Blindness Due to Retinopathy of Prematurity: A Literature Review

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Abstract

Background: Retinopathy of prematurity (ROP) is one of the main causes of blindness in children in developed countries such as the United States, Canada and Western Europe, as well as in developing countries such as India, China, Eastern Europe and Latin America.Purpose: This literature review aims to analyze the incidence, risk factors, and therapeutic management of blindness due to retinopathy of prematurity. Method: Writing a literature review was carried out by searching scientific journals via the Pubmed and Google Scholar databases. The search was carried out using the keywords "Blindness", "Retinopathy Prematurity", , "Risk Factor", "Incidence", "Neonates", "Newborn", "Clinical Study". Inclusion criteria include international published journals, journals published in the 2019-2023 period, as well as research journals related to studies on premature babies. Exclusion criteria included studies on test animals and premature infants with hydrocephalus or major congenital abnormalities. Results: 15 complete journal articles were taken which had been assessed according to the inclusion and exclusion criteria and were used for review. Conclusion: ROP is one of the main causes of blindness in children in developed and developing countries. Low gestational age, low birth weight, and administration of additional oxygen therapy are risk factors for the development of ROP. Laser photocoagulation therapy and anti-VEGF agents (Ranibizumab, Conbercept) are frequently used clinically in the treatment of ROP.

Keywords: Blindness, retinopathy of prematurity, premature infant, incidence, risk factors

1. Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative retinal disorder, occurring in premature infants in which there is abnormal growth of retinal blood vessels due to a complex interaction between vascular endothelial growth factor and insulin-like growth factor 1. The development of retinal blood vessels begins during 16 weeks of gestation and their distribution reaches the nasal retina during 36 weeks of gestation where their development is disrupted by premature birth and as a consequence may progress to retinopathy of prematurity. The incidence and severity of ROP increases with decreasing gestational age and birth weight .(Edgina et al., 2022). The most influential risk factors for ROP are prematurity and low birth weight. Other contributing factors include oxygen supplement therapy, bronchopulmonary dysplasia, maternal preeclampsia,

sepsis, low insulin-like growth factor-1 (IGF-1) levels, hyperglycaemia, nutritional deficiencies and blood transfusions (Yahya., 2020).

Retinopathy of prematurity is one of the leading causes of blindness in children in developed countries such as the United States, Canada, and Western Europe, as well as in developing countries such as India, China, Eastern Europe, and Latin America (Sanggig et al., 2023). In Indonesia, the incidence of ROP in 2016-2017 was 18% in babies born at < 28 weeks gestation, 7% in babies born at 28-32 weeks gestation, and 3.8% in babies born at > 32 weeks gestation. At Cipto Mangunkusumo Hospital, data on the incidence of ROP who came to the polyclinic in 2021 were 227 babies (Kemkes, 2023). This is because currently many premature babies can survive due to the availability of neonatal health services, but the quality of service is not ideal; screening is late or not done and management is late or the quality of therapy is inadequate (Sanggig et al., 2023).

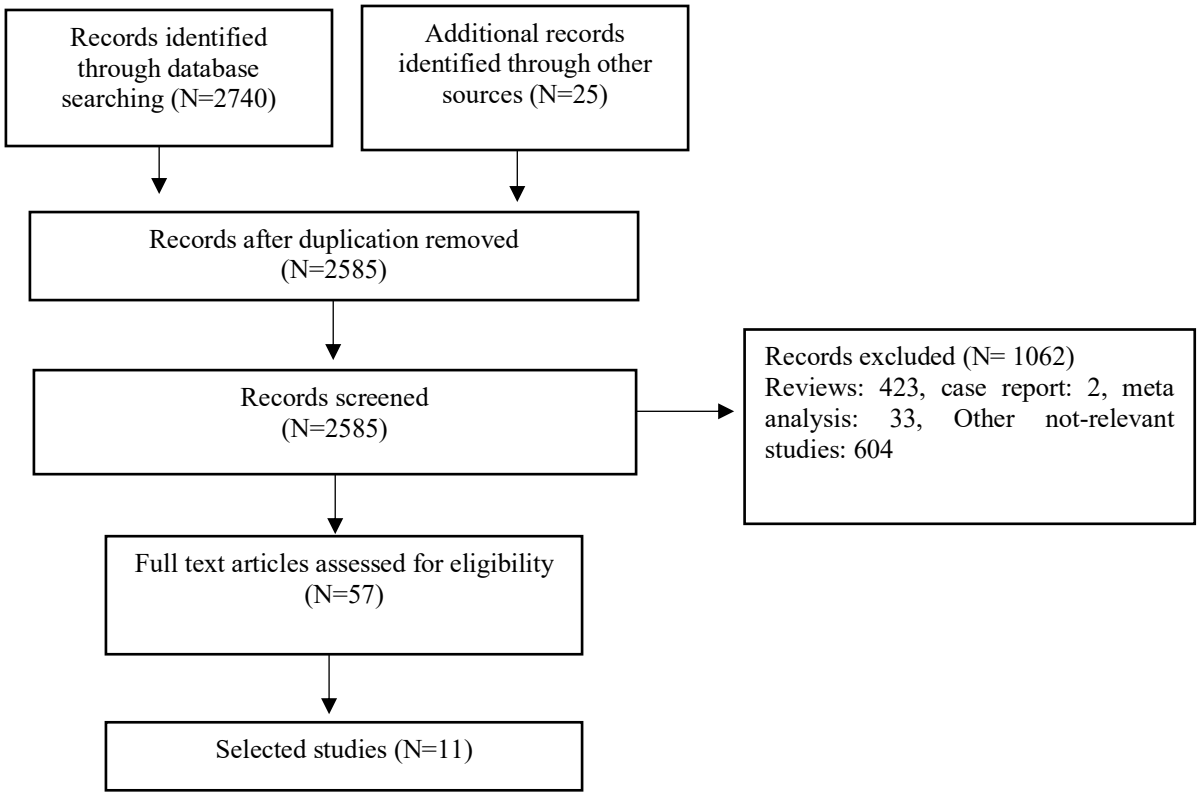
ROP begins with a delay in retinal vascularisation due to relative hyperoxia and continues with the vasoproliferation phase (Yahya, 2020) The retina is the innermost layer of the eyeball that is useful for receiving light and passing it on to the brain so that we can see clearly. Disorders that occur in the retina can cause visual impairment to blindness. So, any visual impairment that occurs must be treated quickly and accurately. Management can be carried out in cases of ROP experienced by premature babies, including cryotherapy, laser photocoagulation, anti-VEGF drugs, and vitrectomy surgery in advanced stages (Sanggig et al., 2023). Although laser photocoagulation can avoid blindness, this treatment modality still leaves vision problems. The study of alternative therapies such as anti-VEGF, IGF-1, and others, opens up the possibility of safer, more effective, and affordable treatments for ROP in the future (Yahya, 2020).

This literature review aims to analyse the incidence, risk factors, and therapeutic management of blindness due to retinopathy of prematurity.

2. Method

The literature review was conducted by searching scientific journals through Pubmed and Google Scholar databases. The search was conducted using the keywords "Blindness", "Retinopathy Prematurity", "Drug Therapy", "Risk Factor", "Incidence", "Neonates", "Newborn", "Clinical Study". Inclusion criteria included international journal publications, journals published in the range of 2019-2023, and research journals related to studies on premature infants. Exclusion criteria included animal studies and premature infants with hydrocephalus or major congenital abnormalities. Based on the search results through Google Scholar and Pubmed of 6,414 journal articles, 15 complete journal articles that have been assessed according to the inclusion and exclusion criteria were taken and used for review.

Study Selection



3. Result

A literature search through the database obtained 11 articles that will be reviewed in this study. A summary of the articles reviewed in this study can be seen in Table 1.

Table 1. Summary of Articles Reviewed

	Location	Recruitment Period	Member of Participants	ROP Incidence	Incidence of Blindness due to ROP	Risk Factors
Asferaw et al,. 2020	Ethiopia	2016 – 2019	93 infants	35.5%	22.6% (vision threatening)	Birthweight (BW), gestational age (GA), postnatal age at first examination, and oxygen exposure.
Trzcionkowska et al., 2023	Neterhlands	2009 – 2018	53 infants (visual impairment)	-	2.02 per 100,000 births	Gestational age (GA), oxygen saturation
Onakoya et al., 2021	Nigeria	2016 – 2020	18 blind infants	-	-	Gestational age, birth weight
Moin et al., 2021	Pakistan	2017 – 2019	51 infants (ROP stage 4 and 5)	-	76.4% blind and 23.6% visual impairment	Gestational age (GA), birth weight (BW), supplemental oxygen, blood transfusion, history of sepsis
Herrod et al., 2022	Sub-Saharan Africa	2019	455 ophthalmologists	-	10%	-
Dalai et al., 2019	India	2016 – 2018	328 infants	29.57%	No data (additional data : 71.13% regression, 18.55% laser, 8.24% laser and intravitreal anti vegf, 2.06% surgery)	Birth weight, gestational age, oxygen therapy, apnea attacks, blood transfusion, Respiratory Distress Syndrome (RDS), maternal anemia, and gestational diabetes mellitus (GDM)
Srinivasa et al., 2019	India	No data	95 infants	15.8%	No data	Gestational age, birth weight, and oxygen therapy
Ndyabawe et al., 2023	Uganda	2022	331 infants	5.7%	No data (additional data : ROP stage1, 10.5%; stage 2, 42.1 %; stage 3, 15.8%; stage 4, 10.5%; stage 5, 5.3%; A-ROP 15.8%)	Birth weight, exclusive breastfeeding, and oxygen therapy
Sheth et al., 2023	India	2021 – 2022	500 infants	8% (ROP incidence)	No data (additional data : ROP stage 2, 2%;	Birth weight, prematurity, respiratory distress syndrome, light, exchange

				25% (AP-ROP incidence among ROP infants)	stage 3, 1%, stage 4, 2%, AP-ROP 2%)	transfusion and age of oxygen therapy are given
Akkawi et al., 2019	Palestine	2016	115 infants	23.5% ROP 11.3% severe ROP	No data	Low gestational age, oxygen supplementation, and bilirubin levels
AlBalawi et al., 2020	Saudi Arabia	2016 – 2018	108 infants	33.3%	No data (additional data : retinal detachment 2.7%, plus disease 2.7%, intervention needed 8.3%)	Birth weight <1000g

4. Discussion

Retinopathy of prematurity (ROP) is a progressive proliferative disorder of the retinal blood vessels of premature infants that can lead to retinal detachment and blindness (Yahya, 2020). Globally, the incidence of ROP occurs in various countries with different incidence rates. Currently, ROP is one of the leading causes of childhood blindness in developed countries such as the United States, Canada, and Western Europe, as well as in developing countries such as India, China, Eastern Europe, and Latin America (Sanggig et al., 2023). The incidence of ROP varies depending on severity, extension, location/zone, presence of enlarged retinal blood vessels/plus disease, and presence of aggressive posterior ROP (APROP) (Yahya, 2020).

A survey of 132 out of 455 ophthalmologists treating ROP cases in 16 sub-Saharan African countries reported that they examined at least one child blinded by ROP during the past 5 years. The incidence of ROP was estimated to be the cause of blindness for 10% of all blind children seen by paediatric retinal surgeons during 2019. Most respondents stated that birth weight and gestational age were the main risk factors as screening criteria for ROP and anti-VEGF was used as the most common modality (Lambert et al., 2022).

Pakistan is now facing its third epidemic of ROP blindness, even in infants receiving neonatal care in small towns. The initial screening criteria for detecting ROP is to check gestational age (GA) ⩽35 weeks and birth weight ⩽2000g. A retrospective study looking at the medical records of premature infants with ROP found 51 children at an average age of 9.7 months. The mean gestational age (GA) was 28.84 weeks, and the mean birth weight (BW) was 1229 grams. Four children (7.8%) had GA >31 weeks plus BW >1501 grams. 40 (76.4%) children were blind and 11 (23.6%) were visually impaired (Mian et al., 2021).

In Nigeria, about 90% of infants who develop ROP-related blindness do not undergo ROP screening. The 18 infants who were screened for ROP blindness showed that they were at a mean gestational age of 28.4 ± 2.2 weeks. The mean birth weight was 1173.7 ± 317.9 grams. Six (33.3%) babies were born in hospital between 28 and 32 weeks. Sixteen (88.9%) children had never undergone ROP examination. Fifteen (83.3%) were blind in both eyes. Six (33.3%) had stage IVb and 12 (66.7%) had stage V (D.S.A et al., 2021). In the Netherlands, the incidence of visual impairment in the form of blindness due to ROP was 2.02 per 100,000 births (2000-2009: 1.84, p = 0.643). Compared to the previous period (1975-2000), a significant decrease was observed (Schalij-Delfos et al., 2023). Another study explained that 39 out of 93 (35.5%) infants with retinopathy of prematurity in Ethiopia, 21 (22.6%) were sight-threatening (blindness) and two with aggressive posterior retinopathy of prematurity, or stage 4/5 (n=12). The mean gestational age of these 33 infants was

29.1 weeks; mean birth weight was 1185.6g. Treatment ranged from anti-VEGF injection; laser; vitrectomy; and lensectomy, depending on the severity (Kerie et al., 2020).

Based on its severity, ROP is divided into 5 stages, namely stage 0; 1; 2; 3; 4; and 5. In stage 0, the retinal blood vessels are immature with no pathological changes. In stage 1, there is a borderline between the vascularised and unvascularised retina. Stage 2 shows a borderline with height, width and volume (ridge); there may be "popcorn", which are small isolated tufts of neovascular tissue located on the surface of the retina. In stage 3, ridge with extraretinal fibrovascular proliferation; divided into mild, moderate, or severe, graded by the amount of proliferative tissue present. In stage 4, there is partial retinal detachment. Ablatio may occur outside the fovea (A) or involve the fovea (B). In stage 5, total retinal detachment with a funnel configuration. APROP is a severe form of ROP. APROP is often referred to by other terms such as type II ROP, rush disease, or fulminate ROP. In this type of ROP, severe dilatation of the blood vessels and meandering can be found. The extent of APROP is usually limited to zone I or II. Other characteristics of APROP are the formation of shunts between intraretinal blood vessels, neovascularisation, bleeding, and rapid deterioration to retinal detachment (Yahya, 2020).

The increase in the number of preterm infants who survive due to advances in the availability of neonatal healthcare in the NICU has increased the number of infants who are likely to develop retinopathy of prematurity. From the review of the 11 journals above, it can be seen that low gestational age and low birth weight are the highest risk factors for blindness due to ROP in premature infants. Srinivasa et al. (2019) in their study explained the significant association of retinopathy of prematurity with gestational age and low birth weight. Prevention of ROP begins with optimal prenatal care of prematurity (Srinivasa, 2019). The process of vascularisation of the healthy fetal retina begins around 16 weeks of gestation progressing from the discus opticus in a peripheral direction. Vascularisation will reach the nasal retina at 36 weeks gestation and temporal at 40 weeks gestation. So that in premature babies born before 28 weeks, the development of the retina is not perfect and is at risk of ROP (Yahya, 2020). Retinopathy of prematurity is also common in infants with a birth weight of <1500 grams (Ndyabawe et al., 2023). This may be because the gestational age at birth is too small so that the birth weight is too small and lower than normal babies, so that various body functions are not fully developed, especially the development of immature retina, and in premature babies themselves can cause retinal damage (Y. Zhang et al., 2022).

The higher prevalence of ROP and severe ROP in the study conducted by Bastola (2023) can largely be attributed to supplemental oxygen therapy (Agrawal et al., 2023). Oxygen therapy contributes to ROP by affecting retinal vascularisation through the regulation of vascular endothelial growth factor (Ndyabawe et al., 2023). Conservative use of supplemental oxygen is a risk factor for developing ROP in premature infants in Palestine ($P < 0.0010$) either by non-mechanical "C-pap or nasal cannula" ($P < 0.0010$) or mechanical ventilation methods ($P = 0.0070$) (Akkawi et al., 2019).

Gestational diabetes is one of the highest risk factors for ROP in one of the hospitals in China. In mothers with gestational diabetes mellitus, due to prolonged hyperglycaemia, the risk of vascular lesions increases, and blood pressure levels rise further, affecting fetal oxygen supply. This inhibits foetal growth and development, including the retina of the foetus.(Zhang et al., 2022) . Infants who are not exclusively breastfed play a role in the development of ROP because the protective role of breast milk by long-chain polyunsaturated fatty acids in counteracting oxygen free radicals is very important in protecting infants from ROP (Ndyabawe et al., 2023). Other risk factors for ROP are anaemia and blood transfusion (Zarei et al., 2019) (AlBalawi et al., 2020) (Shalaby et al., 2021).

Several conditions have also been reported as risk factors for the onset of ROP. However, since not many other researchers have also assessed the same factors, their role as risk factors is not so clear. These risk factors for ROP include respiratory distress syndrome (Pandey et al., 2023), elevated bilirubin levels (Akkawi

et al., 2019, septicemia (Thachil et al., 2019), late-onset sepsis (Tamayo et al., 2022), and bronchopulmonary dysplasia (Shalaby et al., 2021).

5. Conclusion

Retinopathy of prematurity (ROP) is a progressive proliferative disorder of the retinal blood vessels of premature infants that can lead to retinal detachment and blindness. Currently, ROP is one of the leading causes of childhood blindness in developed countries as well as in developing countries. Low gestational age, low birth weight, supplemental oxygen therapy, anaemia, blood transfusion, not exclusively breastfed, respiratory distress, elevated bilirubin levels, late-onset sepsis, septicemia, gestational diabetes and bronchopulmonary dysplasia are risk factors for the development of ROP.

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