Retinopathy of prematurity: Addressing the emerging burden in developing countries

Suraj Singh Senjam¹, Parijat Chandra²

¹Community Ophthalmology, ²Vitreoretina and ROP Services, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Retinopathy of prematurity has emerged and continues to be one of the leading causes of avoidable childhood blindness in low- and middle-income countries over the past few years. A major reason is the lack of adoption of effective and efficient screening for retinopathy of prematurity in various neonatal or newborn units across the countries. At the same time, there is an improvement in the survival rate of high-risk newborn babies which causes a further rise in retinopathy of prematurity. Most of the associated risk factors for retinopathy of prematurity are avoidable, therefore, various preventive strategies can be developed at various levels of healthcare facilities ranging from primary to tertiary level. The integration of appropriate retinopathy of prematurity intervention programs between healthcare departments and partnerships with other non-governmental eye care institutions would be an important as well as critical step to prevent blindness and visual impairment due to retinopathy of prematurity in India and other developing nations.

Keywords: Emerging childhood blindness, India, low-middle income countries, prevention, retinopathy of prematurity

Introduction

In many low and middle-income countries (LMICs), retinopathy of prematurity (ROP) has increasingly been recognized in the past few decades as one of the most important avoidable causes of blindness and visual impairment in children.¹⁻³ The condition is not better even in high-income countries, because of the rising survival of more extremely premature infants, and ROP there remains an important cause of avoidable childhood blindness.¹⁻³ One of the main reasons for rising ROP in developing nations is due to the disparity in quality of care among preterm newborns. With an aim towards achieving the Millennium Development Goals, the child survival rate continues to improve over time due to a dramatic improvement in supportive and therapeutic services, particularly for preterm or small-for-date babies in LMICs.⁴ Subsequently, the number of deaths reduced to 6 million in 2015 from 13 million in 2000.⁵

Several LMICs are observing rapid progress in expanding services for neonates, including a preterm born and high-risk babies to curtail the under 5 mortality rate. For instance, in India, Newborn Care Corners, Newborn Stabilization Units, and Special Newborn Care Units are established across the country which takes care of more than 6 lakhs newborn annually.⁷ This leads to a higher survival rate of high-risk newborns compared to earlier periods while increasing the risk of developing ROP in these children. At the same time, there is also a lack of high-quality ROP care in each neonatal unit or newborn unit – on account of lack of relevant ROP screening guidelines or policies resulting in use of unmonitored oxygen, no screening being conducted for early detection of ROP, etc., thereby, causing the widespread occurrence of ROP across the developing world.⁸ Due to this,
there is a paradigm shift in terms of the most common cause of avoidable blindness in children from infectious and nutritional causes to ROP in India and other developing nations.[9]

**Epidemiology of ROP**

The comparison of epidemiological indicators of ROP from the hospital or population-based studies is the biggest challenge because of substantial variability in screening criteria and study designs. For instance, the reported ROP prevalence ranges from 12.5% (1990–2011) in England[10] and 16% (1990–2011) in the USA[11], where ROP occurs in predominantly extremely low birth weight babies (≤28 weeks gestation and ≤1250 g), whereas, in LMIC, ROP varies from 3 to 44% where wider screening criteria were being employed.[12,13] In a global estimate of ROP in 2010, a total of 184,700 preterm babies developed any form of ROP, of this 20,000 became blind, and a further 12,300 were visually impaired from ROP.[1] A meta-analysis also reported that around 32,300 preterm infants are visually impaired every year due to ROP, including China and India.[9]

India attributed nearly 10% of global estimates of ROP related visual impairment in 2010. It is estimated that around 5000 infants who developed severe ROP required treatment, and 2900 children survived with visual challenges due to ROP.[12,13] Studies across India showed that the incidence of any ROP ranges from 20% to 30% through screening criteria varies in different units across the country.[14] In general, around 50% of preterm infants weighing less than 1250 g at birth show any form of ROP, and these about 10% develop a severe form of ROP.[14] A recent study in a tertiary eye care center in Delhi reported that the incidence of any ROP was 20% with criteria ≤32 weeks gestational age and ≤1500 g at birth.[17]

**Risk factors**

The risk factors of ROP, a noncommunicable disease, can also be described as an epidemiological triad model of disease causation [Figure 1].[18] The triad explains the disease is due to the interaction between the agent (oxygen), susceptible host, and environment (hospital services) within a specific time (dimension). In the West, the risk factor transitions from the first epidemic (the 1940s) to the second epidemic (1970s) of ROP i.e. from preterm to extreme preterm or low birth weight was observed, whereas, in LIC and MIC, mixed risk factors of both epidemics are occurring (third epidemic).[19]

The principal risk factors for ROP are premature birth, low birth weight, prolonged unmonitored oxygen supplementation, sepsis, and other documented risk factors included as in the triad.[6,5,20,21]

**Preventive strategies for ROP in developing countries**

The first and foremost important key step for the prevention of any form of ROP related visual problem is the adoption of an effective and efficient screening strategy. The Government of India recommends ROP screening for babies aged less than 34 weeks of gestational age, and <2000 g of birth weight.[20] However, it could be varied according to the resources and expertise available in the healthcare center. In an apex tertiary hospital in Delhi, a lower cutoff screening criteria is being used in its quality neonatal care unit i.e. (≤32 weeks and ≤BW 1500 g).[17]

The strategy to control the blindness and visual impairment due to ROP should be a multidisciplinary approach from various health and non-healthcare professionals, for instance, pediatricians, neonatologists, ophthalmologists and special counselors, community healthcare workers, etc. The control strategy could be categorized as:

1. **Prevention for ROP development** (primary prevention) - An effort to avoid the development of risk factors like preterm births, e.g. prevention of teenage or adolescent pregnancies, avoidance of substance abuse, etc. This can be considered as “primordial prevention”[22] – steps even before pregnancy which is much earlier than primary prevention. Any prevention once conception happens till delivery and steps to prevent the development of risk factors of ROP after birth is primary prevention such as good neonatal and obstetric care, antenatal steroids to mother, strict oxygen management, education on kangaroo care, etc.

2. **Prevention of outcome of ROP related visual problems** (secondary prevention) - Secondary prevention includes early screening and detection of ROP followed by treatment. Screening is recommended within 4 weeks post-delivery, or earlier between 2–3 weeks after delivery in very preterm and very low birth weight babies. Trained ophthalmologists are required for ROP screening.

![Figure 1: “Epidemiological Triad” representing risk factors for ROP](image-url)
3. **Prevention of further deterioration of function** (tertiary prevention) - Any intervention to restore the vision (like laser/anti-VEGF/surgery) or treating complications as well as function of the visually challenged children - for instance, correction of refractive error, habilitation and low vision service, and visual rehabilitation service.

These prevention strategies can be implemented according to the suitability of healthcare facilities [Table 1]. For example, in a tertiary level of healthcare, all levels of prevention can be employed, whereas in primary level facilities, not all primary prevention strategies are feasible.

**Integration of intervention strategies for ROP**

ROP is rapidly emerging as a leading cause of avoidable blindness among children in India and other LMIC. It is of paramount importance to integrate ROP services into the existing child and newborn services to ensure the healthy growth of preterm infants. Integration can be taken up in both public health facilities and private facilities. However, not all ROP care programs or services will be feasible to integrate into existing health systems. Table 1 shares the specific areas of the ROP program that can be integrated into various levels of prevention strategies at appropriate facilities. So, selective strategies can be considered according to the resources available to these facilities. For instance, organizations dealing with visual rehabilitation can provide few components of tertiary prevention of blind due to ROP such as special education programs, developmental activities, and mobility training.

As part of integration planning, situation analysis and mapping of resources, infrastructure, and caseload are essential before integration which would help in prioritization according to needs and volume of load e.g. number of high-risk newborns in a facility. Later, the integration of various preventive, screening and treatment strategies can be planned in a phased manner- 1st and 2nd phase.

### First phase - secondary and tertiary level health facilities

The ROP screening activities for secondary prevention can be done in secondary and tertiary level health facilities where delivery service is being provided. Since, ROP screening needs a team of trained ophthalmologists, pediatricians or neonatologists, screening may be considered in only selected facilities. In India, the district level center under the Government of India -Special Newborn Care Units for sick and high-risk newborn infants can be effectively taken up for ROP screening activities and is being scaled up in some districts.[24] If ROP is identified, further referral should be done to tertiary eye care equipped with the ROP intervention services.

### Second phase - community level and primary level

The prevention of ROP related visual impairment and blindness is a multidisciplinary team approach. It not only requires specialists but also nurses, healthcare workers including community, Auxiliary Nurse Midwives, and parents of the baby.[7,25] Primordial and primary prevention along with some aspects of tertiary prevention of ROP e.g. vision rehabilitation can be easily integrated at primary and community levels of the healthcare system, which can be incorporated in primary care services.

The primary focus of prevention at this point is to reduce the rates of preterm births with good care before (preconception

| Strategies | Subcomponents (few examples) | Integration to the health care system |
|------------|-----------------------------|--------------------------------------|
| Primary prevention | Prevention of adolescent pregnancies, substance abuse, systemic diseases | Community Primary Secondary Tertiary |
| | High-quality neonatal care | Yes Yes Yes Yes |
| | Sepsis prevention | No Yes Yes Yes |
| | Good obstetric care | Yes Yes Yes Yes |
| | Antenatal steroids to mother | No Yes Yes Yes |
| | Strict oxygen management | No No Yes Yes |
| | Education on kangaroo care | No Yes Yes Yes |
| | Breastfeeding and follow up | Yes Yes Yes Yes |
| | Avoid unnecessary blood transfusion | No No Yes Yes |
| | Hand washing of providers | Yes Yes Yes Yes |
| | Awareness, education on ROP | Yes Yes Yes Yes |
| Secondary prevention | Screening and detection of ROP | Yes Yes Yes Yes |
| | Treatment – laser/anti-VEGF/surgery | No No No Yes |
| | IGL-1 and nutrition supplementation to improve growth | No No No Yes |
| Tertiary prevention | Late-stage of ROP, complications of ROP | Yes No No Yes |
| | Clinical low vision services | No No Yes Yes |
| | Vision rehabilitation | No Yes Yes Yes |
| | Community-Based Rehabilitation | Yes Yes Yes No |
as primordial prevention) and during pregnancy (antenatal); and prevention of risk factors for ROP at the time of birth (intrapartum) and after delivery (postnatal care) as primary prevention. Another important role of primary prevention is to expedite the steps for secondary prevention of ROP i.e. making parents aware of the potential risk of developing ROP in preterm and small for date babies and counseling for the need for screening without delay.

**Primordial prevention**

Strategies to reduce preterm births can be started at preconception or even before pregnancy. There are various reasons for preterm births. Not all, but many factors identified as risk factors for preterm birth, for example, adolescent pregnancy, underweight or obesity of expectant, chronic health condition like diabetes, infections (e.g. HIV), substance abuse, short interval between births, poor psychological health, smoking are associated with preterm births.[26,27] These factors can be dealt with primary care practices by community healthcare providers e.g. health education, family planning, etc. Assisted fertility treatment increases the risk of multiple pregnancies which further invites preterm births. Judicious use of fertility treatment and education about the probability of high-risk newborns and complications, while at the same time encouraging for well-equipped facility-based delivery, will also help to reduce the risk for ROP.[28]

**Primary prevention**

It is the step to be considered from when conception happened until after the delivery of the infant to reduce the risk for ROP. Many of these activities can be a part of primary care practices in the health delivery system. Ensuring good antenatal care, proper nutritional supplementation will help to reduce the preterm births; along with proper screening and management of pregnant women who are at risk of preterm birth e.g. multiple pregnancy, diabetes, and hypertension. Encouraging and motivating the high-risk mothers for facility-based deliveries with neonatal care setup, further retinal screening of preterm babies before and after discharge, the need for follow-up as prescribed, etc., are needed. Additional prevention such as antenatal intramuscular injection of steroid as a pre-referral dose to a pregnant woman in preterm labor (between 24 and 34 weeks of gestation), preventive measures to avoid infection of infants can be provided within the ambit of primary care practices. For example, primary care workers working in the Newborn Care Corners situated at the point of childbirth under the Rashtriya Bal Swasth Karaykram scheme, Government of India, can be educated about ROP and trained to avoid unmonitored 100% oxygen supplementation to newborns.

A study shows that parental ignorance and negligence are some of the key important factors that contribute to the development of ROP.[29] Parents should be counseled and reassured about the importance of screening and the need for multiple screenings for ROP. Community health workers, ASHAs can be trained and educated about ROP screening and the need for strict maintenance of follow-up. Home visits can be done. They will support in improving compliance among parents and follow up. Creating and improving public awareness about ROP also can be a part of primary care services in the community. Children who become blind or visually impaired due to ROP needed to be provided vision rehabilitation and special education to improve academic activities. Awareness about various disability schemes under the Government of India e.g. Assistance to Disabled Persons (ADIP), scholarship for education and assistance in procurement of disability certificate can also be a part of primary care practices.[30]

**Challenges in ROP control program**

The following potential challenges may be faced in developing countries whenever ROP services are planned. Therefore, these challenges must be kept in mind in designing a successful ROP program.

1. **Biological challenges**
   - Many preterm births and small for gestation age births cannot be prevented despite the utmost obstetrics care. This causes persistence in the risk of ROP development.

2. **Programmatic challenges**[31,32]
   - Adherence to screening guidelines may be a challenge because of substantial differences in resources available across various facilities.
   - Shortage of ophthalmologists - As of now screening is to be done by ophthalmologists, and this may increase their workload. This leads to a limitation of the expansion of screening activities.
   - There is a wide gap between the number of babies requiring ROP screening and the number of trained ophthalmologists.
   - Screening by non-opthalmologists – Very few low cost and easy to handle imaging cameras are available that can be used by neonatologists and pediatricians.
   - Improvement of neonatal care- Setting up of high-quality NICU’s is costly. Resource-limited countries may not be amenable for scaling up.
   - Treatment must be started within 48 h, otherwise, a referral may be delayed. Before discharging high-risk babies, the parent must be informed and counseled to get a screening.
   - Lack of awareness among the providers as well as parents which hampers timely screening of ROP.

3. **Database or health management information systems on ROP**
   - Since the ROP control program needs an interdepartmental and multidisciplinary approach, the development of health information systems to monitor the program is a big challenge.

4. **Challenges by parents or family**[32]
   - Since ROP needs follow-up visits, a lot of challenges are also faced by parents for family-related travel and accessibility of the ROP services.
   - They lose an opportunity cost on coming to a highly specialized center e.g. loss of daily wages.
Conclusions

In LMICs, including India, the visual impairment due to retinopathy of prematurity in children is continuously growing over the past many years. The blindness and visual impairment due to ROP is readily avoidable if the necessary steps for early identification are in place in each newborn facility. A multilevel integrated multidisciplinary approach should be a primary focus area in the preventive program of ROP. While implementing, the traditional level of preventive (primary, secondary, tertiary) strategies can be put into place in the various healthcare facilities considering its feasibility and appropriateness. Improving awareness among community healthcare workers, and parents will also be helpful in the effective implementation of the ROP control program.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. 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 Suppl 1:35-49.
2. Blencowe H, Moxon S, Gilbert C. Update on blindness due to retinopathy of prematurity globally and in India. Indian Pediatr 2016;53 Suppl 2:S89-92.
3. Vinekar A, Dogra M, Azad R, Gilbert C, Gopal L, Trese M. The changing scenario of retinopathy of prematurity in middle and low income countries: Unique solutions for unique problems. Indian J Ophthalmol 2019;67:717-9.
4. Tasman W. Retinopathy of prematurity: Do we still have a problem? Arch Ophthalmol 2011;129:1083-6.
5. Hellström A, Smith LEH, Dammann O. Retinopathy of prematurity. Lancet 2013;382:1445-57.
6. Anon. UN Inter-agency Group for Child Mortality Estimation (UN‑IGME). Levels and Trends in Child Mortality. Available from: http://www.who.int/infantfeeding/child‑mortality/en/. [Last accessed on 2019 Mar 20].
7. Kiranmayee PS, Kalluri V. India to gear up to the challenge of “third epidemic” of retinopathy of prematurity in the world. Indian J Ophthalmol 2019;67:726-31.
8. Chattopadhyay MP, Pradhan A, Singh R, Datta S. Incidence and risk factors for retinopathy of prematurity in neonates. Indian Pediatr 2015;52:157-8.
9. Wadhwani M, Vashist P, Singh SS, Gupta V, Gupta N, Saxena R. Prevalence and causes of childhood blindness in India: A systematic review. Indian J Ophthalmol 2020;68:311-5.
10. Painter SL, Wilkinson AR, Desai P, Goldacre MJ, Patel CK. Incidence and treatment of retinopathy of prematurity in England between 1990 and 2011: Database study. Br J Ophthalmol 2015;99:807-11.
11. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptok AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD neonatal research network. Pediatrics 2010;126:443-56.
12. Zin A, Gole GA. Retinopathy of prematurity-incidence today. Clin Perinatol 2013;40:185-200.
13. Bowe T, Nyamai L, Ademola‑Popoola D, Amphornphruet A, Anzures R, Cernichiaro‑Espinosa LA, et al. The current state of retinopathy of prematurity in India, Kenya, Mexico, Nigeria, Philippines, Romania, Thailand, and Venezuela. Digit J Ophthalmol 2019;25:49-58.
14. Blencowe H, Moxon S, Gilbert C. Update on blindness due to retinopathy of prematurity globally and in India. Indian Pediatr 2016;53:S89-92.
15. Ramke J, Petkovic J, Welch V, Blignault I, Gilbert C, et al. Ramke J, Petkovic J, Welch V, Blignault I, Gilbert C, Blanchet K et al. Interventions to improve access to cataract surgical services and their impact on equity in low- and middle-income countries. Cochrane Database Syst Rev. 2017;11(11):CD011307. Published 2017 Nov 9. doi:10.1002/14651858.CD011307.pub2.
16. Chawla D, Agarwal R, Deorari AK, Paul VK. Retinopathy of prematurity. Indian J Pediatr 2008;75:73-6.
17. Sivanandan S, Chandra P, Deorari AK, Agarwal R. Retinopathy of prematurity: AIMs, New Delhi experience. Indian Pediatr 2016;53(Suppl 2):S123-8.
18. Miller RE. Epidemiology for Health Promotion and Disease Prevention Professionals. New York: The Haworth Press; 2002, p. 62.
19. Dutta S, Raghuvbeer T, Vinekar A, Mangat A, Dogra R. Can we stop the current epidemic of blindness from retinopathy of prematurity? Indian Pediatr 2016;53(Suppl 2):S80-4.**
20. Anon. The International Agency for the Prevention of Blindness, Retinopathy of Prematurity-IAFP Resources. Available from: https://www.iapb.org/knowledge/what-is-avoidable-blindness/retinopathy-of-prematurity/[. Last accessed on 2019 Jan 28].
21. Huang J, Tang Y, Zhu T, Li Y, Chun H, Qu Y, et al. Cumulative evidence for association of sepsis and retinopathy of
22. Rashtriya Bal Swasthya Karyakram. Guidelines for Universal Eye Screening in Newborns Including Retinopathy of Prematurity 2017. Ministry of Health and Family Welfare, Government of India. Available from: https://www.nhm.gov.in/images/pdf/programmes/RBSK/Resource_Documents/Revised_ROP_Guidelines-Web_Optimized.pdf. [Last accessed on 2019 Sep 25].

23. Anon. K. Park, Park's Textbook of Preventive and Social Medicine. 23rd ed. Banarsidas Bhanot Publishers; 2016. p. 120-6.

24. Gilbert C, Shukla R, Murthy GVS, Santosha BVM, Gudlavalleti AG, Mukpalkar S, et al. Retinopathy of prematurity: Overview and highlights of an initiative to integrate prevention, screening, and management into the public health system in India. Indian J Ophthalmol 2020;68:S103-7.

25. Shukla R, Murthy GVS, Gilbert C, Vidyadhar B, Mukpalkar S. Operational guidelines for ROP in India: A summary. Indian J Ophthalmol 2020;68:S108-14.

26. World Health Organization G. WHO | New global estimates on preterm birth published. Available from: https://www.who.int/reproductivehealth/global-estimates-preterm-birth/en/ [Last accessed on 2020 March 24].

27. Sen C. Preterm labor and preterm birth. J Perinat Med 2017;45:911-3.

28. Hansen M, Bower C, Milne E, de Klerk N, Bower C. Assisted reproductive technology and birth defects. Hum Reprod Update 2005;20:328-38.

29. Ranjan Padhi T, Badhani A, Mahajan S, Savla LP, Sutar S, Jalali S, et al. Barriers to timely presentation for appropriate care of retinopathy of prematurity in Odisha, Eastern India. Indian J Ophthalmol 2019;67:824-7.

30. Ministry of Social Justice and Empowerment G of I. The Right of Persons with Disabilities ACT, 2016. Available from: http://www.disabilityaffairs.gov.in/upload/uploadfiles/files/RPWD ACT 2016.pdf [Last accessed on 2019 Mar 18].

31. Dogra MR, Katoch D. Retinopathy of prematurity: An emerging and evolving challenge. Indian J Ophthalmol 2017;65:782-4.

32. Vinekar A, Jayadev C, Dogra M, Shetty B. Improving follow-up of infants during retinopathy of prematurity screening in rural areas. Indian Pediatr 2016;53(Suppl 2):S151-4.