Commentary

Retinopathy of prematurity: Addressing the emerging burden in developing countries

Suraj Singh Senjam[1], Parijat Chandra[2]

[1]Community Ophthalmology, [2]Vitreoretina 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.[4,5] 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.[6] Subsequently, the number of deaths reduced to 6 million in 2015 from 13 million in 2000.[2]

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,

Address for correspondence: Dr. Suraj Singh Senjam, Room No. 791, 7th Floor, Community Ophthalmology, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India.
E-mail: drsurajaiims@gmail.com

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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.[3]

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.[14,15] 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.[16] 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.[10] 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.[8,5,20,21]

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.[22] 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"[23] – 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.

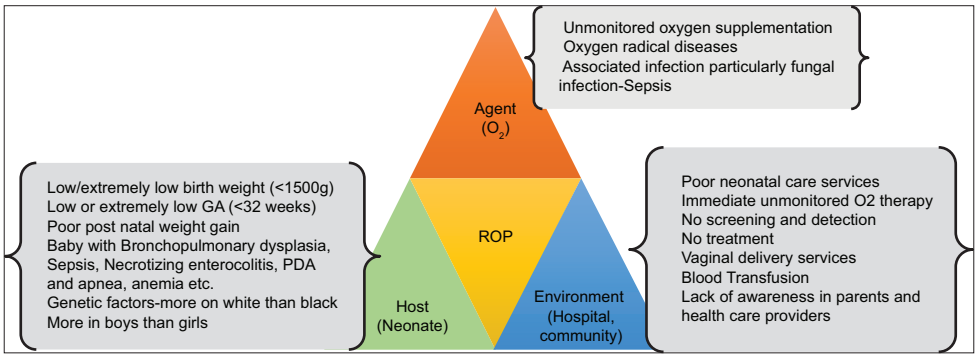

Figure 1: "Epidemiological Triad" representing risk factors for ROP

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

Table 1: Strategies to control retinopathy of prematurity

Strategies	Subcomponents (few examples)	Integration to the health care system			
		Community	Primary	Secondary	Tertiary
Primary prevention	Prevention of adolescent pregnancies, substance abuse, systemic diseases	Yes	Yes	Yes	Yes
	High-quality neonatal care	No	No	No	Yes
	Sepsis prevention	No	Yes	Yes	Yes
	Good obstetric care	Yes	Yes	Yes	Yes
	Antennal 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	No	No	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	No	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 (intranatal) 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**[31,19]
   - 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-ophthalmologists – 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

- Treatment is expensive
- Children with blindness and visually impaired due to ROP need disability certificates. Places to issue such certificates are not widely available, and they also need multiple visits to receive it.

5. **Children with ROP related visual problems**
   - Lack of pediatrics low vision clinic
   - Lack of pediatrics visual rehabilitation services
   - Low vision aids, rehabilitation aids, or assistive technologies are not widely available
   - A very limited number of pediatrics community-based rehabilitation facilities.

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.

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Conflicts of interest

There are no conflicts of interest.

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