International Journal of Community Medicine and Public Health
Alnahdi AT et al. Int J Community Med Public Health. 2024 Jan;11(1):429-433
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20233849

Review Article

Retinopathy of prematurity: prevalence, screening and treatment

Ahmed Thabit Alnahdi[1]*, Alaa Ahmed Althemairi[2], Khalid Mohammed Al-Qahtani[3], Abdulmohsen M. Alharbi[4], Ahmad Alenezi[5], Faisal Sulaiman Alkathery[6], Hussein Ahmed Almahdi[7], Yahya Ayed Al Majbar[7], Hamad Mohammed Asiri[7], Mohammad Rashed Alajmi[8], Abdulaziz Abdullah Alaskar[9]

[1]Department of Ophthalmology, East Jeddah General Hospital, Jeddah, Saudi Arabia
[2]King Fahad General Hospital, Jeddah, Saudi Arabia
[3]Khamis Mushait Maternity and Children Hospital, Khamis Mushait, Saudi Arabia
[4]Department of General Surgery, Jahra Hospital, Al Jahra, Kuwait
[5]Department of Family Medicine, Jahra Health Region, Al Jahra, Kuwait
[6]College of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland
[7]College of Medicine, King Khalid University, Abha, Saudi Arabia
[8]Department of Family Medicine, Jahra Hospital, Al Jahra, Kuwait
[9]Al-Hazemi Medical Center, Al Yamamah Hospital, Riyadh, Saudi Arabia

Received: 30 November 2023
Accepted: 13 December 2023

***Correspondence:**
Dr. Ahmed Thabit Alnahdi,
E-mail: dr_thabit@hotmail.de

ABSTRACT

Retinopathy of prematurity (ROP) is a serious ocular condition arising from improper blood vessel development in the retina, predominantly affecting infants born prematurely or with a birth weight under 1500 g. A global estimate from 2010 indicated that approximately 184,700 infants developed ROP, with around 50,000 progressing to severe stages, yet only 42% received treatment. This article undertakes a thorough review, commencing on 07th November 2023, leveraging databases like Pubmed and Cochrane to synthesize current knowledge and emerging trends in ROP prevalence, screening methodologies, and treatment options. Screening involves repeated eye exams and innovative tools to identify high-risk infants early on. Treatment approaches, encompassing cryotherapy, laser therapy, and anti-VEGF (vascular endothelial growth factor) medications, are tailored to the severity of ROP. Rigorous follow-up assessments are pivotal for tracking progress and ensuring the welfare of infants undergoing ROP interventions. This comprehensive exploration seeks to enhance awareness and understanding of ROP's global prevalence, screening protocols, and evolving treatments, ultimately contributing to informed decision-making and the advancement of best practices in the early identification and management of ROP among premature infants.

Keywords: ROP, Screening, Treatment, Prevalence, Infants, Premature

INTRODUCTION

Retinopathy of prematurity (ROP) is a potentially serious eye disorder that occurs when the blood vessels in the retina do not develop properly. ROP primarily affects infants that are either born prematurely or have a birth weight of less than 1500 grams (3.3 pounds).[1] At the time of premature birth, the vasculature inside the retina of the infant is incomplete, and hence, due to physical immaturity, systemic diseases, and increased oxygen levels pursue abnormal growth of blood vessels in the retina. Induction of oxygen at birth due to respiratory

distress is another leading cause of ROP.[2] Another possible mechanism for ROP is that due to preterm birth, the infant is exposed to higher levels of oxygen than in–utero levels. This causes a disturbance in the VEGF (vascular endothelial growth factor) and IGF-1 (insulin-like growth factor) factors, which are essential and crucial for orderly vascular growth in the retina. The delayed response of this pause is the abnormal development of vessels in the retina.[3]

The severity of ROP ranges between spontaneous resolution and permanent blindness since ROP may regress or worsen over the weeks after the birth of the infant. If left untreated, ROP can lead to serious impacts on the retina, eventually causing issues with vision.[4] ROP can be classified based on severity and its impacts on the eye and vision in five stages, as shown in Figure 1.

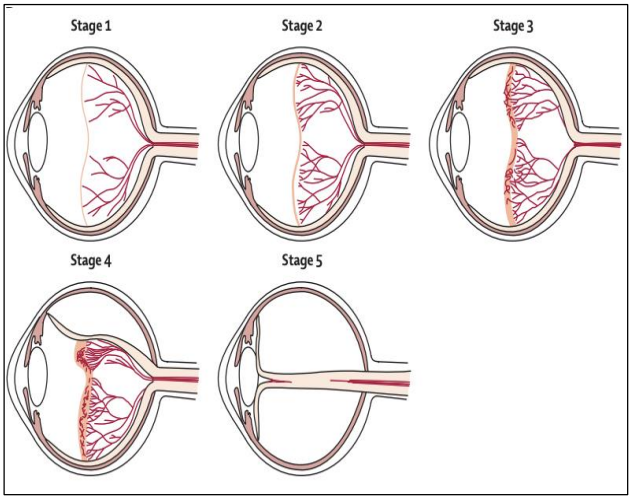

Figure 1: Stages of retinopathy of prematurity.[24]

Stage 1 corresponds to the presence of abnormal vascular structures branching into the space between the vascular and avascular retina. This branching is initially flat and lies adjacent to the retinal plane. However, in stage 2, the proliferation of the blood vessels grows in thickness and height. In stage 3, the vascular growth reaches into the extraretinal space, or in vitreous matter. These blood vessels are now fragile and can bleed and cause scarring. Further fibrovascular proliferation in the extraretinal space, causing initial retinal detachment, is demarcated as stage 4. Stage 5 represents the most advanced and severe form of the condition. In this stage, the retina detaches completely from the walls, collapsing inside the eye and leading to loss of vision.[5] The progression of ROP from one stage to the next is not always linear, and some infants may regress to an earlier stage or progress rapidly. The eventual progression of untreated ROP is known to have a huge impact on the quality of life of infants as well as their caregivers, making ROP a disorder of extreme importance.[6]

ROP is one of the leading causes of childhood blindness around the globe. A study from 184 countries estimated that approximately 184,700 infants developed ROP in 2010. Out of these estimates, ROP in around 50,000 infants progressed to the severe stage however only 42% of them received any treatment.[7] Another study highlighted that almost 32,300 infants around the world are found to have acquired severe ROP, and 62% of them become visually impaired.[8] A US-based study reported that the general prevalence of ROP in the states is around 17.5%, however, an increasing trend has been observed over the years. This increase in the prevalence of ROP can be attributed to the increased rate of survival of preterm babies due to advancements in medicine.[9] A prospective Swedish study estimated a 73% prevalence, with 35% having severe retinopathy.[10] Studies from Norway and Belgium reported a similar estimate of the prevalence of severe retinopathy; 33% and 26%, respectively.[11,12] On the contrary, studies from Australia, New Zealand, Austria, and Finland reported their prevalence of severe ROP to lie between 5 and 16%, which is a considerably lesser estimate than other European regions.[13-15] Although the impact of ROP has reduced since it was first diagnosed, it still secures its position as one of the major leading causes of vision impairment in children in high-income as well as low-middle-income countries. The improvement in the survival rates of preterm babies has had an impact on the rising prevalence of ROP due to the use of supplementary oxygen.[16] In African regions, the prevalence of ROP has been emerging for the past decade. Approximately 14.9% of the general prevalence of ROP was reported in Rwanda and Nigeria.[17] Kenya, on the other hand, estimated that the prevalence of ROP in the country was around 41.7%, out of which 20% had severe disease.[18] The incidence of ROP in Egypt ranged between 19.2% and 70%, based on multiple studies.[17]

A study from Madhya Pradesh, India, observed a 30% prevalence of the ROP, out of which severe ROP was found in 14.2% of the cases.[19] Alarming prevalence in other Asian countries, especially the Middle East, was also reported in the literature. The overall prevalence of ROP in Iran was reported to be 26.1%.[20] On the other hand, an Omani study highlighted that the prevalence of ROP in Oman is approximately 40.4%, majorly identified in infants who had lesser gestational ages.[21] Additionally, studies from Saudi Arabia reported their prevalence to fall between 21.8% and 33.3%, out of which 80% of the cases resolved spontaneously without any treatment, and only 8.3% of the children received any interventional treatment.[22,23]

The rationale for conducting a review article on the prevalence, screening, and treatment of ROP lies in the critical importance of addressing this potentially sight-threatening condition that primarily affects premature infants. ROP is a leading cause of blindness in neonates and given the increasing survival rates of extremely premature babies in neonatal intensive care units, the incidence and significance of ROP continue to rise. Understanding the latest advancements in ROP screening protocols and treatment modalities is vital for healthcare providers, ophthalmologists, and researchers to optimize

clinical practices and enhance outcomes for affected infants. By conducting a comprehensive review, this article aims to synthesize the current state of knowledge and emerging trends in ROP management, thereby facilitating better-informed decisions and promoting best practices in the early detection and treatment of ROP.

METHODS

The research, which began on 7th November 2023, was initiated after a thorough examination of the existing literature. Various databases, including Pubmed, Web of Science, and Cochrane, were utilized to conduct this literature review. The search involved using a wide range of medical terms in different combinations. Manual searches on Google Scholar to identify relevant research terms were also performed. The primary focus of this literature review was on several key areas, including the prevalence of ROP, its common causes, and the screening methods. Additionally, keywords related to the available treatment options and their effectiveness were also added to the search. It is worth noting that the criteria for selecting articles to be included in this study were determined based on multiple factors to ensure a comprehensive and robust review process.

DISCUSSION

The screening and treatment of ROP are crucial aspects of neonatal care, particularly for infants born prematurely who are at an increased risk of developing this vision-threatening condition. Screening protocols are designed to detect ROP early, allowing for timely intervention and the prevention of severe complications.

Screening of ROP

The screening of ROP primarily depends on the identification of infants who are eligible for the screening or are considered high risk for ROP. The standard screening indicator cutoff ranges from the birth of the infant between 30-35 weeks of gestation or 1500-2000 g of birthweight. These cutoffs also depend on the population where the screening is taking place and can be adjusted according to the incidence of preterm births and the demographics of the region. However, there are countries where the standards of screening for ROP are still not practiced. Proper worldwide guidelines for their enforcement are crucial and should be a concern.[24]

Usually, multiple repeated eye exams with dilation, also known as indirect ophthalmoscopy, are required to identify early-stage ROP in a high-risk infant, however, this procedure is known to be extremely painful for preterm infants.[25,26] Since the ratio of children needing extensive treatment after the screening is between 5 and 10%, physicians recommend identifying and applying a screening tool that is less invasive and stressful. In this regard, an algorithm commonly addressed as WINROP was developed to screen high-risk infants for the development of ROP and diagnose it in its early stages.[27,28] WINROP was developed in Sweden and is generally based on the longitudinal measurement of the weight of the preterm infant. It raises an alarm if the risk of the infant developing ROP is increasing.[28,29]

Multiple studies from around the world have endorsed the applicability and validity of WINROP for the screening of ROP, along with suggestions for adjunct clinical examination of the eye to get more robust results. A multicenter study from the USA and Canada estimated that the sensitivity of WINROP is around 98.6%, with a 99.7% negative predictive value (NPV).[30] Various other studies showed that the sensitivity of WINROP in countries such as the UK and Canada was 95% and 81.8%, respectively.[31,32] Additionally, in Asian countries such as India, Turkey, and Saudi Arabia, the sensitivity of ROP was estimated to be 90.32%, 84.3%, and 100%, respectively.[33-35] Although the WINROP tool is capable of identifying ROP in infants as early as one week, the sensitivity of WINROP is highly varied in different regions of the world, so it is recommended to use the algorithm with conventional clinical screening methods.[30] One of the major limitations of WINROP is that it does not include infants who are born at 32 or more weeks of gestation. Moreover, the tool also ignores infants who may have gained weight postnatally but had a low birth weight. Both of these categories are at high risk of ROP, and hence WINROP should be modified to accommodate them.[24] After the screening, the classification of ROP into the correct category is essential since the treatment plan differs for different stages. As illustrated in Figure 1, stages 1 and 2 of ROP are mild, and usually regress without any additional medical intervention. From stage 3 onwards, the chance of retinal detachment increases, and hence, interventional need also becomes crucial.[5]

Treatment of ROP

Initially, when ROP was discovered in preterm infants, treatment modalities for the disorder were limited and only consisted of surgical interventions in stages 4 and 5. Recommendations for the treatment of ROP according to its severity are mentioned in the publication 'International Classification of Retinopathy of Prematurity', which was initially published in 1985, however, later amendments were added in 2005.[36]

In 1988, researchers identified non-surgical treatment options for ROP, which can also prevent progression if done at an early stage. Cryotherapy was one of the first non-progression early-stage treatment options for ROP. Cryotherapy, a therapeutic technique involving the use of extreme cold, has been employed as a treatment modality for ROP. During cryotherapy for ROP, a specialized probe is used to apply freezing temperatures to the peripheral areas of the retina where abnormal blood vessels are present. The goal is to induce the formation of scar tissue, which helps to halt the progression of abnormal blood vessel growth and prevent further complications such as

retinal detachment. The procedure is often performed in a controlled environment, such as an operating room or an ophthalmology clinic, under carefully monitored conditions.[37] However, this approach is still typically reserved for more advanced stages of the condition, specifically Stage 3 ROP, where abnormal blood vessels have proliferated and may pose a risk of retinal detachment. Despite the remarkable results of cryotherapy, several pieces of literature indicate that 21% of the cases treated with cryotherapy still progressed to stage 4 ROP and eventual retinal detachment. Moreover, 80% of the cryotherapy-treated infants had worsened visual acuity at 5 years of age. Furthermore, the procedure was painful and carried the risk of cold burns for the infant on their eyelids and sclera.[16]

In contrast to cryotherapy, transpupillary laser treatment or photocoagulation has shown better long-term outcomes with lesser systemic repercussions. Laser ablation destroys the abnormally formed blood vessels while conserving the visual acuity of the infant.[38] Photocoagulation can also be started in the early stages of ROP, such as stage 1.[39] Another possible treatment venture for ROP has been recently identified, anti-VEGF drugs that can be injected into the eye to reduce the growth of abnormal blood vessels. This treatment option reduces the damage to the peripheral retina and can be administered when the retinal strength is not ideal for photocoagulation.[40] Regardless, the choice between cryotherapy and other treatment options, such as laser therapy or anti-VEGF medications, depends on various factors, including the stage and severity of ROP, the infant's overall health, and the ophthalmologist's judgment. Advances in technology and ongoing research contribute to the refinement of treatment protocols, with the goal of optimizing outcomes for premature infants affected by ROP. Regular follow-up assessments by healthcare professionals are essential to monitor the progress of treatment and ensure the overall well-being of infants who undergo treatment for ROP.

CONCLUSION

In summary, ROP is a critical eye disorder affecting premature infants, characterized by abnormal blood vessel development in the retina. The disorder is closely linked to factors such as prematurity, low birth weight, and exposure to high oxygen levels. If left untreated, ROP can progress through five stages, ranging from mild abnormalities to total retinal detachment and vision loss. The global prevalence of ROP has risen, with substantial variation among regions. Overall, a comprehensive understanding of ROP's prevalence, screening strategies, and evolving treatment modalities is essential to addressing this vision-threatening condition affecting premature infants worldwide.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Dougherty M, Wittenborn J, Phillips E, Swenor B. Published examination-based prevalence of major eye disorders. Centre Dis Control Prev. 2018.
2. Chang JW. Risk factor analysis for the development and progression of retinopathy of prematurity. PLoS One. 2019;14(7):e0219934.
3. Hartnett ME, Lane RH. Effects of oxygen on the development and severity of retinopathy of prematurity. J AAPOS. 2013;17(3):229-34.
4. Garner A, Ben-Sira I, Konen W, Majima A, Mccormick A, Mushin A. An international classification of retinopathy of prematurity. Pediatrics. 1984;74(1):127-33.
5. Agarwal K, Jalali S. Classification of retinopathy of prematurity: from then till now. Community Eye Health. 2017;30(99):4-7.
6. Schwarzer JM, Meyhoefer I, Antonucci LA, Kambeitz-Ilankovic L, Surmann M, Bienek O, et al. The impact of visual dysfunctions in recent-onset psychosis and clinical high-risk state for psychosis. Neuropsychopharmacology. 2022;47(12):2051-60.
7. Loganathan PK, Nair V, Lal MK. Retinopathy of prematurity: overview of new global problem. Paediatrics and Child Health. 2022;32(9):311-23.
8. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2013;74(1):35-49.
9. Aly H, Othman HF, Munster C, Das A, Sears J. The U.S. National Trend for Retinopathy of Prematurity. Am J Perinatol. 2022;29(14):1569-76.
10. Austeng D, Källen KB, Ewald UW, Jakobsson PG, Holmström GE. Incidence of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. Arch Ophthalmol. 2009;127(10):1315-9.
11. Markestad T, Kaaresen PI, Rønnestad A, Reigstad H, Lossius K, Medbø S, et al. Early death, morbidity, and need of treatment among extremely premature infants. Pediatrics. 2005;115(5):1289-98.
12. Allegaert K, de Coen K, Devlieger H, EpiBel Study Group. Threshold retinopathy at threshold of viability: the EpiBel study. Br J Ophthalmol. 2004;88(2):239-42.
13. Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ, et al. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics. 2005;115(4):990-6.
14. Weber C, Weninger M, Klebermass K, Reiter G, Wiesinger-Eidenberger G, Brandauer M, et al. Mortality and morbidity in extremely preterm infants (22 to 26 weeks of gestation): Austria 1999-2001. Wien Klin Wochenschr. 2005;117(21-22):740-6.
15. Tommiska V, Heinonen K, Lehtonen L, Renlund M, Saarela T, Tammela O, Virtanen M, Fellman V. No improvement in outcome of nationwide extremely

low birth weight infant populations between 1996-1997 and 1999-2000. Pediatrics. 2007;119(1):29-36.
16. Asano MK, Dray PB. Retinopathy of prematurity. Dis Mon. 2014;60(6):282-91.
17. Wang D, Duke R, Chan RP, Campbell JP. Retinopathy of prematurity in Africa: a systematic review. Ophthalmic Epidemiol. 2019;26(4):223-30.
18. Onyango O, Sitati S, Amolo L, Murila F, Wariua S, Nyamu G, Lango M, et al. Retinopathy of prematurity in Kenya: prevalence and risk factors in a hospital with advanced neonatal care. Pan Afr Med J. 2018;29:152.
19. Dwivedi A, Dwivedi D, Lakhtakia S, Chalisgaonkar C, Jain S. Prevalence, risk factors and pattern of severe retinopathy of prematurity in eastern Madhya Pradesh. Indian J Ophthalmol. 2019;67(6):819-23.
20. Maroufizadeh S, Almasi-Hashiani A, Omani Samani R, Sepidarkish M. Prevalence of retinopathy of prematurity in Iran: a systematic review and Meta-analysis. Int J Ophthalmol. 2017;10(8):1273-9.
21. Reyes ZS, Al-Mulaabed SW, Bataclan F, Montemayor C, Ganesh A, Al-Zuhaibi S, et al. Retinopathy of prematurity: Revisiting incidence and risk factors from Oman compared to other countries. Oman J Ophthalmol. 2017;10(1):26-32.
22. AlBalawi HB, AlBalawi NS, AlSuhaimi NA, AlBalawi AA, AlAtawi AS, Mirghani HO, et al. Incidence and Risk Factors for Retinopathy of Prematurity in Tabuk City, KSA. Middle East Afr J Ophthalmol. 2020;27(2):105-9.
23. Ahmedhussain HK, Khayyat WW, Aldhahwani BM, et al. Retinopathy of Prematurity: Incidence and Perinatal Risk Factors in a Tertiary Hospital in Saudi Arabia. J Clinic Neonatol. 2021;10(1):31-6.
24. Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. Lancet. 2013 Oct 26;382(9902):1445-57.
25. Trese MT. What is the real gold standard for ROP screening? Retina. 2008;28(3):S1-2.
26. Kleberg A, Warren I, Norman E, Mörelius E, Berg AC, Mat-Ali E, et al. Lower stress responses after Newborn Individualized Developmental Care and Assessment Program care during eye screening examinations for retinopathy of prematurity: a randomized study. Pediatrics. 2008;121(5):e1267-78.
27. Löfqvist C, Andersson E, Sigurdsson J, Engström E, Hård AL, Niklasson A, et al. Longitudinal postnatal weight and insulin-like growth factor I measurements in the prediction of retinopathy of prematurity. Arch Ophthalmol. 2006;124(12):1711-8.
28. Wu C, Vanderveen DK, Hellström A, Löfqvist C, Smith LE. Longitudinal postnatal weight measurements for the prediction of retinopathy of prematurity. Arch Ophthalmol. 2010;128(4):443-7.
29. Löfqvist C, Hansen-Pupp I, Andersson E, Holm K, Smith LE, Ley D, et al. Validation of a new retinopathy of prematurity screening method monitoring longitudinal postnatal weight and insulinlike growth factor I. Arch Ophthalmol. 2009;127(5):622-7.
30. Wu C, Löfqvist C, Smith LE, VanderVeen DK, Hellström A, WINROP Consortium. Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants: a multicenter study analyzing weight velocity deviations for the prediction of retinopathy of prematurity. Arch Ophthalmol. 2012;130(8):992-9.
31. Jung JL, Wagner BD, McCourt EA, Palestine AG, Cerda A, Cao JH, et al. Validation of WINROP for detecting retinopathy of prematurity in a North American cohort of preterm infants. J AAPOS. 2017;21(3):229-33.
32. Ricard CA, Dammann CEL, Dammann O. Screening Tool for Early Postnatal Prediction of Retinopathy of Prematurity in Preterm Newborns (STEP-ROP). Neonatology. 2017;112(2):130-6.
33. Sanghi G, Narang A, Narula S, Dogra MR. WINROP algorithm for prediction of sight threatening retinopathy of prematurity: Initial experience in Indian preterm infants. Indian J Ophthalmol. 2018;66(1):110-3.
34. Koçak N, Niyaz L, Ariturk N. Prediction of severe retinopathy of prematurity using the screening algorithm WINROP in preterm infants. J AAPOS. 2016;20(6):486-9.
35. Raffa LH, Alessa SK, Alamri AS, Malaikah RH. Prediction of retinopathy of prematurity using the screening algorithm WINROP in a Saudi cohort of preterm infants. Saudi Med J. 2020;41(6):622-7.
36. Leviton A, Dammann O, Engelke S, Allred E, Kuban KC, O'Shea TM, et al. The clustering of disorders in infants born before the 28th week of gestation. Acta Paediatr. 2010;99(12):1795-800.
37. Palmer EA, Hardy RJ, Dobson V, Phelps DL, Quinn GE, Summers CG, et al. 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity. Arch Ophthalmol. 2005;123(3):311-8.
38. Houston SK, Wykoff CC, Berrocal AM, Hess DJ, Murray TG. Laser treatment for retinopathy of prematurity. Lasers Med Sci. 2013;28(2):683-92.
39. Emami S, Isaac M, Mireskandari K, Tehrani NN. Laser Treatment for Retinopathy of Prematurity: A Decade since ETROP. Ophthalmology. 2019;126(4):639-41.
40. Wu AL, Wu WC. Anti-VEGF for ROP and Pediatric Retinal Diseases. Asia Pac J Ophthalmol (Phila). 2018;7(3):145-51.

Cite this article as: Alnahdi AT, Althemairi AA, Al-Qahtani KM, Alharbi AM, Alenezi A, Alkathery FS, et al. Retinopathy of prematurity: prevalence, screening and treatment. Int J Community Med Public Health 2024;11:429-33.