RETINOPATHY OF PREMATURITY- A CLINICAL STUDY

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ABSTRACT

BACKGROUND

The aim of the study is to detect the incidence of retinopathy of prematurity among low birth weight and preterm infants and identification of potential risk factors for retinopathy of prematurity.

MATERIALS AND METHODS

It was a prospective cohort study enrolling all neonates who presented for retinopathy of prematurity screening with birth weight ≤1750 g and/or neonates born at less than 34 weeks gestational age and neonates with gestational age between 34 to 37 weeks gestational age or a birth weight between 1750 and 2000 g, if high-risk factors like history of prolonged oxygen therapy, mechanical ventilation and haemodynamic instability is present. A total of 100 infants had retinal evaluation by indirect ophthalmoscopy and were followed up periodically. Prenatal and postnatal risk factors for ROP were assessed.

RESULTS

Out of the 100 infants screened, 37 had ROP. Of the 74 eyes screened, stage 1 was seen in 41 eyes, stage 2 in 19 eyes and stage 3 in 14 eyes. Zone 1 disease was seen in 10 eyes, zone 2 in 24 eyes and zone 3 in 40 eyes plus disease was seen in 10 infants. Lower birth weight (P<0.001), lower gestational age (P<0.001), oxygen therapy, (P=0.001), respiratory distress syndrome (P<0.001), multiple gestation (P<0.001) long length of ICU stay (P<0.001) were significant risk factors in this study. No significant association was detected between maternal age, diabetes, hypertension, treatment for infertility, mode of delivery, sex of infant, mechanical ventilation, 1 minute Apgar score, phototherapy, sepsis and PDA.

CONCLUSION

The incidence of ROP is 37%. Lower birth weight, prematurity, compromised pulmonary function, multiple gestation, long length of ICU stay were significant risk factors in this study.

KEYWORDS

Retinopathy of Prematurity, Oxygen Therapy, Prematurity, Risk Factors.

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BACKGROUND

The major causes of blindness in children vary widely from region to region being largely determined by socioeconomic development and the availability of primary healthcare and eye care services. Retinopathy of Prematurity (ROP) is more important in high-income countries, while acquired conditions in childhood are more important in low-income countries. In middle-income countries, the picture is mixed, but ROP is emerging as an important potentially avoidable cause of blindness.[1]

Retinopathy of Prematurity (ROP) is a vasoproliferative disorder of the developing retina that accounts for over 50,000 blind children worldwide.[2] Since 1942 when ROP was first recognised, advances have been made both in understanding the aetiology and characterising the pathological progression of ROP as well as establishing interventions timed to prevent or even reverse visual loss.

Screening for retinopathy of prematurity was started in many countries at the end of the 1980s, when the American CRYO-ROP study reported its first positive results of cryotherapy.[2] With the advent of the results of ETROP trial advocating early treatment for high-risk prethreshold ROP, also the importance of early detection of ROP has increased.[3]

Three factors have shown consistent and significant association with ROP in different studies- low gestational age, low birth weight and prolonged exposure to supplementary oxygen. Other risk factors propounded by various studies include apnoea and mechanical ventilation, sepsis and frequent blood transfusions. However, the precise roles of these factors individually in the progression of the disease have not yet been determined.

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Aim of Study

The principal aims of conducting this study were-

- To detect the incidence of retinopathy of prematurity among low birth weight and preterm infants presenting for retinopathy of prematurity screening.
- Identification of potential risk factors for retinopathy of prematurity.

MATERIALS AND METHODS

Patients

All neonates presenting to the Ophthalmology Department for retinopathy of prematurity screening during the study period selected on a non-random sequential basis.

Inclusion Criteria

All neonates with birth weight ≤1700 g and/or neonates born at less than 34 weeks gestational age. Neonates with gestational age between 34 to 37 weeks gestational age or a birth weight between 1750 and 2000 g are included if high-risk factors like history of prolonged oxygen therapy, mechanical ventilation and haemodynamic instability is present.

Exclusion Criteria

Infants with congenital anomalies, any retinal or choroidal disease (other than ROP) or a media opacity precluding fundus visualisation are excluded from the study. Infants who did not complete the required follow up examinations were also excluded from the study.

Methodology

Examination was done by the principal investigator at the ophthalmology clinic or the NICU (for incubator dependent infants). The method of examination was by indirect ophthalmoscopy using 20D condensing lens after dilating the infant's pupils with 0.5% tropicamide and 2.5% phenylephrine. An infant eye speculum and scleral indentation were used to view the retinal periphery after topical anaesthesia using 2% proparacaine drops. The place of examination was the retina clinic of the Ophthalmology Department or the NICU depending on the clinical status of the infant.

The first ophthalmological examination was done at 31 weeks post-conceptional age or 3 to 4 weeks chronological age whichever is earlier. Periodic follow up was done on a weekly or biweekly basis until the retina is vascularised or till 45 weeks post-conceptional age.

The retinopathy was classified by location on the retina (zone 1-3) and severity (stage 1-5) according to the criteria established by the International Committee for Classification of ROP.

The patient's medical records were examined and data collected regarding the proposed risk factors of ROP. This includes-

- Maternal variables such as maternal age, maternal diabetes, preeclampsia, history of infertility treatment, multiple gestation and mode of delivery.
- Prenatal variables such as gestational age, birth weight and sex of infant.
- Postnatal variables include oxygen therapy, documented 1 minute Apgar score, history of mechanical ventilation, blood transfusions, phototherapy for jaundice, documented sepsis and length of stay at a Neonatal ICU >15 days.

Informed written consent in regional language was taken from the parents of all babies fulfilling the screening criteria.

Duration of Study- 1 year.

Study Design- A prospective cohort study.

Ethical Clearance and Conflict of Interest

Study proposal was cleared by institutional research board prior to beginning of data collection. Expense of study was met by principal researcher. There was no conflict of interests involved.

Statistical Analysis

Statistical analysis was performed using standard statistical variables using Microsoft Excel 2010 and Epi Info 7 software.

Mean and standard deviation was calculated in quantitative variables. Relative risk was calculated in qualitative data. Continuous quantitative variables were analysed using Student's t-test. Qualitative variables were assessed using chi-square test. Yates correction was performed in situation where individual values were less than 5. Fisher exact test was done in case of qualitative variables with columns having zero value.

A p value less than 0.05 was considered as significant result.

All data collected was entered in Microsoft Excel spreadsheet to create a master chart.

RESULTS

A total of 100 infants were included in this study. The mean gestational age of the screened population was 32.08 weeks ±2.32 weeks. The mean birth weight was 1436.7 g ±290.25 g. There were 52 females and 48 males. The incidence of ROP was 37%.

Result	Frequency
ROP	37
No ROP	63

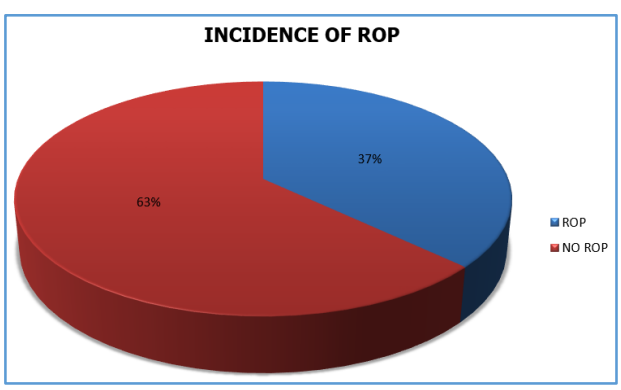

Figure 1. Incidence of ROP

Characteristics of ROP

1. Stage of Disease

Of the 200 eyes screened, stage 1 disease was seen in 41 eyes, stage 2 disease in 19 eyes, stage 3 disease in 14 eyes.

Stage 1	41 eyes
Stage 2	19 eyes
Stage 3	14 eyes

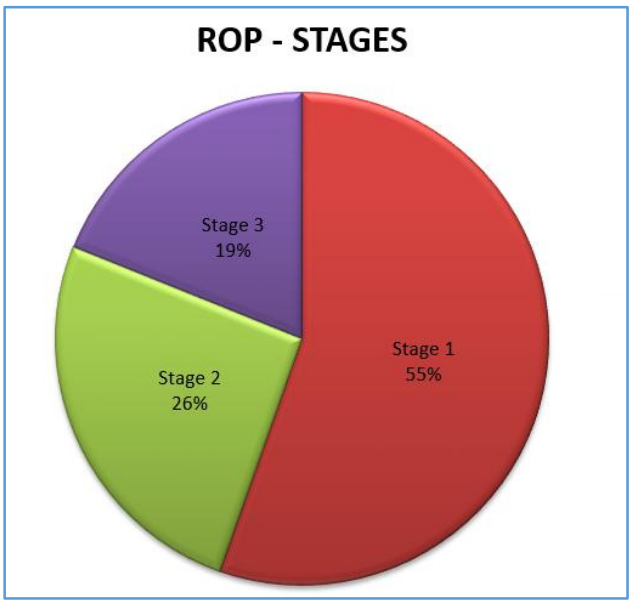

Figure 2. ROP Stages

2. Zone of Disease

Of the 200 eyes screened, zone 1 disease was seen in 10 eyes, zone 2 disease in 24 eyes, zone 3 disease in 40 eyes.

Zone 1	10
Zone 2	24
Zone 3	40

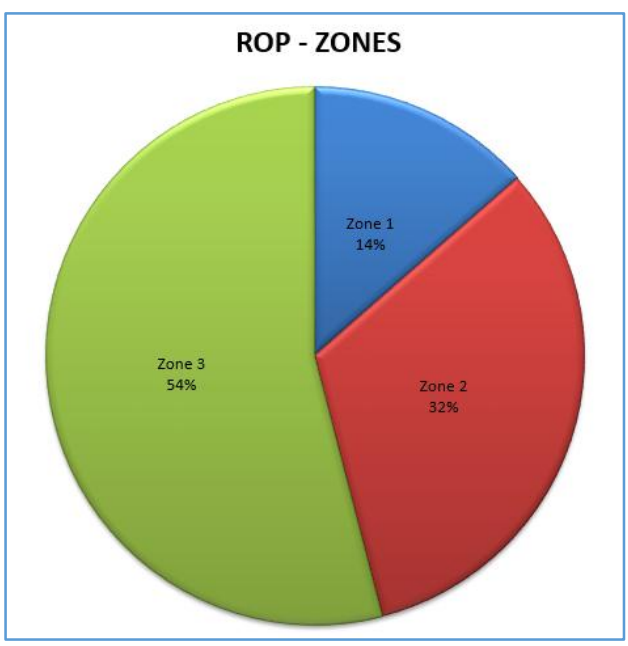

Figure 3. ROP Zones

3. Incidence of plus Disease

Plus disease was found in 10 eyes out of the 37 eyes with ROP.

Result	Frequency
Plus	10
No Plus	27

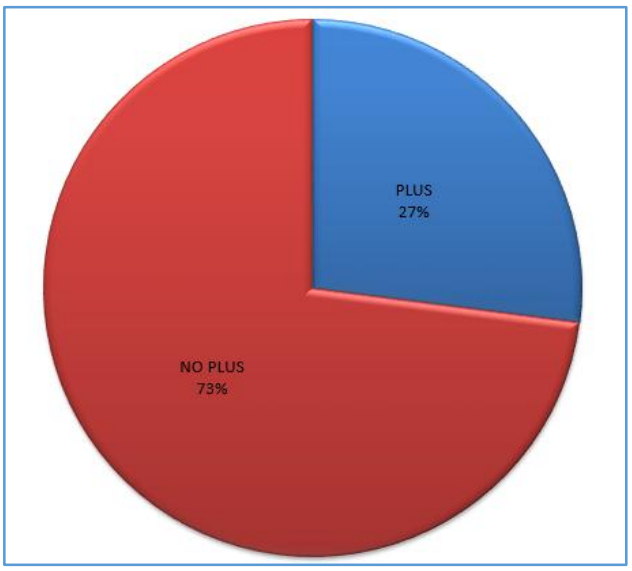

Figure 4 Incidence of plus Disease

4. Disease Symmetry

Disease was symmetric in 29 cases. Asymmetric disease was found in 8 cases.

Result	Frequency
Asymmetric	8
Symmetric	29

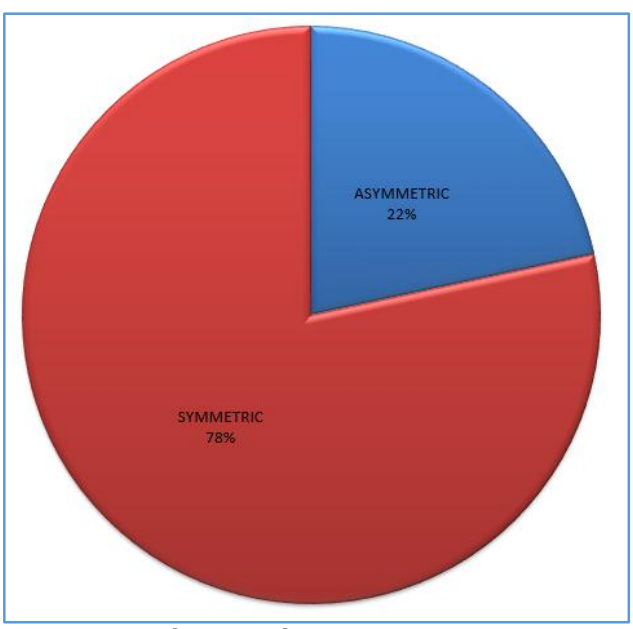

Figure 5 Disease Symmetry

5. Severe ROP

12 patients had severe ROP requiring laser.

Result	Frequency
Severe ROP	8
Not severe	29

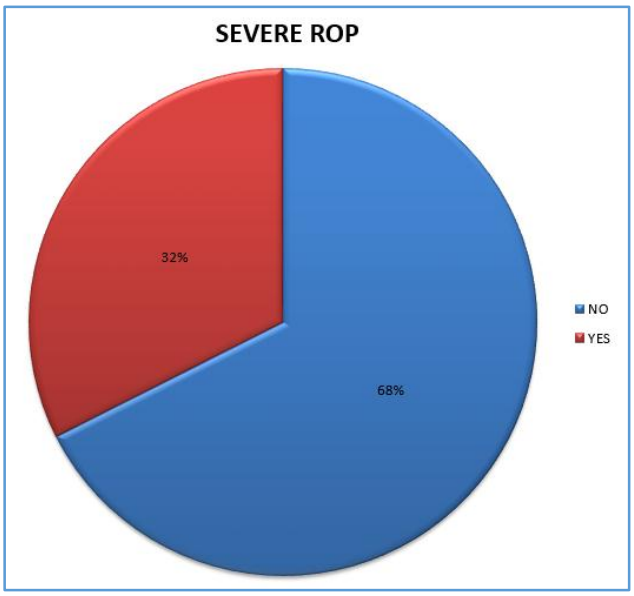

Figure 6. Severe ROP

6. Risk Factors

1. Maternal Risk Factors

a. Maternal Age

Incidence of ROP was found to be 40% when maternal age more than 30 and 36.25% in maternal age <30. Relative risk calculated was 1.0625 (p=0.756).

	ROP	No ROP
Age >30	8	12
Age <30	29	51
RR=1.0625	Chi=0.0965	p=0.756

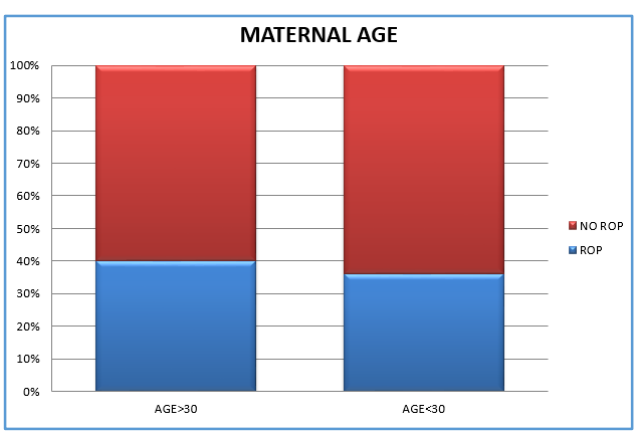

Figure 7. Maternal Age

b. Maternal Diabetes

Incidence of ROP was found to be 50% in the presence of maternal diabetes and 36.45% in children of non-diabetics. Relative risk calculated was 1.2708 (Fisher exact p=0.6252).

	ROP	No ROP
Diabetic	2	2
Non-diabetic	35	61
RR 1.2708		p=0.6252

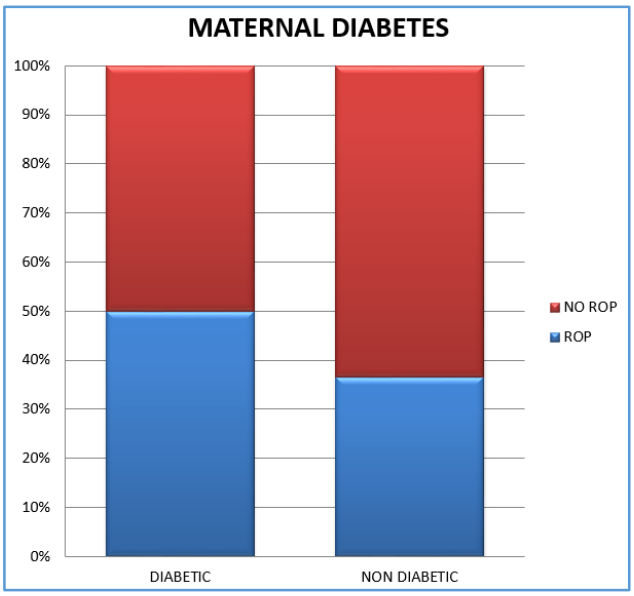

Figure 8. Maternal Diabetes

c. Maternal Preeclampsia

Incidence of ROP was found to be 30.77% in the presence of preeclampsia in mother and 39.19% in children of non-hypertensives. Relative risk calculated was 0.8784 (p=0.4442).

	ROP	No ROP
PIH	8	18
No PIH	29	45
RR 0.8784	Chi=0.5852	p=0.4442

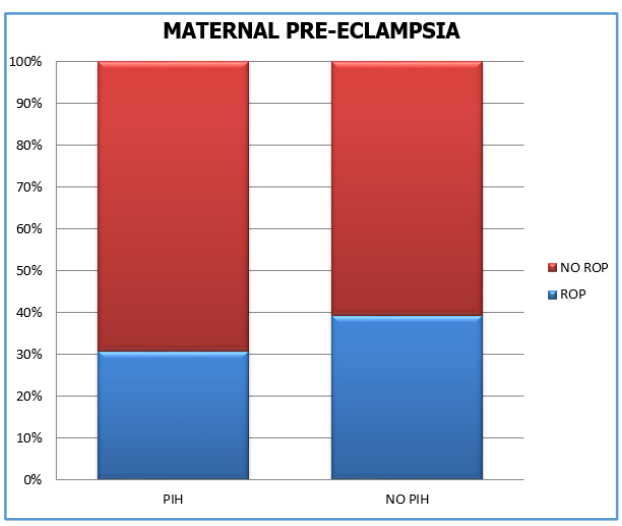

Figure 9. Maternal Preeclampsia

d. Maternal History of Infertility Treatment

Incidence of ROP was found to be 66.67% in children of mothers with history of infertility treatment and 35.1% in those without. Relative risk calculated was 1.9468 (Fisher exact p=0.1205).

	ROP	No ROP
Infertility Treatment	4	2
No Treatment	33	61
RR 1.9468		p=0.1901

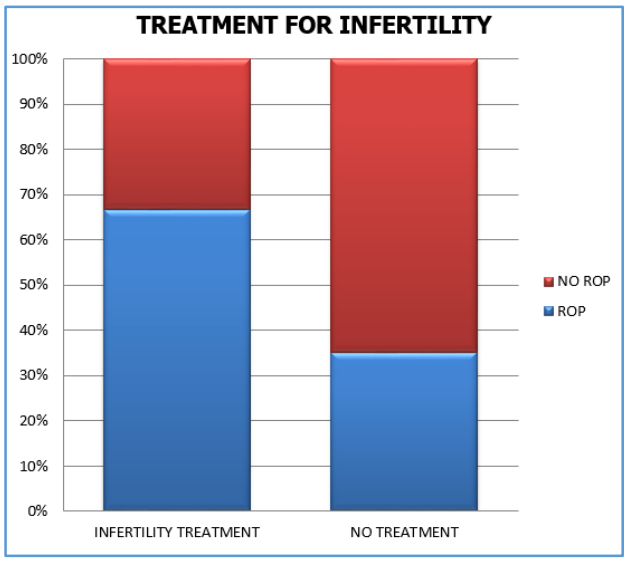

Figure 10. Treatment for Infertility

e. Multiple Gestation

Incidence of ROP was found to be 84.21% in multiple gestation as compared to 25.92% in singleton pregnancies. Relative risk calculated was 4.6914. This result was statistically significant with a p value of 0.000004106.

	ROP	No ROP
Multiple Gestation	16	3
Single Gestation	21	60
RR 4.6914	Chi=22.4287	p<0.0001

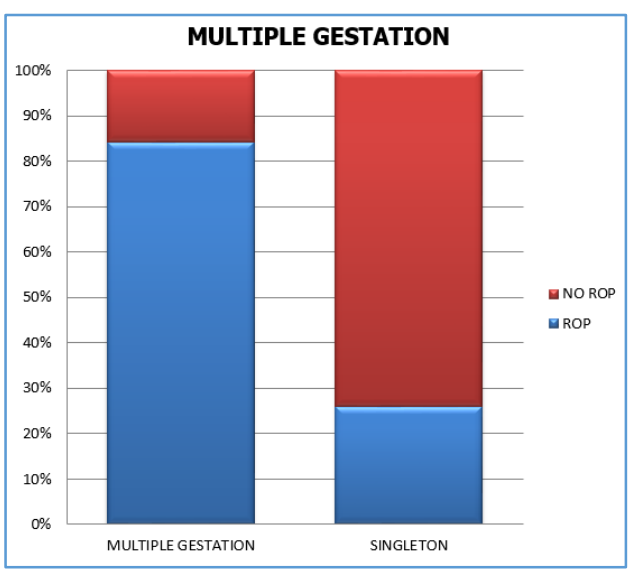

Figure 11. Multiple Gestation

2. Natal Risk Factors

A. Mode of Delivery

Incidence of ROP was found to be 34.42% in vaginal delivery as compared to 41.02% in caesarean section. Relative risk calculated was 0.8994 (p=0.5049).

	ROP	No ROP
Vaginal	21	40
Caesarean Section	16	23
RR 0.8994	Chi=0.4445	p=0.5049

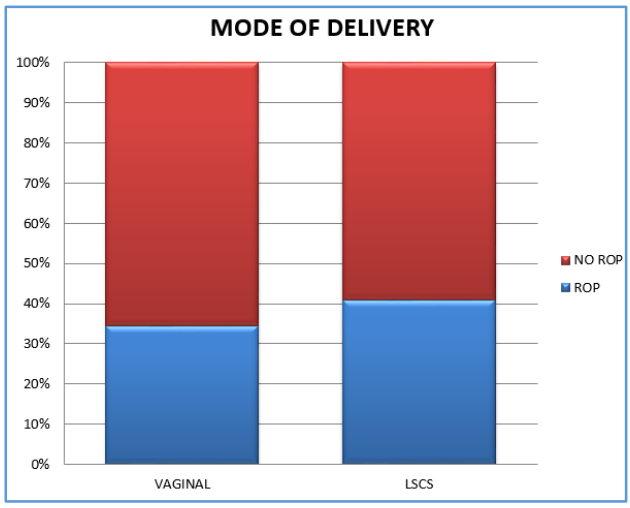

Figure 12. Mode of Delivery

B. Sex of Infant

Incidence of ROP was found to be 32.69% in female babies as compared to 41.67% in male babies. Relative risk calculated was 1.1538 (p=0.3530).

	ROP	No ROP
Female	17	35
Male	20	28
RR=1.1538	Chi=0.8624	p=0.3530

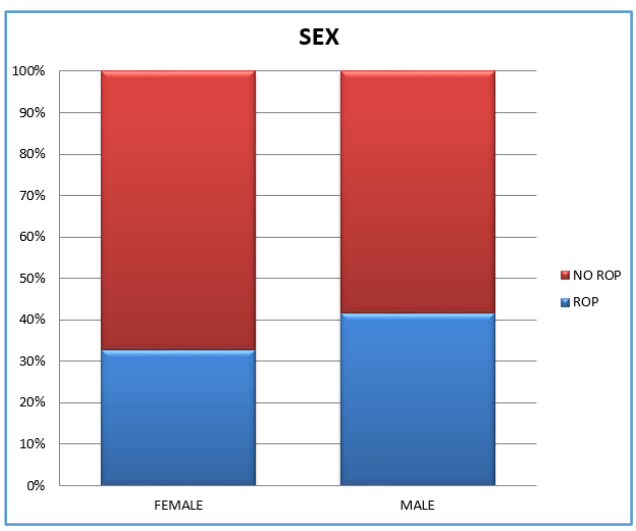

Figure 13. Sex

C. Gestational Age

The mean gestational age in children with ROP was 30.83 weeks (S.D=2.42) while those with no ROP was 32.81 (S.D=1.94).

The following is the incidence of ROP in various gestational age-

Grouping	ROP	No ROP	Total	Incidence of ROP
<=28 wks.	6	1	7	85.71%
28-30 wks.	8	2	10	80.00%
30-32 wks.	12	17	29	41.38%
>32 wks.	11	43	54	20.37%

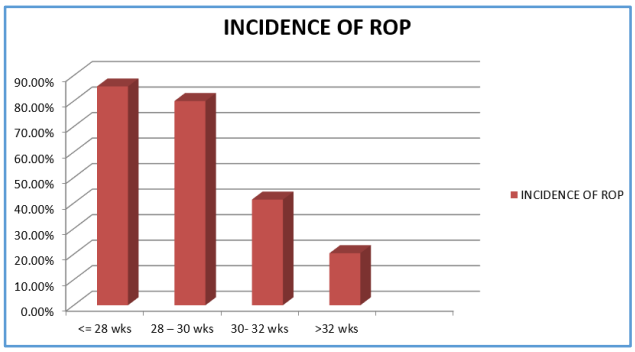

Figure 14. Incidence of ROP

Thus, the incidence of ROP increases with decreased gestational age. This was significant with a p value of 0.000049.

D. Birth Weight

The mean birth weight in children with ROP was 1309.32 g (S.D=251.33) while those with no ROP was 1512.22 (S.D=285.83).

The following is the incidence of ROP in various groups-

Birth WT	ROP	No ROP	Total	Incidence of ROP
ELBW	2	2	4	66.67%
VLBW	24	21	45	52.17%
LBW	11	40	51	21.57%

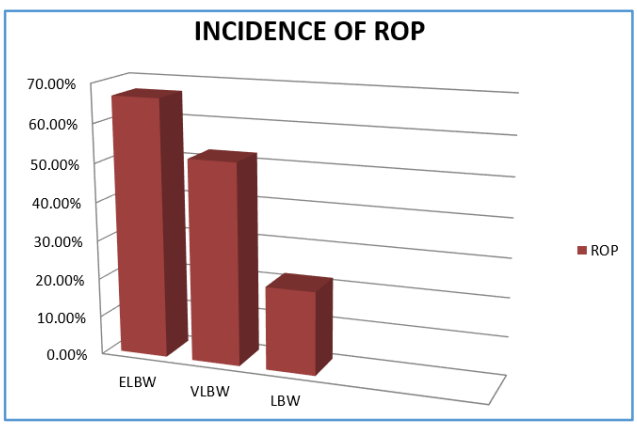

Figure 15. Incidence of ROP

Thus, the incidence of ROP increased with decrease in birth weight. This was significant with a t value of 3.5795 and a p value of 0.000384.

E. Oxygen Therapy

Incidence of ROP was found to be 50.76% in infants with oxygen therapy as compared to 11.11% in those without. Relative risk calculated was 1.7991. The result was significant with a p value of 0.0001028.

	ROP	No ROP
Oxygen Therapy	33	32
No Oxygen	4	31
RR=1.7991	Chi=15.1051	p=0.0001028

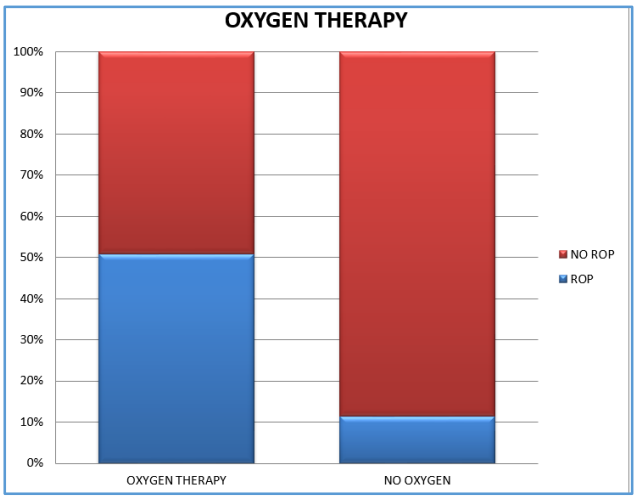

Figure 16. Oxygen Therapy

F. Mechanical Ventilation

Incidence of ROP was found to be 72.72% in infants with mechanical ventilation as compared to 32.58% in those without. Relative risk calculated was 2.4719 (p=0.01704).

	ROP	No ROP
Mechanical Ventilation	8	3
No Ventilation	29	60
RR=2.4719		p=0.01704

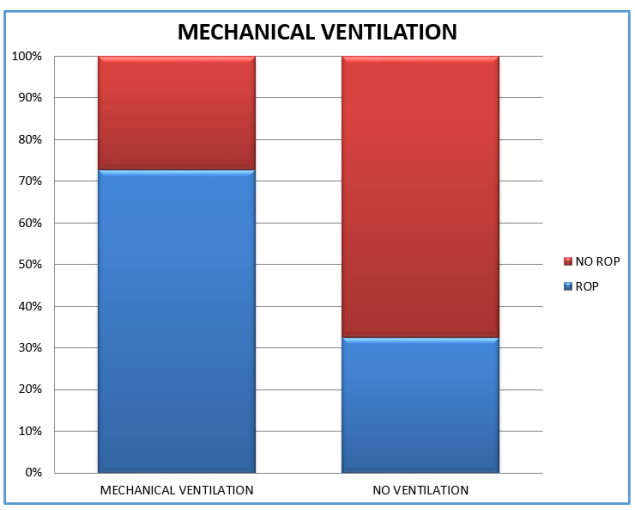

Figure 17. Mechanical Ventilation

G. Blood Transfusion

Incidence of ROP was found to be 52.63% in infants with mechanical ventilation as compared to 33.33% in those without. Relative risk calculated was 1.7991 (p=0.5049).

	ROP	No ROP
Blood Transfusion	10	9
No Transfusion	27	54
RR=1.7991	Chi=0.4445	p=0.5049

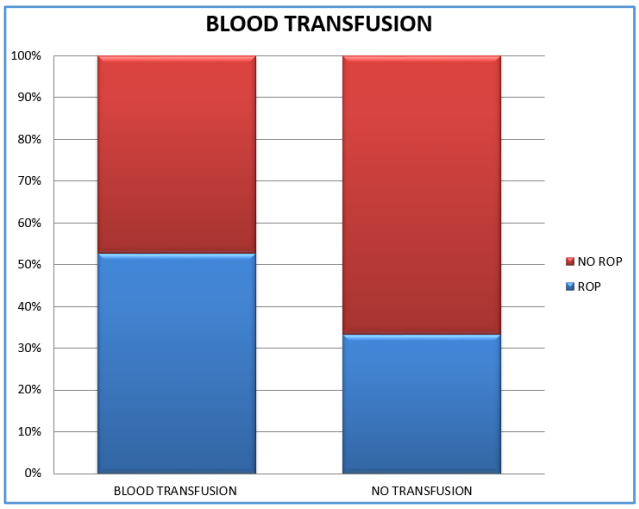

Figure 18. Blood Transfusion

H. Documented 1 Minute Apgar

Incidence of ROP was found to be 35.71% in infants with Apgar <7 as compared to 37.20%. Relative risk calculated was 0.9767 (p=0.9144).

	ROP	No ROP
Apgar <7	5	9
Apgar >7	32	54
RR=0.9767	Chi=0.0115	p=0.9144

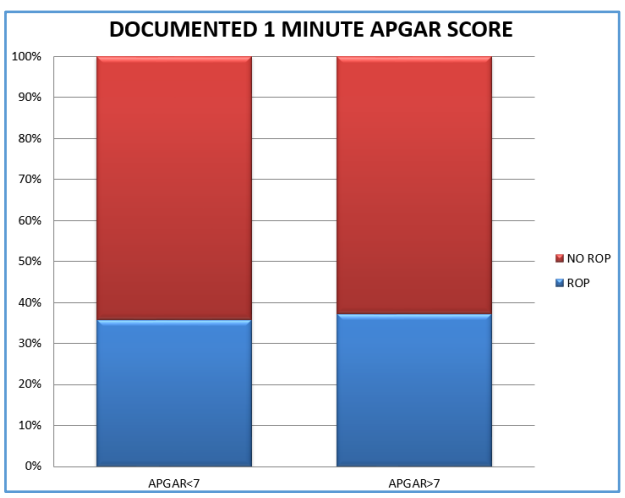

Figure 19. Documented 1 Minute Apgar Score

I. Phototherapy

Incidence of ROP was found to be 45.65% in infants who underwent phototherapy as compared to 29.62% in those who did not. Relative risk calculated was 1.2948 (p=0.09812).

	ROP	No ROP
Phototherapy	21	25
No Phototherapy	16	38
RR=1.2948	Chi=2.7357	P=0.09812

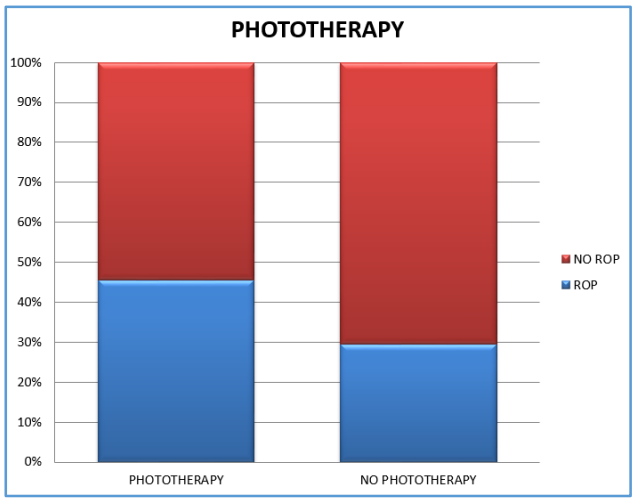

Figure 20. Phototherapy

J. Sepsis

Incidence of ROP was found to be 37.14% in infants with sepsis as compared to 36.92% in those who did not. Relative risk calculated was 1.0035 (p=0.9826).

	ROP	No ROP
Sepsis	13	22
No Sepsis	24	41
RR=1.0035	Chi=0.0005	p=0.9826

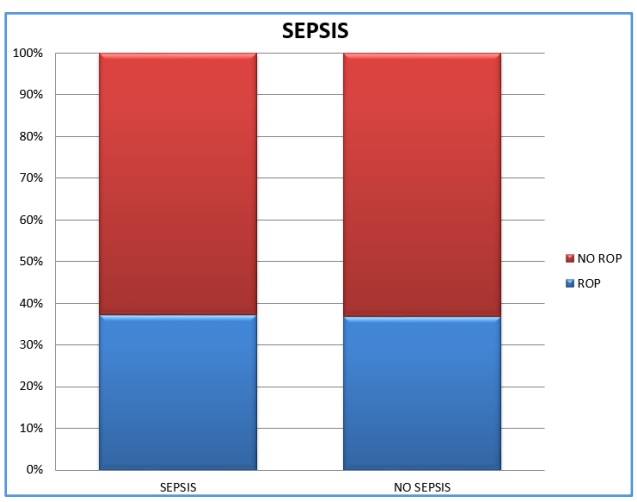

Figure 21. Sepsis

K. Respiratory Distress Syndrome

Incidence of ROP was found to be 75.86% in infants with RDS as compared to 21.12% in those without. Relative risk calculated was 3.2676. The result was statistically significant with a p value of 0.000001437.

	ROP	No ROP
RDS	22	7
No RDS	15	56
RR=3.2676	Chi=26.46	P<0.0001

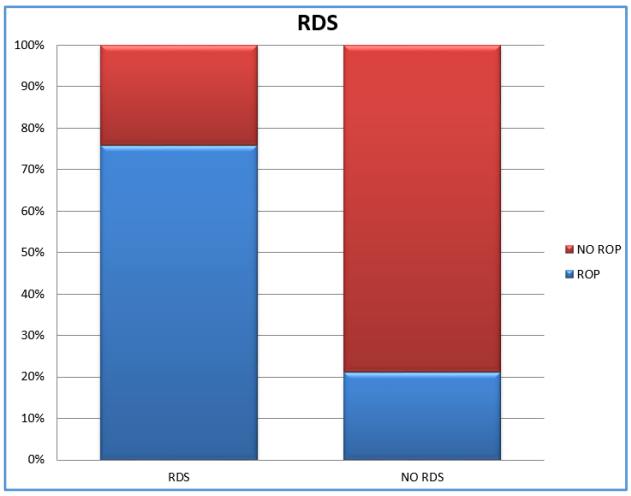

Figure 22. RDS

L. Patent Ductus Arteriosus

Incidence of ROP was found to be 60% in infants with PDA as compared to 35.79% in those without. Relative risk calculated was 1.6053 (P=0.2744).

	ROP	No ROP
PDA	3	2
No PDA	34	61
RR=1.6053	Chi=1.1944	p=0.2744

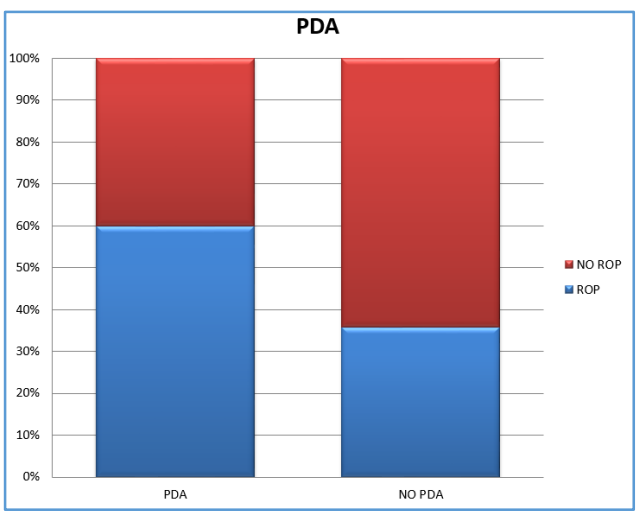

Figure 23. PDA

M. Length of ICU Stay

Incidence of ROP was found to be 52.46% in infants with long ICU stay as compared to 12.82% in those without. Relative risk calculated was 3.2676. The result was statistically significant with a p value of 0.00006333.

	ROP	No ROP
ICU Stay >15 Days	32	29
ICU Stay <15 Days	5	34
RR=3.2676	Chi=16.0357	P<0.0001

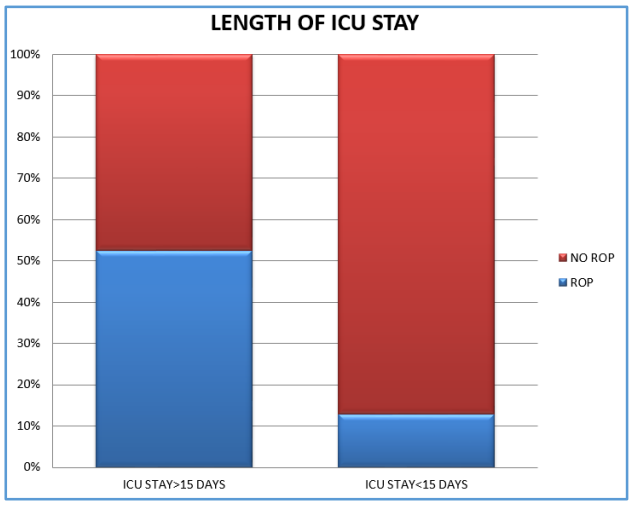

Figure 24. Length of ICU Stay

DISCUSSION

Incidence

Incidence of retinopathy of prematurity detected in our study was 37%. This value was comparable with many studies conducted in the past. Different authors have detected an incidence of retinopathy of prematurity in India ranges from 19.7% to 52%.[4-11] Closest result to our findings detected in literature review was 41.5% by Hungi et al.[4] The incidence of retinopathy of prematurity in this study was comparable to previous studies accessible in literature.

The mean gestational age of the screened population was 32.08 weeks ± 2.32 weeks. The mean birth weight was 1436.7 g ± 290.25 g. There were 52 females and 48 males.

Risk Factors

ROP is a multifactorial disease involving many factors. In our study, low birth weight, low gestational age, oxygen therapy, mechanical ventilation, respiratory distress syndrome, multiple gestation and length of ICU stay >15 days were significant risk factors.

With regards to the inverse relationship between gestational age and ROP, we found it a significant risk factor for ROP. This was in agreement with different studies of worldwide. This was explained by immaturity of vascularisation that induces an increased susceptibility of the retina to oxidative damage and to a number of perinatal factors, which include hypertension, hypoxia, blood transfusions and sepsis.

We found that birth weight to be significant factor for occurrence of ROP. This was in agreement with many studies, which reported a significant association between lower birth weight and development of ROP. This can be explained by an increased susceptibility for oxygen therapy, prolonged ventilation, sepsis and blood transfusion in very low birth weight infants.

Oxygen therapy was an independent risk factor for the development of ROP in different studies.

We found a significant relationship between the occurrence of ROP and use of oxygen therapy. On the other hand, Palmer et al[8] reported that that ROP may develop in cases that did not receive oxygen therapy.

Another significant risk factor for ROP in our study was multiple gestation. This was in concordance with the study of Motta et al,[9] which showed higher frequency of any stage of ROP in twins and triplets.

Respiratory distress syndrome was a risk factor in our study. This has been previously seen in the different studies, which have suggested immaturity and compromised pulmonary function to be the important aetiological factors for ROP. The relationship between RDS and ROP maybe that due to systemic hypoxia results in retinal hypoxia and more need for oxygen therapy.

Long length of NICU stay was another risk factor in this study. This may not be an independent risk factor, but a sign of the increased severity of illness associated with those infants who are born earlier with a lower birth weight.

Among the postnatal risk factors, mechanical ventilation had increased risk of ROP, but it was not significant. Study by Hakeem et al[10] had similar results.

In this study, we found that sepsis was not significantly associated with the development of ROP. We also did not find frequency of blood transfusions as a risk factor for development of ROP. This was in disagreement with the studies of Hakeem et al. No significant relationship was found between phototherapy and ROP as in the study by Hakeem et al.

We did not find any significant relationship between maternal age and development of ROP. This was in contrast with the results of Wu W.C. et al.[11]

In this study, we found no significant association between maternal preeclampsia and ROP. This was in contrast with the studies of Fortes Filho JB et al who found preeclampsia to be a protective factor for retinopathy of prematurity.[12] Our findings were in agreement with the studies of Mehmet et al.[13]

Maternal diabetes and ROP was also not significantly linked in this study. This is in agreement with the studies of Kavurt et al.[14] Our study also did not find any link between ROP and maternal infertility treatment. This was in contrast with the study by Paul-Chan RV et al,[15] which linked assisted reproduction to retinopathy of prematurity.

It is suggested that the higher incidence of ROP in multiple birth neonates maybe secondary to lower birth weight and gestational age.[16]

Our study had more males with ROP than females. However, result was not statistically significant.

Though more number of ROP babies were delivered by caesarean section, the relationship between the mode of delivery and occurrence of ROP was insignificant.

PDA and ROP also did not have a significant relationship in our study.

Since the survival rate of premature infants is better with improved PICU care, prompt correction of modifiable risk factors can decrease the incidence of ROP and early diagnosis prevent blindness and provide better visual rehabilitation in premature infants.

CONCLUSION

The incidence of ROP in patients undergoing screening in Government Medical College, Thrissur, is 37%. This was on par with national statistics.

Lower birth weight, lower gestational age, oxygen therapy, respiratory distress syndrome, multiple gestation, long length of ICU stay were significant risk factors in this study.

No significant association was detected between maternal age, maternal diabetes, maternal hypertension, treatment for infertility, mode of delivery, sex of infant, 1 minute Apgar score, mechanical ventilation, phototherapy, sepsis, PDA.

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