**Original Article**

**Ocular Morbidity of Preterm Infants Screened for Retinopathy of Prematurity at 2 Years of Age – A Prospective Follow up Study**

**Authors**

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**Abstract**

**Background:** Prematurity by itself carries a lifelong increased risk of ocular morbidity, regardless of whether the baby developed acute phase ROP. When visual acuity and contrast sensitivity are measured later in life for children born prematurely compared to term birth, median values are significantly lower. Prematurity can later lead to sequelae which is mainly divided into 4 categories; visual functions, strabismus, refractive errors mainly myopia and those affecting the ocular structure like retinal detachment, glaucoma, cataract.

Thus we can infer that, ROP as such is not preventable but the blindness from ROP is one of the few causes of childhood visual disability in which blindness should, by timely treatment, be prevented. There is also need for long term follow up of these children to detect any sequelae.

**Materials and methods**- Prospective consecutive case series of preterm infants screened for ROP at a tertiary eye care center over a period of 2 years.

**Results**- Refractive errors occurred more frequently in the premature babies as compared to the general population. Among refractive errors, myopia predominated in all groups. The prevalence of refractive errors and the degree of myopia were significantly affected by the presence of ROP, severity of ROP, decreasing birth weight and gestational age. Astigmatism also occurred more frequently in the ROP group. Degree of astigmatism was also higher in the ROP group as compared to the premature babies without ROP.

Among other problems affecting ocular structure, Strabismus had a significant association to the presence of ROP. All other sequelae like cataract, nystagmus, retinal detachment and anterior segment problems were only seen in the cicatricial ROP group.

**Conclusions**- This study stresses the need for early screening of premature babies for the presence of refractive errors and other problems of ocular structure like strabismus, nystagmus, cataract which can enable these babies to have a normal visual development especially in developing countries where there is a rise in neonatal services.

**Key Words** – Prematurity, Retinopathy of prematurity, Strabismus, Refractive errors.

**Introduction**

Retinopathy of Prematurity (ROP) is a vasoproliferative disorder of retina primarily affecting premature infants. The incidence of Retinopathy of Prematurity as one of the leading causes of blindness in children is on the rise. Worldwide
there are an estimated 50,000 children at least blinded, and many more disabled, by this condition. Although in the beginning it was more prevalent in developed countries, with the advances in neonatal care and increased survival of low birth weight infants it is now gaining significance in developing countries as well. In India, the incidence of ROP is estimated to be about 20% according to recent studies. ROP has been reported in preterm infants of larger birth weight and older gestational ages in Asians compared to those in the US, possibly because of variations in ethnic groups, regulation and monitoring of oxygen delivery, and the availability of prenatal care. Preterm infants with birth weight less than 32 weeks and/or gestational age less than 32 weeks need to be screened for development of Retinopathy of Prematurity. Blindness from ROP is increasingly restricted to the most immature babies less than 1000g. In developed countries blindness from ROP is stable despite the increasing survival of low birth weight babies because of the sophisticated neonatal care and awareness of this blinding disease. But in the developing countries, as the neonatal services are increasingly being provided, the number of cases of ROP is also increasing because of the lack of proper screening programs. ROP can later lead to sequelae which is mainly divided into 4 categories; visual functions, strabismus, refractive errors mainly myopia and those affecting the ocular structure like retinal detachment, glaucoma, cataract. Thus we can infer that, ROP as such is not preventable but the blindness from ROP is one of the few causes of childhood visual disability in which blindness should, by timely treatment, be prevented. A proper protocol for the screening of babies for ROP. There is also need for long term follow up of these premature children with particular emphasis to ROP babies to detect any sequelae.

Aim and Objectives
1. To study the occurrence of ocular problems like refractive errors, strabismus, nystagmus and cataract at 2 years of age in preterm children screened for retinopathy of prematurity.
2. To study the effect of stage of ROP, gestational age and birth weight on the development of refractive errors at 2 years of age.

Materials and Methods
Study Design: Prospective follow up study
Study Setting: Regional institute of ophthalmology
Study Population: Consecutive preterm infants screened for ROP in Regional institute of Ophthalmology
Study Duration: The study duration is 2 yrs
Sample Size: The sample size has been calculated to select a sample for this study using the formula:

\[ N = \frac{Z_2 PQ}{d^2} \]

Where \( N \) = sample size
\( Z_2 = 1.96 \) for a significance level of 95%
\( P \) = proportion of strabismus among ROP children (30%)
\( Q = 100 - P \) (70%)
\( D = 20\% \) of \( P \)

Substituting these values in the equation, the sample size for this study was calculated as 224.

Inclusion Criteria
1. All preterm infants who were screened at RIO, TVM with gestational age less than 35 weeks
2. Those willing for follow up

Exclusion Criteria
1. Preterm infants with other morbidities not related to prematurity
2. Those not willing for follow up

Methodology
The study is conducted on preterm infants screened for ROP in our institute. Of these the ROP infants are categorized according to the ‘International Classification of Retinopathy of Prematurity’. The screening is done at 4 weeks of age or 31 weeks of gestational age.
(whichever is later) and then followed up at 6 months, 1, and 2 years of age to detect the development of refractive errors, strabismus or cataract or any other sequelae.

- At each follow up, the following details are observed:
  - visual acuity in terms of visual behavior, fixation to light, following light beam and appropriate age matched testing strategies
  - Presence of other problems like strabismus, nystagmus or cataract.
  - Then they are called for refraction by retinoscopy. For this the pupils are
  - dilated using homatropine eye drops on the day of refraction or atropine 1% once daily three days prior to refraction.

**Statistical Analysis**

Statistical analysis was done using SPSS software. Quantitative variables are summarized (days of IBN admission, birth weight, gestation age, astigmatism, myopia) using mean and standard deviations or median with interquartile range (IQR). Qualitative variables (type of premature infants, sex, gestational age, comorbidities, strabismus presence & type, ocular morbidities, stage of ROP) are summarized using proportions. Chi-square test is used for testing association between qualitative variables like spherical equivalent category and ROP category, birth weight category, gestational age category, astigmatism. Non parametric tests (Mann Whitney test, Wilcoxon sign rank test, Kruskal Wallis test) were applied used to compare quantitative variables following non-normal distribution

**Results**

A total of 250 infants were eligible and enrolled into the study over a period of 6 months. Of this, 2 infants had died due to respiratory distress 1 month postnatally. 20 infants did not turn up for follow up and thus were dropped from the study. Thus a total of 228(454 eyes) infants were studied and followed up over a period of 2 years. Out of the total of 228 infants, 47% were males while 53% were females.

Of the total of 228, 183 had no retinopathy of prematurity (ROP) and 45 infants had ROP. Thus the incidence of ROP in our study was 19.7%. Among the ROP infants enrolled in our study, all infants had ROP in both eyes.

**Gender Distribution**

<table>
<thead>
<tr>
<th>Type of ROP</th>
<th>male n(%)</th>
<th>female n(%)</th>
<th>total n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROP</td>
<td>27 (60%)</td>
<td>18 (40%)</td>
<td>45 (20%)</td>
</tr>
<tr>
<td>No-ROP</td>
<td>80 (43.7%)</td>
<td>103 (56.3%)</td>
<td>183 (80%)</td>
</tr>
<tr>
<td>Total</td>
<td>107 (47%)</td>
<td>121 (53%)</td>
<td>228 (100%)</td>
</tr>
</tbody>
</table>

n=no. of eyes

**Gestational Age Distribution**

The mean gestational age of the ROP group was 30 weeks with a standard deviation of 2.2 weeks, and 33 weeks in the no-ROP group with a standard deviation of 2.1 weeks. In the ROP group, 37 eyes out of the 45 babies (82.2%) belonged to the less than 1.5 kg category. While in the No-ROP group majority were in the more than 1.5 kg category.

The mean gestational age of the ROP group was 30 weeks with a standard deviation of 2.2 weeks, and 33 weeks in the no-ROP group with a standard deviation of 2.1 weeks. In the ROP group, majority of the infants (21 babies) belonged to the 30-32 weeks while 12 were less than <29 weeks. No cases were reported after 34 weeks of gestation. The most immature baby screened was at 27 weeks.

In the No-ROP group, only 4.9% belonged to the <29 weeks and more than 50% belonged to the 33-35 weeks.

The mean gestational age of the ROP group was 30 weeks with a standard deviation of 2.2 weeks, and 33 weeks in the no-ROP group with a standard deviation of 2.1 weeks.
In the ROP group, 37 eyes out of the 45 babies (82.2%) belonged to the less than 1.5 kg category. While in the No-ROP group majority were in the more than 1.5 kg category. That is, most of the ROP babies were in the category of very low birth weight. This agrees with earlier studies that quote low birth weight to be a risk factor for ROP.

Relation between Spherical Equivalent and the Birth Weight at 2 Years

Table 3

<table>
<thead>
<tr>
<th>Birth weight (gm)</th>
<th>Type of refractive error</th>
<th>Myopia</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High (&gt;6D) n (%)</td>
<td>Medium 3 to 6D n (%)</td>
<td>Low &lt;3D n (%)</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>8</td>
<td>27</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>3.7%</td>
<td>12.4%</td>
<td>53.2%</td>
</tr>
<tr>
<td>1500 or above</td>
<td>0</td>
<td>8</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>3.4%</td>
<td>62.7%</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>35</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td>1.8%</td>
<td>7.7%</td>
<td>58.1%</td>
</tr>
</tbody>
</table>

Chi-square p value< 0.05, n=no. of eyes
The above table shows that the spherical equivalent increased with increasing birth weight. It is noteworthy that high myopia was found only in the group of birth weight less than 1500g.

**Relation of Spherical Equivalent to the Gestational Age At 2 Yrs**

Table 4

<table>
<thead>
<tr>
<th>Type of refractive error</th>
<th>Myopia</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>medium myopia (&gt;-6D) n (%)</td>
<td>low myopia (-3D to 6D) n (%)</td>
</tr>
<tr>
<td>Gestational Age(In weeks)</td>
<td>high myopia (&gt;6D) n (%)</td>
<td></td>
</tr>
<tr>
<td>29 wks and less</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>30 to 32 wks</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>33 to 35 wks</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>26</td>
</tr>
</tbody>
</table>

Chi square p value=0.006

At two years, spherical equivalent had a significant relation to the gestational age.(p=0.006)
There was a definite gradient of degree of myopia in each category with medium and high myopia occurring in the more immature babies.

**Relation between Myopia and ROP at 2 yrs**

Figure 3 : Myopia and ROP AT 2 YR(% of eyes)

Myopia occurred in both ROP infants and premature infants without ROP, it was more commonly seen in the ROP category. That is, 91% of ROP eyes were myopic as against only 75% of the without ROP category. ROP babies had 1.2 times more chance to have myopia than the control group. (RR=1.21)
This association of ROP to myopia was statistically significant (p= 0.0001).

**Analysis of Other Ocular Sequelae**

**Strabismus: Relation of Strabismus to ROP**

Figure 4: Strabismus among ROP category

Strabismus occurred in 38% of ROP babies which was nearly 3 times the incidence in the no-ROP babies.

**Type of Strabismus**

Figure 5: Type of strabismus

In both groups, exotropia was the predominant type of strabismus. The proportion of the two types were similar in both groups; 7:1. The mean age at detection of strabismus was 15.9 months with a standard deviation of 5.9 months.
Other Sequelae
The occurrence of other sequelae was seen only in the severe ROP group, who required treatment.

Figure 6: other sequelae
n=no of rop babies(45)

Out of the 45 babies, nystagmus occurred in 4 babies. Among the anterior segment problems, cataract occurred in 2 patients and micro cornea in 1 patient. The one patient who had micro cornea had cataract, nystagmus, exotropia and total RD. This one patient may be a standing example for the extent of sequelae of cicatritial ROP. One patient had undergone cataract surgery. No cases of glaucoma were reported.

Posterior segment problems included 5 cases of RD (3 cases of total RD and 2 cases of focal TRD). One of the cases underwent sclera buckling. The other fundus problems included macular drag in 3 eyes.

Discussion
Prematurity as such predisposes a child to developing refractive errors and ROP in particular is associated with many other ocular problems. The study aims at underlining the fact that premature babies, especially ROP children need long term follow up to address future ocular problems.

This study was conducted to study the ocular morbidity in the children born premature. It also looks into the sequelae occurring in the ROP infants per se. the long term ocular morbidity in premature infants can be mainly discussed in 4 regions: refractive errors, ocular structure, visual function and other problems like strabismus, nystagmus. This study has evaluated the refractive status and the ocular structure in detail.

The study was conducted on 228 infants of which 45 had ROP and 183 did not have ROP. These infants were followed up over a period of 2 years at 6 monthly intervals. Our results have been discussed in detail below.

Gender
ROP occurred in the males more commonly in our study (60%). There is no definite gender predilection for ROP noted.

Incidence
Out of the 228 infants, 45 were having ROP. Thus the incidence of ROP in our study was 19.7%. In India, many studies on incidence of ROP have been done that has reported an incidence between 20-50%. More recent studies by Gupta et al and Aggarwal et al and Maheshwari et al has shown an incidence of around 20%. This is similar to our study. Such large variation of incidence is probably because of geographical variation, the quality of neonatal services and the criteria for screening used.

In our study out of the 45 babies with ROP, all babies had ROP in both eyes and it was symmetrical in all babies except two cases where it was asymmetrical. One case had stage 5 in one eye and stage 3 in the other. The other case had stage 3 and stage 1 in either eye. It outlines the fact that ROP is usually symmetrical in both eyes.

Overview of the risk factors of ROP in our study
Gestational age
The mean gestational age of the ROP group was 30 weeks with a standard deviation of 2.2 and that of the no-ROP group was 33 weeks (standard deviation 2.1). Nearly 70% of the ROP occurred at gestational age less than 32 weeks as compared to 40% of the No-ROP group. So as the gestational age decreases, the incidence of ROP increases. This re asserts the findings of earlier studies that gestational age is a major risk factor for ROP.

The earliest case reported was at 27 weeks and no case was reported after 34 weeks. The mean age...
was 30 weeks. This forms the basis of many screening programs, that changes of ROP are rarely detected at less than 30 weeks and unlikely above 35 weeks.

**Birth weight**

Refractive errors has an increased incidence with a decrease in birth weight.

**Analysis of refractive errors**

The aim of our study was to assess the refractive errors occurring in preterm infants and to further analyse whether the presence of ROP, its severity or the stage of ROP had any relation to the refractive status of the eye. We also observed the progress of these errors over a period of 2 years.

**Spherical equivalent**

The mean spherical equivalent in our study was 0.22 at 6 months and 0.52 at 2 years and the predominant refractive error in all groups was myopia. 70% of the preterm infants in our study were myopic which is far higher than the prevalence of myopia in the corresponding full terms (10%). The spherical equivalent showed a correlation to the occurrence of ROP. It was significantly higher in the ROP group. The SE showed significant association to the birth weight and gestational age. But there was no significant correlation between the treated and spontaneously regressed group and no significant relation to stage of ROP.

The results of the current study indicate a disruption of the emmetropization process in low birth weight preterm infants. Whereas there is a reduction in the prevalence of both myopia and hyperopia over the course of the first year in full-term infants, preterm infants show only a modest reduction in the prevalence of hyperopia.

Myopia was the predominant refractive error in our study; it occurred in 70% of eyes of premature babies. This confirms the findings of earlier studies.

Hence further analysis of myopia was done. As we have discussed earlier, the presence of ROP (p=0.001), lower gestational age (p.001) and lower birth weight (p=0.002) were found to be significantly associated with refractive errors (SE), particularly myopia. Further we have also attempted to study the degree of myopia in various groups. For this we had divided Myopia into 3 categories namely High, Medium and Low myopia.

ROP was definitely a risk factor for the development of myopia, with myopia occurring 90% of the ROP group and only 75% of No-ROP cases. These results are similar to that found by G Holmstrom ET al10 in Stockholm where the incidence was higher in the ROP eyes as compared to the No-ROP eyes. Another study by Nissenkorn and Yassur et al122 also found a relation between the two though the incidence of myopia in the two groups were less than the present study (50% in ROP and 16% in the no ROP eyes).

Regarding the stages of ROP, Myopia occurred in nearly all stages of ROP in almost the same frequency (90%) but the severity of Myopia differed in each group. As the severity of ROP increased, the degree of myopia also increased. The average myopia in the mild ROP was -1.51D whereas in the severe ROP it was -5.63D. This was statistically significant (p<0.001). This agrees with the findings of Quinn et al12 who reported that cicatricial ROP was associated with higher degrees of myopia. The prevalence of myopia and high myopia also is highly related to the severity of retinal residua of ROP. It is unclear whether the scarring phases of retinopathy contribute substantially to the development of abnormal refractive states, either the anterior segment effects or the shorter eye, or whether both the scarring and the increased prevalence of myopia are independent sequelae of ROP and prematurity.

As to the relation of myopia to the gestational age and birth weight, the prevalence of myopia was more in the lower birth weight babies and the more immature babies in both the ROP and no ROP babies. This is similar to earlier studies which have proved conclusively an association of myopia to the lower gestational age and birth weight11,12,13.
The degree of myopia also showed a correlation to the birth weight and gestational age. The average myopia increased alongside with a decrease in the gestational age (p<0.001) and birth weight (p=0.002). This was statistically significant. And it is in lines with that reported by Nissenkorn et al.11

In our study the prevalence of myopia in the treated ROP group was 92% and 89% in the eyes with spontaneously regressed ROP. But this difference was not statistically significant. This is not in agreement with recent studies which have dealt with the possibility of laser treatment contributing to the occurrence of myopia 14-16. But on analysing the degree of Myopia, it was higher in the treated group than in the spontaneously regressed group, thus outlining that laser treatment was significant in determining the severity of Myopia. The ETROP study had also reported that 80% of threshold ROP infants and 65% of treated high risk pre-threshold infants had myopia. Many other studies also quote similar results. Thus in our study though there was no significant difference in the incidence of myopia between the treated and the spontaneously regressed group, but the degree of myopia was definitely higher in the treated group.

Astigmatism was found more frequently in the eyes with ROP (p< 0.05). Thus ROP was a risk factor for the occurrence of astigmatism (p<0.05). The occurrence of high astigmatism (>2D) was highest in the treated ROP group (37%) at 2 yrs than the untreated eyes. This is similar to the results of G Holmstrom et al 10 performed in Stockholm.

**Strabismus**

Out of the 228 babies, 28 had strabismus. Thus an overall incidence of strabismus in our study was 14.9%. This is higher than the incidence in normal population of 3%. There are many other studies that report similar incidences. It was 13.5% in study by Holmstrom et al10 and 22% by Brian et al.

The prevalence of strabismus in ROP babies was more than double of that in babies without ROP (37% in ROP vs. 9% in babies without ROP). This again is similar to the study by Holmstrom et al18 which reported 40% in ROP and 5.9% in children without ROP.

As to the type of strabismus, exotropia predominated in both the groups at a proportion of 7:2. But this is against observations made earlier that convergent squint is more commonly seen in premature babies. The ratio of convergent to divergent strabismus in the UK Caucasian population 17,18 is about 3:1 but for those born preterm far more are divergent and the convergent: divergent ratio becomes 1:1. One reason why this didn’t agree with our study might be because of the relatively shorter follow up period in our study.

**Other sequelae**

In our study all the other sequelae were exclusively found in the ROP group. Nystagmus occurred in 4 children, one of which also had associated micro cornea and total cataract. There were two cases of cataract one of which underwent cataract surgery at 6 months. Retinal detachment occurred in 4 cases. Three were total RD. Two were focal RD, one of which underwent sclera buckling. Other fundus sequelae were macular drag in 3 cases and patients who underwent cryotherapy also had increased pigmentation and peripheral chorioretinal atrophy. Thus we conclude that the treatment of ROP must not stop with laser treatment but it is a grave responsibility of the treating ophthalmologist to follow up these children further to manage the forthcoming sequelae of refractive errors and others. It is also to be kept in mind that it is not just the ROP infants but those born premature should also be followed for the occurrence of refractive errors and adequately treated.

**References**

2. Fledelius HC. Ophthalmic changes from age of 10 to 18 years. A longitudinal study of sequelae to low birth weight. II. Visual


