

## A Recent Review of Retinopathy of Prematurity : Scenario in South East Asia

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### Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative ocular condition that appears due to inappropriate vascularization of the immature retina of preterm neonates . If it progresses , it may cause visual morbidity even permanent blindness . South East Asian Countries like Bangladesh, Pakistan, India etc had improved medical services now a days . With modified medical cares and lowering infant mortality rate they are facing new threats like ROP . But it's very warm and encouraging that these countries are defending with all their resources and engaging more each day to prevent visual morbidity and blindness due to ROP .

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### Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative ocular condition that appears due to inappropriate vascularization of the immature retina of preterm neonates<sup>1</sup>. Terry<sup>2</sup> initially identified the ailment as retrolental fibroplasia in 1942. Owens and Owens noted in 1949 that the illness might potentially manifest during the postnatal phase, and Campbell proposed in 1951 that oxygen therapy might be a major contributing cause<sup>3,4</sup>. Three "epidemics" of ROP-related blindness have been reported thus far<sup>5,6</sup>. The first epidemic, which was mostly caused by unmonitored supplementary oxygen,

struck developed nations in the 1940s and 1950s. Premature infants survived at earlier gestational ages and with lower birth weights due to advancements in neonatal care, which caused ROP to virtually vanish. However, ROP resurfaced as a significant issue, causing the second epidemic to start in industrialized nations in the 1970s. Then, in the mid-1990s, the third epidemic started in low- and middle-income nations (first in Latin America and Eastern Europe, then in East and South Asia, and finally in sub-Saharan Africa) as a result of high preterm birth rates and disparities in neonatal care. ROP is frequently observed in larger and older newborns exposed to unregulated oxygen (similar to what had occurred in the US decades earlier), and certain countries or regions within countries lack the resources and technology necessary to maximize their care<sup>7</sup>. Preterm infant survival has grown dramatically as a result of improvements in neonatal care. However, there are still risks associated with this accomplishment, one of which being the emergence of retinopathy of prematurity. ROP is a disorder that affects preterm, low birth weight babies and is made worse by exposure to uncontrolled supplementary oxygen and other risk factors<sup>8</sup>. ROP is a fast expanding public health issue in low-middle-income nations. ROP is typically seen in over 50% of preterm children weighing less than 1,250 g at delivery, and it usually regresses on its own. However, the condition advances to the severe,

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vision-threatening phases in about 10% of newborns, necessitating immediate care and regular monitoring. Globally, 20,000 preterm babies are estimated to become blind from ROP every year and another 12,300 survive with visual impairment. The most significant risk factor for ROP is prematurity, whose incidence rises as gestation and birth weight decrease. Along with poorly controlled supplemental oxygen, anemia requiring blood transfusions, sepsis, and apnea, poor early weight development during the first few weeks of birth is also a risk factor for ROP. However, even in the absence of oxygen exposure or other risk factors, a very preterm, extremely low birth weight neonate may develop ROP<sup>9-14</sup>.

## Materials and Methods

This review is based on an in-depth study of the literature available, which was conducted (starting from 2023 until January 2025) in databases such as PubMed and Google Scholar using term such as: “retinopathy of prematurity”.

## Retinopathy Of Prematurity

A vaso proliferative condition of the immature retinal vasculature in premature infants is called retinopathy of prematurity (ROP). The line separating the vascularized retina from the avascular retina is where the defects associated with ROP arise. ROP has two separate phases and can develop between the third and fourth CA before 31 to 33 weeks of post conception age after conception, independent of gestational age at delivery. The relative hyperoxia of the extrauterine environment disrupts the normal vasculo-genesis of the retina during the acute initial phase. Certain regions of the anterior retina become non-vascularized and experience vaso obliteration as a result. A second chronic phase is brought on by the ensuing hypoxia and is marked by the creation of arteriovenous shunts and the growth of vascular and glial cells. Vascular endothelial growth factor (VEGF) overproduction is the cause of the second phase; other growth factors, including placental growth factor and insulin-like growth factor 1, are also involved. If the vascular changes are severe, especially if scar tissue forms, they may result in retinal detachment and blindness<sup>15,16,17,18</sup>.

## Core Causes of ROP

According to the World Health Organization

(WHO), a baby delivered before 37 weeks of pregnancy is considered premature, and if born before 28 weeks, it is considered severe. Less than 2,500 grams is considered low birth weight (LBW), while less than 1000 grams is considered very LBW.

Prematurity is the main risk factor for ROP, and its prevalence increases with decreasing gestation and birth weight. Poor early weight development during the first few weeks of life is another risk factor for ROP, along with extended and poorly managed supplementary oxygen, anemia necessitating blood transfusions, jaundice, phototherapy, sepsis, and apnea. Thrombocytopenia, failure to gain weight, and early cord clamping are additional risk factors. It is estimated that there are 9.7 trained ophthalmologists for every million people in Bangladesh. One of the contributing factors to the increase in ROP rates is the shortage of qualified ophthalmologists and staff<sup>8,19,20</sup>.

## ROP Screening

Babies with birth weight (BW)  $\leq 2000$ g

Babies born at gestational age (GA) of  $\leq 35$  weeks  
Selected preterm ( $>35$ - $<37$  weeks) infants who are sick and have needed extensive cardiorespiratory support and prolonged oxygen therapy, or who had apnea of prematurity, anemia needing blood transfusion, thrombocytopenia or neonatal sepsis should also be screened if the attending pediatrician or neonatologist considers them to be at high risk<sup>8</sup>.

## Location and Staging of ROP

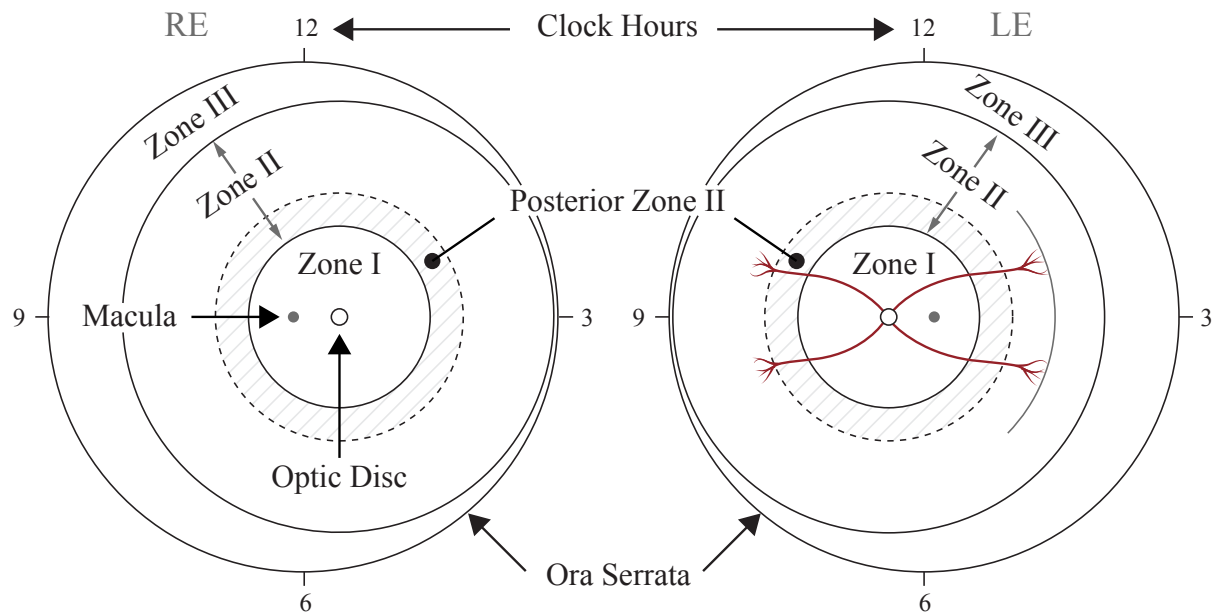
### Location :

Zone I is circular area surrounding the optic disc which has a radius of twice the distance from the optic nerve to fovea.

Zone II is circular band of retina which extends from the edge of Zone 1 to the ora serrata nasally and to the equatorial arc temporally.

Posterior Zone I is circular band of retina which extends from the edge of Zone 1 into Zone 2 with a width of 2 disc diameters.

Zone III is crescent shaped area on the temporal side which extends from Zone 2 to ora-serrata<sup>8,21</sup>.



**Figure 1 : Zones of ROP<sup>21</sup>**

**Stages :**

Stage 1 is thin white line which separates the vascular from the avascular retina

Stage 2 is ridge develops from the demarcation line, which has both height and width. May have isolated tufts of neovascular tissue on the surface of the retina (popcorn)

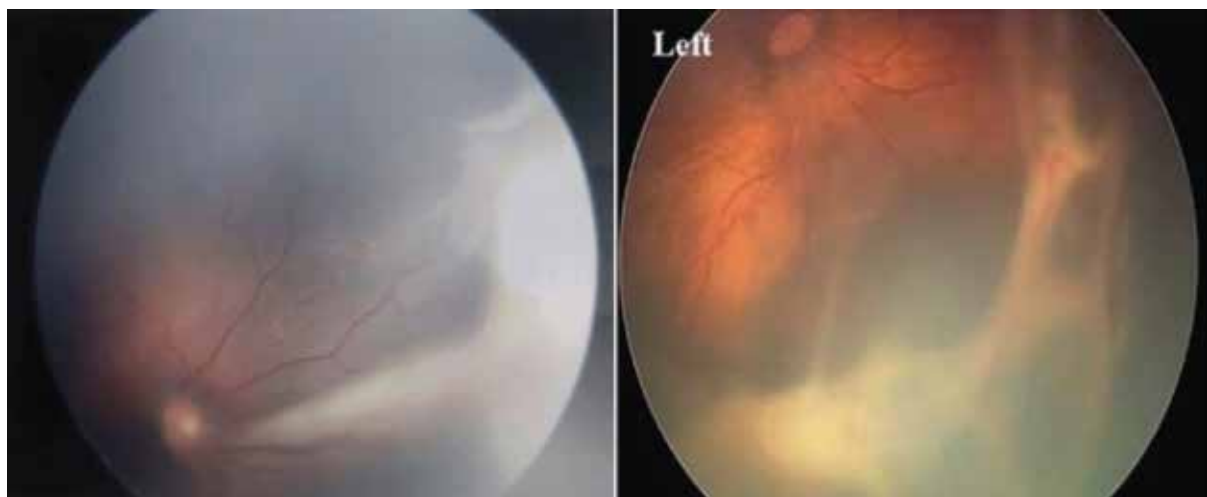
Stage 3 is extraretinal neovascular proliferation with abnormal vessels and fibrous tissue arising from the ridge and extending into the vitreous

Stage 4 partial retinal detachment; not involving the fovea (4a) or involving the fovea (4b)

Stage 5 is complete retinal detachment

Aggressive ROP (A-ROP) is severe form of ROP which develops rapidly.

Plus disease is presence of venous dilatation and tortuosity of retinal vessels. May be associated with vitreous haze and pupillary rigidity<sup>8,21</sup>.



**Figure : Stage 4 ROP (2 separate patients)**

## Screening

20-day strategy : Babies with a GA of  $\leq 30$  weeks or a BW of  $\leq 1500$ g

30-day strategy : Babies with a GA of  $\leq 35$  weeks or a BW of  $\leq 2000$ g 8.

## Treatment and Follow up Schedule

### Follow up Schedule :

Follow-up visit within 1 week:

Zone I: immature vascularization, stage 1 or 2 ROP

Posterior zone II: immature vascularization

Suspected presence of A-ROP

Recommended follow-up visit in 1–2 weeks:

Zone I: unequivocally regressing ROP

Posterior zone II: immature vascularization

Zone II: stage 2 ROP

Recommended follow-up visit in 2 weeks:

Zone II: immature vascularization, stage 1 ROP, or unequivocally regressing ROP

Recommended follow-up visit in 2–3 weeks:

Zone II: regressing ROP

Zone III: stage 1 or 2 ROP

## ROP Management Planning<sup>8</sup>

### End of screening

- Mature retinal vessels in both eyes i.e., extend into Zone 3 or to the ora and around the expected birth date
- ROP in Zones 1 and 2 is present but has definitely regressed or vessels are mature
- ROP in Zone 3 is present but is definitely regressing on at least two successive examinations

### Re-screen in 1 Week

- No previous ROP, immature retinal vessels in one or both eyes in Zone 1

### Re-screen in 2 Week

- No previous ROP, immature vessels in one or both eyes in Zone 2

| Zone   | Presence of Plus Disease | Stage 1                     | Stage 2                     | Stage 3                     |
|--------|--------------------------|-----------------------------|-----------------------------|-----------------------------|
| Zone 1 | Plus disease present     | Urgent Treatment            | Urgent Treatment            | Urgent Treatment            |
|        | No plus disease          | Re-screen in 1 week or less | Re-screen in 1 week or less | Urgent Treatment            |
| Zone 2 | Plus disease present     | Re-screen in 1 week or less | Urgent Treatment            | Urgent Treatment            |
|        | No plus disease          | Re-screen in 1- 2 week      | Re-screen in 1- 2 week      | Re-screen in 1 week or less |
| Zone 3 | Plus disease present     | Re-screen in 1 week or less | Re-screen in 1 week or less | Re-screen in 1 week or less |
|        | No plus disease          | Re-screen in 2 weeks        | Re-screen in 2 weeks        | Re-screen in 2 weeks        |

### Urgent Treatment within 24 hours :

- A-ROP
- Cannot assess stage or zone and plus disease is present
- Stage 4 and Stage 5 ROP

### Laser Photocoagulation

Zone I: any-stage ROP with plus disease or stage 3 ROP without plus disease

Zone I: stage 3 ROP without plus disease

Zone II: stage 2 or 3 ROP with plus disease

### Intravitreal Anti-VEGF

Intravitreal bevacizumab or ranibizumab for treatment of stage 3 ROP with plus disease in zone I

### Vitrectomy

Stage 4 and above needs Vitrectomy procedure<sup>8,21,22.</sup>

### Complications

Vitreous hemorrhage and retinal detachment are deadliest forms of complications that may lead to diminished vision and even blindness . Patients may also present with myopia, strabismus, amblyopia and anisometropia even after proper treatment<sup>22</sup> .

## ROP Prevention<sup>8</sup>

### Preterm birth prevention :

- Birth spacing
- Proper use of fertility treatments;
- Proper antenatal care for mothers at risk of preterm birth.

### Prevention of ROP:

- Ensuring high quality Neonatal intensive care unit (NICU) with regulated oxygen supplementation in health care facilities
- Antenatal steroids for fetal development in preterm birth

### In the delivery room and NICU:

- Very gentle resuscitation
- Avoid 100% supplemental oxygen (optimal levels 89% to 94%)
- Delayed cord clamping
- Provide swaddling and kangaroo care

### Prevention of visual impairment due to ROP:

- Follow scheduled screening for ROP
- Urgent treatment in advanced ROP
- Regular and long-term follow up according to schedule

## Recent ROP Scenario in Bangladesh

In Bangladesh, ROP is also a developing issue. Follow-up eye examination of preterm newborns under 33 weeks showed an incidence of 4.4% in few studies<sup>23,24</sup>. Bangladesh gives birth to about 3.75 million newborns annually. With a preterm birth rate of 14.5%, approximately 424,100 babies are born before 37 weeks of pregnancy<sup>25</sup>. Approximately 45,000 babies are born before 28 weeks of pregnancy or with low birth weight (less than 2,500 grams). Approximately 25,000 of them weigh 1,500 grams or fewer and are at high risk of ROP<sup>26</sup>.

Like other growing economies, health care services are growing day by day in Bangladesh. Improved special child care unit (SCANU) and neonatal intensive care unit (NICU) services increase specialized care for preterm, low birth weight and ill newborns.

Recently many studies were conducted in multiple tertiary hospitals and super specialty eye hospitals. These studies projected that maximum patients are coming from 28-32 weeks

gestational age (GA) group with mean GA extending from 30-31 years<sup>27-29</sup>. Maximum cases got birth weight between 800-1500 gm<sup>27,29</sup>. Maximum patient had come for first examination in or after 4 weeks, as their attendant were instructed by pediatrician or gynecologist. ROP in Bangladesh showed female predominance. Majority of the patients were hospital born and significant number of them had history of SCANU or NICU stay with heavy flow oxygen therapy. More than 20% ROP cases were twin or triplets. 80% or above ROP cases presented with neonatal multiple complications (jaundice / respiratory distress / blood transfusion/ sepsis/ congenital heart disease/ anemia/ respiratory distress syndrome) These co morbidities influence duration of hospital stay and also stimulate appearance of ROP. Among the presented cases more than 50% presented with A-ROP and plus disease. ROP laser and intravitreal antiVEGF injections are widely available treatment procedures in Bangladesh. Pars plana vitrectomy is also applicable here when needed<sup>27-30</sup>.

## Recent ROP Scenario in India

India reports the highest incidence of global preterm births, totaling 3.5 million annually, and is currently experiencing its third epidemic of ROP. Investigations carried out throughout India have indicated that the occurrence of ROP ranges from 2.3% to 47.2%. In 2010, India represented approximately 10% of the estimated global cases of visual impairment attributed to ROP. Given that 1 in 6 preterm births in India takes place at a gestational age of less than 32 weeks, and 40% of these require admission to a neonatal intensive care unit (NICU), with an 80% survival rate, it can be deduced that approximately 190,000 neonates are at risk of developing ROP. Based on the assumption that 10% of at-risk infants necessitate intervention, it can be estimated that approximately 20,000 infants in India will need ROP treatment annually<sup>31-37</sup>.

Screening usually begins at six postnatal weeks or 31 weeks post menstrually. Inspections occur every 1-2 weeks during screening until ROP diminishes or retinal blood vessels fully form, often between 40-50 weeks postmenstrual age. Telemedicine for ROP has been implemented



worldwide to address the shortage of ROP-trained ophthalmologists, and artificial intelligence (AI) as a screening tool may improve ROP screening and lead to automated, quantifiable, and objective ROP diagnosis. AI in ROP is used to diagnose plus illness, stage it, and create an automated severity score. i ROP DL system with 93% sensitivity and 94% specificity. AI-based computer assisted diagnosis can balance clinical screening sensitivity with manpower needs. 15% advanced to severe ROP and necessitated intervention. 35% of stage II and 40% of stage III Retinopathy of Prematurity. There were very few instances of stage IV and V Retinopathy of Prematurity. Ninety-five percent of the subjects were within a gestational age range of 28 to 31 weeks. 67.50% of the subjects had a birth weight of less than 1250 grams. Sixty percent of the participants were male. Risk factors include oxygen supplementation (73%), respiratory distress syndrome (48.5%), multiple births (22.5%), and sepsis (42%)<sup>38-42</sup>.

### Recent ROP Scenario in Pakistan

In 2023, Pakistan's infant mortality rate decreased to 55.7 per thousand live births, down from 82.5 per thousand live births in 2000, which increases its vulnerability to the ROP epidemic<sup>43</sup>. Retinopathy of prematurity (ROP) frequently remains unrecognized in Pakistan, attributed to the elevated incidence of low birth weight (LBW) and preterm births, the absence of standardized protocols, inadequate awareness among family physicians, and subpar neonatal care. The occurrence of ROP in Pakistan ranges from 10.5% to 24.6%. The elevated incidence of preterm births in Pakistan, coupled with significant healthcare disparities, presents critical challenges in the management of Retinopathy of Prematurity (ROP)<sup>44-47</sup>.

In Pakistan, Males accounted for 60.5% of ROP cases in Pakistan. The average birth weight was  $1.3 \pm 0.28$  kg, and the average gestational age was  $30.4 \pm 2.36$  weeks. Approximately 40%, 35%, and 20% of all premature newborns developed Grades I, II, and III. 32–34 weeks gestation was present in 60% of cases. Over 80% of the cases received oxygen therapy, and the majority had hospital deliveries<sup>48-50</sup>.

### Recent ROP Scenario in Nepal

In Nepal, incidence of retinopathy of prematurity

in Nepal is around 20%<sup>51,52</sup>. Maximum patients diagnosed with ROP had mean gestational age around 32 weeks and mean birth weight of 1600gm. Maximum cases were female. Hospital delivery was commonest among ROP cases. Majority of ROP cases came with 1001-1600gm body weight. Highest number of cases had gestational age of 30-32 weeks<sup>53-55</sup>.

### Recent ROP Scenario in Sri Lanka

Sri Lanka had developed modern medical services. With increased civilization, they were also suffering from raised number of ROP. They presented with around 20% ROP incidence there. They have huge number of ophthalmologists and retina specialists to overcome their ROP situations<sup>56,57</sup>.

### Limitations:

This study was conducted from publications from 2023. Long term evaluation must be necessary .

### Conclusion

Infant mortality rate is reducing day by day in South East Asia. High risk neonates are getting more sophisticated treatment and medical attentions. As a result, more preterm alive babies came with more risk of ROP development. Proper national policies with adequate implementation is necessary to combat this hazardous situation. Ophthalmologists with retina specialists together with gynecologists and pediatrician can function together as super hero here.

### Data Availability

Data used to support the findings of this study were included within this article.

### Ethical Aspect

Patient's confidentiality was ensured

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### Conflict of interest

None

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