Journal of Medical and Health Studies
ISSN: 2710-1452
DOI: 10.32996/jmhs
Journal Homepage: www.al-kindipublisher.com/index.php/jmhs

JMHS
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| RESEARCH ARTICLE

Retinopathy of Prematurity: A Review of Risk Factors, Oxygen Targets, Screening Criteria

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| ABSTRACT
Retinopathy of Prematurity (ROP) is a disease of immature retinal tissue that is strongly associated with prematurity, low birth weight, and prolonged oxygen exposure. The purpose of this review is to evaluate published literature to determine which factors can be linked to the development of ROP, which factors are protective against ROP, and which factors are still unclear. It also sought to review the major oxygenation trials in premature infants to establish the recommended oxygen saturation targets in premature babies and what criteria are useful in evaluating infants for ROP. Databases (PubMed, Medline, PubMed Central, and Google Scholar) were used to obtain relevant literary articles. Key findings suggested that major risk factors for ROP were prematurity, low birth weight, and prolonged oxygen exposure. Evidence suggests that maternal diabetes, maternal smoking, prolonged rupture of membranes, lack of antenatal steroids, ethnicity, multiple births, low Apgar scores, and sepsis are risk factors for the development of ROP. Evidence suggests that maternal hypertensive disorders, mode of birth, and chorioamionitis are not associated with ROP. Recommendations of oxygen saturations in the neonate include targets of 90-95% and 90-94%. Screening for ROP is dependent on birth weight, gestational age, and risk factors, with recommendations varying according to pediatric societies.

| KEYWORDS

Infant, Premature, Diseases, Infant, Newborn, Diseases, Congenital, Hereditary, and Neonatal Diseases and Abnormalities, Retinal Diseases, Eye Diseases, Infant, Premature, Infant, Extremely Premature, Infant, Newborn

| ARTICLE DOI: 10.32996/jmhs.2022.3.2.5

1. Introduction

Retinopathy of Prematurity (ROP) is a disease of the immature retina (the light-sensitive part of the eye) that occurs in a sequential manner and can lead to severe morbidity, including retinal detachment, visual impairment, and blindness (Fierson et al., 2018). With adequate and timely screening for ROP in the Neonatal Intensive Care Unit (NICU), these detrimental consequences can be avoided through efficient identification and prompt treatment (Fierson et al., 2018) (Blencowe et al., 2013). ROP screening is based on a combination of factors, including prematurity, low birth weight, and other risk factors (Blencowe et al. 2013), which are discussed below.

ROP develops due to factors that encourage retinal new blood vessel growth, known as "neovascularization" (Smith, 2003). Neovascularization is a result of the combination of many complex risk factors which we do not yet fully understand (Kaur et al., 2022). Once neovascularization occurs, this can lead to fibrovascular retinal detachment and subsequently lead to decreased visual acuity and blindness (Hartnett, 2015).

ROP often occurs in infants with lower birth weights, with estimates suggesting that 65% of infants with a birth weight of <1,250g are affected, and 80% of infants <1,000g are affected (Quimson, 2015). It has been estimated that every year as many as 20,000 infants may be blinded by ROP, and approximately 12,300 more may suffer mild to moderate visual impairment (Blencowe et al., 2013). Increasing numbers of premature births have led to ROP becoming a significant source of morbidity (Hartnett, 2015). The

prevalence varies by region, with the greatest disease burden being seen in places with rapidly growing economies such as India, China, parts of Asia, and South America (Blencowe et al., 2013). Well-established NICU and ophthalmology services have correlated with the disease burden being greatest in neonates with lower gestational age (<28 weeks), while in countries with less established services, infants of higher gestational age (up to 37 weeks) and weight (up to 2,000g) were also at increased risk for severe ROP (Chan-Ling et al. 2018).

This review aims to evaluate the evidence available for or against risk factors related to the development of retinopathy of prematurity, to evaluate the various trials which occurred in establishing the benefits and risk of oxygen in premature infants, to review what result this has had in terms of current guidance of maintaining oxygen saturation in infants admitted to the Neonatal Intensive Care Unit, and which infants the pediatric societies recommend for screening of ROP.

2. Method & Search Strategy

Databases (PubMed, Medline, PubMed Central, and Google Scholar) were used to obtain the literary articles used in this review. Keywords such as "neonate", "ROP", "retinopathy of prematurity", "risk factors", "gestational age", "birth weight", "maternal hypertensive disorder", "maternal diabetes", "maternal age", "maternal smoking", "assisted reproductive technology", "mode of birth", "prolonged rupture of membranes", "chorioamnionitis", "antenatal corticosteroids", "ethnicity", "multiple births", "low Apgar scores", "Pulse Oximetry Saturation Trial for Prevention of ROP", "Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial", "Canadian Oxygen Trial", "Benefits of Oxygen Saturation Targeting II", "Neonatal Oxygenation Prospective Meta-analysis", "American Academy of Pediatrics", "European Consensus Guidelines", "Canadian Paediatric Society", "Royal College of Paediatrics and Child Health", "World Health Organization" and "ROP screening" were used in various combinations, together with the Boolean operator "AND", in the search criteria to generate the list of articles.

The list of results was then screened, and articles were selected based on the relevance of the title. The abstracts of the selected articles were then screened to determine relevance, and finally, the full texts were perused to obtain the necessary information. Only articles relevant to the research topic and available in the English language or with an English translation were used. Priority was given to more recently published articles.

3. Results and Discussion

3.1 Risk Factors & Determinants

Table 1: Evidence Supporting Major/ Well-established Risk Factors

Risk Factor	For	Result
Prematurity /decreased birth weight	(Razak & Faden, 2019) (Kim et al., 2018) (Freitas et al., 2018) (Alajbegovic-Halimic, et al. 2015) (Lundgren et al., 2014)	Positive correlation
Prolonged oxygen exposure	(Schmidt et al., 2013) (The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups, 2013) (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, et al. 2010)	Positive correlation

Table 2: Evidence for and Against Maternal Risk Factors

Maternal risk factors	For	Against/unable to establish link	Correlation
Hypertensive disorders	(Zayed et al. 2010)	(Alshaikh et al., 2017) (Zhu et al., 2017) (Chan et al., 2016)	No correlation
Diabetes	(Opara et al., 2020) (Tunay et al., 2016)	-	Positive correlation
Maternal age	(Wu et al., 2010)	(Uchida et al., 2014)	Unclear correlation
Maternal smoking	(Hudalla et al., 2021) (Spiegler et al., 2013)	(Hirabayashi et al., 2010)	Positive correlation

Table 3: Evidence for and Against Prenatal and Perinatal Risk Factors

Prenatal and Perinatal Risk Factors	For	Against/unable to establish link	Most likely
Assisted reproductive technology	(Frilling et al., 2007)	(Slaveykov et al., 2021) (Barker et al., 2016)	Unclear correlation
Mode of birth	(Manzoni, et al., 2007)	(Awad, et al., 2021) (Nugud, et al., 2019)	No correlation
Prolonged rupture of membranes	(Alsammahi & Basheikh, 2021) (Ozdemir et al., 2012)	-	Positive correlation
Chorioamnionitis	-	(Villamor-Martinez, E., et al., 2018) (Yim et al., 2018) (Mitra et al., 2014)	No correlation
Not receiving antenatal corticosteroids	(Zeng et al., 2022) (Alsammahi & Basheikh, 2021) (Yim et al., 2018)	-	Positive correlation

Table 4: Evidence for and Against Infant Risk Factors

Infant Risk Factors	For	Against/unable to establish link	Most likely
Ethnicity	(Janevic et al., 2018) (Wallace et al., 2017) (Tawse et al., 2016) (Aralikatti et al., 2010)	-	Positive correlation
Multiple births	(dos Santos Motta, et al., 2011) (Motta et al., 2006)	(Riazi-Esfahani et al., 2008)	Positive correlation
Lower Apgar scores	(Ranjan et al., 2019) (Marinov et al., 2017)	-	Positive correlation
Blood transfusion	(Lust, et al., 2019)	-	Positive correlation
Sepsis	(Wang, et al., 2019) (Huang, et al., 2019) (Tolsma, et al., 2011)	-	Positive correlation

3.1.1 Major risk factors

The risk factors and determinants for the development of ROP are many, some of which are documented in Tables 1-4. The major risk factors (Table 1) have been well-established, and these include early gestational age (≤30 weeks), low birth weight <1,500g, and excessive or prolonged exposure to oxygen (Alajbegovic-Halimic et al. 2015) (Kim et al. 2018).

Gestational age and decreased birth weight are discussed together because they are often interlinked. A 2018 study of 602 newborns of birth weight <1,500g or <32 weeks, or with weight and gestational age above these criteria, with risk factors, followed over the course of 10 years, showed that 33.9% developed ROP. Of the 520 neonates whose gestational age was <32 weeks or whose birth weight was <1,500g, 37.6% of the cohort developed ROP (Freitas et al. 2018). In 2014, another evaluation of 2,941 infants of <32 weeks gestational age also linked low birth weight as a major factor (Lundgren et al. 2014).

It has also been shown that an infant being small for gestational age increases the risk of ROP (Razak & Faden, 2019) (Kimyon, 2019). The link between ROP and oxygen exposure was explored in the SUPPORT, COT, and BOOST trials which are detailed below (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, et al., 2010) (Schmidt, B. et al., 2010) (The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups, 2013) and supported in a 2019 retrospective study of 438 infants (Kimyon, 2019).

3.1.2 Parental Risk Factors

Maternal risk factors (Table 2) may include hypertensive disorders, diabetes, medications, age, and smoking (Kim et al., 2018). There was no relationship between paternal demographics and the presence of ROP (Kimyon, 2019).

Most evidence indicates that maternal hypertensive disorders are not linked to the development of ROP in neonates. A 2017 meta-analysis (Zhu et al., 2017) of 45,082 infants, a 2016 meta-analysis (Chan et al., 2016) of 45,281 infants, and a 2017 retrospective cohort study (Alshaikh et al., 2017) of 97 infants all showed that hypertensive disorders of pregnancy were not able to be linked to the development of ROP. In contrast, an earlier study in 2010 - a retrospective study of 5,143 infants, showed that infants born to mothers with maternal new-onset gestational hypertension were more likely to show ROP at their initial screen. Of note, this study also found no association between ROP severity and erythropoietin treatment. (Zayed et al., 2010).

The presence of maternal diabetes has been shown to be associated with the development of neonatal ROP according to a 2020 retrospective cohort study (Opara et al., 2020) of 883 neonates and a 2016 retrospective case-control study (Tunay et al., 2016) of

78 premature infants. The 2020 retrospective cohort study considered neonates weighing <1,500g, whereas the 2016 retrospective case-control study was of infants with a birth weight of 1,500g or more; it found that maternal diabetes is associated with ROP, and the strength of association increased with increasing severity of ROP, establishing it as an independent risk factor. The retrospective case-control study done in 2016 analyzed data of 78 premature infants from diabetic mothers and compared it with data of 258 controls. The rate of ROP (78.2% in the case group and 14.7% in the control group) and the rate of type 1 ROP (20.5% in the case group and 4.7% for controls) were found to be significantly higher in the case group. Therefore, maternal diabetes was shown to be an independent risk factor.

Regarding maternal age as a risk factor, a 2010 retrospective case-control study (Wu et al., 2010) of 144 patients showed that mothers who were older than 30 had an increased risk of development of ROP. However, in a 2014 retrospective study (Uchida et al., 2014) of 197 premature infants, there was seen that younger maternal age was associated with a higher risk of ROP and older maternal age was associated with a lower risk of ROP; a finding that they suggested may be complicated by older mothers having higher rates of pregnancy failure, and younger mothers having other complicating factors resulting in premature births. The 2019 retrospective study (Kimyon, 2019) by Kimyon showed that maternal as well as paternal age was not significantly associated with the presence of ROP.

The risk between maternal smoking and neonatal ROP has been shown to be directly linked. In a 2020 retrospective case-control study (Hudalla et al., 2021) of 751 premature infants, a total of 397 infants were deemed to have ROP, of whom 81 were identified as having a severe condition (stage ≥3). Sixty-three (8.3 percent) mothers reported smoking during pregnancy, consuming a median of 10 cigarettes per day. These infants were classified according to their mothers' smoking status during pregnancy, and the frequency distribution of ROP stages was noted. Stage ≥3 (22 percent vs 10 percent) and stage 2 (24 percent vs 20 percent) ROP occurred more frequently in neonates born to smoking mothers (Kimyon, 2019). In addition, a 2013 multicenter study (Spiegler et al., 2013) of 2,475 parents of infants who were very low birth weight reported that in mothers who smoked during pregnancy, there was an increased rate of ROP in the infants. However, a small case-control study in 2010 (Hirabayashi et al., 2010) of 86 premature infants showed that maternal smoking was associated with a lower rate of severe ROP.

3.1.3 Prenatal and Perinatal Risk Factors

The prenatal and perinatal risk factors (Table 3) include assisted conception, hospital of birth, mode of delivery, premature rupture of membranes, chorioamnionitis (Kim et al., 2018), and lack of antenatal steroids (Console et al., 1997).

The largest study we encountered was a 2019 meta-analysis (Friling et al., 2007) of 10,392 assisted reproductive technology (ART) cases and 39,474 spontaneous conception cases. This study showed that ART, particularly in vitro fertilization, was likely to result in higher risk and severity of ROP, thus establishing a good basis to support the association. Several smaller studies have found inconsistent evidence, including a 2016 retrospective audit (Barker et al., 2016) which did not find a significant difference between ART and non-ART groups but could not rule out a possible association, a 2021 retrospective analysis (Slaveykov et al., 2021) of 419 infants which found that ART is a risk factor but indirectly, due to association with lower birth weight and gestational age.

In assessing the risk of the mode of birth, an earlier study in 2007; a prospective (Manzoni et al., 2007) cohort analysis of 174 neonates, showed that 40.9% of the infants who delivered vaginally developed ROP versus 17.5% of those delivered via C-section, thus suggesting vaginal birth to be a risk factor for ROP. However, more recent data, such as from a 2019 retrospective study (Nugud et al., 2019) of 163 patients and a 2021 prospective study (Awad et al., 2021) of 100 neonates, showed that mode of delivery was a non-significant risk factor.

Prolonged rupture of membranes (PROM) is a significant risk factor for ROP, as evidenced by a 2021 retrospective chart study (Alsammahi & Basheikh, 2021) of 229 preterm babies and a 2012 study (Ozdemir et al., 2012) of 25 infants.

Chorioamnionitis was not a significant risk factor according to a 2014 meta-analysis (Mitra et al., 2014) of 10,590 preterm neonates, a 2018 meta-analysis (Villamor-Martinez et al., 2018) of 38,986 infants, and a 2020 retrospective study (Yim et al., 2018) of 221 preterm infants. A 2018 systematic review and meta-analysis (Villamor-Martinez et al., 2018) of 38,986 infants sought to establish Chorioamnionitis as a risk factor for retinopathy of prematurity, and their data found a positive correlation between the two.

Evidence shows that receiving antenatal corticosteroids results in decreased incidence of ROP in these infants, according to a 2021 study (Alsammahi & Basheikh, 2021) which showed that more neonates who received antenatal steroid therapy did not develop ROP, a 2018 meta-analysis (Yim et al., 2018) of 20,731 neonates showed that receiving antenatal steroids results in a decreased risk of development of ROP, and a 2022 meta-analysis (Zeng et al., 2022) of 196,264 infants.

3.1.4 Infant factors

Factors related to ROP that vary according to the infant (Table 4) include ethnicity, gender, multiple births, low Apgar score, and neonatal comorbidities and treatments.

Black and Asian infants may be at increased risk of developing ROP. A 2009 retrospective observational study (Aralikatti et al., 2010) of 1,690 preterm infants showed that Asian and Black infants have an increased risk of developing threshold ROP when compared with White infants. A 2016 retrospective review (Tawse et al., 2016) of 1,303 infants showed that Black neonates were less likely than Asian neonates to develop Type 1 ROP. In a 2018 retrospective cohort study of 582,297 infants, Asian infants were determined to be at an increased risk for ROP (Janevic et al., 2018). In a 2016 retrospective cohort study (Wallace et al., 2017) of 19,325 patients, Black infants were found to be at greater risk of ROP than White infants.

The development of ROP may be higher in multiple births but may be secondary to low birth weight and lower gestational age seen in multiple births. In 2006, Motta et al. in a study (Matta et al., 2006) of 159 newborns, it was shown that ROP was significantly higher in twins. A 2008 study (Riazi-Esfahani et al., 2008) of 99 neonates revealed no significant difference and suggested that any apparently higher rate may be secondary to other factors such as lower birth weight and gestation in multiple births. A 2011 prospective cohort study (dos Santos Motta et al., 2011) of 159 newborns showed a higher frequency of ROP in twins and triplets.

Lower Apgar scores are linked to the development of ROP. In a 2019 study of 107 neonates, low Apgar scores at 1 and 5 minutes were linked to a higher risk of ROP (Ranjan et al., 2019). In a 2017 study of 132 preterm infants, a low 5-minute Apgar (6 or less) was linked to ROP progression to a stage needing treatment (Marinov et al., 2017).

Neonatal comorbidities and treatments which are linked to the development of ROP include (Kim et al., 2018) pulmonary (apnea and caffeine, respiratory distress syndrome, respiratory support, bronchopulmonary dysplasia), anemia/transfusion/erythropoietin (Lust et al., 2019), thrombocytopenia, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, sepsis (bacterial and fungal) (Wang et al., 2019), and postnatal weight gain and insulin-like growth factor-1 (Hård et al., 2013).

A 2018 retrospective study (Lust et al., 2019) of 1,635 infants revealed that receiving a blood transfusion in the first 10 days of life was a significant risk factor (almost four-fold increase) for the development of severe ROP.

Two meta-analyses carried out in 2019 by Wang et al. (Wang et al., 2019) and Huang et al. (Huang et al., 2019), respectively, showed a close relationship between the development of ROP and the presence of sepsis. An analysis in 2011 of 1,059 infants showed a similar result (Tolsma et al., 2011). It is suggested that vasoproliferation in ROP may be promoted by angiogenesis mediated by neutrophils and vascular endothelial growth factor (VEGF) (Gong & Koh, 2010).

3.2 Oxygen saturation levels and monitoring alarms

The importance of studying the effects of oxygen and oxygen toxicity on premature neonates was recognized, and the need for a large-scale study was born. In the effort to establish a study of this magnitude, the Pulse Oximetry Saturation Trial for Prevention of ROP (POST ROP) was planned to include 4,000 infants. However, due to issues of funding, the study was broken up into five smaller studies (Cole et al., 2003) which are outlined below. These studies - SUPPORT, COT, BOOST II Australia, BOOST II New Zealand, BOOST II the United Kingdom, evaluated two groups of infants: those assigned to a lower oxygen saturation level of 85-89% versus a higher oxygen saturation level of 91-95% (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, et al. 2010) (Schmidt et al. 2013) (The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups, 2013).

The Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial (SUPPORT) (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, et al. 2010) was started in early 2005 and evaluated 1,316 infants between 24 to 28 weeks gestational age. The trial found that in the lower oxygen saturation group, severe retinopathy occurred less often as compared to the group with higher oxygen saturation. However, there was also an increased incidence of death before discharge in this same group (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, et al. 2010).

The Canadian Oxygen Trial (COT) (Schmidt et al. 2013) was started in late 2006 and evaluated 1,200 infants between 23 to 28 weeks of gestational age. The study found no significant difference in death and disability in the infants at 18 months and no significant difference in the occurrence of ROP between the 2 groups (Schmidt et al., 2013).

The Benefits of Oxygen Saturation Targeting II (BOOST II) (The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups, 2013) trials were three international randomized, controlled trials started in 2006 and 2007 in Australia, New Zealand, and the United Kingdom; it recruited 2,448 infants. The results showed that the mortality was significantly increased in the group with

the lower oxygen saturation (23.1%) versus, the higher oxygen saturation group (15.9%) (The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups, 2013). However, results also showed a smaller percentage of patients with ROP (10.6%) in the lower saturation group than in the higher saturation group (13.5%) (The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups, 2013).

The results of the five studies outlined above were analyzed as part of a meta-analysis known as the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) Collaboration (Lisa et al., 2018). In addition to no significant difference found between the 2 groups in terms of death or disability at 18-24 months of corrected gestational age, there was also an increased risk of ROP in infants allocated to the higher oxygen saturation group (Askie et al., 2018).

3.2.1 Clinical Relevance

The American Academy of Pediatrics (AAP) released documentation in 2016 (Cummings et al., 2016) which stated that the ideal oxygen saturation range for extremely low birth weight neonates was likely to be very patient-specific and depends on several different factors including gestational age, age, and clinical well-being. It goes on to say that the ideal saturation range is a compromise between complications arising from either hyperoxemia or hypoxemia. The AAP notes that an oxygen saturation range of 90-95% may be safer than 85-89% but stresses that despite the randomized controlled trials mentioned above, we still do not know the ideal oxygen saturation range in extremely low birth weight infants. In terms of the alarm limits, the AAP suggests that an upper alarm limit of 95% is reasonable while the infant still requires supplemental oxygen. As for the lower target, it simply reasons that the lower limit should be somewhat below the chosen oxygen saturation range (Cummings et al., 2016).

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome, updated in 2019, while it still acknowledges that the ideal range is unknown, have given recommendations for targeting oxygen saturations of 90-94% and setting alarm limits at 89-95% (Sweet et al., 2019).

3.3 Screening Criteria

The AAP "Screening Examination of Premature Infants for Retinopathy of Prematurity", released in 2018 (Manja et al., 2017), recommends that the criteria for screening of premature infants should include:

1. All infants with a birth weight of ≤1,500g.
2. All infants born at ≤30 weeks gestational age.
3. Infants with birth weight 1,500-2,000g or >30 weeks gestational age with risk factors for ROP (such as prolonged oxygen supplementation).

The Canadian Paediatric Society "Retinopathy of prematurity: An update on screening and management", released in 2016 (Jefferies et al., 2016), recommends screening:

1. All infants born at ≤30 weeks and 6 days gestational age.

2. All infants with birth weight ≤1,250g.

3. More mature infants with risk factors for ROP.

The Royal College of Paediatrics and Child Health released guidelines "Screening and Treatment of Retinopathy of Prematurity - clinical guideline", which was published in 2008 and reviewed in 2013 (Royal College of Paediatrics and Child Health, 2022), developed together with the Royal College of Ophthalmologists, British Association of Perinatal Medicine, and BLISS.

This guidance is given in two parts for the screening criteria. They stated that the following babies MUST be screened for ROP:

1. All infants born at ≤30 weeks and 6 days gestational age.

2. All infants with birth weight ≤1,250g.

They also suggested that infants <32 weeks and <1,501g SHOULD be screened for ROP.

The Pan American Health Organization (PAHO) and the World Health Organization (WHO), in 2017 (Pan American Health Organization, 2019). "Clinical practice guidelines for the management of retinopathy of prematurity" have suggested implementing

the recommendation to screen infants with a birth weight of <2,000g and/or <36 weeks gestational age of any birth weight who present with risk factor(s) for developing ROP.

3.4 Recommendations

Recommendations for future research include allowing this paper to serve as a building block, whereby more studies, databases, and risk factors are collated, with updated articles depending on when this is done. This review is valuable for parents, doctors, and other healthcare providers of NICU babies and graduates so that they can note which factors are linked to ROP, and hence reduce or avoid them, and know when to screen these babies.

3.5 Strengths and Limitations of the Study

This review was able to adequately fulfil its study objectives by exploring each section in detail. However, a limitation is that more databases were not included. Another limitation is that for each risk factor, a thorough search of every article was not carried out due to the sheer volume this would entail, thus allowing for the possibility of articles being missed. Because non-English studies were excluded, other relevant articles may have also been missed. Quality checks were not performed on the articles reviewed.

4. Conclusions

Retinopathy of Prematurity (ROP) is a disease of immature retinal tissue. This review sought to explore a number of concepts, including which risk factors are suggestive of or unrelated to the development of ROP, what were the results of the oxygen clinical trials and how they translated into clinical practice, and what criteria are used when evaluating infants for ROP. To accomplish this goal, databases (PubMed, Medline, PubMed Central, and Google Scholar) were used to obtain relevant literary articles.

ROP is strongly associated with prematurity, low birth weight, and prolonged oxygen exposure. Evidence suggests that maternal diabetes, maternal smoking, prolonged rupture of membranes, lack of antenatal steroids, ethnicity, multiple births, low Apgar scores, and sepsis are risk factors for the development of ROP. Evidence also suggests that maternal hypertensive disorders, mode of birth, and chorioamionitis are not associated with ROP. Recommendations of oxygen saturations in the neonate include targets of 90-95% and 90-94%. Screening for ROP is dependent on birth weight, gestational age, and risk factors, with recommendations varying according to pediatric societies.

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Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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Ethical approval: Due to the nature of the research being a review article, the authors did not seek ethical approval.

Informed consent: Due to the nature of the research being a review article, the authors did not seek informed consent

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