Review Article

A review on retinopathy of prematurity

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is a leading cause of childhood blindness. It predominantly affects preterm infants with very low birth weights or extreme prematurity. Aberrant retinal vascular development, driven by hyperoxia and hypoxia-induced neovascularization, is central to ROP pathogenesis. This review explores the relationship between maternal health and ROP, evaluates current prevention strategies, assesses innovations in diagnostic and screening technologies, reviews contemporary treatments, and identifies future research directions.

Methods: A literature review was conducted in the PubMed / MEDLINE, Scopus, Web of Science, and Google Scholar databases using related keywords, i.e., "retinopathy of prematurity," "retinal development," "pathophysiology," "vascular growth," "complications," "visual outcomes," "maternal health factors," "obstetrics," "preeclampsia," "risk factors," "preterm birth," "corticosteroids," "oxygen management," "treatment strategies," "laser therapy," "anti-VEGF agents," "surgical approaches", and "artificial intelligence (AI)" and targeting English studies published in the last 20 years. Additionally, the references from the selected articles were manually reviewed. Clinical trials, meta-analyses, systematic reviews, case–control studies, case series, narrative reviews, pilot studies, and relevant animal studies were included.

Results: Maternal factors, such as diabetes, smoking, and preeclampsia, along with neonatal factors, such as low gestational age and extreme prematurity, are critical contributors to ROP. Key preventative strategies to reduce the risk of ROP and improve neonatal outcomes include: 1. prenatal care involves screening and managing maternal conditions, providing maternal education, and administering antenatal corticosteroids. 2. Neonatal care encompasses nutritional support, supplementation with essential fatty acids, and regulated oxygen administration. By focusing on these strategies, we can enhance the health of newborns at risk for ROP. Advances in screening, including artificial intelligence (AI)-assisted diagnostics and advanced imaging, are improving early detection. Treatment modalities such as laser photocoagulation, cryotherapy, and anti-vascular endothelial growth factor therapies have shown promise but pose challenges, including recurrence risk and systemic side effects.

Conclusions: ROP continues to pose a major threat to the vision of preterm infants, particularly in regions with limited healthcare resources. Addressing ROP requires multidisciplinary team approaches that integrate obstetric and neonatal care. Preventative strategies, including prenatal care optimization, oxygen management, and nutritional support, are essential. Future efforts should focus on integrating emerging technologies and recent findings to ensure global relevance and currency.

KEYWORDS

obstetrics department, ophthalmology, health, maternal, prematurity retinopathy, low-birth-weight infant, very-low-birth-weight infant, gestational ages, laser therapies, photocoagulation, cryotherapies, vascular endothelial growth factor

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INTRODUCTION

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness, predominantly affecting preterm infants who require intensive neonatal care [1]. This condition arises from aberrant development of retinal vasculature, with preterm infants of very low birth weight or extremely early gestational age being most at risk [1]. Globally, each year, approximately 20 000 preterm infants experience blindness due to ROP, with over half of these cases occurring in middle-income countries, where healthcare infrastructure and technological advancements often lag behind those of high-income nations [2]. The pathophysiology of ROP is biphasic: the initial phase is characterized by inhibited retinal vascular development due to hyperoxia, which is followed by a phase of abnormal neovascularization prompted by hypoxia and elevated levels of intraocular growth factors, such as vascular endothelial growth factor (VEGF) [3]. This pathological signaling is further exacerbated by factors such as oxidative stress, inflammation, and compromised nutritional support, all of which contribute to the progression of ROP [4].

While advancements in neonatal care have significantly improved the survival rates of preterm infants, progress in ROP screening and management has lagged behind these achievements. In middle-income nations, where a substantial number of preterm infants are born annually, the ROP incidence continues to rise due to inadequate screening programs [5]. Given that ROP is associated with an increased risk of other ocular disorders, such as myopia, strabismus, glaucoma, and retinal detachment, early detection of at-risk neonates and timely interventions are essential [6, 7].

Guidelines for screening vary globally, and establishment of unified international standards remains a challenge, given the diverse healthcare resources and neonatal intensive care capabilities in different countries [8, 9]. A thorough understanding of ROP risk factors is imperative for developing effective prevention and treatment strategies [10].

In this review, we provide an overview of recent advancements in understanding the etiology, pathogenesis, diagnostic approaches, interventions, and outcomes of ROP. We explore the intersection of maternal health and ROP development, evaluate current preventive strategies, discuss innovations in diagnostic and screening technologies, review contemporary management practices, and highlight future research directions and opportunities for innovation in ROP care.

METHODS

A literature search was conducted using related keywords, i.e., “retinopathy of prematurity,” “retinal development,” “pathophysiology,” “vascular growth,” “complications,” “visual outcomes,” “maternal health factors,” “obstetrics,” “preeclampsia,” “risk factors,” “preterm birth,” “corticosteroids,” “oxygen management,” “treatment strategies,” “laser therapy,” “anti-VEGF agents,” “surgical approaches”, and “artificial intelligence (AI)”.

The literature search was conducted in four major electronic databases: PubMed / MEDLINE, Scopus, Web of Science, and Google Scholar. The search interval spanned from January 1, 2004, to December 31, 2024, and included studies published in English. References cited in the retrieved articles were manually reviewed to identify additional relevant studies not captured during the initial database search. This process ensured selection of English literature for inclusion in the review. Eligibility criteria for study inclusion were defined to encompass a wide range of research designs (clinical trials, meta-analyses, systematic reviews, case-control studies, case series, narrative reviews, pilot studies, and letters to the editor), provided that they offered meaningful insights into ROP. Human studies were prioritized, focusing on clinical data and patient outcomes. However, animal studies were also reviewed where they contributed critical insights into the mechanisms of ROP or informed treatment approaches, particularly in areas where human data were unavailable.

To ensure methodological rigor, two researchers (S.K. and S.A.S.) conducted the data collection process. Each researcher independently screened the titles and abstracts of the retrieved studies to identify eligible articles. Discrepancies were resolved through discussion, and a third reviewer (P.R.) was consulted in cases where consensus could not be reached. Duplicate studies were excluded during the screening process, and irrelevant articles that did not meet the eligibility criteria were removed.

RESULTS and DISCUSSION

Pathophysiology and Associated Complications

The pathogenesis of ROP remains incompletely understood [11]; however, several factors are believed to contribute to the risk of ROP development. These include retinal vessel immaturity, oxygen therapy, fluctuations in oxygenation, intermittent hypoxia, oxidative stress and inflammatory cytokines, inflammation, and dysregulation of several factors, primarily vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) [12].

ROP occurs in two distinct phases: phases 1 and 2 [13]. Most preterm infants weighing less than 1.5 kg require supplemental oxygen for respiratory support at birth due to their underdeveloped cardiopulmonary systems [13]. In phase 1, from birth to roughly 30 weeks' postmenstrual age, relative hyperoxia exists (due to supplemental oxygen therapy, insufficient nutrition, and maternal growth hormones), as compared to the typical intrauterine environment [14]. This relative hyperoxia results in reduced retinal oxygen demand and subsequently interrupts retinal blood vessel growth, primarily due to decreased levels of growth factors, such as VEGF and IGF-1 [13].

When the infant is transitioned from respiratory support to room air, insufficient oxygenation and increased metabolic demands can lead to hypoxia [13]. This condition subsequently stimulates the release of growth factors, primarily VEGF and IGF-1 [13]. During this phase, low IGF-1 levels progressively increase to levels sufficient to activate VEGF pathways [13]. This leads to abnormal retinal vascularization and proliferation, which along with oxidative damage to endothelial cells results in capillary obliteration and decreased perfusion [15]. Consequently, apoptosis of vascular endothelial cells results in the cessation of normal vessel development and elimination of the existing immature vasculature, ultimately leading to retinal avascularity [16]. Subsequently, this process caused formation of visible flat (stage 1 ROP) or raised (stage 2 ROP) whitish tissue, which is termed the demarcation line and visible ridge, respectively [17]. Restoring IGF-1 levels to normal through physiological replacement while the baby is still in the uterus may help prevent ROP [18].

As the disease progresses, vascular growth proliferates into the vitreous cavity (stage 3 ROP) [19]. If aberrant neovascularization advances through the retina into the vitreous, and if these fragile neovascular tufts remain untreated, blood and fluid leaks will disseminate throughout the retina [20]. This results in scar development (cicatrix) and traction on the retina, subsequently causing sub-total (stage 4 ROP) or total (stage 5 ROP) retinal detachment, macular dragging, and eventually, irreversible blindness and visual loss [16, 20, 21].

Besides oxygen, various inflammatory proteins and biomarkers, including elevated interleukin-6 (IL-6) levels [22], lowered lymphocyte counts, reduced lymphocyte-to-monocyte ratios (LMR), and higher neutrophil-to-lymphocyte ratios (NLR) [23] noted early in life among extremely preterm infants, have been linked to an increased risk of ROP [24]. A recent study has indicated that increased levels of the pro-inflammatory cytokine IL-6 exhibited a negative correlation with circulating IGF-I levels in preterm newborns and were linked to ROP onset. Notably, babies who subsequently required therapy for ROP had elevated IL-6 levels in the first few weeks post-birth, indicating that inflammation may play a role in ROP pathophysiology, possibly via its interaction with IGF-I [25]. Another study revealed that elevated levels of proinflammatory proteins, such as TNF-alpha, IL-6, and myeloperoxidase (MPO), were linked to a higher risk of ROP. Conversely, neurotrophic and angiogenic proteins, such as brain-derived neurotrophic factor (BDNF), neutroponin-4 (NT-4), and angiopoietin-1 (ANG-1) had protective effects against ROP, particularly in the absence of increased inflammation markers, indicating the complex etiology of ROP [26]. Enhanced complement activation in the retina/vitreous stimulates the microglia, resulting in inflammation. A quantitative evaluation of inflammatory markers in tears may aid in the early prediction of ROP development and facilitate timely disease therapy, therefore minimizing visual impairment [27].

Maternal Risk Factors for ROP

To manage ROP better, we need to study the disease as an event affected by various factors occurring before, during, and after birth. Numerous studies have identified neonatal risk factors associated with ROP, including low gestational age (particularly birth at 28 weeks or less of gestation [28]), low birth weight (LBW), prolonged oxygen exposure, lower Apgar score in the first and fifth minute [29], sepsis, interventricular hemorrhage [30], patent ductus arteriosus [31], and invasive ventilator duration [31, 32].

Studies have indicated a correlation between ROP and maternal risk factors, such as maternal age, smoking, and mode of delivery [31-33]. A higher incidence of any stage of ROP in infants born through vaginal delivery than in those born by cesarean section was observed [30, 33]. Recent meta-analyses indicated that ROP risk is associated with chorioamnionitis [34] and pregnancies related to induced fertility [28]. One significant risk factor for the occurrence of severe ROP in premature children, delivered before 32 weeks of gestation, is maternal smoking during pregnancy [32]. Moreover, maternal diabetes was shown to correlate with ROP, and the strength of this correlation escalates with the severity of ROP [35].

Additionally, various studies have identified other maternal risk factors associated with ROP, including advanced maternal age (particularly age over 30 years) [36], lower socioeconomic status [37], placenta dysfunction [38], and

maternal systemic inflammation [39]. Furthermore, multiple pregnancies generally lead to infants having a lower gestational age and birth weight, both of which are critical risk factors for the onset of ROP [40].

Preeclampsia shows a controversial association with ROP: some studies have indicated an inverse correlation [41], while others have identified an elevated risk of ROP [42, 43]. Maternal diseases linked to placental circulation abnormalities resulting in fetal hypoxia have also garnered attention. A comprehensive investigation revealed an increased incidence of ROP in newborns whose mothers had difficulties during pregnancy, namely second or third-trimester hemorrhaging and premature ruptured fetal membranes [44], with or without infection [30]. Maternal iron insufficiency is a risk factor for ROP onset, and maternal iron supplementation during gestation may reduce the likelihood of developing this condition [45].

Strategies for Prevention

Table 1 outlines key preventative strategies aimed at reducing the risk of ROP and improving neonatal outcomes as described in literature [14, 46-54].

Advances in Screening and Diagnostic Techniques

Screening guidelines: Given that ROP can possibly jeopardize the future sight of an infant, screening for this condition is necessary [55]. First, it is essential to identify which infants should be screened: all infants with a birth weight of ≤ 1500 grams or a gestational age of ≤ 30 weeks must be screened for ROP [56]. Furthermore, among infants with a birth weight between 1500 and 2000 grams or a gestational age >30 weeks, those with additional risk factors, should be screened [56]. These risk factors are the following: hypotension requiring inotropic support, prolonged oxygen supplementation, and oxygen supplementation without proper saturation monitoring [56]. The screening examination should be performed by an ophthalmologist experienced in examining preterm infants for ROP. The common methods of screening infants include binocular indirect ophthalmoscopy and pupillary dilation [8, 57].

Diagnostic tools: The diagnosis of ROP relies on several imaging tools to visualize the retina and assess disease severity; the gold standard for ROP diagnosis, as mentioned above, is the indirect ophthalmoscopic examination performed by an experienced ophthalmologist during screening for ROP [8, 57]. An ophthalmologist should use a binocular indirect ophthalmoscope with a condensing lens to examine the retina, often accompanied by scleral depression, to view the peripheral retina. This provides a wide field of view and is essential for accurate staging and detection of ROP. However, the procedure requires significant expertise and can be uncomfortable for infants [58].

Wide-angle contact fundus cameras are another important tool [59]. These cameras capture high-resolution images of the retina, including the peripheral areas, and are useful for remote diagnosis or follow-up comparisons. The images can be reviewed by ophthalmologists to obtain a second opinion or to monitor disease progression. While effective, this method involves contact with the infant's eye and requires skilled personnel to operate the camera [59].

Table 1. Preventative strategies for retinopathy of prematurity (ROP)

Time Frame	Preventative strategies	Details
Prenatal care	**Screening and management of maternal conditions.**	Early identification and management of conditions such as gestational diabetes and hypertension reduce the risk of preterm labor and ROP [46, 47].
	Maternal education.	Educating mothers on preterm labor signs enables early medical intervention, lowering preterm birth rates [48].
	Antenatal corticosteroids.	Administration of corticosteroids enhances fetal lung maturity and reduces ROP severity [49].
Neonatal care	**Nutritional support.**	Breast milk provides bioactive factors that lower ROP risk. Human milk significantly reduces ROP incidence in extremely premature infants [50, 51].
	Essential fatty acid supplementation.	Preterm infants are often deficient in docosahexaenoic acid and arachidonic acid; supplementation with these fatty acids reduces severe ROP incidence [52, 53].
Oxygen therapy	**Regulated oxygen administrations.**	Oxygen saturation should be maintained at 90–95% to balance sufficient oxygen supply and minimize ROP risk [14, 54].

Another tool that is primarily used for research purposes, is optical coherence tomography (OCT). OCT is a non-invasive imaging method that provides high-resolution cross-sectional images of the retina. This technique provides the clinician with valuable data on retinal thickness and structure that can be used in monitoring ROP progression [60]. These diagnostic tools, combined with the International Classification of Retinopathy of Prematurity [61], enable accurate diagnosis and staging of ROP, ensuring timely intervention to prevent severe visual impairment.

***Role of artificial intelligence*:** Diagnostic performance of AI-based methods has been investigated for various anterior segment ocular entities [62]. Recently, AI has demonstrated the potential to enhance ROP screening and diagnosis processes, helping to address limitations in clinical assessments that are subjective and dependent on the availability of practitioners who are trained to examine and treat infants [63]. Manual feature extraction techniques have been employed in historical machine-learning methodologies, whereby parameters of retinal vessel dilation and tortuosity were calculated; however, these methods were time-consuming and not sufficiently accurate for clinical workflows [64]. The introduction of deep learning and, in particular, convolutional neural networks (CNN), has changed this situation markedly [65]. Deep-learning methods have rapidly developed and can learn relevant features from the images of the retina automatically, without any human guidance, and have shown the capability for more accurate and efficient diagnosis [66].

The first fully automated system for detecting ROP using deep learning was introduced in 2016 by Worrall et al. [64]. Their CNN-based model demonstrated the ability to distinguish between ROP-affected and healthy cases with accuracy comparable to that of human graders [64]. Other examples are the DeepROP and the i-ROP systems [67, 68]. The DeepROP system [67], trains two CNN to extract ROP features and to grade disease severity, respectively, while the i-ROP Deep Learning (i-ROP DL) system [68] uses a U-net CNN for vessel segmentation and classification, achieving performance on par with that of expert ophthalmologists [67, 68]. Such AI tools improve diagnostic accuracy and provide objective, quantitative measures of disease severity, which may alleviate interobserver variability [63].

Despite these advances, challenges remain in translating AI technologies from research and discovery to clinical implementation. This is of great relevance for generalizability, since AI models trained on a particular dataset might not be able to reproduce an acceptable performance when challenged with images acquired from different cameras, populations, or with questionably high or low image quality [64]. Additionally, incorporating AI technologies with existing clinical processes would require overcoming practical barriers with respect to the cost of imaging equipment and standardizing of imaging protocols [63]. AI-assisted ROP screening could markedly reduce the number of patients to be evaluated by clinicians through automated detection of severe cases, allowing ophthalmologists to concentrate on patients at the highest risk [69]. Additionally, AI can help in obtaining retinal images for examination in real time, which could yield clearer retinal images and make examinations easier [70]. With ongoing AI development, the future of ROP care, integrated with automated systems, holds promise for decreasing the prevalence of preventable blindness, particularly in resource-constrained settings where access to specialized care is limited [71]. In this respect, achieving this goal requires collaboration between researchers, clinicians, and regulatory bodies to ensure the effectiveness and accessibility of these technologies.

Current Approaches to Management

ROP can be categorized based on treatment requirements [72]. The primary objective of ROP treatment is to prevent abnormal blood vessel growth and retinal detachment, diminish the occurrence of blindness, and enhance visual outcomes [72]. Interventions for ROP can significantly improve visual results and prevent blindness [73]. Management may include pharmaceutical treatments, such as intravitreal injections of anti-VEGF, as well as non-pharmacological interventions, including peripheral retinal ablation with either cryotherapy or laser photocoagulation therapy, vitrectomy, and scleral buckling [13, 20].

The conventional treatment for ROP in the past was cryotherapy, which employs a probe chilled to subzero temperatures, and which necessitates general anesthesia. Cryotherapy is associated with increased inflammation and requires more analgesia than laser treatment [16]. Cryotherapy has not been widely used to treat ROP since the late 1980s because it induces more inflammation than laser therapy [74]. Laser photocoagulation of the avascular retina is performed using diode or argon lasers [74]. Laser therapy demonstrates superior ocular outcomes and improved long-term structural and visual results compared to cryotherapy [75]. It is applicable in less-severe ROP, reducing adverse outcomes in approximately 10% of cases and achieving a disease regression rate of 71–100% post-treatment [76, 77]. Both cryotherapy and laser therapy effectively ablate a significant proportion of peripheral retinal cells responsible for

VEGF production; however, these treatments do not fully lower the VEGF levels [20].

Numerous studies have demonstrated a success rate exceeding 90% after laser therapy, establishing it as a primary treatment option for ROP [78, 79]. Laser therapy minimizes systemic side effects and decreases the occurrence of recurrent or persistent avascular zones [78]. Delayed laser therapy and more advanced disease at the start of treatment could significantly reduce the treatment success rate [80]. Complications that may arise following laser therapy include new-onset hemorrhage, anterior segment ischemia, cataract [81], corneal burns, myopia, iris burns, and vitreous hemorrhage [20, 77]. Laser therapy requires skilled practitioners [73], demands an extended duration [73], and may correlate with increased levels of myopia, resulting in poor structural outcomes and loss of the peripheral visual field [73, 76, 82, 83]. Consequently, interventions with minimal side effects and more safety are under investigation.

In cases where ROP progresses to end-stage retinal detachment, classified as stage 4 or 5, surgical interventions, such as scleral buckling or vitrectomy may be employed to alleviate vitreoretinal traction and can reattach the retina to preserve vision and prevent blindness [74]. Research findings regarding the impact of surgery on retinopathy exhibit significant variability across different studies [84, 85]. The Early Treatment for Retinopathy of Prematurity (ETROP) Study indicated that reattachment was achieved with the scleral buckle technique in 67% of cases, whereas reattachment was achieved in only 33% by vitrectomy [84]. However, several other studies on vitrectomy for stage 4 ROP have reported favorable reattachment rates, from 80% to over 90% [85-88].

In recent decades, intravitreal anti-VEGF agents have been recognized as a beneficial treatment option for managing ROP in premature infants. Anti-VEGF agents inhibit elevated VEGF levels in the retina and vitreous while addressing the abnormal vascularization associated with ROP [20]. Bevacizumab [89], ranibizumab [89], pegaptanib [89], and aflibercept [89] are among the most common anti-VEGF agents.

The recombinant humanized antibody bevacizumab is more effective than laser treatment in stage 3 ROP with plus disease in zone I [90]. In contrast to laser treatment, intravitreal bevacizumab has been shown to decrease ROP recurrence and poor ocular outcomes, including macular dragging, in infants [90]. In the follow-up Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) clinical study, bevacizumab reduced high myopia more than laser therapy [74, 91].

Ranibizumab is a recombinant, humanized monoclonal IgG1 anti-VEGF antibody that exhibits stronger VEGF affinity and fewer systemic effects compared to bevacizumab [92]. A recent study found that high-dose ranibizumab had a greater treatment success rate and fewer ocular side effects than those of laser therapy [93]. ROP therapy using pegaptanib sodium, an RNA aptamer targeting VEGF-165, is being investigated One study found that pegaptanib combined with laser treatment improved ocular outcomes in stage 3 ROP and led to more ROP patients experiencing regression compared to laser therapy alone [94]. Laser treatment was associated with a greater ROP recurrence rate than that of the combined therapy [74]. The most effective anti-VEGF agent currently available is the novel drug aflibercept. Multiple trials have shown that intravitreal aflibercept is safe and beneficial for managing type 1 ROP [95, 96]. In one trial, ranibizumab had a greater ROP recurrence rate than that of aflibercept [97]. Conbercept is a new anti-VEGF drug with a 50-fold greater binding affinity than bevacizumab and a long vitreous half-life. It inhibits VEGF-A and VEGF-B isoforms, producing substantial anti-angiogenic effects [98]. A study has indicated that 0.15 mg intravitreal conbercept is effective for stage 2 or 3 ROP with plus disease in zone II, with no adverse ocular outcomes observed during the follow-up period [99].

A recent systematic review indicated that anti-VEGF therapy effects on serum VEGF levels last up to 2 months, potentially influencing neurodevelopmental outcomes [100]. While anti-VEGF treatment is beneficial for ROP, a systematic review has shown that it carries a higher risk of recurrence compared to laser photocoagulation [101]. Conbercept showed greater effectiveness in reducing the risk of recurrence and prolonging the retreatment interval than ranibizumab [101]. No significant difference in recurrence rates was observed between bevacizumab and ranibizumab [101]. Recurrences were observed at a significantly later time with anti-VEGF therapy in comparison to laser photocoagulation. The retreatment rates for bevacizumab and laser photocoagulation were similar [101].

Several studies have claimed that anti-VEGF drugs are more effective than laser treatment in less severe cases [102, 103]. They increase vascularization in the peripheral avascular retina, which reduces the likelihood of further reactivation and improves the visual field. Additionally, these drugs are associated with a decrease in myopia [73, 104]. However, a meta-analysis revealed a treatment success rate of 89% for laser therapy, whereas the success rates for different anti-VEGF agents varied between 74% and 87% [93]. Other medications targeting ROP formation and

progression, including erythropoietin (EPO) and IGF-1, are being studied alongside VEGF inhibitors. Recombinant human EPO was tested for preventing ROP in preterm newborns but did not significantly reduce ROP incidence or severity [77, 105].

Final Message

Pregnancy induces a series of significant physiological transformations within the ocular system, influencing both maternal and neonatal vision [1, 106, 107]. Consequently, the prevention and treatment of ROP could be significantly enhanced by collaboration in multidisciplinary teams, including primary eye care providers, ophthalmologists, ophthalmic nurses, neonatologists, and gynecologists, ensuring comprehensive care for both mother and infant [108-111].

A key strength of this review is the inclusion of emerging innovations, such as AI, which hold the potential to enhance ROP care. Furthermore, the integration of findings from both human and animal studies in the last two decades facilitates a wider and deeper understanding of ROP pathogenesis, supporting treatment development. The literature search process in this study, conducted by two independent researchers, minimized bias and strengthened the rigor of the review. Nevertheless, some limitations must be acknowledged. First, the review included only studies published in English, potentially excluding relevant research in other languages. Second, despite the extensive search interval, recent or unpublished findings may have been missed. Lastly, the review primarily addressed maternal and neonatal health in middle- and high-income countries, with a limited focus on low-income settings where the ROP incidence is increasing, but where research remains scarce. Future research should aim to include studies published in multiple languages and from diverse geographical regions to capture a more global perspective. Emphasis should be placed on addressing the research gaps in low-income countries [112]. Additionally, incorporating emerging technologies and ensuring that both published and unpublished recent findings are integrated will help to maintain the currency and relevance of future research.

CONCLUSIONS

ROP continues to pose a major threat to the vision of preterm infants, particularly in regions with limited healthcare resources. This condition results from disrupted retinal vascular development, influenced by multiple maternal and neonatal factors, including systemic inflammation, oxygen management, and nutritional deficiencies. Despite progress in ensuring neonatal survival, advancements in ROP prevention and management remain insufficient. Enhancing prenatal care, promoting breastfeeding, and refining oxygen therapy protocols are critical for reducing ROP incidence. Innovations, such as AI-driven diagnostic tools and anti-VEGF therapies, offer new opportunities to improve detection as well as treatment outcomes. However, challenges persist in addressing global disparities in screening programs and standardizing care protocols. A coordinated, multidisciplinary approach involving the fields of obstetrics, neonatology, and ophthalmology is imperative to address this complex issue comprehensively. Future efforts must focus on integrating research-driven strategies and innovative technologies to reduce the burden of ROP and improve lifelong outcomes for the affected infants. Incorporating emerging technologies and integrating both published and unpublished recent findings will help maintain the currency and relevance of future research.

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