RETINOPATHY OF PREMATURITY: A REVIEW OF RISK FACTORS AND COMORBIDITIES

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ABSTRACT

Retinopathy of prematurity (ROP) is a disorder of the developing blood vessels in the premature retina and is a very important and preventable cause of childhood blindness. It usually affects premature babies who are exposed to certain risk factors to which it is found to be associated with. Recent advancements in neonatal care have led to an increase in the survival of low birth weight and premature infants, resulting in a rise of ROP incidence. This article aims to review studies done to find out risk factors and comorbidities associated with ROP.

KEYWORDS: Retinopathy of Prematurity, gestational age, childhood blindness, low birth weight, sepsis, oxygen therapy, apnea, blood transfusion.

Retinopathy of prematurity (ROP) was first described by Terry in 1942 as retrolental fibroplasia.[¹] Globally at least 50,000 children are blind from retinopathy of prematurity (ROP).²] In India alone, 500 children are estimated to become blind from ROP every year.

Earlier ROP was thought to be mainly associated with oxygen therapy. Later it was also reported in several cases without oxygen therapy, and even after oxygen therapy, all premature infants didn’t developed ROP. Finally, it was concluded that etiology of ROP is multifactorial occurring most frequently in the small and sick infants[³], but following three factors were found to be consistently and significantly associated with ROP: low gestational
age (LGA), low birth weight (LBW) and prolonged exposure to supplementary oxygen after delivery. Other putative risk factors are mechanical ventilation, sepsis, intraventricular hemorrhage, surfactant therapy, apnea, and anemia.

Two epidemics of retinopathy of prematurity (ROP) have been described till now in industrialized countries. The “first epidemic” occurred in the 1940s and 1950s, and affected mainly premature babies in USA and Western Europe. Unmonitored higher concentration of supplemental oxygen was the principal risk factor at that time. The "second epidemic" started in the 1970s, as a consequence of increased survival rates of extremely premature babies. Currently available data suggests that the proportion of blindness as a result of ROP varies greatly among countries, influenced by the levels of neonatal care and the availability of effective screening and treatment programmes. Now many developing countries like India and China are introducing or expanding intensive neonatal care services in the private as well as the government sectors, leading to an increase in ROP prevalence. This has now been referred to as the “third epidemic”.

Screening

ROP is amongst the leading causes of childhood blindness worldwide. Proper screening is necessary for early detection of cases and timely intervention when required to reduce this burden of blindness. This makes screening an important aspect of ROP. Various screening guidelines have been developed in different countries according to the incidence of ROP and the level of neonatal care facilities available. In India, according to RBSK, screening should be done for infants with either of the following.

1. Birth weight < 2000 gm
2. Gestational age < 34 weeks
3. Gestational age between 34 to 36 weeks with risk factors such as.
   Prolonged oxygen therapy, Cardio-respiratory support, Respiratory distress syndrome, Chronic lung disease, Fetal hemorrhage, Blood transfusion, Neonatal sepsis, Exchange transfusion, Intraventricular hemorrhage, Apneas, Poor postnatal weight gain.
4. Infants with an unstable clinical course who are at high risk (as determined by the neonatologist or pediatrician).

ROP screening should be done at 4 weeks after birth. But for infants of gestational age 28 weeks or birth weight less than 1200 gm screening should be done 2-3 weeks after birth.
This screening should continue at least every two weeks until.[9]

- Vascularization of the retina reaches normal completion, or
- Until ROP regresses, or
- Until ROP requiring treatment develops

Some studies on ROP

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Inclusion Criteria</th>
<th>Incidence of ROP</th>
<th>Risk factors</th>
</tr>
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<tbody>
<tr>
<td>Charan R et al[10] 1995, Chandigarh, India</td>
<td>BW ≤ 1700 gm.</td>
<td>47.27% (78/165)</td>
<td>LBW, LGA</td>
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<tr>
<td>Rekha et al[12] 1996, Banglore, India</td>
<td>BW &lt; 1500gm or GA ≤ 34 week</td>
<td>46 % (46/100)</td>
<td>GA ≤ 32 weeks, anemia, duration of oxygen therapy</td>
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<tr>
<td>Prendiville A et al[13] 1988, London</td>
<td>BW &lt; 1500gm</td>
<td>30% (42/140)</td>
<td>LGA, Acidosis (number of times that the pH was &lt;7.2), Hyperoxia (number of times that arterial oxygen tension was greater than 12 kDa)</td>
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<td>Wallace DK et al[14] 2000, USA</td>
<td>GA ≤ 30 week</td>
<td>Not studied</td>
<td>LGA, Sepsis, Rate of postnatal weight gain, Volume of transfused erythrocyte</td>
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<tr>
<td>Yang CS et al 2001[15], China</td>
<td>BW &lt; 2000 gm or GA &lt; 36 week</td>
<td>25% (27/108)</td>
<td>Artificial ventilation, sepsis, Chronic lung disease, Periventricular leukomalacia, RDS, IVH, Congenital heart disease</td>
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<tr>
<td>Tae-im Kim et al3 2004, Korea</td>
<td>BW ≤1500 gm or GA of ≤28 week</td>
<td>21.1% (83/392)</td>
<td>LGA, LBW, Sepsis, Apnea, Prolonged use of a ventilator, Surfactant therapy</td>
</tr>
<tr>
<td>Gupta VP et al[16] 2004, New Delhi, India</td>
<td>GA ≤35 weeks or BW ≤1500 gm</td>
<td>21.7% (13/60)</td>
<td>Oxygen therapy, sepsis, apnea</td>
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<tr>
<td>Dutta S et al[17] 2004, Chandigarh, India</td>
<td>GA ≤32 week or BW ≤1,700 gm or preterm with oxygen therapy ≥30 days</td>
<td>Not studied</td>
<td>LGA, LBW, Administration of packed cells and double-volume exchange transfusion</td>
</tr>
<tr>
<td>Shah et al[18] 2005, Singapore</td>
<td>BW &lt; 1500 gm</td>
<td>29.2% (165/564)</td>
<td>LBW, maternal preeclampsia, pulmonary hemorrhage, duration of ventilation, CPAP</td>
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<tr>
<td>Study ID</td>
<td>Authors</td>
<td>Year, Location</td>
<td>Criteria</td>
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<td>11</td>
<td>Akkoyun I et al.</td>
<td>2006, Turkey</td>
<td>GA ≤ 32 weeks</td>
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<tr>
<td>12</td>
<td>Anand vnekar et al.</td>
<td>2007, Chandigarh, India</td>
<td>Preterm babies with ROP</td>
</tr>
<tr>
<td>13</td>
<td>Austeng et al.</td>
<td>2009, Sweden</td>
<td>GA &lt;27 weeks</td>
</tr>
<tr>
<td>14</td>
<td>Chaudhari S et al.</td>
<td>2009, Pune, India</td>
<td>GA ≤32 week or BW &lt;1,500 gm</td>
</tr>
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<td>15</td>
<td>Kumar et al.</td>
<td>2011, New Delhi, India</td>
<td>BW ≤1,500 gm or GA ≤32 week, BW 1,501–1,800 gm or GA 33–34 weeks if associated with oxygen use or mechanical ventilation.</td>
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<tr>
<td>16</td>
<td>Hakeem A.A et al.</td>
<td>2012, Egypt</td>
<td>GA ≤ 32 weeks or BW ≤ 1500 gm or oxygen therapy for more than 7 days</td>
</tr>
<tr>
<td>17</td>
<td>Krishna A Rao et al.</td>
<td>2013, Karnataka, India</td>
<td>BW &lt; 1500 gm and/or GA ≤ 32 weeks and also those who were at risk for ROP</td>
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<td>18</td>
<td>Hadi et al.</td>
<td>2013, Egypt</td>
<td>GA &lt; 32 weeks BW &lt; 1250 gm</td>
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<tr>
<td>19</td>
<td>Shivaprasad B et al.</td>
<td>2014, Karnataka, India</td>
<td>GA &lt; 35 weeks and/or BW &lt; 1750 gm</td>
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<td>20</td>
<td>Yousef Alizadeh et al.</td>
<td>2015, Iran</td>
<td>BW ≤2500 gm and/or GA ≤36 weeks</td>
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<tr>
<td>21</td>
<td>Chattopadhyay et al.</td>
<td>2015, Sikkim, India</td>
<td>GA 35 to 37 week or BW &lt; 1700 gm and BW less than 2000 gm with risk factors for ROP</td>
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<tr>
<td>22</td>
<td>Crystal Le et al.</td>
<td>2016, Telangana, India</td>
<td>GA ≤ 34 week and/or BW ≤1750 gm and infants with sepsis, respiratory distress syndrome, or long-term oxygen therapy</td>
</tr>
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</table>

**Risk factors and comorbidities**

According to a WHO report, India is having the highest number of preterm babies being delivered every year i.e. 3,519,100 which along with the lack of good neonatal care and proper screening program results in high incidence of ROP in India. Various risk factors and comorbidities have been found to be associated with ROP and the role of many others is being studied.

**Risk factors**

1) **Prematurity (Low birth weight and low gestational age)** - As ROP is a disease of the premature retina so in almost all the studies prematurity (LBW and LGA) has been found as the most important risk factor for ROP. Shah VA et al in their study conducted in Singapore reported a 29.2% incidence of ROP among VLBW and found a strong association of ROP with smaller, more immature and sicker infants.

2) **Oxygen**- In many studies oxygen was established as an important risk factor causing ROP. Norman Ashton et al in their randomized controlled trial which was published in 1956 stated that the severity of the vaso-obliterative effect of oxygen is directly proportional to the concentration and duration of oxygen administered. Flynn et al. conducted a study in 1992 and found a significant association between the duration of time the transcutaneous PO2 was greater than or equal to 80 mm Hg and the incidence and severity of ROP. Later STOP ROP study was conducted in 2000 to compare the efficacy and safety of 96%-99% SaO2 (conventional) vs 96%-99% SaO2 (supplemental) for infants with prethreshold ROP to reduce the likelihood of progression to threshold ROP. It was
reported that supplemental oxygen didn't cause a further progression of prethreshold ROP but also didn't significantly reduce the number of infants requiring peripheral ablative surgery.\[46\] The Surfactant, Positive Airway Pressure, Pulse Oximetry Randomized Trial (SUPPORT) and Benefits of Oxygen Saturation Targeting Study II (BOOST-II) compared 85-89% SaO2 vs. 91-95% SaO2 and found that the lower oxygen levels were associated with increased mortality, but lower rates of ROP.\[47\] Mccolm et al in their study in 2001 found that oxygen variability, rather than a high level of oxygen is associated with the severity and incidence of ROP.\[48\]

3) **Multiple birth-** Multiple gestation is usually associated with increased risk for preterm birth, LBW, anemia, and perinatal morbidities, which may affect the risk of ROP in such babies.\[34,49,50\] In some studies it is found to be significantly associated with ROP.\[39–42,51,52\] while in many others no differences between singleton and multiple births were found.\[53–55\]

**Systemic comorbidities**

Infants with ROP generally have other systemic abnormalities also, like anemia, sepsis, necrotizing enterocolitis, cardiac defects, bronchopulmonary dysplasia, intraventricular hemorrhage\[56\], cerebral palsy and developmental delay.\[57\] The severity of ROP can also be considered as a predictor of neurodevelopmental outcome later in life.\[58\]

1) **Pulmonary complications** like Apnea of prematurity\[3,16,22,25,27,29,31,33,41,52\], respiratory distress syndrome\[15,20,23,27,30,52\], bronchopulmonary dysplasia\[33,43,51\], chronic lung disease\[15\] requires prolong oxygen therapy and mechanical ventilation\[3,15,18,25–27,39,41,43\], both of which are established risk factors of ROP. So, infants with such complications are more prone to the development of ROP.

2) **Anemia of Prematurity-** Anemia is much more common among preterm babies because of the lack of impaired erythropoiesis which is termed as Anemia of prematurity. In many studies, it is established as a risk factor for ROP.\[12,27,30,42,59\] Such babies often require blood transfusion and recombinant erythropoietin (EPO) transfusion both of which are found to be associated with ROP.\[17,20,22,24–26,33\] Although there are some other studies that found no significant relationship between ROP and blood transfusion and EPO administration.

3) **Patent Ductus arteriosus-** In many studies, PDA has been established as a risk factor of ROP.\[15,23,26,27,33,39\] This can be explained by the fact that in such patients there is a bypass of
systemic blood flow which may render retina hypoxic, and this can be a cause of the
development and progression of ROP. Indomethacin used in such patients is also found as a
risk factor for ROP.\(^{60}\) But in many other studies no significant relationship between ROP
and PDA was found, so much more studies and research are needed to find the strength of the
association of ROP and PDA.

4) Sepsis- Sepsis is established as a risk factor for ROP in many studies.\(^{3,15,22,24,26,27,30,32,33,52,61,62}\) Perinatal infection and inflammation are suggested as a
reason for increased incidence of ROP in such patients. Still, more research is awaited in this
field.

5) Intraventricular hemorrhage (IVH)- IVH is a complication of prematurity and in many
studies it has been found to be significantly associated with ROP.\(^{15,25,27,51,52}\)

6) Poor postnatal weight gain- A few studies have shown a significant relationship
between poor postnatal weight gain and an increased risk of developing ROP.\(^{63–66}\) Wallace
et al\(^{14}\) in their study found poor postnatal weight gain as a risk factor for the development of
severe (stage 3 or greater) ROP. They concluded that special attention should be taken for
infants who gain less than 50% of their birth weight in the first 6 weeks of life. In many
studies, it has been found that WINROP (Weight, insulin-like growth factor, neonatal
retinopathy of prematurity) algorithm can predict the occurrence of ROP in infants.\(^{67–72}\)
Gaurav Sanghi et al\(^{53}\) (2018) conducted a study to find its efficacy in detecting sight-
threatening type 1 retinopathy of prematurity (ROP) in Indian preterm infants. They enrolled
70 infants out of which 31 (44.28%) developed Type 1 ROP. They found its sensitivity in
detecting Type 1 ROP to be 90.32% and overall specificity was found to be 38.46%.

CONCLUSION
We can see noticeable variation in incidence and risk factors of ROP in various studies
conducted in different countries and even in same country. This can be explained by
following reasons.

1) Heterogeneity of subjects in terms of race and ethnicity 2) Differences in inclusion criteria
used in different studies 3) Diagnostic disagreement among ophthalmologists 4) Differences
in screening guidelines and level of neonatal care.

Screening has a very crucial role in ROP management for early detection of cases and timely
intervention if needed to prevent poor sequelae of disease. Considering the poor outcome of
the surgery in later stage early intervention in the form of laser or Anti VEGF is the best treatment available. There should be a good communication and cooperation between a neonatologist and an ophthalmologist for proper and timely screening of high risk babies and whenever possible ROP screening should be done before discharging such babies. A proper record must be maintained of all babies who require review and further follow up must be ensured. Parents must be counseled properly about the prognosis of disease and importance of screening. Its medico legal importance must not be neglected, because if a child goes blind due to late or missed screening then both the neonatologist and the ophthalmologist will be at very high risk of getting into a lawsuit. Also there is need of much more research work to be done in this field to find out many other risk factors and co morbidities associated with ROP.

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BIBLIOGRAPHY


