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Retinopathy of Prematurity: A Review of Risk Factors and their Clinical Significance

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Abstract

Retinopathy of prematurity (ROP) is a retinal vasoproliferative disease that affects premature infants. Despite improvements in neonatal care and management guidelines, ROP remains a leading cause of childhood blindness worldwide. Current screening guidelines are primarily based on two risk factors: birth weight and gestational age; however, many investigators have suggested other risk factors, including maternal factors, prenatal and perinatal factors, demographics, medical interventions, comorbidities of prematurity, nutrition, and genetic factors. We review the existing literature addressing various possible ROP risk factors. Although there have been contradictory reports, and the risk may vary between different populations, understanding ROP

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VIII. DISCLOSURES

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risk factors is essential to develop predictive models, to gain insights into pathophysiology of retinal vascular diseases and diseases of prematurity, and to determine future directions in management and research in ROP.

Keywords

pediatric ophthalmology; preterm infant; retina; retinopathy of prematurity; risk factor; risk model

I. RETINOPATHY OF PREMATURITY

A. Introduction

1. Introduction—Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy affecting premature infants that is a leading cause of childhood blindness worldwide. As premature births increase and survival rates improve due to advances in neonatal care, the number of infants at risk for ROP has been increasing worldwide, especially in middle-income countries including India and China.[50,51,139]

2. Epidemiology—In the Early Treatment for Retinopathy of Prematurity (ET-ROP) study in the United States, the incidence of any stage ROP was 68% among infants weighing <1251 g.[144] Among infants with ROP, clinically-significant (prethreshold) ROP developed in 36.9%.[144] Globally, in 2010, an estimated 184,700 babies of 14.9 million preterm babies developed any stage of ROP, 20,000 of whom became blind (visual acuity <20/400) or severely visually impaired (visual acuity from <20/200 to ≥20/400) from ROP, and of whom 12,300 others developed mild-moderate visual impairment (visual acuity from <20/40 to ≥20/200).[50] In high-income countries, it was estimated in 2010 that 6,300 of 32,700 babies with any ROP developed treatment-requiring ROP, and 1,700 babies became blind or severely visually impaired from ROP. [50]

B. Screening

1. Current screening guidelines—Most guidelines use birth weight (BW) and gestational age (GA), which are major risk factors, to identify infants in need of ROP screening. Current guidelines by the American Academy of Pediatrics, American Academy of Ophthalmology, and American Association for Pediatric Ophthalmology and Strabismus stipulate that all infants ≤30 weeks GA or ≤1500g BW should be screened for ROP, as well as selected larger infants based on clinical course.[115] According to the United States National Vital Statistics Reports in 2015, there were about 56,000 very low BW infants (BW <1500g) and about 27,000 and 36,000 infants with gestational age of ≤ 27 and 28–31 weeks, respectively, most of whom required screening examinations for ROP.[270] On average, each infant requires 3.4 serial examinations, meaning that several hundred thousand ROP screening exams are performed annually in the United States.[100]

2. Limitations of current screening program—Current screening protocols in the United States and United Kingdom are effective at identifying clinically significant disease with high sensitivity, but are not generalizable to other regions with different standards of neonatal care. Several published series have shown that infants with ROP in low- and

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middle-income nations have a higher average BW and GA than infants with ROP in the United States.[23,39,47,50,71,75,102,139,140,245,313,391] In addition, current screening guidelines, though highly sensitive, result in screening of many infants who never develop clinically significant disease. Recent reports suggest between 9–40% of screened infants will develop ROP, and an even smaller number will require treatment.[78,135,136,230,239,255] ROP examinations can cause significant morbidity in neonates, including decreased oxygen saturation levels, increased heart rate, and increased apnea events. Also, unnecessary examinations may increase the medical costs for ROP screening. Therefore, although over-screening ROP has been considered acceptable because missing severe ROP can cause devastating results, developing novel screening protocols with both high sensitivity and specificity across various populations would be ideal.[261,320] For this purpose, understanding risk factors for ROP is essential.

II. MAJOR RISK FACTORS

A. Prematurity: GA and BW

GA and BW are the two strongest known risk factors for development of ROP. The multicenter study of cryotherapy for ROP (CRYO-ROP) followed 4,099 infants with BW ≤1251g, and found that lower BW and younger GA were strongly associated with developing “threshold” ROP.[328] In the CRYO-ROP cohort, each 100g increase in BW decreased the odds of reaching threshold ROP by 27%, and each week increase in GA decreased the odds of reaching threshold disease by 19%.[328] These results have been replicated in multiple subsequent studies, both for the risk of incident ROP and of treatment-requiring ROP.
6,10,11,13,14,17,18,21,47,57,65,75,77,94,102,109,114,122,125,135,138,143,147,152,157,174,202,204,216,228,231,233,236,240,246,255,263,2

B. Oxygen

The use of supplemental oxygen, oxygen concentration, duration, and prolonged mechanical ventilation were among the most frequently identified risk factors for severe and treatment-requiring ROP. The first randomized-controlled trial in ROP published in 1956 based on the preclinical work of Ashton and Patz[25,293–297] found that exposure to >50% oxygen increased the incidence of ROP compared to a curtailed-oxygen group.[213] In 1992, Flynn and coworkers[118] found that for every 12-hour period with a tcPO2 ≥80mmHg, the risk of severe ROP nearly doubled. In addition to high oxygen itself, fluctuations in oxygen saturation have been found to be an independent risk factor for severe ROP.[88,419] A number of subsequent studies found the duration of oxygen therapy to be a significant risk factor for severe ROP.
10,13,39,57,71,74,109,114,131,149,152,167,231,236,257,264,276,283,312,313,315,364,401,412,428 Similarly, many studies identified prolonged mechanical ventilation as a risk factor for any or severe ROP.
11,12,36,39,53,57,106,120,157,167,187,211,232,263,266,274,275,286,335,337,345,348,368,370,405,406,412,417

Despite several large randomized-controlled studies comparing different target ranges for oxygen saturation, the ideal range remains controversial. The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial studied the effects of

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89–94% SaO2 vs. 96–99% SaO2 on ROP incidence, and found no significant difference.[2] The Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial (SUPPORT) and Benefits of Oxygen Saturation Targeting Study II (BOOST-II) compared 85–89% SaO2 vs. 91–95% SaO2, and found that the lower oxygen levels were associated with increased mortality, but lower rates of ROP.[64,353] The Canadian Oxygen Trial (COT) also compared 85–89% vs 91–95%, but found no significant difference in either the rate of death or disability between the two groups.[332]

III. ALTERNATIVE RISK FACTORS

A. Introduction

Since ROP was first described over 75 years ago, there have been thousands of papers published on the disease. In our review of the literature, we have identified over 300 papers that identify distinct putative risk factors for ROP. Individual risk factors are discussed in detail below.

B. Maternal factors

1. Hypertensive disorders of pregnancy (HDP)—HDP is often associated with perinatal morbidities,[130] but is also known to be associated with higher levels of anti-angiogenic factors such as sFlt-1 (soluble fms-like tyrosine kinase-1), an antagonist of vascular endothelial growth factor (VEGF), and placental growth factor.[105,310,322,327] Several studies found HDP including preeclampsia-eclampsia to be a significant risk factor for ROP by either univariate or multivariate analysis;[39,129,254,287,337,405] however, other large-scale studies found that preeclampsia was not associated with ROP or associated with reduced risk of ROP.[23,121,180,412,422] Recently, a meta-analysis on HDP and ROP that included 13 cohort studies with a total of 45,082 babies revealed no clear association.[429] Variable study quality and various possible confounding factors such as antenatal medication, associated maternal conditions, and postnatal oxygen treatment may explain the conflicting results.

2. Maternal diabetes mellitus (DM)—Diabetes may have both direct (e.g. increased retinal VEGF by hyperglycemia) and indirect (e.g. association with respiratory distress syndrome) impact on ROP development;[317,333] however, there are conflicting results on the association between maternal DM and ROP. The National Collaborative Trial on Patent Ductus Arteriosus in the United States from 1979 to 1981 found a higher incidence of ROP among babies of diabetic mothers.[309] Recently, a Turkish retrospective study identified maternal DM as an independent risk factor for both ROP and type 1 ROP in infants with BW ≥ 1500g;[374] however, neither a prospective population-based Swedish study (1988–1990) of maternal risk factors for ROP nor a prospectively collected Israeli national database study (1995–2007) confirmed these findings.[43,175] There is large heterogeneity in study period, baseline subject characteristics, and diabetes management among these studies, and degree of glycemic control was not considered in most studies, which limits interpretation.

3. Maternal medication use—Studies have found associations between maternal medication use and ROP, including beta blockers[131] and antihistamine use late in pregnancy.

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[309] A Swedish population-based study, however, failed to identify any association between maternal medication use and ROP.[175] Further studies involving various medications are warranted.

4. Maternal age—Advanced maternal age has been associated with various adverse outcomes including miscarriage,[83,278] intrauterine growth restriction,[279] preterm births, low birth weight,[83,349] and chromosomal abnormalities.[83] The association of maternal age and ROP has been examined, with conflicting results including studies showing increased incidence with increasing maternal age,[402] decreased incidence with increased maternal age, [375] and no association with maternal age in a large Canadian cohort study.[200] There is wide variability in the range of maternal age among studies that may partly explain the conflicting results.

5. Smoking—Tobacco smoke exposure during pregnancy has been associated with low birth weight,[227] and nicotine has been reported to upregulate VEGF in *in vitro* studies.[306,425] There are conflicting results on the association of maternal smoking and ROP.[3,24,170,175,351] A large-scale German study found that maternal smoking was associated with growth restriction and development of ROP.[351] Most of these studies did not examine the amount of smoking, which may be an important factor to consider in future studies.

6. Other maternal factors—A Turkish study showed that maternal iron deficiency anemia was associated with development of ROP.[89] One study investigated relationship between average day length during early gestation and development of severe ROP and showed that each additional hour of day length during the first 90 days after conception decreased the likelihood of severe ROP by 28%.[410] Two studies on maternal and neonatal factors showed that maternal blood leukocyte count was significantly associated with ROP. [399,400]

C. Prenatal and perinatal factors

1. Assisted conception—Although the exact mechanism is not clear, association between assisted reproductive technology (ART) including in vitro fertilization (IVF) and ROP has been studied with conflicting results.[34,67,125,256,259,394] Some studies identified ART as an independent risk factor for ROP, but it is difficult to draw definite conclusions because ART is also associated with factors including low BW, early GA, and multiple births. Two United Kingdom studies suggest that improvements in IVF may have reduced the additional risk of severe ROP. [127,256]

2. Hospital of birth—Higher-level hospitals or study centers of large clinical trials showed lower rates of ROP.[94,144,328,367,384] The CRYO-ROP study found that infants born outside study centers were at greater risk of developing threshold ROP.[328] The ET-ROP study also showed greater risk for severe ROP among outborn infants.[144] This finding could be explained by probable higher level of infant care with more experience managing premature infants in higher-level hospitals or by the baseline characteristics of transferred infants with higher-level morbidities.

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3. Mode of delivery—Several studies have studied the association of mode of delivery and ROP, with conflicting results, including studies showing increased risk for ROP with vaginal birth,[95116,248] increased risk with Caesarean section,[397] and no associations.[5,325] There were variations in perinatal medications, indications for delivery mode, and maternal factors such as preeclampsia and chorioamnionitis that may have affected the discrepancy.

4. Premature Rupture of Membranes—Published data are conflicting on the association of preterm premature rupture of membranes (PPROM) and ROP risk.[95,226,243,286,397] A Turkish single-center study found that PPROM >18 hours was independently associated with an increased risk of type 1 ROP;[286] however, a Swedish matched case-control study on WINROP (Weight, Insulin-like growth factor-1, Neonatal, ROP) alarm system found PPROM to have a protective effect against ROP stage ≥3.[397] These conflicting results might be explained by different outcome measures, small sample size, and different confounding factors adjusted in those studies. Two studies in United States showed reduced incidence of severe ROP in preterm PPROM groups compared with other causes of preterm birth such as preterm labor, suggesting possible roles of perinatal therapies (such as corticosteroids) for PPROM in ROP and a possibility of “prenatal phase” of ROP.[226,243]

5. Chorioamnionitis—Intrauterine inflammation including chorioamnionitis has been associated with various perinatal morbidities including bronchopulmonary dysplasia and cerebral palsy,[386] and several studies suggest association of chorioamnionitis with ROP. Animal studies also showed that systemic inflammation impaired retinal angiogenesis in newborn animals.[177,372] A meta-analysis of 27 studies in 2014 revealed that chorioamnionitis was significantly associated with ROP by univariate analyses, but no association was found on multivariate analysis correcting for GA.[262] A recent study suggested an association between aggressive posterior ROP (APROP) and chorioamnionitis.[9]

D. Infant factors

1. Race/ethnicity—The CRYO-ROP study found that black infants had a lower incidence of threshold ROP compared to white infants.[326,328] This finding has been confirmed in multiple subsequent North American studies.[78,159,308,358,409] On the contrary, the study by Aralikatti and coworkers in the United Kingdom found black infants to have a higher risk of severe ROP than white infants.[22] Asians and Alaskan natives also appear to have a greater risk of ROP than white infants.[22,181,224] This racial variation suggests a genetic predisposition to ROP. Also, the difference in findings between different countries might be explained by racial variation in socioeconomic status, which has been associated with low BW, small for GA and preterm birth.[291]

2. Gender—In other ocular vascular diseases, gender differences due to different blood flow have been suggested, but there are few clinical studies supporting the association.[330] Also, a study showed that male fetal sex was associated with higher maternal levels of proinflammatory cytokines and angiogenic factors including VEGF during pregnancy, suggesting potential harmful effects on development of ROP in male infants.[108] Studies on

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gender and ROP risk have also been conflicting. The CRYO-ROP study and New York cohort study found no difference in the incidence of ROP by gender;[78,288] however, other studies have reported that male sex is a significant risk factor for ROP.[95,240,348,368,378,409,417]

3. Twin/multiple births—Multiple gestation is associated with increased risk for preterm birth, smaller BW, and perinatal morbidities, which may affect ROP risk.[1] In the CRYO-ROP study, singleton infants were found to have less risk of ROP than twins or multiplets.[328] Other studies have also found multiple gestation to be significantly associated with ROP.[53,217,231,234,254,276,409,413] Multiple birth has also been associated with treatment-requiring ROP in a series by Yang and coworkers[409] and in a cohort study by Port and coworkers;[308] however, several studies reported higher incidence of ROP in singletons,[125] or no differences between singleton and multiple births.[52,126] This inconsistency may be due to variations in mode of delivery, variable maternal factors and perinatal therapy, natural vs. assisted conception, and lack of adjustment for known risk factors, which is especially important because multiple gestation is associated with known risk factors of ROP such as smaller BW.

4. Apgar score—It has been suggested that lower Apgar scores, as a general indicator of poor neonatal health, may be associated with higher rates of ROP. Studies from China,[207] Australia and New Zealand,[95] United States,[264] Hungary,[110] Bosnia and Herzegovina,[13] Korea,[400] and Iran[39] found lower Apgar scores among infants with ROP; however, on multivariate regression analysis, the relationship between Apgar scores and ROP was not significant in most studies. It should be noted that it is important to recognize the limitations of the Apgar score: it does not predict individual neonatal neurologic outcome, and it is inappropriate to use the Apgar score alone to establish the diagnosis of asphyxia.[4]

E. Comorbidities and treatments

1. Pulmonary complications and treatments

a. Apnea and caffeine: Infants with apnea of prematurity are more likely to require mechanical ventilation and supplementary oxygen, and may be more likely to develop ROP.[23,70,71,75,148,149,179,207,211,254,257,274,309,423,428] A large-scale Turkish study found apnea to be independently associated with greater risk of ROP.[23]

Caffeine, a xanthine derivative, has been commonly used for the treatment and prophylaxis of apnea of prematurity and has been associated with improved neonatal outcomes such as decreased incidence of bronchopulmonary dysplasia (BPD).[98,292] A randomized multicenter study in 2007 found that severe ROP was less common in infants assigned to caffeine,[331] and an animal model of ROP study showed caffeine ameliorated hyperoxia-induced vaso-obliteration as well as hypoxia-induced pathologic angiogenesis.[424] There have, however, been conflicting results on caffeine use and development of ROP with both positive and negative associations reported.[14,157,182,237,331] Differences in caffeine dosage, different outcome measures, and lack of control group or adjustment for known risk factors might explain the conflicting results. Two recent meta-analysis studies identified a lower association of ROP with early caffeine use.[219,289.331]

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b. Respiratory distress syndrome (RDS) and surfactant: RDS is caused by a surfactant deficiency in the neonate. With RDS, the infant may become hypoxic and require mechanical ventilation and oxygen therapy, both of which are associated with increased incidence of ROP. Not surprisingly, therefore, RDS is associated with increased risk of developing ROP.[10,11,23,85,102,174,220,233,290,336,362,406,428] Many of these infants require surfactant, and several studies investigated the association between surfactant therapy and ROP.[27,85,186,211,220,229,257,290,314,335,337,365,366,391,412,413,423] Some of these studies found surfactant therapy to be an independent risk factor for ROP, which can be interpreted as higher ROP risk in infants with RDS requiring surfactant therapy.

c. Respiratory support: Prolonged mechanical ventilation (PMA), often defined as >7 days of ventilator dependence, is among the most frequently identified risk factors for ROP.[12,24,26,35,54,106,117,120,137,148,157,174,184,187,211,220,233,254,257,263,266,286,345,348,370,397,405,412,413,417]

A recent cohort study including 979 infants revealed that the need for respiratory support including mechanical ventilation and high-frequency oscillatory ventilation at time of first study-related examination (median 33 weeks PMA) was an independent risk factor for referral-warranted ROP.[417] Several studies have found that, like traditional mechanical ventilation, the need for nasal CPAP also increases the risk of ROP,[150,174,220,233,275,337,363] and delays involution of ROP.[273]

d. Bronchopulmonary dysplasis (BPD): BPD (also known as chronic lung disease), defined as supplemental oxygen dependence beyond 28 postnatal days, a confounding clinical diagnosis associated with prolonged oxygen exposure by definition, been associated with ROP.[85,135,174,290,308,315,373,398,412] Although corticosteroids to prevent or treat BPD are controversial due to possible adverse effects such as cerebral palsy, corticosteroids remain a common treatment in preterm infants.[37,38,252,393] Studies evaluating corticosteroids and ROP have found conflicting results as an independent risk factor.[36,57,85,159,204,235,401] Different time periods between studies, early vs. late administration of steroids, different dosage, and different baseline subject characteristics may have affected these study results. A recent data analysis of 1,472 infants with birth weight <500g showed that steroid treatment was an independent risk factor for any stage and stage ≥3 ROP after controlling for confounders such as BPD, sepsis, and oxygen use.[268]

2. Anemia, transfusion and erythropoietin (EPO)—Decreased hemoglobin concentration after birth is particularly pronounced among preterm infants, because of impaired erythropoiesis due to inadequate production of EPO, and is termed anemia of prematurity. Blood transfusions, recombinant EPO to treat or prevent anemia, and anemia itself have been implicated as ROP risk factors. Because EPO, regulated by oxygen in both kidney and retina, is an important proangiogenic factor and has been associated with retinal vascular stability in a mouse model of ROP,[63,73,392] levels of EPO and anemia due to low EPO might be associated with development of ROP. In addition, the iron load from transfusions may catalyze the formation of reactive oxygen species, and accelerate oxidative damage, predisposing to ROP;[171,357] however, the results of studies evaluating presence and/or treatment of anemia as risk factors for ROP have been inconsistent.

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Several studies reported significant association between anemia and ROP,[32,313] but other studies found that anemia was not an independent risk factor.[106,414] Moreover, Englert and coworkers reported that infants with prolonged severe anemia developed milder ROP than less anemic infants.[106] Variations in severity, time, and duration of anemia, treatment strategy for anemia, and degree of prematurity might have affected the inconsistent results.

Transfusion of RBCs appears to be a risk factor for the development of ROP.[5,11,20,39,40,65,82,86,101,102,106,116,122,123,137,143,148,150,152,167,180,202,207,208,220,229,246,257,283,315,334,346,348,356,367,38]

Four randomized controlled trials and a meta-analysis on the effect of transfusion protocols suggest the amount of transfusion may not be associated with ROP.[42,56,72,112,214]

Although administration of EPO has been reported to increase the incidence of ROP in some studies,[116,122,199,250,257,318] there are conflicting results including those from meta-analysis on the association between EPO and ROP. We have identified 5 recent (2014 or later) meta-analyses on this topic: 4 of them found that early (before 8 days after birth) or late EPO did not influence the risk of any stage or stage ≥3 ROP.[7,81,112,403] In one meta-analysis, however, *post hoc* analysis including all studies that reported on stage ≥3 ROP regardless of timing of EPO revealed an increased risk.[280] The major limitation of included studies for meta-analysis is that few studies primarily aimed to examine the relationship between EPO and ROP.

3. Thrombocytopenia—In addition to their wound healing function, platelets are regulators of angiogenesis: platelets store, transport, release angiogenic factors such as VEGF, and can enhance or inhibit local angiogenesis by adhering to endothelium.[69,188] Several studies suggested an association between thrombocytopenia and severe ROP including APROP[241,385] and zone I ROP.[192] An Indian case-control study[385] and a Swedish cohort study[241] showed that the mean platelet count of APROP infants was significantly lower than that of control infants.

4. Patent ductus arteriosus (PDA)—Studies have demonstrated associations between PDA and neonatal morbidities such as necrotizing enterocolitis, intraventricular hemorrhage, and BPD.[62,158] In infants with PDA, reduced perfusion due to by-pass of systemic blood flow might result in retina hypoxia, which may affect development or progression of ROP.[62] Several studies have reported that presence and/or treatments for PDA are risk factors for ROP.[36,150,184,189,220,257,266,367,387] A study of 487 infants in Turkey found that PDA was an independent risk factor for severe ROP.[29]

Management of PDA, which is still controversial, includes cyclooxygenase inhibitors and surgical closure, both of which have been associated with ROP.[12,94,122,191,195,260] Jegatheesan and coworkers[191] conducted a randomized controlled trial, and found that administration of high dose indomethacin was independently associated with severe ROP. Analysis of Canadian Neonatal Network data revealed surgical ligation was associated with higher frequency of severe ROP compared with infants who received indomethacin;[260] however, other studies revealed no effects for surgical ligation on ROP.[80,396] Current data are inconclusive as to whether infants treated with surgical ligation were sicker than those without surgery, or whether the surgery itself results in worse outcome.

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5. necrotizing enterocolitis (NEC)—NEC is a serious intestinal complication of prematurity that can be life-threatening. The pathophysiology of NEC may involve innate immune responses to intestinal microbiota, leading to inflammation.[359] Animal model studies showed that systemic inflammation affects retinal angiogenesis,[132,177,372] suggesting possible association between NEC and ROP. Epidemiologic studies have shown that NEC might increase ROP risk.[78,187,220,229,233,241,263,315,398] In a New York cohort study, Chiang and coworkers found NEC to be associated with an increase in the risk of developing ROP.[78] A study of 423 infants in Canada also reported that NEC was an independent risk factors for ROP.[187]

6. intraventricular hemorrhage (IVH)—IVH is an important complication of prematurity that often results in neurodevelopmental impairment.[269] IVH occurs in 25–30% of all preterm infants <1,500 g.[344] For unclear reasons, IVH has repeatedly been associated with ROP and appears in many of the articles reviewed.[12,14,23,35,58,68,76,122,174,220,235,266,272,311,336,337,387,395,398,405,414,415] An epidemiologic analysis of 2,950 infants in Turkey revealed that any IVH was associated with greater risk of ROP.[23]

7. Bacterial and fungal sepsis—Neonatal sepsis is among the most frequently identified risk factors for any ROP and severe ROP.[5,10,14,23,35,57,65,68,114,137,143,149,150,152,205,208,220,229,235,245,249,257,263,264,266,271,277,283,301,309,315,362,367,377,391,41

It has been suggested that perinatal infection and inflammation may play important roles in ROP.[91] A New York state cohort study reported that the presence of neonatal sepsis was associated with an elevated risk of ROP.[78] The Extremely Low Gestational Age Newborns (ELGAN) study also revealed that late bacteremia is an independent risk factors for prethreshold/threshold ROP.[369] Studies evaluating fungal sepsis and ROP have found conflicting results as an independent risk factor for severe ROP.[203,277] A Swedish cohort study suggested an association between sepsis and APROP.[241]

8. Postnatal weight gain and insulin-like growth factor 1 (IGF-1)—Poor postnatal weight gain may be indicative of poor overall health in the neonate. Poor postnatal weight gain, and slower postnatal growth velocity have been associated with ROP.[29,45,119,165,210,238,242,379,380,388,390,418] Wallace and coworkers found that each 60g below an infant's expected weight at 6 weeks was associated with a 20% increase in ROP risk.[388] The ELGAN study group reported that infants in the lowest quartile for growth velocity were at higher risk of developing any ROP and type 1 ROP.[379] Additionally, a study showed that slow postnatal weight gain is associated with a lower postnatal increase of serum IGF-1.[107] IGF-1 is an anabolic hormone promoting development of many tissues including retinal vessels, and early postnatal low serum IGF-1 is associated with development of ROP.[164,166,193,302,383] Prediction models including weight gain with or without serum IGF-1 level are shown in Table 1.

9. Nutrition

a. Human milk: Human milk increases IGF-1 level and contains docosahexaenoic acid (DHA), antioxidants like inositol, vitamin E and carotenoids.[44] These factors may help

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protect against ROP. Several studies have shown that human milk feeding decreases the incidence of any-stage or severe ROP, although conflicting results have been reported.[141,162,185,201,251,281,307,352] Three recent meta-analyses found a protective effect of human milk on development of ROP.[44,112,426] One meta-analysis in 2015 included 5 observational studies comparing the incidence of any stage and severe ROP in infants who were fed human milk and formula, and revealed that exclusive and mainly human milk feeding protected from any and severe ROP.[426] Another recent meta-analysis including 9 observational studies showed that any amount of human milk feeding, even if not exclusive, was significantly associated with lower ROP incidence.[44]

b. Parenteral nutrition and fish oil: Omega-3 long-chain polyunsaturated fatty acids reduce pathological angiogenesis in an animal model of ROP.[84] DHA is an omega-3 fatty acid that is one of the major components of the retina.[324]

For parenteral nutrition, lipid emulsion (LE) containing fish oil shows higher DHA level than that in conventional soybean oil LEs, and may reduce incidence of ROP.[41,298,299] A Turkish randomized controlled study showed that fish oil LE was associated with lower incidence of any-stage ROP,[41] and a recent meta-analysis revealed that the pooled relative risk of severe ROP was lower in fish oil LE group than that in soybean oil LE group;[382] however, prolonged parenteral nutrition has been suggested as a risk factor for ROP.[14,35,275,307,346]

c. Energy intake: A Swedish population-based study showed that higher intakes of energy, fat, and carbohydrates during the first 4 weeks of life were associated with lower risk of severe ROP, suggesting that providing adequate energy from parenteral and enteral sources may be important for reducing the risk of stage ≥3 ROP.[354]

d. Inositol: Inositol, a component of membrane phospholipids, has an important role in cell signaling and maturation of pulmonary surfactant.[156,247] Serum levels of inositol are higher during the fetal period than postnatal period,[155] and lack of supplementation such as human milk feeding results in decreased inositol levels.[153] A randomized controlled trial in 1992 and a prospective cohort study in 2000 found that inositol supplementation was associated with decreased incidence of ROP;[124,154] however, a recent phase 3, randomized, placebo-controlled trial to determine the effectiveness of myo-inositol injection on increasing the incidence of survival without severe ROP was terminated early due to safety concerns.[A]

10. Hyperglycemia and insulin—Hyperglycemia, commonly seen in extremely low BW infants especially during the first week of life, is a risk factor for mortality and morbidity of premature infants.[161] An animal model study suggested that under hypoxic condition, retinal Müller cells, which are known as major sources of VEGF in retina, produced more VEGF when glucose level was high.[55] Several reports have found hyperglycemia increases the risk of developing ROP,[8,49,110,133,196,266,267,321,397] but a retrospective database study including 24,548 preterm infants in United States and a recent meta-analysis study did not find hyperglycemia to be a definite risk factor for ROP.[28,225] Variations in confounding factors, definitions of hyperglycemia, number and timing of measurements, and management for hyperglycemia may account for the inconsistent results.

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In addition, studies looking specifically at insulin use for treatment of hyperglycemia found borderline significance.[196,225]

11. Length of hospital stay—Longer length of initial hospital admission has been associated with higher rates of ROP.[14,57,106,233,254,378,391] The association between length of hospital stay and ROP, however, may arise because length-of stay is a proxy for cumulative illness burden, with the most ill infants requiring the longest hospital stays.

12. Serum/plasma factors—Several serum/plasma factors including VEGF,[145,163,198,223,300,303,427] bilirubin,[96,113,134,169,178,201,258,416] sE-selectin,[66,304] CRP,[186] apelin,[16] vitamin D,[194] trace elements such as zinc,[407] and inflammatory cytokines such as IL-6[350] have been studied. Although VEGF is a key factor in retinal angiogenesis, studies on systemic levels of VEGF and related factors such as soluble VEGF receptors showed contradictory results.[145,163,198,223,300,303,427] A study on serum cytokine levels in cord blood showed that interleukin-7, monocyte chemotactic protein-1, and macrophage inflammatory proteins 1 alpha and 1 beta were associated with risk of ROP.[421]

13. Other factors—A number of other infrequently studied factors include inhaled nitric oxide use,[31,212,355,376,378,411] dopamine,[19,133,182,265] phototherapy,[17,23,209,335] sildenafil treatment,[111,128,190,253,323] twin-twin transfusion syndrome,[146] fresh-frozen plasma transfusion,[93] myocardial injury after birth,[236] elevated mean platelet volume,[360,361] and serum neutrophil-to-lymphocyte ratio.[221]

IV. Genetic risk factors

Though there is strong evidence for a genetic predisposition for ROP, specific genetic variants with strong association with ROP have not been detected.[160,176,340] Racial differences in ROP (See **Section III, D-1**) and a high concordance rate among monozygotic twins[48,284] both strongly suggest a genetic predisposition to ROP. Most studies have dealt with only a few SNPs from small number of candidate genes, often those in the angiogenesis signaling pathways such as VEGF and Wnt. Genetic association studies with ROP and VEGF gene have been contradictory.[15,33,87,99,142,176,197,206,222,223,305,339,343,381] The Wnt signaling pathway genes previously identified in familial exudative vitreoretinopathy, including *FZD4* and *LRP5*, and Norrie Disease Protein (NDP) gene have also been explored with positive associations with ROP including stage 4/5 ROP in several studies;[90,97,104,172,173,218,244,342] however, there have been only a few genetic studies with adequate sample size and refined inclusion criteria. A large genetic cohort study identified SNPs in the intronic region of brain-derived neurotrophic factor (BDNF) gene as associated with treatment-requiring ROP, which warrants further studies on functional effects of intronic variants of *BDNF* and replication studies. Studies on other genes including *ACE*,[151,305] *AGT*,[305] *AGTR1*,[305] *ANGPT2*,[33,339] *NOS3*,[305,319,341,404,420] *FLT1*,[222] *KDR*,[222] *HMOX1*,[305] *IGF1R*,[338] *IL10*,[92] *IL1B*,[92] *TGFB1*,[87] *TLR4*,[92] *TNF*,[87,92] *TSPAN12*,[218] and *F5* (Factor V Leiden)[30,215] have not shown clear associations with ROP in clinical studies.

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V. RISK PREDICTION MODELS

Predictive models have been developed to identify high-risk infants and to reduce the number of unnecessary screening examinations. In addition to GA and BW, the models have incorporated other factors such as weight gain rate, which are shown in Table 1.[45,46,60,61,103,165,181,238,285,316,329,336,347,365,377,408,417,418] A 2016 American Academy of Ophthalmology report systematically reviewed 23 studies including both development and validation studies to evaluate the accuracy of prediction models and suggested that the models cannot be widely used because of limited generalizability and small sample size, although some models showed reduction in screening burden without missing treatment requiring ROP in some cohorts.[183]

VI. CONCLUSIONS AND FUTURE DIRECTIONS

There have been many putative risk factors for ROP identified in clinical studies. Some of these results are contradictory, unreplicated, and/or limited by confounding with other known risk factors. There are several reasons for contradictory results: (1) heterogeneity of study subjects: differences in race or ethnicity, and differences in baseline characteristics of included infants such as GA and BW may affect the clinical outcomes of ROP. (2) Differences in neonatal care between study hospitals or countries may affect results of studies: there is considerable variation in neonatal care protocols such as oxygen target and in clinical outcomes such as survival rate and morbidities of prematurity, (3) Diagnostic disagreement between ophthalmologists may also affect outcome measures of ROP studies. Clinical experience of ophthalmologists may vary between studies or between physicians in the same study. Moreover, it is well-known that even experts in ROP have disagreements in diagnosis.[59,79,168] (4) As a result of changes in screening and treatment guidelines since the 1980's, there may be differences in outcome measures. (5) There are limitations of study designs in a considerable number of included articles. Retrospective nature, small sample size, a lack of consideration of confounding factors, and inadequate control groups may influence the conclusions.

Incorporating risk factors into ROP management may improve screening methods and enhance understanding of pathophysiology. Some investigators have developed risk prediction algorithms to better predict ROP. Although these algorithms are not incorporated into current screening guidelines, the algorithms have shown fair prediction of treatment requiring ROP while reducing number of examinations. An ideal screening algorithm for ROP must have near-100% sensitivity so as not to miss a single case of treatment-requiring ROP. While current risk models such as WINROP have approached this ideal in initial testing, their sensitivity has fallen when applied to other populations and would miss some infants with severe disease if applied broadly. Incorporating more risk factors and validation studies with adjustment to various populations may improve diagnostic accuracy of prediction algorithms.

Understanding risk factors for ROP is essential to develop sophisticated predictive models and to gain insights into pathophysiology of retinal vascular diseases such as diabetic

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retinopathy, and co-morbidities of prematurity. In addition, finding risk factors may also help to determine future directions in management and research in ROP.

VII. METHODS OF LITERATURE SEARCH

The PubMed was queried from January 1990 to August 2017. The following search terms were used: *retinopathy of prematurity AND risk factors, retinopathy of prematurity AND risk analysis,* and *retinopathy of prematurity AND prediction*. Criteria for inclusion included the relevance, clinical importance, and scientific importance of articles to the subject of this paper. Articles cited in the reference lists of other articles were reviewed and included when considered appropriate. All articles with English abstracts were reviewed, and foreign-language articles were included when the abstract contained sufficient information for use in this paper. A select number of articles have been included before 1990 for historical purposes.

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Table 1

ROP prediction models and their covariates

Predictive Model	Variables or criteria	Reference
Safety index model	BW, GA, days on oxygen use	Schalij-Delfos et al. 1996[329]
Utrecht model	BW, GA, number of erythrocyte transfusions within the first 4 weeks of life.	Termote et al. 2005.[365]
WINROP1	BW, PMA, postnatal weight gain (weight measured once every postnatal week from birth), serum IGF-1 and IGFBP3 level	Löfqvist et al. 2006.[238]
WINROP2	BW, PMA, weight measured once every postnatal week from birth until 35 to 36 postmenstrual weeks	Hellström et al. 2009.[164]
UHC Model	BW, GA, race (Black vs. non-Black), gender, multiple birth	Yang and Donovan. 2009.[408]
Denmark model	BW, GA	Slidsborg et al. 2011.[347]
PINT model	BW, GA, daily weight gain rate	Binenbaum et al. 2011.[45]
CHOP model	BW, GA, daily weight gain rate	Binenbaum et al. 2012.[46]
ROP Score	BW, GA, weight at completed 6 weeks of life, oxygen in mechanical ventilation, transfusion up to 6 week of life	Eckert et al. 2012.[103]
NEDROP	BW < 1250g, GA < 30 weeks, a selection of infants with GA 30–32 weeks and/or BW 1250–1500 g, with at least one of the following risk factors: artificial ventilation, sepsis, necrotizing enterocolitis, postnatal glucocorticoids or cardiotonica	van Sorge et al. 2013.[377]
UK model	BW, GA, early weight gain, maternal ethnicity	Husain et al. 2013.[181]
e-ROP study	GA, fundus findings (pre-plus/plus disease, stage and zone of ROP, blot hemorrhage) and medical conditions (respiratory support and weight growth rate) at the first image session (32–34 weeks PMA)	Ying et al. 2015.[417]
Malaysia model	BW, GA, intraventricular hemorrhage, respiratory distress syndrome	Senthil et al. 2015.[336]
CO-ROP model	BW ≤ 1500g, GA ≤ 30 weeks, net weight gain ≤ 650g between birth and 4 weeks of age	Cao et al. 2016.[61]
University of Utah Model	BW, GA, the need for any surgery, and maternal magnesium prophylaxis	Owen et al. 2017.[285]
STEP-ROP model	BW, GA, respiratory distress syndrome, non-Hispanic ethnicity, multiple gestation	Ricard et al. 2017.[316]

BW, birth weight; GA, gestational age; PMA, postmenstrual age; IGF-1, insulin-like growth factor-1; IGFBP3, insulin-like growth factor-1 binding protein 3.