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Risk factors for retinopathy of prematurity: a current literature review

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ABSTRACT

Aim of the study: To present the primary and secondary risk factors for the development of retinopathy of prematurity (ROP), as reported in the literature to date.

Material and methods: Analysis of scientific papers and articles available in the PubMed, Google Scholar and UpToDate databases devoted to the study of risk factors involved in the development of retinopathy in premature infants, with attention given to the WINROP and G-ROP algorithms used in ophthalmic screening tests.

Conclusions: The best documented risk factors with a direct impact on ROP include low birth weight and preterm birth, low IGF-1 level, chorioamnionitis, and neonatal sepsis, while factors with an indirect impact on the development of ROP comprise bronchopulmonary dysplasia, necrotizing enterocolitis, apnea of prematurity, and respiratory distress syndrome (RDS).

KEY WORDS: screening, preterm birth, primary and secondary risk factors for retinopathy of prematurity, ROP..

INTRODUCTION

Retinopathy of prematurity (ROP) is a condition associated with excessive vascular proliferation in the immature retina of preterm infants. Despite good outcomes achieved in the care of prematurely born infants, ROP remains a major cause of visual impairment and blindness in children. Global statistics show that at least 50,000 children to date have lost vision due to ROP [1]. Thanks to the application of the latest guidelines addressing such aspects as optimal oxygen therapy, ROP screening strategies, and effective treatment modalities, the number of cases of stage 1 ROP has decreased significantly in recent years, while the total number of premature infants requiring treatment is equivalent to 3-5% of children undergoing screening [1]. Current ophthalmic screening guidelines are based primarily on two risk factors: birth weight and fetal age [2]. Nonetheless, many researchers argue that there are also other risk factors that need to be considered, including maternal factors, prenatal and perinatal factors, demographics, medical interventions, nutrition, comorbidities, and genetic background. Exploring and understanding the factors that contribute to ROP is key to developing effective therapeutic models.

PATHOPHYSIOLOGY

The immature retinas of preterm infants are susceptible to factors that disrupt retinal vascular growth, leading to retinopathy. The process takes place in two stages. In the first stage, the normal development of retinal vasculature is disrupted due to premature birth. During this period, the newborn's retina is exposed to hyperoxic conditions, leading to a decrease in the levels of insulin-like growth factor (IGF-1) and vascular endothelial growth factor (VEGF). This stage leads to the narrowing or obliteration of the retinal vessels. The second stage of ROP begins at a gestational age of approximately 32-34 weeks. Increased hypoxia of non-vascularized retina leads to increased production of VEGF and erythropoietin, which in turn induces pathological neovascularization and fibrous proliferation that may even result in retinal detachment [3].

PRIMARY RISK FACTORS

While many different factors are known to contribute to the risk of developing ROP, two of them carry the greatest importance: low gestational age and low birth weight. Others include anemia, exchange blood transfusions, respiratory failure, and poor general condition of the premature infant. In the 1940s and 1950s, respiratory support with high oxygen levels was used in intensive care units in order to increase neonatal survival rates [29]. At that time, an increased prevalence of a condition initially referred to as retrolental fibroplasia began to be observed. It was later correlated with the use of high oxygen concentrations. Over the past few decades, the incidence of ROP has decreased because of the introduction of more effective ventilation methods and less aggressive oxygen therapy provided to preterm infants [5].

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Fetal age and birth weight

Both are recognized as the most important risk factors for retinopathy of prematurity. A multicenter study (CRYO-ROP) that enrolled 4,099 preterm infants with birth weights of less than 1251g showed that lower birth weight and lower gestational age significantly contributed to the development of retinopathy in preterm infants [6]. The thesis has been corroborated by the results of numerous metaanalyses reported in scientific studies [7-9].

Oxygen therapy

The duration and level of oxygen therapy as well as prolonged mechanical ventilation are among the most common causes underlying the development of severe retinopathy of prematurity requiring treatment. The first randomized studies, with results published in 1956, showed that the infant's exposure to oxygen in an incubator at a saturation level in excess of 50% increased the risk of ROP compared to a group of infants receiving low-concentration oxygen therapy. To date, a number of scientific studies that have corroborated the theses that were initially put forward in 1956, provided evidence that the duration of oxygen therapy and prolonged mechanical ventilation are important risk factors for ROP [5]. In addition to high oxygen concentrations, oxygen fluctuations and the retinal response to hypoxia after the discontinuation of therapy have also been revealed as vital factors in the pathogenesis of retinopathy. Hence, it is so important to constantly monitor oxygen pressure and maintain its level at 30-40%. High oxygen concentrations are known to increase the formation of oxygen free radicals that cause peroxidation of lipids in the retinal vascular endothelial cell membrane and lead to their destruction [10].

Screening tests

According to the 2020 consensus statement of the Polish neonatologists and ophthalmologists from the Pediatric Ophthalmology Section, screening should be provided to preterm infants born at ≤ 33 weeks of gestational age with a birth weight ≤ 1800 g, and preterm infants born over the age of 33 weeks and weighing over 1800 g with cardiovascular respiratory failure, low weight gain and other pathologies associated with prematurity, identified as eligible for screening by a neonatologist considering the child's general condition and high risk of ROP. It was agreed that the first ophthalmic examination should be performed in the child's 4th week of life based on the chronological birth age. According to the recommendations of the American Academy of Pediatrics (AAP) as well as the guidelines issued by other neonatological and ophthalmic societies, the date of the first ophthalmic examination should depend on the neonate's maturity [2].

NEW CRITERIA REGARDING RISK FACTORS

New observations suggest that accurate weight measurement in hospital neonatal units may play a major role in predicting the development of ROP. Slow and insufficient neonatal weight gain has been shown to be linked to the emergence of retinopathy of prematurity [11, 12]. Slow weight gain is associated with lower plasma IGF-1 levels [13]. IGF-1 is an anabolic hormone that promotes the development of many types of body tissues including the retinal vasculature. An association has been found between early postnatal decrease in IGF-1 levels and the development of retinopathy of prematurity [14].

WINROP

WINROP is an algorithm proposed by Hellström *et al.* [15] that takes into account birth weight (BW), gestational age (GA), and postnatal weight gain as parameters for the assessment of ROP. The determined parameters allow the estimation of the IGF-1 level, which in turn enables the prediction of the risk factor for the development of ROP. The algorithm has been found to be particularly useful in predicting stage 1 ROP [16-18]. Recent studies indicate that WINROP needs additional revisions that would complement the existing screening criteria. Lung *et al.* argued that the WINROP algorithm should be used as a complement to the risk factors included in the full screening criteria already in use in different countries [19]. In the Polish study by Jagła *et al.* [20], the algorithm was found to be characterized by lower sensitivity compared to that used in other highly developed countries. To improve the usefulness of WINROP, it was proposed that the identified criteria should be combined with other, complementary procedures used in premature infants (such as surfactant therapy) [20].

G-ROP

G-ROP is an algorithm that comprises more recent criteria, with the following six risk factors: (1) GA < 28 Hbd; (2) BW < 1051 g; body weight gain (3) < 120 g during days 10-19 of life, (4) < 180 g during days 20-29 of life, (5) < 170 g during days 30-39 of life and/or (6) occurrence of hydrocephalus [21]. Many studies to date have shown high rates of correct diagnoses on the basis of compliance with the above criteria [22-24]. Furthermore, G-ROP has been found to reduce costs associated with the process of ROP detection following the inclusion of the above parameters in the diagnostic work-up [24]. A recent study (2021) by Almeida *et al.* [25], which compared the risk parameter criteria in the G-ROP and WINROP algorithms, demonstrated that both procedures were simple and reliable, and even mutually complementary in ROP detection. In their study, Binenbaum *et al.* [26] expanded the generalized G-ROP criteria. According to the risk factor scheme developed by these authors, the assessment of premature infants' eligibility for ophthalmic examination would help eliminate a certain number of unnecessary ophthalmic evaluations in children who are at a low risk of ROP. This scheme consists of seven criteria which, when met in the given order, determine the infant's eligibility for an ophthalmic examination [26].

PRENATAL, PERINATAL AND MATERNAL FACTORS

Assisted reproductive technologies

Based on the studies reviewed by the authors of this paper, there is no conclusive evidence to determine whether there is a link between conception using assisted reproductive technologies (ART) and the development of ROP. The study by Gao *et al*. [27] showed a greater risk of ROP and more severe retinopathy among children born of pregnancies achieved with the help of ART. In contrast, Alsammahi *et al*. in their 2021 article [28] categorically rejected any association between ROP and conception using assisted reproductive technologies.

Pregnancy-induced hypertension

Pregnancy-induced hypertension affects approximately 6-10% of pregnancies. It is defined as early systemic hypertension with systolic blood pressure (RRs) ≥ 140 mmHg and diastolic blood pressure (RRd) ≥ 90 mmHg, diagnosed in a pregnant woman after 20 weeks of gestation. Two stages of PIH can be distinguished, including mild PIH with RRs and RRd values in the range of 140-159 mmHg and 90-109 mmHg, respectively, and severe PIH with RRs ≥ 160 mmHg and RRd ≥ 110 mmHg. The diagnosis also includes preeclampsia, i.e. a severe form of PIH diagnosed on the basis of hypertension and the presence of proteinuria > 300 mg in a 24-hour urine collection without a prior diagnosis of hypertension or kidney disease. Literature reports on the correlation between PIH and ROP contain contradictory results and conclusions. The development of pregnancy-induced hypertension is associated with elevated levels of antiangiogenic factors including soluble fms-like tyrosine kinase 1 (sFlt-1), vascular endothelial growth factor (VEGF) antagonist, and placental growth factor [29]. Some authors have claimed that PIH and preeclampsia represent significant risk factors for ROP [30], but other studies have shown that pregnancy-induced hypertension is not associated with a higher incidence of ROP [31,32]. Such contradictory findings in the published studies can be attributed, among other factors, to the varying quality of research and the presence of confounding factors such as prenatal therapy, maternal comorbidities, and postnatal oxygen therapy.

Thyroid diseases

Hormonal disturbances associated with the dysfunction of the thyroid gland have been growing in prevalence in the female section of the society. Since the issue that has been gaining more and more attention recently, it seems pertinent to address it the context of ROP as well. Healthy thyroid function is known to be essential for cerebral and retinal development. Laboratory studies have shown no significant decrease in the risk of ROP in preterm infants in association with thyroid hormone supplementation used in hypothyroidism, but clear evidence has been found for a link between brain damage and hyperthyroidism coexisting with an ongoing inflammatory body response [33]. Only scarce reports can be found in the literature regarding possible links between thyroid diseases in pregnancy and the development of ROP. One of them is the study by Männistö *et al*. [34], which identified a relationship between hyperthyroidism and the development of ROP in children born prematurely. In another study, conducted by Korkmaz *et al*. [35] on a group of children diagnosed with thyroid hormone deficiency (mainly correlated with the maternal use of thyreostatics, the presence of maternal autoantibodies or iodine deficiency), an elevated risk of developing ROP was noted. However, further studies are needed to explore this aspect.

Gestational diabetes

Studies have pointed towards a possible correlation between gestational diabetes and ROP, either directly through an increase in retinal VEGF levels due to hyperglycemia or indirectly through respiratory failure secondary to respiratory distress syndrome (RDS). However, there are still doubts about the link between gestational diabetes and the development of ROP. The retrospective cohort studies by Opara *et al*. [36] showed that maternal diabetes was an independent risk factor for severe or clinically significant ROP (stage 3 or higher) in neonates with a body weight of less than or equal to 1,500 g, when adjusted for a number of relevant covariates, while the power of the association between ROP and maternal diabetes increased along with the progression of ROP stages. In contrast, Razak and Faden [37], in their meta-analysis of data derived, among others, from the PubMed database, spanning a period from 1 January 2000 to 19 August 2019, found no significant association between the occurrence of ROP and gestational diabetes.

Smoking

Exposure to tobacco smoke during pregnancy is associated with lower birth weight and, according to in vitro fertilization studies, with altered regulation of VEGF secretion in retinal cells [38]. Maternal smoking has been linked to stunted growth and the development of ROP [39, 40]. Different results were obtained in the study by Hirabayashi *et al*. [41], where the incidence of ROP was lower among the children of women who smoked during pregnancy compared to the children of maternal non-smokers. However, it must be noted that the majority of studies do not analyze the amount of cigarettes smoked or the duration of exposure to tobacco smoke. These factors would need to be considered in further explorations of the association between smoking and ROP.

Chorioamnionitis

Chorioamnionitis is a consequence of intrauterine inflammation caused by bacteria, occurring in the perinatal period. The infection represents a maternal response that manifests as the presence of white blood cells in the chorion and the placental fetal membranes. Based on the studies evaluating the composition of amniotic fluid, a link has been shown between high levels of endoglin, interleukin-6 and interleukin-8

(IL-6, IL-8) contained in it, and the development of ROP [42]. In the recent literature, attention has been focused on the relationship between the pre-existing diagnosis of maternal chorioamnionitis (especially associated with funisitis) with systemic inflammatory response/infection in the premature infant's body. The markers listed above have been shown to coexist with major ROP risk factors, markedly increasing the risk of developing the condition [43]. A link has also been suggested between the occurrence of APROP (aggressive posterior-ROP) and inflammation of the fetal membranes [44].

Preterm premature rupture of membranes

Preterm premature rupture of membranes (PPROM) is a common cause of premature birth. Little literature can be found on the association between PPROM and ROP, except for the link between an increased risk of ROP1 development and the duration of PPROM over 18 hours [45]. It has been hypothesized that treatment with certain medicines including steroids or antibiotics prevents preterm labor and later inhibits the development of ROP in premature infants [46].

NEONATAL FACTORS

Multiple pregnancy

Multiple pregnancy is a factor that can increase the risk of both preterm labor and lower birth weight and perinatal conditions, all of which may have an impact on the development of retinopathy of prematurity. Numerous studies have observed a higher incidence of ROP in premature infants born from multiple pregnancies [47, 48]. In contrast, a more recent (2018) study by Petriçli *et al.* [49] showed that multiple births exhibited no significant correlation with the development of ROP in very low-weight premature infants.

Apgar score

Studies show that premature infants diagnosed with ROP have lower Apgar scores compared to the infants without a diagnosis of ROP. However, the correlation was not significant in most studies [50, 51]. Marinov *et al.* [52] found no statistically significant association between low Apgar scores and the incidence of ROP. However, the authors demonstrated that the Apgar score was a significant risk factor for ROP progression to more severe stages requiring treatment.

Ethnicity

Black infants have been reported to be less commonly diagnosed with ROP compared to white infants [53, 54]. Evidence for this thesis can be found in the studies by Reddy *et al.* [55], which focused on assessing IGF-1 levels in the blood of preterm infants of different ethnicities. The lowest IGF-1 levels were noted in black children, but the ROP prevalence was also the lowest in this group [55], which is in disagreement with previous studies exploring the effect of IGF-1 on the development of ROP [14]. It was also highlighted that IGF-1 levels varied across ethnicities and could often pose a problem when adjusting risk factors in the WINROP algorithm. Another finding, made by Ludwig *et al.* [54], is that even though ROP is generally less common in preterm infants of black ethnicity, when they are diagnosed with the condition, it is more often at a severe stage. The observation is attributed to lower IGF-1 levels in their blood. The prevalence of retinopathy in Asian children was found to be considerably higher as well. In contrast to the above claims, Aralikatti *et al.* [56] reported that both ethnicities, black and Asian, represented factors increasing the risk of ROP. The ethnic variation described above may suggest a genetic predisposition to retinopathy of prematurity. It may be an important diagnostic factor in countries with highly ethnically diverse populations with a high percentage of immigrants.

COMORBIDITIES OF PREMATURITY

Systemic bacterial or fungal infection during the postnatal period

Neonatal sepsis is one of the most commonly reported risk factors for ROP. Perinatal infection and associated postnatal inflammation have been identified to play an important role in the development of retinopathy of prematurity [57]. According to Wu T. *et al.* [58], VLBW preterm infants are a group particularly prone to various types of infections, including severe ROP. Studies to date indicate that the inflammatory condition with the best known and proven role in ROP pathogenesis is currently late-onset sepsis (LOS), particularly in VLBW preterm infants born less than 32 weeks into gestation [59]. Similar conclusions come from a 2019 meta-analysis by Wang *et al.* [60], which also found evidence for the role of sepsis in the development of ROP, though the stage and severity of ROP were not determined. In addition, links between sepsis and the development of AP-ROP have been suggested [61].

Apnea of prematurity

Apnea of prematurity requires mechanical ventilation and oxygen therapy, which may result in an increased incidence of ROP [62, 63]. Prolonged mechanical ventilation (>7 days) is claimed to be a factor predisposing to ROP [64], as shown in a Turkish metaanalysis [62]. Caffeine citrate is used to prevent apnea in premature infants, but there have been contradictory views about this therapy in the context of ROP.

Respiratory distress syndrome

Respiratory distress syndrome (RDS) is caused by pulmonary surfactant deficiency in neonates. It may lead to hypoxia requiring oxygen therapy and/or mechanical ventilation, both of which predispose the infant to the development of ROP. Not surprisingly, then, RDS is associated with an increased risk of ROP [62, 65].

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is associated with prolonged oxygen dependence, beyond 28 days after birth,

Table I. Pathomechanism and clinical significance of risk factors directly or indirectly related to the development of ROP

Risk factor	Pathomechanism	Indirect/ indirect effect (on the retina)	Clinical relevance for the development of ROP	Literature
Primary factors				
Early gestational age and low birth weight	Immaturity	Direct	High	[6–9]
Oxygen therapy	Free radical production, impact on stage 1 ROP	Direct	High	[5, 10]
IGF-1 factor level	Postnatal decline in IGF-1 affects the development of ROP	Direct	High	[11–14]
Maternal factors				
Assisted reproductive technologies	Impact on preterm labor	Indirect	Low	[27, 28]
Pregnancy-induced hypertension (PIH) and preeclampsia	Possible impact on preterm labor	Indirect	Low	[29–32]
Thyroid diseases	Effects of thyroid hormonal function on cerebral and retinal development	Direct	Further studies are required	[33–35]
Gestational diabetes	Hyperglycemia contributes to an increase in retinal VEGF levels and respiratory distress syndrome (RDS)	Direct and indirect	Low	[36, 37]
Smoking	Impact on the regulation of VEGF production and low birth weight in preterm infants	Direct and indirect	Further studies are required	[38–41]
Chorioamnionitis	Correlation between elevated inflammatory markers in amniotic fluid and the development of ROP	Direct	High	[42–44]
Preterm premature rupture of the membranes (PPROM)	Unknown	Indirect	Low	[45, 46]
Neonatal factors				
Multiple pregnancy	Effect on preterm labor, low birth weight, and perinatal conditions	Indirect	Low	[47–49]
Apgar score	ROP development – a factor determining progression to a more severe stage	Indirect	Further studies are required	[50–52]
Ethnicity	Dependent on IGF-1	Indirect	Relevant in countries with ethnically diverse populations with a high proportion of immigrants	[14, 53–56]
Comorbidities of prematurity				
Neonatal sepsis	Systemic inflammation in premature infants	Direct	High	[57–61]
Apnea of prematurity	Indication for prolonged mechanical ventilation and oxygen therapy	Indirect	High	[52–64]
Respiratory distress syndrome (RDS)	Surfactant deficiency	Indirect	High	[62, 65]
Bronchopulmonary dysplasia (BPD)	Prolonged oxygen dependence > 28 days after birth, impact on ROP severity	Indirect	High	[65, 66]
Necrotizing enterocolitis (NEC)	Abnormal innate immune response, changes in gastrointestinal microbiota, systemic inflammation	Direct and indirect	High	[67, 68]
Intraventricular hemorrhage (IVH) and leukomalacia	Based on neurodevelopmental factors	Direct and indirect	Further studies are required	[69–71]
Morphological factors				
Anemia	Retinal effects of erythropoietin as a proangiogenic factor and vascular stabilizer	Direct	Further studies are required	[72–75]
Thrombocytopenia	Reduced elimination of VEGF by platelets, no inhibition of local angiogenesis	Direct	Further studies are required	[76–80]
Elevated inflammatory parameters (CRP, procalcitonin, IL-6, NLR)	Systemic inflammation in premature infants	Direct	Further studies are required	[81–84]

which increases the predisposition to retinopathy in such premature infants [65]. A Polish study by Podraza *et al.* [66], showed that dysplasia also had an effect on the severity of ROP.

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is a serious complication of prematurity. The condition is attributed, among other factors, to anomalies in the innate immune response that alter the intestinal microbiota. There is evidence based on animal models showing that generalized inflammation affects retinal angiogenesis [67], which may suggest a link between NEC and the development of ROP. In their large 2021 metaanalysis, Fundora *et al.* [68], compared cases of NEC treated with surgery at different times after diagnosis to determine possible links with the development and stage of ROP. Premature infants with NEC were shown to be at a high risk of severe ROP compared to the children without a diagnosis of necrotizing enterocolitis.

Intraventricular hemorrhage and leukomalacia

Intraventricular hemorrhage (IVH) and leukomalacia, regarded as significant complications of prematurity, cause brain dysfunction, which is often associated with neurodevelopmental changes in preterm infants. IVH is associated with ROP, as shown in many papers addressing the underlying causes of ROP [69, 70]. However, no clear correlation has been reported between cerebral leukomalacia and ROP [71].

Morphological factors: anemia, transfusions, and erythropoietin

Anemia is a common complication of prematurity. Blood transfusions, erythropoietin products used for anemia treatment or prevention, and anemia are recognized as risk factors for ROP. Regulated by cellular oxygen levels in the kidneys and retina, EPO is an important proangiogenic factor associated with retinal vascular stability [72].

Several studies have found evidence for a significant link between anemia and severe ROP requiring treatment, but at the same time, no association has been identified between ROP and elevated erythropoietin levels [73]. Other studies have found no relationship between anemia and the development of retinopathy [74]. In their metaanalysis published in 2020, Zhu *et al.* [75] reported that blood transfusions were an independent risk factor for the development of ROP especially among younger preterm infants.

Thrombocytopenia

Thrombocytopenia is another important marker of ROP. In addition to their essential role in the coagulation cascade, blood platelets store, transport and release angiogenic agents, e.g. VEGF, and via adhesion to endothelial cells, can either enhance or inhibit local angiogenesis [76, 77]. Under conditions of thrombocytopenia, the functions of VEGF removal in the vessels of the growing retina and the transport of IGF-1 (during phase 2) decrease, thus contributing to the development of ROP [78, 79]. It has been shown that the most important measurement of platelet levels is that obtained during the first 24 hours of the infant's life, as it can be predictive of the development of ROP [78]. A link between thrombocytopenia and AP-ROP has also been suggested [80].

Elevation in inflammatory markers

Elevation in inflammatory markers determined in laboratory test results of premature infants treated in neonatal units has also been correlated with the development of ROP. One of such markers is CRP, which frequently becomes elevated in response to inflammation and infection. Its impact is controversial, as research findings point both towards the link between CRP and development of ROP [81] and the inferior specificity of the marker compared to procalcitonin and IL-6 [82]. Another marker is NLR (neutrophil-to-lymphocyte ratio), with relatively recent studies reporting a link between ROP and NLR level determined immediately after birth. High NLR levels indicate physiological stress affecting the child's body during prenatal development, possibly contributing to the prenatal onset of ROP. Nonetheless, many studies have failed to provide any evidence for a correlation between ROP development and NLR [83, 84] (Table I).

CONCLUSIONS

Gaining insights into the impact of various risk factors on the development of ROP is still a current topic, as they may contribute to improving the diagnostic work-up for ROP even before the onset of the first symptoms of the condition. To date, many studies have been published that examine the role of different risk factors in the development of retinopathy of prematurity. The best evidence exists for the effects of low birth weight and premature age. However, in addition to these primary risk factors, there are also other documented factors having a direct impact on the development of ROP (including postnatal decrease in IGF-1 level, chorioamnionitis, and neonatal sepsis) as well as a range of risk factors with an indirect effect on ROP (bronchopulmonary dysplasia, necrotizing enterocolitis, apnea, and respiratory distress syndrome (RDS)). As the literature shows, studies are underway to determine the impact of other risk factors, mentioned above, on the development of ROP, as their contributory role in the emergence of retinopathy has not been proven so far.

DISCLOSURE

The authors declare no conflict of interest.

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