Risk Factors of Retinopathy of Prematurity among Very Preterm and Very Low Birth Weight Infants

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Abstract

This comprehensive literature review critically examines the incidence and pivotal risk factors contributing to retinopathy of prematurity (ROP) among very preterm and very low birthweight infants. Synthesizing a spectrum of studies, it meticulously evaluates the multifaceted roles of gestational age and birthweight as primary determinants influencing the vulnerability of premature infants to ROP. Furthermore, it delineates the intricate relationship between oxygen supplementation, a critical clinical intervention, and its impact on ROP pathogenesis, emphasizing the importance of optimal oxygen management strategies. Additionally, the review elucidates the association between respiratory distress syndrome (RDS), a common complication in premature neonates, and the heightened risk of ROP development. Investigating sepsis and blood transfusion as potential contributors, it scrutinizes their influence on ROP incidence and severity within this fragile population. This synthesis underscores recent advancements in preventive measures, screening protocols, and tailored management approaches, highlighting the significance of early detection and targeted interventions. However, persistent gaps in the literature advocate for further research to elucidate additional risk factors and refine neonatal care practices. This review underscores the urgent need for ongoing research endeavours to enhance understanding, optimize care strategies, and mitigate the burden of ROP among these high-risk infants.

Keywords: Retinopathy of Prematurity; Premature Infants; Risk Factors; Low Birthweight Infants

1. Retinopathy of Prematurity

1.1. Definition

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder predominantly affecting newborn preterm infants, particularly those born before 31 weeks of gestation and weighing less than 1250 grams. This potentially blinding eye condition, identified in 1942, significantly impacts vision in children, often affecting both eyes. Various study highlighted a correlation between lower birth weight and increased ROP susceptibility. ROP stands as a prevalent cause of visual impairment in children, potentially leading to permanent vision loss or blindness [19].

1.2. Epidemiology

Approximately 32,300 infants globally endure irreversible vision impairment annually due to Retinopathy of Prematurity (ROP), with 20,000 of these children experiencing severe blindness or impairment [9]. ROP stands as a leading cause of childhood blindness worldwide, stemming from historical instances of unrestricted oxygen use in the late 1940s and early 1950s, subsequently connected to the rising survival rates of premature infants. Varied studies worldwide highlight the prevalence of ROP among premature infants: in the UK in 2011, incidence was 12.6% among infants with GA<32 weeks and/or BW<1,501 g, while Taiwan recorded 36.6% between 2002 and 2011. Similarly, South Korea reported 29.8% among infants with a gestational age of less than 37 weeks from 2007 to 2018, and other studies indicated a 31.7% incidence among infants weighing <1,500 g between 2006 and 2014 [11]. A study in an Indonesian NICU from 2009 to 2011 identified a 12.9% ROP incidence among 248 preterm infants, pinpointing oxygen therapy, sepsis, and low gestational age as independent risk factors [22].

1.3. Pathophysiology

The development and progression of Retinopathy of Prematurity (ROP) manifest through abnormal neovascularization, unfolding in two distinct postnatal phases. Initially, from birth to approximately 32 weeks' postmenstrual age, normal retinal vascular growth halts due to hyperoxia-induced oxygen toxicity. Premature infants, even in ambient air, encounter a hyperoxic environment compared to the intrauterine setting, accentuated by oxygen supplementation during respiratory distress. Hyperoxia triggers both the cessation of retinal vessel growth and the partial regression of existing vessels in this phase. Subsequently, the second phase ensues, marked by hypoxia-induced pathological vasoproliferation. Inadequate vascularization prompts retinal hypoxia, prompting the release of angiogenic factors such as vascular endothelial growth factor (VEGF) and erythropoietin, culminating in neovascularization, intraocular fibrosis, and retinal detachment [9].

1.4. Risk Factors of ROP

To this date, the known causes for the development of Retinopathy of Prematurity remain unclear. Although many studies have suggested that several risk factors have a direct correlation to the incidence of ROP. Majority of the studies have made several risk factors to show a dominant correlation with the incidence of ROP. Gestational age of under 28 weeks, birth weight of < 1500 g, oxygen therapy and sepsis are known to be among the most prominent risk factors today.

1.4.1 Gestational Age

The development of Retinopathy of Prematurity (ROP) occurs in two phases: initially, from birth to around 32 weeks postmenstrual age, retinal vessel growth stops due to oxygen toxicity in premature infants, leading to partial vessel regression. Subsequently, hypoxia-induced vasoproliferation triggers neovascularization, intraocular fibrosis, and retinal detachment [9]. Gestational age, measured in weeks from conception, categorizes pregnancies. Approximately 15 million babies are born preterm annually, with rates between 5% to 18% worldwide. Different gestational age categories correlate with ROP risk, guiding screening guidelines globally; for instance, in the US, infants <30 weeks require eye screening, and recommendations align around infants <1500 g or <32 weeks' gestation [13][16].

1.4.2. Birth Weight

Birth weight, measured within the first hour of life, categorizes infants into low birth weight (<2500 g), very low birth weight (<1500 g), and extremely low birth weight (<1000 g), while normal birth weight ranges between 2500 g to 4000 g [12]. Numerous studies highlight birth weight as a significant risk factor associated with the development of retinopathy of prematurity (ROP). Wu et al. discovered that poor weight gain during early infancy marked a severe ROP risk, observed in approximately 50% of affected infants. In India, a study screening 704 infants with gestational age ≤ 32 weeks or birth weight ≤ 1500 g found 11.9% and 4.7% incidence of ROP and severe ROP, respectively, with significant correlation between risk factors and ROP development [15]. Indonesian studies also reported higher ROP incidence in infants <1500 g, with 17% of those <1000 g affected, showcasing a higher overall incidence compared to developed countries [8].

1.4.3. Oxygen Supplementation

Excessive oxygen supplementation significantly increases the risk of retinopathy of prematurity (ROP), a neovascular pathology in immature retinal vessels linked to prematurity and oxidative injury from oxygen therapy. ROP progresses from a vaso-obliterative phase to a vaso-proliferative disease, potentially causing blindness [1]. Studies confirm that limiting oxygen in the initial post-delivery weeks reduces ROP occurrence [18]. In Indonesia, inadequate control of oxygen delivery to preterm infants led to a high ROP incidence, emphasizing the need for enhanced awareness and better monitoring equipment for optimal oxygenation [6].

1.4.4. Sepsis

Sepsis, a severe response to infection, poses a life-threatening medical emergency triggering a systemic chain reaction [2]. It stands as a significant contributor to neonatal inflammation, impacting morbidity in newborns. Studies have identified bacterial sepsis as a potential risk factor for retinopathy of prematurity (ROP), particularly in cases of low gestational age (GA) and birth weight (BW) [5]. Recent research underscores the association between neonatal inflammation and ROP, especially in very low birth weight infants. Conflicting findings persist regarding the independent role of fungal sepsis in severe ROP risk. However, bacterial sepsis emerges as an independent risk factor, particularly in extremely low gestational age newborns. Studies suggest that the impact of sepsis on retinal vascularization may exacerbate when combined with other risk factors. The connection between sepsis and ROP development may be attributed to the relationship between inflammation and angiogenesis, where certain proinflammatory proteins and angiopoietins potentially influence abnormal retinal angiogenesis, fostering ROP progression [10].

1.4.5. Blood Transfusion

Blood transfusion, encompassing various transfusion therapies during hospitalization, emerges as a significant factor in the progression of retinopathy of prematurity (ROP). Studies highlight its association with ROP progression, particularly in relation to the duration of oxygen administration and the number/volume of blood transfusions given during the first weeks or month of life [5]. Research conducted in China involving over 1,000 infants at risk showcased a notable 21.7% incidence of ROP among those who received blood transfusions compared to 2.0% without transfusions [4]. A comprehensive systematic review incorporating 18

studies and over 15,000 preterm infants confirmed the significant association between red blood cell (RBC) transfusions and ROP, further emphasizing the role of transfusions in ROP development [24].

1.4.6. Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), primarily affecting premature newborns due to surfactant insufficiency, presents with respiratory distress and increased oxygen needs after birth. Its diagnosis relies on criteria such as increasing oxygen dependency in the first 24 hours, absence of infection signs, and specific radiological lung patterns. RDS prevalence decreases with gestational age and weight, affecting 60-80% of infants born before 28 weeks and 15-30% between 32-36 weeks [8]. A study found a 20.6% incidence of ROP in infants with RDS compared to 2.0% without RDS, indicating a significant correlation between RDS presence and ROP development [4].

2. Very Preterm Infants

2.1. Definition

Every year witnesses an estimated 15 million babies born prematurely, occurring before 37 completed weeks of gestation, a trend escalating due to advancements in medical technology. Across 184 countries, preterm birth rates vary from 5% to 18% of all births. Preterm birth categorization follows gestational age: infants born between 32 – 36 weeks are termed moderate to late preterm; those between 28 to 32 weeks are termed very preterm, while infants born in less than 28 weeks of gestation are classified as extremely preterm [16].

2.2. Epidemiology

Globally, over 15 million babies are born prematurely each year, accounting for an 11% preterm birth rate. In France, among roughly 60,000 births, approximately 85% fall within the moderately preterm to late preterm range (32-36 weeks), while 10% are very preterm (28-31 weeks), and 5% are extremely preterm (under 28 weeks). Neonatal mortality rates, though decreasing, remain substantial and largely hinge on gestational age at birth, with mortality rates exceeding 10% for infants born before 28 weeks, 5-10% for those born between 28 and 31 weeks, and 1-2% for infants born between 32 and 34 weeks [20]. Conversely, in Indonesia, the prevalence of low birthweight (LBW), prematurity, and small for gestational age (SGA) births is high, leading to significant morbidity and mortality among these infants. In 2010, Indonesia ranked fifth globally for premature births, exhibiting a preterm birth rate of 15 per 100 live births [6].

2.3. Etiology

Until now, the precise causes of very preterm birth remain elusive, yet they are commonly linked with factors such as premature rupture of membranes, preterm labour, and various maternal medical conditions. Identified risk categories associated with preterm delivery encompass maternal demographic characteristics such as young or advanced maternal age, black race, and low socioeconomic status. Unhealthy lifestyle habits including tobacco use, substance abuse, and extreme pre-pregnancy body mass index are also recognized risks. Pregnancy history elements like short interpregnancy intervals, prior preterm delivery, and multiple gestations contribute to these risks. Complications during pregnancy, such as placental abruption or

previa, polyhydramnios, and oligohydramnios, are implicated. Maternal medical disorders like thyroid disease, obesity, asthma, diabetes, and hypertension elevate the risk. Mental health aspects like psychological or social stress and depression are also linked. Fertility treatments, whether assisted-reproductive technology or non-assisted-reproductive technology fertility treatments, play a role. Intrauterine infection, particularly premature rupture of membranes, and fetal abnormalities also contribute to these risk factors [23].

2.4. Morality

Survival rates for very preterm infants differ worldwide, contingent upon the availability of obstetric and neonatal care resources as well as perspectives on viability. In developed countries, notably, survival rates for preterm infants at the earliest gestational ages have notably increased. In such settings, the threshold of viability has been extended to 22 to 23 weeks of gestation, leading to improved survival rates. However, in developing countries, survival at these gestational ages remains considerably low [23].

3. Very Low Birth Weight Infants

3.1. Definition

Birth weight, defined as the initial weight of a fetus or newborn upon birth, is ideally measured within the first hour of life, according to WHO guidelines, to ensure accuracy before significant postnatal weight fluctuations occur. It is categorized into low birth weight (LBW), very low birth weight (VLBW), and extremely low birth weight (ELBW). LBW refers to infants weighing less than 2500 g, VLBW less than 1500 g, and ELBW less than 1000 g, while normal birth weight falls within the range of 2500 - 4000 g [12]. The current classification, adopted during the 29th World Health Assembly in 1976, replaced the previous LBW definition of "less than 2500 grams." VLBW (1500 g) and ELBW (1000 g) serve as subcategories within the LBW classification. Causes of LBW typically involve preterm birth (gestational age < 32 weeks), intrauterine growth restriction (IUGR), or a combination of both [3].

3.2. Epidemiology

According to Unicef in the year 2020, approximately 19.8 million new-borns, accounting for 14.7% of all births, experience low birth weight (LBW) globally [21]. LBW prevalence varies across regions, ranging from 6% in East Asia and the Pacific to 28% in South Asia [14]. The survival rate of infants with very low birth weight (VLBW; <1500 g) has notably increased to 80% to 90% in developed countries due to medical advancements [7]. Premature births before 37 weeks of gestation and the associated low birth weight contribute significantly to neonatal morbidity and mortality, as well as being major risk factors for other causes of mortality [17]. The rising survival rate among VLBW infants has also led to an increase in the incidence of retinopathy of prematurity (ROP). For instance, in a Korean study involving 2,009 VLBW infants has an incidence rate of 34.9% [11].

3.3. Etiology

The precise causes of low birth weight remain elusive, although intrauterine growth retardation (IUGR) and premature birth are considered primary factors. IUGR results from inadequate uterine-placental perfusion and prenatal nutrition, impacting the overall anthropometric measurements of the fetus. Infants

affected by IUGR typically display normal nutritional symptoms. Factors like extra-uterine infection, trauma, illness, fetal infection, and abnormalities contribute to preterm birth, which in turn leads to growth retardation and ultimately, low birth weight [14].

3.4. Mortality

Indonesia, based on 2015 statistics, holds the tenth-highest newborn mortality rate globally, standing at 14 deaths per 1,000 live births. In rural areas, this rate significantly escalates to 24 fatalities per 1,000 live births. A substantial portion of this mortality is attributed to preterm newborns. A retrospective cohort study utilizing data from the Indonesia Demographic and Health Survey 2007 indicated a direct correlation between lower birth weight and decreased chances of neonatal survival. Despite insufficient financial backing, the expansion of neonatal intensive care units (NICUs) in Indonesia is anticipated to aid in reducing this high infant mortality rate [6].

4. Conclusion

The search into retinopathy of prematurity (ROP) encompasses critical facets such as its definition, epidemiology, and etiology. ROP, a significant cause of childhood blindness, predominantly affects very preterm and very low birth weight infants. Understanding its incidence requires a nuanced exploration of risk factors including gestational age, birth weight, oxygen supplementation, blood transfusion, sepsis, and respiratory distress syndrome. Within the subcategories of very preterm and very low birth weight infants, insights into their definitions, epidemiology, etiologies, and associated mortalities highlight their vulnerability to ROP. This comprehensive understanding emphasizes the need for ongoing research, tailored preventive measures, and enhanced care interventions to address ROP's prevalence and impact in these at-risk populations.

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