

Prevention of Retinopathy of Prematurity: A Perinatal approach

Dharmapuri Vidyasagar

ABSTRACT

Retinopathy of prematurity (ROP) is a multifactorial vasoproliferative retinal disorder in the premature infant exposed to high oxygen therapy. Retinopathy of prematurity is a major contributor to childhood blindness. Whereas ROP in high-income countries is decreasing, it is increasing in the low and middle-income countries, such as India. On the other hand, ROP is also a preventable disease. So far, preventive programs have focused on pediatric, neonatal, and nursing practices: Minimizing exposure to oxygen of premature babies admitted to neonatal intensive care unit (NICU) in respiratory distress (RDS) and early detection of ROP and treatment by the ophthalmologists.

Prematurity is the major risk factor for ROP. Decreasing the risk of prematurity requires a perinatal approach. Evidence shows that good antenatal care, managing preterm labor, and administration of antenatal steroids decrease respiratory complication and the need for oxygen therapy in the premature infants. There is also a need for decreasing the elective cesarean sections (ECS) which add to iatrogenic preterm births and associated respiratory complications. New research shows that inflammatory factors that lead to premature labor also make the premature retinal vessels susceptible to developing ROP. These scientific findings lay ground for a stronger perinatal approach to prevent ROP in future. This article attempts to highlight the perinatal approach to prevent ROP.

Keywords: Childhood blindness, Global burden of ROP, Perinatal inflammation, Prevention of prematurity, Prevention of ROP, Retinopathy of prematurity.

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INTRODUCTION

Retinopathy of prematurity (ROP) is an endovascular proliferative disease in the premature infant who has been exposed to high oxygen concentration treatments in the immediate neonatal period. The cause and effect

of oxygen therapy and ROP have been established over 70 years ago.¹ Since then several epidemics of ROP have occurred in the industrialized Western World.² With changes in practices of managing infants with respiratory disease, improved surveillance of oxygen administration, early detection of ROP by screening, and implementation of several new therapies, ROP has steadily decreased over the last 30 years, specifically in the industrialized high-income countries. Recently ROP was declared as an avoidable disease by the World Health Organization.³

However, low and middle-income countries (LMICs) are suffering from the third epidemic of ROP. Countries, such as India and China together account for more than half of the total number of premature infants born in the world.⁴ India alone accounts for 3.5 million preterm infants annually. The incidence of ROP in India varies from 38 to 52% of "at-risk" babies in urban areas, and in rural areas the incidence of ROP is similar to urban population.⁵ The incidence of treatable ROP is 10% and this accounts for >60,000 infants annually who may progress to treatment requiring disease in India alone.⁶ Unfortunately, the impact of this disability will last through the life span (60–70 years) of the surviving premature newborn causing collective loss of productivity of millions of years. Retinopathy of prematurity is a lifelong disease. These staggering numbers will soon add to personal, social, and national economic burden particularly in the LMICs. Therefore, there is an urgent need to develop programs to prevent ROP and associated related visual disabilities and blindness.

IS ROP PREVENTABLE?

Experience over the last three decades in the industrialized countries tells us that ROP is a preventable disease. The prevention of ROP depends on many factors and many disciplines of medicine. Retinopathy of prematurity is primarily the disease of premature infants who develop respiratory complications requiring oxygen and ventilator support which are responsible for causing ROP. Figure 1 shows the potential role of various disciplines in the prevention of ROP: Obstetricians in the management of preterm labor and preterm deliveries, pediatricians and neonatologists in the management of premature infant during their early life with respiratory problems (hyaline

Professor Emeritus

Department of Pediatrics and Center for Global Health
University of Illinois at Chicago, Chicago, IL, USA

Corresponding Author: Dharmapuri Vidyasagar, Professor Emeritus, Department of Pediatrics and Center for Global Health University of Illinois, Chicago, IL, USA, Phone: (312) 9964185 Mobile: (630) 290 1153, e-mail: dvsagarmd@yahoo.com

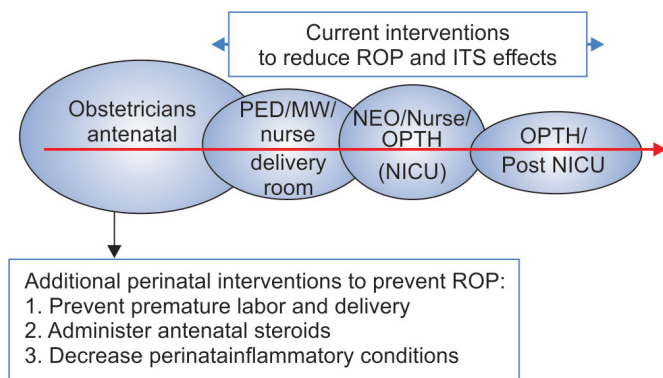


Fig. 1: The disciplines involved and their respective roles in the prevention and management of preterm babies and ROP. As stated in the text, each of the disciplines in the continuum of care of mother and the baby has important roles in prevention of ROP. As shown in the upper box, currently the disciplines of pediatrics, neonatologists, nursing, and ophthalmologists are fully engaged in prevention of ROP. The lower box identifies the perinatal interventions that may lower the incidence of ROP. The concept of the role of perinatal inflammation on ROP (shown in red) is a new one and needs further studies. See text for details

membrane disease), and early recognition and treatment of ROP by the ophthalmologist. Indeed prevention of ROP is the continuum of care of fetomaternal dyad from antenatal period to delivery and after delivery the care of the premature baby by the pediatricians and nurses in the neonatal intensive care unit (NICU). This is supplemented with the expert services of ophthalmologists in early diagnosis and treatment of ROP.

Preterm infants are at a high-risk for developing ROP, a multifactorial, severe, vasoproliferative retinal disorder that may lead to blindness. With the increasing survival rate of preterm infants, ROP has become a leading cause of childhood blindness. Blindness due to ROP is estimated to be 6–18% in industrialized countries, whereas in developing countries it may reach 38%. The incidence of ROP in the developed countries has been decreasing steadily, whereas the incidence of ROP is increasing steadily in developing countries. Indeed the incidence of ROP and blindness is much higher in developing countries than in developed countries. The reason for this includes (1) the high rates of premature birth, (2) lack of ROP awareness, lack of skilled personnel, or financial constraints, and (3) lack of screening and treatment programs in most neonatal units.

In order to develop a meaningful approach to prevent ROP, we need to understand the underlying risk factors that lead to ROP in premature infants. Prematurity and low birth weight are the basic causes of ROP. More the prematurity, higher the risk of developing RDS because of immaturity of lungs. Infants with RDS require administration of higher oxygen concentrations and other ventilator support to maintain normal oxygenation of blood. The immature retinal vasculature of premature

infant is susceptible to higher blood oxygen levels causing immediate vasoconstriction of retinal vessels followed by vasoproliferation resulting in ROP. There is a critical role of pediatricians and the neonatologists in providing optimal respiratory care and monitoring blood oxygenation in premature infants in RDS and avoid hyperoxia, a cause for ROP.

Role of Pediatricians, Neonatologists, and Nurses

So far the efforts to prevent ROP have focused on postdelivery management of premature baby in RDS and in the NICU and postdischarge of the baby. Pediatricians involved in caring for the premature babies must be trained in proper use of oxygen therapy in neonatal resuscitation of the premature babies in the delivery room. Oxygen should be used with caution as a drug with toxicity. They must avoid use of 100% oxygen as a routine for resuscitation. Lower concentration of O_2 can be delivered using oxygen blenders. Oxygen saturations of the baby should be monitored using pulse dosimeter. Once the baby is resuscitated and shifted to delivery room, the infant should be continuously monitored with pulse oximeter and maintain oxygen saturators between 88 and 92%. Adherence to these guidelines is very difficult but critical. In the NICU, it is the Nursing staff that monitors the infant closely; therefore, it is important to train the nursing staff to maintain oxygenation within the set limits of alarm. Nurses are key to prevention of ROP.

Both doctors and nurses must be oriented to proper use of oxygen therapy in the NICU. They must have proper training and orientation in the use of pulse oximetry. These include:

- All nurses in the NICU must be trained to operate pulse oximetry, setting up high and low limits, set the alarms, and know what to do when alarms ring.
- Written protocols must be available for oxygen therapy and use of pulse oximetry.
- All premature infants requiring oxygen therapy should have blender to deliver desired fraction of inspired oxygen. And infants must be placed on pulse oximeter.
- Extremely premature infants receiving oxygen and ventilator care (continuous positive airway pressure (CPAP)/ventilator) should have 1:1 patient nurse ratio.
- Nurse should keep records of pulse oximeter on hourly basis.

A recent study⁷ showed that a higher nurse to patient ratio leads to better control and higher proportion of time within target limits of oxygen saturation than with lower nurse to patient ratio. This improvement was mainly due

to reduction in hyperoxemia. In NICUs where the nurse to patient ratio was less (1:3), babies spent significantly more time in higher oxygen saturations, a potent cause for developing ROP.

Role of Ophthalmologists

Each NICU caring for high-risk infants requiring oxygen therapy and ventilator care must have the support of an ophthalmologist to initiate infant screening for ROP while the babies are still in the NICU. There should be well-written ROP screening protocols along with the ophthalmologist. Nurses must be trained to prepare the babies for ROP screening.

In addition, the ophthalmologists play a very important role in early recognition by universal screening of all premature infants at risk usually less than 32 weeks and birth weight <1,500 gm. The universal criteria for ROP screening have been established by various professional organizations. The classification of stages of ROP and appropriate treatment protocols have been defined.⁸ It has been shown in high-income countries that there is a close adherence to above guidelines for oxygen therapy, strict screening criteria, and close follow-up by a dedicated retinal ophthalmologist. These policies have decreased the incidence of ROP and prevented the poor sequel of ROP.

Castillo et al⁹ in South America have shown a significant decrease in the rate of severe ROP in very low birth weight infants in association with an educational program provided to all NICU staff and the implementation and enforcement of clinical practices of O₂ management and monitoring.

Role of the Obstetricians in the Prevention of ROP

Although ROP is primarily a disease of the premature infant after birth, we must focus on the subject of prevention of prematurity as much as we have focused on postdelivery care. Prevention of prematurity and therefore ROP also falls in the domain of the obstetricians. Improved obstetric care of mothers at risk of delivering premature babies is critical. Use of tocolytic agents to prevent preterm labor and use of antenatal steroids to enhance lung maturity are some of the obstetric strategies that will lower the risk of developing ROP. In addition, care given by the neonatologists in the NICU and involvement of ophthalmologists in the nursery and postdischarge care are important to have a good outcome of infants diagnosed to have ROP in the nursery. As stated in the document *Born Too Soon*,⁴ the new paradigm of care of the premature babies include: manage preterm labor with antenatal steroids, and babies in RDS with

oxygen and CPAP in developing countries. It also sets a new paradigm of intense training of health care personnel involved across the span of preconception, antenatal, delivery room, and NICU care in safe use of oxygen and proper use of pulse oximeter.

In general, the role of obstetricians in the prevention of ROP falls into three categories:

1. Prevention of preterm labor and preterm birth
2. Antenatal steroid treatment of mothers coming in premature labor.
3. Preventing perinatal inflammation.

Indeed all these efforts will have an impact on reduction of ROP.

Obstetricians have an important role in decreasing premature labor and preventing iatrogenic prematurity—a major consequence of nonmedically indicated elective cesarean sections (ECS)—and enhancing lung maturity using antenatal steroids in mothers who come in premature labor. Higher rate of prematurity¹⁰ and surfactant deficiency¹¹ are associated with babies delivered by ECS. Respiratory morbidity in ECS is inversely related to gestational age at the time of ECS.¹² Tests to assess lung maturity to the occurrence of iatrogenic RDS syndrome although useful are not in vogue nowadays even in developed or developing countries. The American College of Obstetricians and Gynecologists¹³ recommends that ECS be considered at 39 weeks or later at the onset of spontaneous labor to avoid iatrogenic RDS.

In spite of the association of higher rates of RDS with ECS and iatrogenic prematurity, there are no data regarding the rates of ROP among the iatrogenic premature babies. The data on the association of ECS and iatrogenic prematurity in LMICs are hard to come by. But it can be argued that since premature babies with RDS invariably are treated with oxygen therapy and some form of respiratory support without proper monitoring of oxygenation, there is a potential risk of developing higher rates of ROP. This is one the several areas where the obstetricians in LMICs should pay greater attention and avoid iatrogenic prematurity, thereby avoiding the associated problem of ROP.

DO ANTENATAL STEROIDS DECREASE ROP?

Higgins et al¹⁴ were the first to document the beneficial effects of antenatal steroids in reducing ROP in premature infants. They analyzed the risk factors in a group of premature infants with a birth weight of <1,250 gm who had undergone screening for ROP. They found that mothers who received antenatal steroids developed significantly less ROP that was stage 2 or higher than infants without a history of antenatal dexamethasone exposure—8.7 vs 35% respectively.

More recently Gyamfi-Bannerman et al¹⁵ published their results of randomized controlled trial of antenatal administration of betamethasone to women at risk for late preterm delivery. The results showed that there was a decreased need for substantial respiratory support during the first 72 hours after birth. Betamethasone administration also resulted in reduced rates of severe respiratory complications, including RDS. Reduction in the above-mentioned respiratory complications of premature infants would decrease the need for oxygen therapy and respiratory support.

Although the impact of dexamethasone on ROP was not the aim of their study, it showed that there was a significant decrease in bronchopulmonary dysplasia (BPD) in the dexamethasone treatment group. Thus, it can be assumed that shorter duration of exposure to oxygen and decreased incidence of BPD will also reduce the incidence of ROP. It will be of interest to further analyze this large data set to study the impact of antenatal steroids on the development of ROP.

PERINATAL INFLAMMATION AND ROP

There is increasing interest to study the relationship of perinatal inflammation and ROP since perinatal inflammation is also an underlying cause for preterm delivery. Sood et al¹⁶ measured several inflammatory cytokines in the blood obtained from infants with <1,000 gm birth weight and assessed the ROP staging during the first three postnatal weeks. Infants were grouped into three ROP groups: No ROP, mild, and severe ROP. They found that ROP was associated with eight inflammatory cytokines, suggesting a relationship of perinatal inflammation and ROP.

Later, Hellström et al¹⁷ concluded that “antenatal factors, such as placental infection and inflammation might predispose the fetal retina to severe ROP, and such a sensitization effect might constitute a prephase of the disease.” They also speculated that “by reducing risk factors that disrupt normal retinal vascularization (inflammation) is likely to be more effective than late treatment of neovascularization.” These interesting findings and speculations remain to be investigated further.

In conclusion, while the roles of pediatricians, nurses, and the ophthalmologists in the prevention of ROP and the role of perinatal services to decrease preterm births are well established, there are emerging new concepts of perinatal interventions to prevent ROP.

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