WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 5, 1235-1248. Review Article ISSN 2277– 7105

RETINOPATHY OF PREMATURITY: A REVIEW OF RISK FACTORS AND COMORBIDITIES

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Article Received on
20 Feb. 2019,
Revised on 10 March 2019,
Accepted on 31 March 2019
DOI: 10.20959/wjpr20195-14593

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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.[4] 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.[5] The "second epidemic" started in the 1970s, as a consequence of increased survival rates of extremely premature babies.[6] 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.[7] 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”.[7]

Screening

ROP is amongst the leading causes of childhood blindness worldwide.[8] 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[9], 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

	Author and year	Inclusion Criteria	Incidence of ROP	Risk factors
1	Charan R et al[10] 1995, Chandigarh, India	BW ≤ 1700 gm.	47.27% (78/165)	LBW, LGA
2	Gopal L et al[11] 1995, Madras, India	BW <2000 gm	38% (19/50)	LGA, LBW Oxygen supplementation
3	Rekha et al[12] 1996, Banglore, India	BW < 1500gm or GA ≤ 34 week	46 % (46/100)	GA ≤ 32 weeks, anemia, duration of oxygen therapy
4	Prendiville A et al[13] 1988, London	BW < 1500gm	30% (42/140)	LGA, Acidosis (number of times that the pH was <7.2), Hyperoxia (number of times that arterial oxygen tension was greater than 12 kDa)
5	Wallace DK et al[14] 2000, USA	GA ≤ 30 week	Not studied	LGA, Sepsis Rate of postnatal weight gain, Volume of transfused erythrocyte
6	Yang CS et al 2001[15], China	BW < 2000 gm or GA < 36 week	25% (27/108)	Artificial ventilation, sepsis Chronic lung disease, Periventricular leukomalacia, RDS, IVH, Congenital heart disease
7	Tae-im Kim et al[3] 2004, Korea	BW ≤1500 gm or GA of ≤28 week	21.1% (83/392)	LGA, LBW, Sepsis, Apnea, Prolonged use of a ventilator, Surfactant therapy
8	Gupta VP et al[16] 2004, New Delhi, India	GA ≤35 weeks or BW ≤1500 gm	21.7% (13/60)	Oxygen therapy, sepsis, apnea
9	Dutta S et al[17] 2004, Chandigarh, India	GA ≤32 week or BW ≤1,700 gm or preterm with oxygen therapy ≥30 days	Not studied	LGA, LBW, Administration of packed cells and double-volume exchange transfusion
10	Shah et al[18] 2005, Singapore	BW < 1500 gm	29.2% (165/564)	LBW, maternal preeclampsia, pulmonary hemorrhage, duration of ventilation, CPAP

11	Akkoyun I et al[19] 2006, Turkey	GA ≤ 32 weeks	Not studied	LBW, RDS, volume of blood transfusion, duration of artificial ventilation
12	Anand vnekar et al.[20] 2007, Chandigarh, India	Preterm babies with ROP	Not studied	Out born RDS, Exchange Transfusion
13	Austeng et al[21], 2009 Sweden	GA <27 weeks	72.7% (368/506)	LGA, LBW
14	Chaudhari S et al[22] 2009, Pune, India	GA ≤32 week or BW <1,500 gm	22.3% (123/552)	Oxygen therapy, sepsis, Apnea
15	Kumar et al[23] 2011, New Delhi, India	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.	11.9% (84/704)	RDS, PDA requiring medical or surgical management, meningitis
16	Hakeem A.A et al[24] 2012, Egypt	GA ≤ 32 weeks or BW ≤ 1500 gm or oxygen therapy for more than 7 days	19.2% (33/172)	LGA, Sepsis, Oxygen therapy Frequency of blood transfusions
17	Krishna A Rao et al[25] 2013, Karnataka, India	BW < 1500 gm and/or GA ≤ 32 weeks and also those who were at risk for ROP	21.6% (61/282)	LBW Prematurity, IVH, Apnea, CPAP duration, Packed red blood cell transfusion
18	Hadi et al[26] 2013, Egypt	GA < 32 weeks BW < 1250 gm	34.2% (52/152)	LBW, LGA, packed red blood cell and/or plasma transfusion, sepsis, duration of ventilation, intraventricular hemorrhage, PDA
19	Shivaprasad B et al 2014[27], Karnataka, India	GA < 35 weeks and/or BW < 1750 gm	13 % (13/100)	LGA, LBW, Ventilation exposure to oxygen, RDS, Hyperoxia (>150 mmHg), hypoxia (<40 mmHg), IVH, Apnea, Sepsis, PDA, Shock, Anemia,
20	Yousef Alizadeh et al[28] 2015, Iran	BW ≤2500 gm and/or GA ≤36 weeks	20.6% (64/310)	LBW and LGA
21	Chattopadhyay et al[29] 2015, Sikkim, India	GA 35 to 37 week or BW < 1700 gm and BW less than 2000 gm with risk factors for ROP	44% (22/50)	LBW, LGA, Apnea
22	Crystal Le et al 2016[30], Telangana, India	GA ≤ 34 week and/or BW ≤1750 gm and infants with sepsis, respiratory distress syndrome, or long-term oxygen therapy	2.3% (66/2910)	LGA, LBW RDS, Oxygen therapy, Sepsis Anemia of prematurity

23	Ashwani Kumar et al[31] 2017 Punjab, India	BW ≤ 1500 gm and/or GA ≤32 weeks	40.3% (31/77)	LBW, LGA, Apnea of prematurity
24	Reyes et al[32] 2017, Oman	GA < 32 weeks BW < 1500 gm	40.4% (69/171)	LBW, LGA, prolong of oxygen therapy, late-onset sepsis
25	Tian Wu et al 2018,[33] China	GA < 32 weeks BW < 1501 gm	26.0% (131/504)	LGA LBW, in vitro fertilization, apnea of prematurity, sepsis, BPD, PDA, volume of blood transfusion

BW: Birth weight, GA: Gestational age, PDA: Patent ductus arteriosus, CPAP: Continuous positive airway pressure, IVH: Intraventricular hemorrhage, BPD: Bronchopulmonary dysplasia, RDS: Respiratory distress syndrome.

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[34] which along with the lack 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.[3,10,12,16,18,18,19,21,25,26,28–30,32,33,35–43] Shah VA et al[18] 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.[3,3,3,11,12,16,18,22,24,25,32,35,40,41] 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.[44] 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.[45] 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[3,16,22,25,27,29,31,33,33,41,52], 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 VEFG 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.

Financial support and sponsorship- Nil.

Conflicts of interest- There are no conflicts of interest.

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