Review Research

RETINOPATHY OF PREMATURITY, AN IMPORTANT PUBLIC HEALTH PROBLEM IN PAKISTAN: A REVIEW

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ABSTRACT

Introduction: Retinopathy of Prematurity (ROP) is the significant cause of blindness in children globally. Although the incidence of ROP is greater in premature infants worldwide, statistics show that it is more common in low-middle-income countries. Multiple causes and complications of ROP in low middle-income countries have been reported therefore the purpose of this literature review was to review the findings from literature about the burden, causes, outcomes, and important preventive measures of ROP for low middle-income countries, especially in Pakistan. **Methods:** A comprehensive review of the literature was conducted from published articles. Research studies were selected that included risk factors of ROP, screening, and diagnosis of ROP, treatment of ROP, and prevention of ROP. **Results** The cause of the high rate of ROP in Low-middle income countries (LMICs) includes a high rate of preterm babies, lack of awareness regarding ROP, financial instability, and insufficient treatment and screening programs at the newborn units. ROP is found to be the significant cause of preventable blindness in South Asia. There are three different levels of prevention aimed at reducing the burden of ROP in LMICs. Primary prevention aims at reduction in preterm births, secondary prevention aims at early diagnosis of the disease and tertiary prevention aims at reducing deterioration of conditions due to disease. **Conclusion:** The emphasis on preventive measures especially primary and secondary level prevention can help in decreasing the burden of ROP. This requires a multidisciplinary approach at all levels including at the level of policymaking, program implementation, health care providers, and community level.

Keywords: ROP, LMICs, Pakistan, Prevention, Literature review

Introduction

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy affecting neonates. It is a significant cause of blindness in children globally (Blencowe, Lawn, Vazquez, Fielder, & Gilbert, 2013). According to the WHO report of 2012, around 1 in 10 preterm babies are born globally (Organization, 2012).

Research shows that ROP affects around 300,000 infants globally (Wheatley, Dickinson, Mackey, Craig, & Sale, 2002). In the US the incidence of having any stage of ROP was 68% among infants with weight <1,251 gms, and 36.9% among them were those who developed clinically significant ROP (Group, 2005). According to the global estimate of 2010, around 184,700 out of 14.9 million preterm babies developed any stage of ROP, among them 20,000 were blind having Visual Acuity (VA) <20/400, some of them had severely impaired VA and among them, 12,300 had a mild or moderate visual disability (Blencowe et al., 2013).

Among the developed countries, the estimates of 2010 showed that 6,300 babies out of 32,700 had ROP requiring treatment and data shows around 1,700 of them had severely impaired vision resulting from ROP (Blencowe et al., 2013). In 2010 around 170,000 premature babies developed ROP globally, and 54,000 among them were those who required immediate treatment for the disease and only 40% among them received the treatment (Blencowe et al., 2012) In comparison to high-income countries, where the incidence of ROP was found 13.2-46% (Brown et al., 1998), (Rodríguez-Hurtado & Cañizares, 2006), (Holmström, Broberger, & Thomassen, 1998).

The incidence of ROP in LMICs is greater than 40% with more survival rate of premature babies and with limited diagnostic services (Gilbert et al., 2005) (Austeng, Källen, Ewald, Jakobsson, & Holmström, 2009); (Blencowe et al., 2013; Blencowe, Lawn, Vazquez, Fielder, & Gilbert, 2013);(Gilbert et al., 2005). Research evidence from schools demonstrates that 50,000 children aged 15 years were blind because of ROP worldwide, with the highest ratio from Latin America (Gilbert, 2008). As per the 2005 International Classification of ROP, the disease has been described based on Zones (location of disease) and stages (severity of abnormal vascularization) (Jefferies, Society, Fetus, & Committee, 2016) that are mentioned below:

Stages (1 to 5) and description of retinopathy of prematurity:

Stage 1: A line segregating avascular retina from vascularized one

Stage 2: Rising elevations in the section of segregating line

Stage 3: Additional retina fibrovascular proliferation outspreading into the vitreous

Stage 4: Partial retinal detachment

Stage 5: Complete retinal detachment

Plus Disease: Increased vascular dilatation and tortuosity of posterior retinal vessels in at least two quadrants of the retina

Pre-Plus Disease: More vascular dilatation and tortuosity than normal but insufficient to make the diagnosis of plus disease (Jefferies et al, 2016)

Furthermore, Retinopathy of prematurity has been classified into five stages depending on the severity of the disease (Reynolds, 2014)

- Stage I is the condition with mildly abnormal blood vessel growth. Stage I mostly improve without treatment and develop normal vision without further progression.
- Stage II is the condition with moderate abnormal blood vessel growth. This condition also mostly improves without treatment, to normal vision.
- Stage III has severely abnormal blood vessel growth. The blood vessels grow towards the center of the eye instead of along the surface of the retina. Infants who develop stage III ROP develop normal vision without treatment, however, an infant with stage III ROP and the plus disease requires treatment. Plus disease is the disorder when blood vessels of the retina enlarge and become twisted.
- Stage IV is the condition in which the retina is partially detached that results in bleeding and abnormal vessels pull the retina away from the wall of the eye.
- Stage V is the complete detachment of the retina and the end-stage of the disease. The preterm infant with grade V ROP suffers from visual impairment and permanent blindness.

ROP is a significant cause of blindness (Reynolds, 2014). The development in neonatal care around the world has improved the survival rate of premature infants (Organization, 2000). These infants are at high risk of the development of ROP. The infants with mild ROP improve without any treatment (Holmström et al., 1998).However, infants with severe disease may require treatment and can develop permanent blindness (Blencowe, 2016). Although the incidence of ROP is greater in premature infants worldwide, statistics show that it is more common in low-middle-income countries (Blencowe et al., 2012). Multiple causes and complications of ROP have been reported in the literature which is not established in one place. Hence, the purpose of this literature review was to review and demonstrate the findings from literature about the burden, causes, outcomes, and important preventive measures of ROP for low middle income countries, especially in Pakistan.

Methods

Search strategies and data sources

A comprehensive review of the literature was conducted from articles using PubMed, Google Scholar, Science Direct, International Council of Ophthalmology, and WHO databases using terms such as Retinopathy of prematurity, LMICs, South Asia, Pakistan, Pre-term births, visual impairment, ophthalmology, and etcetera. Moreover, links to “related articles” were accessed in electronic databases.

Eligibility criteria

The studies included were descriptive, observational studies, comparative studies, and correlational studies. Inclusion criteria included only full-text papers in the English language. All relevant articles were preferred and there was no restriction on publication date as few older articles contained important content relevant to the subject. Research studies were selected that included risk factors of ROP, screening, and diagnosis of ROP, treatment of ROP, and prevention of ROP.

Results

A total of 40 peer-reviewed papers were selected for literature review. 28 papers were eligible for the review that included risk factors of ROP, screening, and diagnosis of ROP, treatment of ROP, and prevention of ROP. 12 papers were excluded from the selected papers based on the criteria that: 1) they were not generalizable and were context-specific; 2) included interventional studies and 3) qualitative studies to explore experiences of ROP. The eligible papers were reviewed to understand the background, context, causes, treatment, and complications of ROP.

The epidemics of ROP have been comprehended in three different periods (Gilbert, 2008). The first epidemic was during the 1940s and early 1950s when the association of ROP with oxygen administration was acknowledged. Due to the association of high oxygen to the development of ROP, oxygen use was restricted (Quinn, Gilbert, Darlow, & Zin, 2010). During that time, there was a significant decrease in ROP blindness but an increase in high infant mortality due to restricted oxygen administration.

In the late 1960s and 1970s, the second epidemic of ROP was seen when the development of neonatal units in most high-income countries increased the survival of low birth weight and very premature infants (Hellström, Smith, & Dammann, 2013). This increased the survival of premature infants while resulted in an increased rate of cases of ROP.

The third epidemic of ROP was recorded in 1990s (Hellström et al., 2013).The countries including China, Russia, European countries, and Southeast Asian countries developed well-established neonatal care units (Hellström et al., 2013). It is estimated from the records of 2010, that around 2.6 million premature infants were born with a gestational age of less than 32 weeks. Around 20,000 infants had blindness and many infants had mild to moderate ROP (Hellström et al., 2013).

Global situation analysis

According to WHO, 1.4 million children are visually disabled globally, among them 2/3rd are from low-middle-income countries (Organization, 2012). Because of improved neonatal care, the survival rate of preterm babies has been enhanced, and the risk of preterm-related ROP has been increased globally, particularly among the middle-income countries including Pakistan, China, and India (Blencowe et al., 2013). The cause of high rate of ROP among these countries is the high rate of preterm babies born in these countries, lack of awareness regarding ROP, financial instability, and insufficient treatment and screening programs at the new-born units (Blencowe et al., 2012).

Among many countries around the globe, the incidence of premature infants is higher which is 13.3% in South Asia and poses a significant public health concern for the development of ROP (Murthy, 2017). ROP is found to be the significant cause of preventable blindness in South Asia. Alongside, there is limited literature available on ROP from low-income countries (Adams, Bunce, Dahlmann-Noor, & Xing, 2016).

Pakistan is suffering from poor health resources and facilities related to screening, diagnostics, and treatment procedures (Taqui, Syed, Chaudhry, Ahmad, & Salat, 2008). Also, the actual incidence of ROP is still not known because of limited studies (Chaudhry et al., 2014). Few of the studies have represented the incidence of ROP within their clinical settings. A cross-sectional study conducted at a private hospital in Karachi reported 32.4% of ROP incidence (Taqui, 2008). Another study was conducted in the same setting to measure the frequency of ROP in preterm babies. Study results showed that the incidence of ROP in premature neonates is 10.5% (Sohaila et al., 2014). A study conducted at an Ophthalmology department of a tertiary care hospital in Lahore found the incidence of Retinopathy of prematurity around 24.6% (Jamil, Tahir, Ayub, & Mirza, 2015)

Risk factors for ROP

The major risk factors for ROP were recognized during three epidemics of ROP (Gilbert, 2008). The causes of ROP have been demonstrated by the causal model. This model in epidemiology was introduced in 1976 by Rothman (Rothman & Greenland, 2005) *(Figure 1)*. This model is used to reflect the variety of causes among the components of the disease. Considering the risk factors for ROP, each pie in the causal model is a sufficient cause to develop the disease. The major causes of ROP include low gestational age, low birth weight, and prolonged exposure to supplementary oxygen following birth (Rodriguez-Hurtado & Canizares, 2006).

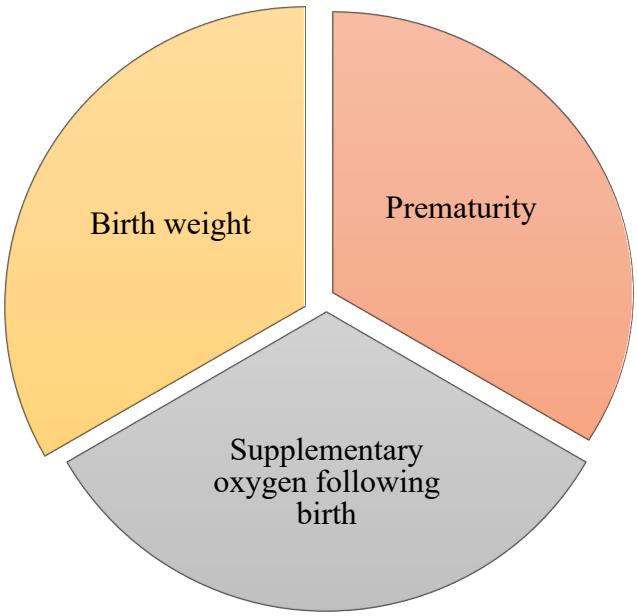

Figure 1. Causal model" representing sufficient causes of ROP

Screening and Diagnostic Procedures for ROP

The first-line management for ROP is screening. The management demands good training and skilled individuals along with suitable and proper screening equipment (Chan-Ling, Gole, Quinn, Adamson, & Darlow, 2018). Nearly all of the guidelines use birth weight and gestational age as an indicator for the screening of ROP as both of these are the major risk factors of ROP(Gilbert et al., 2005). The latest guidelines by the American Academy of Pediatrics, American Academy of Ophthalmology, and American Association for Pediatric Ophthalmology and Strabismus recommends screening of ROP to all newborns who are born at 32 weeks or less than 32 weeks gestational age; and born with a birth weight of 1,500 grams or less (Gilbert et al., 2005)

Treatment of ROP

Retinopathy of prematurity is classified by its zone, severity, and presence of plus disease. Based on the classification and severity of ROP, the Royal College of Ophthalmology provides the guidelines for the treatment of Retinopathy of prematurity demonstrated in *Table 1*(Chan-Ling, 2018).

Table 1: Guidelines for treatment of ROP

Treatment indicated	Zone I, any ROP with plus Zone I, stage 3 without plus disease Zone II, stage 3 with plus disease
Treatment should be considered	Zone II, stage 2 with plus disease
Time from diagnosis to treatment	48 hours
Treatment modality	Trans pupillary diode laser therapy first line (argon laser second line)
Treating surgeon	Babies with ROP should be treated by ophthalmologists who have appropriate competency

Options to address the problem of ROP

Preventive services are an essential part of the health care system and include a diverse range of activities aimed at decreasing risks and health problems (Offord, 2000). There are three different levels of prevention aimed at reducing the burden of ROP in LMICs *(Figure 2).*

Primary prevention

Primary prevention prevents the disease before its occurrence (Offord, 2000). This is done by preventing exposures to the cause of disease. The major cause of ROP is preterm births. The major risk factors for preterm births include maternal weight, short birth intervals, maternal infections during pregnancy, and maternal chronic conditions. Antenatal care is preventive healthcare and it helps women in the prevention of potential health problems through prenatal screening (Gullotta & Bloom, 2003). Evidence suggests that there is a lack of ANC services utilized by women in LMICs. A study examining coverage of ANC services demonstrated that around 29.9% of women in Nigeria, 34.4.% in

Rwanda, 30.4% in Zambia, and 30.3% women in Nepal utilized ANC services (Benova, Tunçalp, Moran, & Campbell, 2018). The data from Pakistan Demographics and Health Survey shows improvement in the trend of antenatal care services utilized by women in Pakistan, however, there is still a need for improvement for utilization of ANC services. ANC services are important to prevent the risk factors of ROP including low birth weight and premature infants.

Secondary prevention

Secondary prevention reduces the consequences of an occurred disease. This is done by detection of disease at an earlier stage to prevent complications of the disease. Blindness is the major complication of ROP. To prevent the complication of blindness due to ROP, regular examinations and screening tests are important for a preterm infant (Gilbert et al., 2005). Regular ophthalmic examinations of a premature infant can help in early detection and the prevention of long-term complications. Screening of ROP requires proper infrastructure, coordination, planning, and skilled ophthalmologists to perform specialized procedures (Woolf, 2008). Most of the LMICs lack health care infrastructure, proper planning, and coordination, and skilled health care providers. This is the reason for the high incidences of ROP in LMICs (Peters et al., 2008).

Tertiary prevention

Tertiary prevention aims to reduce the long-term complications of the disease (Offord, 2000). This is achieved by preserving the quality of life and permanent impairments. Timely interventions within 48 hours to 72 hours are essential to save infants from visual impairments (Peters et al., 2008). Laser therapy is the gold standard treatment for retinopathy. In the absence of laser therapy, cryotherapy may be considered (Azad & Chandra, 2003). Evidence suggests the positive role of antivascular endothelial growth factor injection in the treatment of ROP (Azad & Chandra, 2003). Surgical intervention like scleral buckle and vitrectomy is performed for retinal detachment due to ROP (Azad & Chandra, 2003). These interventions require financial considerations. The countries like Pakistan where people pay out-of-pocket payments for health care services utilization, treatment of ROP remains a challenge.

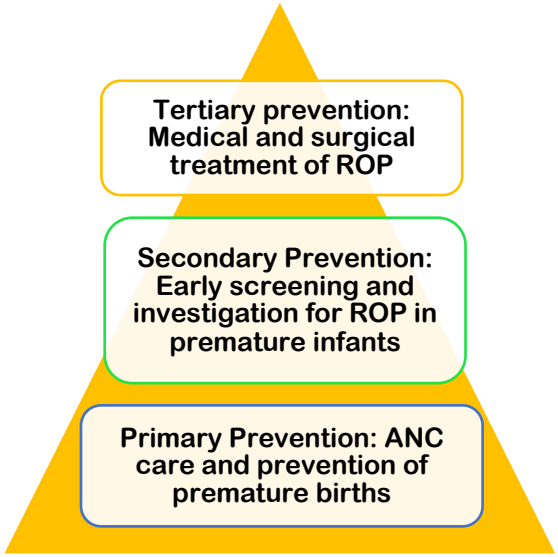

Figure 2. Levels of prevention for ROP

Discussion

The cases of ROP are increasing in LMICs leading to blindness among children (Brown et al., 1998). Neonatal care has been improved in recent years and have improved the survival rate of neonates which has correspondingly increased the risk of preterm-related ROP globally and extensively among LMICs. The major risk factors for ROP include prematurity, low birth weight, and oxygen administration to neonates. Therefore, birth weight and gestational age are important indicators for the screening of ROP as both of these are the major risk factors of ROP.

To decrease the burden of this important disease, it is important to integrate ROP screening services in every neonatal unit to timely diagnose and treat the problem. There are three different levels of prevention aimed at reducing the burden of ROP in LMICs. Primary prevention can be done by utilizing ANC services to prevent premature births. Secondary prevention can be done by detection of disease at an earlier stage to prevent complications of the disease through regular examinations and screening tests. And tertiary prevention can be achieved by preserving the quality of life and permanent impairments through procedures like laser therapy and cryotherapy.

Therefore the policymakers in these countries should establish newborn health policies for ROP prevention, the level of staffing of health care providers should be ensured by hospital administrators, the referral mechanisms for premature infants should be channelized and the guidelines for ANC care should be strengthened.

The program implementers in these countries need to build the capacity of health care providers for screening and treatment of ROP and there should be proper procurement of types of equipment required for ROP screening and they should develop region-specific ROP guidelines according to incidence and causes of ROP. The health care providers should educate mothers and parents about complications of preterm births before delivery and should emphasize the need for screening and diagnostic investigations required for preterm infants.

Conclusion

The incidences of ROP in premature children especially in LMICs are continuously increasing (Organization, 2012). The emphasis on preventive measures especially primary and secondary level prevention can help in decreasing the burden of ROP. This requires a multidisciplinary approach at all levels including at the level of policymaking, program implementation, health care providers, and community level. The health system of the countries should strengthen their emphasis on health care infrastructure, health care services, and preventive strategies rather than emphasizing curative services.

Conflicts of Interest

The author declares no conflicts of interest.

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