplementation, RDS, and maternal complications to be potential risk factors in the development of this disease. Recognizing the complexity of ROP risk factors is pivotal, not only for the development of predictive models but also for gaining profound insights into the pathophysiology of retinal vascular diseases and conditions associated with prematurity. This review aims to provide a better understanding that can guide future clinicians and researchers to treating and studying ROP. This study is a literature review, where researchers systematically examined articles aligning with pre-established criteria. The screening process involved assessing titles, abstracts, keywords, inclusion criteria, and the entire text contents of relevant previous articles for review.

Keywords: Pediatric Ophthalmology; Retinopathy of Prematurity; Preterm Infants; Risk Factors; ROP

1. Retinopathy of Prematurity (ROP)

1.1. Definition

Retinopathy of Prematurity (ROP) is vasoproliferative disease of the retina that is unique to premature infants and is considered to be the leading cause of childhood blindness worldwide. In 1942, Terry initially referred to ROP as Retrolental Fibroplasia (RLF) and defined it as a progressive disease that was primarily present in preterm infants with low birth weight. He noticed that in a series of preterm infants, a form of fibrous and dense tissue formed behind their lens [38]. In the past, ROP was not a primary concern for both ophthalmologists and pediatricians, but a decade later this issue progressed on to be a serious problem worldwide as incidences increase each year.

1.2. Epidemiology

It is estimated that around 14 million of the world's children suffer from blindness [43]. Among others, ROP remains to be one of the most common preventable diseases causing blindness and visual impairment in children around the world. In the year 2010, a global number of 184,700 infants and 14.9 million preterm infants

developed any stage ROP [12]. The first ever case of ROP was back in the 1940s and 1950s, reportedly due to unmonitored oxygen supplementation in Europe and North America. Every year in the United States, around 14,000 preterm infants are diagnosed with ROP. Of these infants, approximately 90% experience spontaneous regression, and between 1,100 and 1,500 develop a disease severe enough to require medical treatment [9]. ROP is also increasingly reported in developing countries, particularly in Asian countries such as India and China. Emerging cases from Latin America and Eastern Europe further confirm that this disease is currently a very important cause of blindness in middle-income countries, as neonatal intensive care units (NICUs) expand rapidly, but still fail to apply proper monitoring for oxygen delivery in premature babies.

One study reported the incidence of ROP within an eleven-year period at Harapan Kita Hospital in Jakarta, which is known to be one of the largest and oldest NICU in Indonesia; this study included all preterm infants admitted with GA of ≤32 weeks and birth weight (BW) of less than 1500 g for the period of January 2005–December 2015. In the <1000 g group, 27 (46%) infants had no ROP, 22 (37%) had ROP 1–2 and 10 (17%) had ROP 3–5. In the 1000–1500 g group, 172 (68%) infants had no ROP, 71 (28%) had ROP 1–2 and nine (4%) had ROP 3–5 [42].

1.3. Clinical Features and Classification

In 1979, a group of international committees formulated the International Classification for Retinopathy of Prematurity (ICROP). Five years later, this classification was later modified, taking into account certain aspects of the disease: severity, location, extent, and documentation of the status of the blood vessels in the posterior pole (plus disease).

1.3.1 Severity of ROP

There are five stages to describe the degree of severity in ROP as mentioned. Each of these stages represents ophthalmologic findings at the junction between the vascularized and avascular retina, and denotes the degree of vascular changes within the retina.

- **Stage 1 – Demarcation Line**
  In the first stage, there is a presence of a thin and delicate-line-like structure that separates the vascular and avascular retina. This structure lies flat with abnormal branching vessels leading up to it, in the plane of the retina.

- **Stage 2 – Ridge**
  Following the development of the demarcation line, in the following stage the presence of a ridge can be seen in the region of the demarcation line, extending above the retinal plane. Small tufts called “popcorn” vessels can also be found posterior to the ridge.

- **Stage 3 – Extraretinal Neovascular Proliferation**
  This stage features the extraretinal fibrovascular proliferation which can be seen rising into the vitreous and extends with the posterior aspect of the ridge, causing a ragged appearance as proliferation becomes more extensive. The development may be continuous or non-continuous.

- **Stage 4 – Partial Retinal Detachment**
  In this stage, there may be an appearance of partial retinal detachment which may be exudative or tractional. Stage 4 ROP may be extra foveal; partial retinal development not involving the fovea (stage 4A), or partial retinal detachment involving the fovea (stage 4B), occurring in treated or untreated eyes, it varies depending on the tractional vectors and presence of exudates. The clinical features suggesting partial retinal detachment includes loss of fine detail of choroidal vasculature

or of granular pigment epithelium, a ground-glass appearance relative to adjacent attached retina, or both.

- **Stage 5 – Total Retinal Detachment**
  The last stage of ROP progression is considered to be the most severe, as it features a tractional total retinal detachment, detachments are often funnel-shaped or concave. The clinical presentation of this stage can be identified by the presence of leukocoria (white pupillary reflex). Total retinal detachment is currently classified by configuration of the funnel: open-open (open anterior and posteriorly), open-closed (open anteriorly and closed posteriorly), closed-open (closed anteriorly and open posteriorly), or closed-closed (closed anteriorly and posteriorly). Furthermore, the Committee now recommends that total detachment be subcategorized into 3 configurations: stage 5A, in which the optic disc is visible by ophthalmoscopy; stage 5B, in which the optic disc is not visible secondary to retrolental fibrovascular tissue or closed-funnel detachment; and stage 5C, in which findings of stage 5B are accompanied by anterior segment abnormalities (e.g., anterior lens displacement, marked anterior chamber shallowing, irido-capsular adhesions, capsule-endothelial adhesion with central corneal opacification, or a combination thereof.

1.3.2 Zones of ROP

The zones of ROP are located between the anterior and posterior retina, which can be divided into 3 zones:

- **Zone I**
  The area surrounding the optic nerve and macula, measuring in twice the distance from the center of the optic nerve (posterior retina within a 60° circle centered on the optic nerve).

- **Zone II**
  Extends from the edge of zone I centrifugally to the nasal part of *ora serrata*.

- **Zone III**
  The residual crescent of retina anterior to zone II.

1.3.3 Extent of ROP

The extent of ROP takes into account the condition of the blood vessels. The degree of the disease is determined by measuring it in clock hours, divided into 12 consecutive areas, with each area ranging by 30°.

1.3.4 Plus Disease

Another factor also taken into account is the presence of plus disease within the patient. Plus disease is characterized by vascular dilatation (venous) and tortuosity (arteriolar) of the posterior retinal vessels in at least 2 quadrants of the retina. The presence also describes the increase in blood flow passing through the retina.

1.3.5 Plus Disease

Vascular abnormalities of the posterior pole that are insufficient to be diagnosed as plus disease, however, indicate more venous dilatation and arteriolar tortuosity than normal.

1.3.6 Aggressive Posterior ROP (AP-ROP)

Also known as rush disease, AP-ROP is an unusual, progressive, severe form of ROP that is characterized by posterior location, rapidly evolving plus disease, and neovascularization that may be subtle or intraretinal in nature. AP-ROP does not undergo the same classic development as the typical ROP and can become stage 5 if not treated immediately. This condition is often seen in babies with very low birth weight and early gestational age.

1.4. Types of ROP

Current guidelines show that ROP is divided into two types [2]. Type 1 ROP (high-risk ROP), as defined by the Early Treatment for ROP (ETROP) study, is a severe ROP that requires prompt treatment to prevent progression to retinal detachment and blindness [51]. According to Shan et al., type 1 ROP can be defined according to these conditions: (1) any ROP with plus disease in zone I; (2) stage 3 ROP in zone I; (3) stage 2 or 3 ROP with plus disease in zone II. Infants with type 1 ROP have a strong risk of developing blindness, currently treatment is recommended within 72 hours for type 1 disease. Furthermore, some studies have also referred to the more severe spectrum of this disease as advanced ROP. Advanced ROP includes stages 4A, 4B, 5 all with plus disease and AP-ROP [1]. Meanwhile, type 2 ROP disease requires observation, it is defined as zone 1-stage 1 or 2-without plus disease, and zone 2-stage 3-without plus disease. Patients with type 2 ROP usually have a low-risk pre-threshold of ROP.

2. Risk Factors

Until today the specific cause of ROP remains unclear, however, it is believed that several risk factors have a direct correlation with the incidence of ROP. Most studies review three dominant risk factors that are substantial to the development of ROP. The two strongest known risk factors for ROP are gestational age (GA) and birth weight (BW) [12]. Other commonly associated risk factors include oxygen therapy supplementation, respiratory distress syndrome (RDS), and apnea of prematurity (AOP) [38].

2.1. Prematurity: GA and BW

Factors such as GA and BW are inversely correlated with the incidence of ROP. Babies who are smaller in size and those born at an earlier gestational age are at higher risk of developing this disease. One study reported that premature infants with lower GA had a higher incidence of Type 1 ROP and that no infants with a GA >26 weeks or BW >1000 g developed Type 1 ROP [25]. This report was then confirmed by another study, as they also found no data on infants developing type 1 ROP requiring treatment in infants with GA >27 weeks or BW >900 g [50]. Various existing literature highlights the vulnerability of extremely premature infants to ROP due to the incomplete development of retinal blood vessels, especially those with a smaller gestational age. Furthermore, aligned with previous studies, more recent studies have consistently revealed BW to be an important risk factor in the development of ROP [34]. The multicenter study of cryotherapy for ROP (CRYO-ROP) followed 4,099 infants with BW ≤1,251 g and found that lower BW was strongly associated with developing “threshold” ROP [27]. Notably, in the CRYO-ROP cohort, a 100-gram increase in birth weight was associated with a 27% reduction in the odds of reaching threshold ROP, highlighting the inverse relationship between birth weight and ROP risk. The consistency of these findings with established studies reinforces the link between low birth weight and an increased risk of ROP, underscoring the importance of birth weight as a

critical factor in understanding and mitigating ROP risk in preterm infants, especially those with very low birth weight.

2.2. Oxygen Supplementation

The immature retina of a preterm infant is highly susceptible to any disruption that might hinder neurovascular growth compared to those of an at-term infant. The suppression of growth factors induces a high metabolic activity in the retina, however, the poorly vascularized retina becomes hypoxic. This condition leads to a stimulation of growth-factor-induced vasoproliferation, which as a result could potentially trigger retinal detachment [43].

The use of supplemental oxygen, oxygen concentration, duration and prolonged mechanical ventilation were among the most frequently identified risk factors for treatment-requiring ROP [27]. This was in agreement to a study conducted by Shah et. al in 2016; in which out of the 90 newborns screened for ROP, 35 came out to be positive with the maximum being in stage 1, among the ROP-positive newborns, most had received oxygen exposure. Another study conducted at a tertiary care center in Northeast India in 2017, also found a strong association between ROP incidence and oxygen supplementation, with results of oxygen supplementation (p-value = 0.0182) with a significant relative risk factor of 0.8104 [16]. A comparative study by Chaudhri S et al., also revealed p-value of <0.05 for oxygen supplementation association in infants that were screened for ROP. Hence, the development of ROP also remains to be one of the key factors in disease progression.

2.3. Multiple Gestations

Multiple gestations, characterized by the concurrent development of two or more fetuses, have been identified as a significant risk factor in the development of Retinopathy of Prematurity (ROP). This association is rooted in the increased susceptibility of multiples to preterm birth, smaller birth weight, and perinatal morbidities, all of which contribute to the heightened risk of ROP. The findings from the CRYO-ROP study conducted by Kim et al. in 2018 underscored this link, revealing that singleton infants exhibited a lower risk of ROP compared to their counterparts in twin or multiple pregnancies. The magnitude of the concern is further emphasized by the prevalence of multiple births, constituting approximately 3% of live births in the United States alone [20]. This statistical representation underscores the broader implications of the association between multiple gestations and ROP, as it speaks to a sizable portion of the population at risk for this potentially sight-threatening condition.

One study on 153 Chinese infants born of multiple gestations. The results indicated an incidence of ROP and Type 1 ROP at 11.8% and 3.9%, respectively, within this cohort [50]. These findings parallel those from other studies, reinforcing the notion that multiple gestations are linked to very low birth weight and preterm births—two independent risk factors strongly associated with the development of ROP. The interplay between multiple gestations and ROP risk is multifaceted. The increased likelihood of preterm birth and lower birth weight in multiples creates an environment conducive to the development of ROP. Prematurity exposes the immature retina to external stimuli prematurely, while lower birth weight may signify inadequate intrauterine growth, both contributing factors to ROP pathogenesis.

In conclusion, the association between multiple gestations and ROP risk is a complex interplay of factors involving preterm birth, smaller birth weight, and perinatal morbidities. The evidence from studies such as the CRYO-ROP study and investigations by other studies collectively supports the notion that multiple

gestations significantly elevate the risk of ROP [50]. As twin births continue to represent a notable percentage of live births, understanding and addressing the specific challenges posed by multiple gestations is crucial for effective preventive strategies and early intervention in the context of ROP.

2.4. Sex

According to WHO, the term sex refers to the biological characteristics that define humans as female or male. Linear to this, the American Psychological Association (2015) also described it as something that is assigned since birth (or before during ultrasound) based on the sets and appearance of external genitalia that a male or female possesses, whereas gender refers to a person's inner feeling of being male, female, or something else. Several studies conducted in the past have revealed that the incidence of ROP was more common in males than in females. In 2018, Wu et al. screened a total of 535 preterm infants, of whom the remaining 504 were eligible and found that the sex distribution was 261 (51.8%) male and 243 (48.2%) female for ROP [48]. This claim was in agreement with a previous study conducted by Darlow et al. (2005) in Badriah et al. (2012), which reported that male infants were more vulnerable to ROP (OR 1.67; 95% CI 1.34 to 2.09; $p = 0.001$). However, more recent studies have revealed results to be contradictory. Braimah et al. in 2020, stated that there was a higher risk of ROP ($p = 0.004$) in females with >27 weeks GA compared to males, similar to an observation by Shim et al. Studies regarding sex have always been conflicting in the development of ROP, many have linked it due to an elevated maternal concentration of proinflammatory cytokines and angiogenic factors, notably vascular endothelial growth factor (VEGF), during the gestational period may indicate the presence of factors that could potentially exert adverse effects on the progression of ROP in male neonates [27].

2.5. Blood Transfusion

The association between blood transfusions and the risk of Retinopathy of Prematurity (ROP) has been a subject of significant research, yielding diverse findings that underscore the complexity of this relationship. One study in India in a tertiary care hospital reported a striking increase in the risk of ROP, revealing that infants receiving blood transfusions were at a staggering 13.169 times higher risk compared to those not requiring transfusions. The statistical significance of this association, marked by a p-value of < 0.0001, underscores the robustness of the link between blood transfusions and ROP risk [33].

Corroborating these findings, Wu et al. in China provided additional evidence supporting the independent association between blood transfusions and ROP development (OR = 1.819; 95% CI 1.046–3.163), with statistical significance reflected in p-values < 0.05 [48]. This convergence of results across different studies and populations reinforces the notion that blood transfusions indeed play a role in influencing the risk of ROP. Notably, packed red blood cell (RBC) transfusions administered within the first ten days of life have been strongly correlated with an increased risk of severe ROP development. Remarkably, each transfusion during this critical period is associated with a 9% higher risk of severe ROP. However, it is essential to recognize a temporal dimension, as later transfusions do not carry the same heightened risk. This temporal variation in risk emphasizes the need for careful consideration of the timing of blood transfusions in the neonatal period.

Interestingly, a counter-narrative exists within the body of literature, where some studies assert that blood transfusions are not a significant risk factor in the development of ROP. The apparent contradiction might stem from variations in the severity, time, and duration of anemia, as well as the treatment strategy employed.

One study highlighted that the degree of prematurity could also contribute to the inconsistent results observed across studies [27].

In conclusion, the relationship between blood transfusions and ROP is complex, with conflicting evidence highlighting the need for a better understanding of the factors influencing this association. The temporal aspect of transfusions, variations in anemia management, and the degree of prematurity collectively contribute to the conflicting findings.

2.6. Respiratory Distress Syndrome

Several studies have consistently underscored Respiratory Distress Syndrome (RDS) as a significant risk factor in the progression and development of Retinopathy of Prematurity (ROP). RDS is characterized by a deficiency in surfactant levels in neonates, leading to potential complications that elevate the risk of ROP [27]. Three studies have all independently identified the association between the presence of RDS and the use of mechanical ventilation and oxygen therapy as key risk factors for ROP [10, 11, 46]. Their multiple logistic regression analyses consistently emphasize the significance of these interrelated factors in contributing to the development of ROP in neonates.

A recent nation-based cohort study conducted in Taiwan further delves into the intricate relationship between RDS and ROP [28]. This study sheds light on the consequences of RDS, emphasizing the imperative nature of extended Neonatal Intensive Care Unit (NICU) stays under ventilation and oxygen supplementation. In the presence of RDS, infants often require prolonged NICU care, and this extended duration significantly elevates the risk of exposure to high concentrations of oxygen. Such exposure can have deleterious effects on the delicate and developing retinal capillaries, potentially leading to ROP.

The NICU environment, while essential for the care of preterm infants, is also associated with hyperoxia—an excessive supply of oxygen. This hyperoxia can suppress crucial growth factors in the retina. Consequently, the retina, which is still poorly vascularized but increasingly metabolically active, becomes hypoxic. This hypoxia triggers the growth factor-induced proliferation within blood vessels, ultimately increasing the risk of severe complications such as retinal detachment and blindness.

2.7. Sepsis

A study identified neonatal sepsis as a recurrently recognized risk factor for both any Retinopathy of Prematurity (ROP) and severe ROP, underscoring its clinical relevance and implying a substantial association between systemic infection and the pathogenesis of retinopathy. In a study targeting very low birth weight (VLBW) and low birth weight (LBW) preterm infants, reported a notable prevalence of sepsis at 48.39% within the study population [33]. This finding accentuates the importance of sepsis in the ROP context, particularly

among preterm infants characterized by low birth weight, thereby signifying a vulnerable demographic with heightened susceptibility.

Several research have independently corroborate the notion that sepsis is a significant risk factor for ROP [22,45]. These studies explain the relationship between sepsis, the inflammatory process, and retinal angiogenesis into potential mechanisms through which sepsis may contribute to ROP development.

In contrast, one study reported conflicting results, characterizing sepsis as an inconsequential independent risk factor for ROP based on their multivariate analysis [27]. The divergent outcomes across studies imply a nuanced and multifactorial nature of the association between sepsis and ROP, potentially influenced by variations in study populations, methodologies, and the specific criteria employed for sepsis definition and diagnosis. The literature on sepsis as a risk factor for ROP still remains to be conflicting.

2.8. Maternal Complications

Studies have revealed a clear association between maternal complications and the development of ROP. Notably, preeclampsia, a hypertensive disorder during pregnancy, has emerged as a significant risk factor for ROP. Hartnett et al. (2016) established a compelling link between maternal preeclampsia and the elevated risk of this severe ROP stage. Preeclampsia's impact on placental development and fetal vascular growth can create an environment conducive to the pathological changes in the retina seen in ROP. Wang et al. (2018) revealed very low birth weight (VLBW) infants whose mothers experienced preeclampsia encountered a significant elevation in their susceptibility to developing ROP. Moreover, studies such as Penn et al. (2017) have underscored the role of gestational diabetes in increasing the likelihood of type 1 ROP development. Elevated maternal blood glucose levels in diabetic pregnancies can lead to fetal hyperinsulinemia and adverse alterations in retinal vascular development, contributing to the progression of ROP towards its severe manifestation.

Furthermore, maternal chorioamnionitis, a condition characterized by infection of the fetal membranes, has also been identified as a potential contributor to type 1 ROP, through inflammatory processes and angiogenic mediators in developing treatment-requiring ROP [17]. These findings collectively emphasize the paramount significance of maternal health management, particularly in cases involving preeclampsia, gestational diabetes, and chorioamnionitis, to mitigate the risk of preterm infants progressing to the severe stage of type 1 ROP, thereby reducing the potential for profound visual impairment in these vulnerable neonates. Studies have proven maternal complications can alter the intrauterine environment inducing inflammatory processes that could potentially lead to aberrant blood vessel growth [47].

3. CONCLUSION

In conclusion, the literature on retinopathy of prematurity (ROP) reveals a complex landscape marked by the identification of putative risk factors. However, the findings are characterized by contradictions, lack of replication, and limitations inherent in study design. Heterogeneity in study subjects, variations in neonatal care practices, and diagnostic discrepancies among ophthalmologists contribute to the inconsistencies. Additionally, changes in guidelines over time and the retrospective nature of many studies further complicate the interpretation of results. Despite these challenges, incorporating risk factors into ROP management holds promise for refining screening methods and advancing our understanding of pathophysiology. Notably, researchers have developed risk prediction algorithms showing potential in predicting treatment-requiring ROP

and reducing unnecessary examinations. Nevertheless, current models face challenges in maintaining sensitivity across diverse populations, prompting ongoing efforts to enhance diagnostic accuracy through the inclusion of additional risk factors and validation studies. Beyond ROP, unraveling these risk factors carries broader significance, providing insights not only into retinal vascular diseases but also influencing future directions in the management and research of related conditions such as diabetic retinopathy and prematurity-associated comorbidities. Thus, addressing the complexities within ROP research is pivotal for improving both clinical practices and the broader landscape of retinal disease understanding.

4. METHODS OF LITERATURE RESEARCH

This study is a literature review, where researchers systematically examined articles aligning with pre-established criteria. The screening process involved assessing titles, abstracts, keywords, inclusion criteria, and the entire text contents of relevant previous articles for review. Articles were obtained from PubMed, Google Scholar, and Science Direct by filtering criteria from the year 2012 to 2023. Criteria for inclusion were the relevance, clinical importance, and scientific importance of articles to the subject of this article. Articles cited in the reference lists of other articles were reviewed and included when considered appropriate. All articles with English abstracts were reviewed and used in this article.

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