“A STUDY ON FACTORS AFFECTING THE OUTCOME OF RETINOPATHY OF PREMATURITY – A CROSS SECTIONAL ANALYTICAL STUDY WITH INTERNAL COMPARISON, AT A TERTIARY CARE CENTER IN NORTH CHENNAI”

A Dissertation submitted to THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY in partial fulfilment of the regulations for the award of degree of

M.D DEGREE (PEDIATRICS)

BRANCH VII

INSTITUTE OF SOCIAL PEDIATRICS

GOVERNMENT STANLEY MEDICAL COLLEGE

CHENNAI – 600 001

May 2019

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation / thesis entitled "**A STUDY ON FACTORS AFFECTING THE OUTCOME OF RETINOPATHY OF PREMATURITY – A CROSS SECTIONAL ANALYTICAL STUDY WITH INTERNAL COMPARISON, AT A TERTIARY CARE CENTER IN NORTH CHENNAI"** is a bonafide and genuine research work carried by me, **DR VIJAYALAKSHMI M**, under the guidance of **Prof. Dr.M.A.ARAVIND, M.D.**, Professor in Department of pediatrics.

The dissertation is submitted to **The Tamilnadu Dr.M.G.R. Medical University** towards the partial fulfillment of the rules and regulations for the **M.D Degree Examination – Branch VII – in pediatrics.**

Signature of the Canditate

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Place : CHENNAI

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This is to certify that the dissertation entitled "**A study on factors affecting the outcome of retinopathy of prematurity – a cross sectional analytical study with internal comparison, at a tertiary care center in north Chennai"** is a bonafide record of work carried out by **DR.M.VIJAYALKSHMI**, in the Department of pediatrics, Government Stanley medical college, under my guidance and supervision during the period of her post graduate study for M.D. pediatrics from MAY 2016 to May 2019.

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CERTIFICATE BY THE INSTITUTION

This to certify that the dissertation titled "**A study on factors affecting the outcome of retinopathy of prematurity – a cross sectional analytical study with internal comparison, at a tertiary care center in north Chennai"** is a bonafide record of work carried out by **DR. M.VIJAYALAKSHMI**, in the Department of paediatrics under our direct supervision and guidance, during the academic year 2016 -2019 submitted to **The Tamilnadu Dr.M.G.R Medical University, Chennai** in partial fulfillment of the requirement of the award for the degree of **M.D BRANCH VII (PEDIATRICS).**

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ACKNOWLEDGEMENT

It is with immense pleasure and gratitude that I thank **Dr. PONNAMBALA NAMASIVAYAM, M.D.,D.A.,D.N.B., THE DEAN, STANLEY MEDICAL COLLEGE** for bestowing me the permission and privilege of presenting this study and for enabling me to avail the institutional facilities.

It is with great pleasure that I express a deep sense of gratitude to my teacher and **Guide**, **Prof. Dr.M.A.ARAVIND, M.D.,** Professor, Department of pediatrics, for his valuable guidance and support during the preparation of this dissertation and also inspiring me at every step of this study, for without his this study wouldn't be possible.

I express my gratitude to my **Co- guide, Dr.Ekambaranath M.D,** Assistant Professor of PICU for his valuable help and guidance throughout this study.

I am very grateful to all my chiefs, **Prof.Dr Ravi Chandran T.,M.D., Prof.Dr.J.Ganesh M.D, D.C.H, Prof. Dr.Jayakumar M., M.D., and Prof. Dr Poovazhagi V, M.D,D.C.H., Dr.Meghalai S, M.D.,** for their valuable guidance and motivation.

I sincerely thank my Assistant Professors **Dr.P.Sankaranarayanan M.D, Dr.Venkatesh P. M.D, Dr.Vinodh M. M.D, Dr.Parveen kumar M.D, Dr. Senthilkumar and Dr Rajesh, Dr.Selvi M.D, Dr.Anandhi M.D,** for their valuable support throughout the course of this study.

I thank all the post graduates in the Department of Pediatrics in our Stanley Medical College who have helped me and it was an immense pleasure working with all.

Finally I wish to express my whole-hearted thanks to all the Emergency and PICU nurses and all the patients who participated in the study.

Dr.M.VIJAYALKSHMI

CERTIFICATE II

This is to certify that this dissertation work titled "**A study on factors affecting the outcome of retinopathy of prematurity – a cross sectional analytical study with internal comparison, at a tertiary care center in north Chennai"** of the candidate **Dr. M.VIJAYALAKSHMI** with registration Number……for the award of the degree **M.D.,** in the branch of **PAEDIATRICS (BRANCH VII).** I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows ……percentage of plagiarism in the dissertation.

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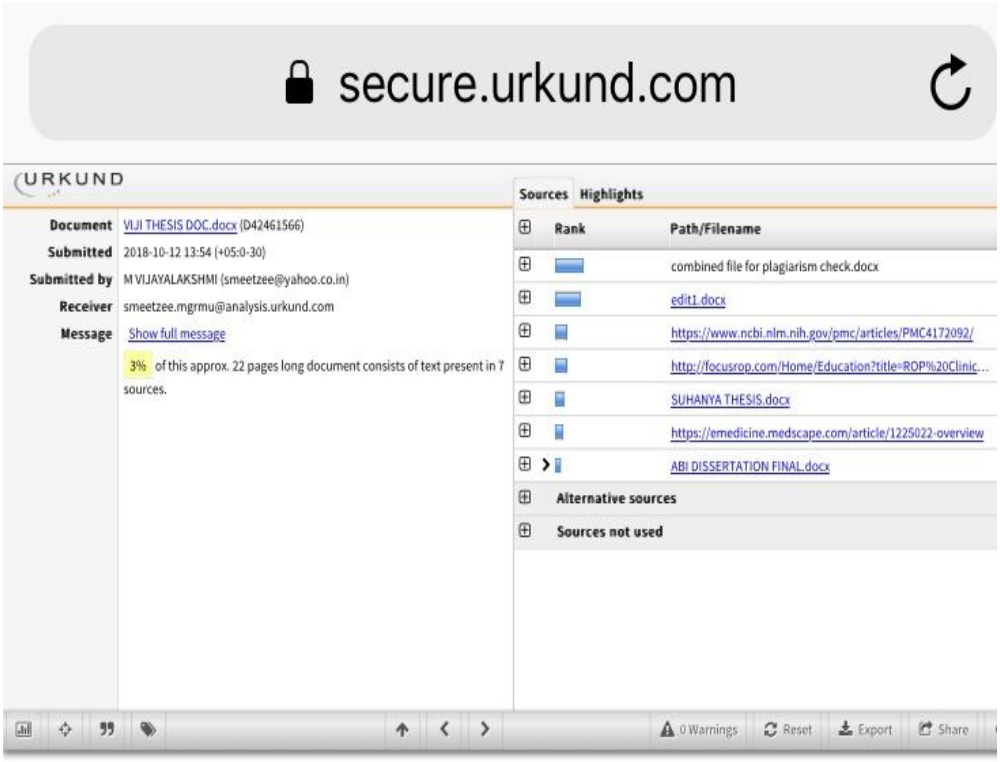

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DEGREE (PEDIATRICS) BRANCH VII

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April 2019 TABLE OF CONTENTS CERTIFICATE ACKNOWLEDGEMENT TABLE OF CONTENTS LIST OF TABLES LIST OF FIGURES ABBREVATIONS AND ACRONYMS 1. INTRODUCTION 2. REVIEW OF LITERATURE 3. AIMS AND OBJECTIVE 4. SUBJECTS AND METHODOLOGY 5. RESULTS 6. DSCUSSION 7. CONCLUSION 8. BIBLIOGRAPHY 9. ABSTRACT 10. APPENDICES • ETHICAL COMMITTEE CERTIFICATE • INFORMATION SHEET • CONSENT FORM • DATA COLLECTION PROFORMA • MASTER CHART • PLAGIARISM CERTIFICATE

ETHICAL COMMITTEE APPROVAL CERTIFICATE

GOVERNMENT STANLEY MEDICAL COLLEGE& HOSPITAL,CHENNAI -01
INSTITUTIONAL ETHICS COMMITTEE

Title of the Work : A study on factors affecting outcome of Retinopathy of Prematurity- A cross sectional analytical study with internal comparison, at a Tertiary care Centre in North Chennai.
Principal Investigator : Dr.M.Vijayalakshmi
Designation : PG (MD Paediatrics)
Department : Department of Paediatrics, Govt. Stanley Medical College.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 11.10.2017 at the Council Hall, Stanley Medical College, Chennai-1 at 11am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY, 3/11/17
IEC, SMC, CHENNAI

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ABBREVATIONS AND ACRONYMS

ROP	-	Retinopathy of prematurity
RLF	-	Retro-lental fibroplasia
VLBW	-	Very low birth weight
GDM	-	Gestational diabetes mellitus
VEGF	-	Vascular endothelial growth factor
RDS	-	Respiratory distress syndrome
PIH	-	Pregnancy induced hypertension
AN	-	Antenatal
ELBW	-	Extremely low birth weight
LBW	-	Low birth weight
PROM	-	Premature rupture of membranes

INTRODUCTION

There has been a dramatic increase in the survival of extremely preterm, extremely low birth weight and sick neonates, due to better newborn facilities, care and monitoring. This has led to the slow emergence of the diseases among preterm and the low birth weight neonates.

Retinopathy of prematurity (ROP) is a retinal vascular disease that predominantly affects these preterm neonates. ROP can be considered as a slowly emerging leading cause of preventable blindness in India. Newborns not only born <32 weeks of gestation are at risk of developing ROP, but also those who are born >32 weeks if they were sick, subjected to hyperoxia. Out of all the neonates screened positive for ROP only about 10% progress to severe stages with retinal detachment and blindness[1]. In the remaining majority of the neonates, ROP spontaneously regresses. Timely screening and early intervention can prevent blindness and minimize visual handicap. There are various known and proven risk factors for ROP including very low birth weight (VLBW) neonates weighing <1500g, prematurity (<32-34 weeks of gestation),hyperoxia, prolonged oxygen exposure , neonatal hyperbiluribinemia, intraventricular hemorrhage, poor post natal weight gain, infants born to mothers with Gestational diabetes mellitus (GDM), etc.

But the risk factors leading on to severe stages of ROP are still very unclear. This study aims to bring in to light those less studied neonatal and maternal risk factors in association with developing severe stages of ROP. If one could predict the outcome of ROP based on these available risk factors for severe ROP, early intervention can be done to prevent the same.

REVIEW OF LITERATURE

DEFINITION

Retinopathy of prematurity, previously called as retro-lental fibroplasias (RLF)[1], is an ischemia induced vasoproliferative multi-factorial disorder of the developing retina, most commonly occurring in the preterm.[2]

EPIDEMIOLOGY

Out of 26 million annual live births in India, 8.5% weigh <2kgs, thus making 2 million newborns at risk for ROP[3].The overall incidence of ROP varies from 20-52%[2]. 65% of infants with birth weight < 1.25kg, 80% of those with birth weight <1kg will develop some degree of ROP[1,2]. Only about 10% of the infants progress to severe ROP[3,4], implying that the rest regress spontaneously.

The incidence of ROP is relatively low in developing countries when compared to the industrialized nations, because of lack of adequate ventilator facilities reducing the chances of oxygen exposure, high mortality of VLBW babies in whom incidence of ROP is the most, lack of ophthalmological monitoring of newborns[2]. The incidence of ROP can vary within the same unit at different time periods[3]. A new unit that initially has lower rates of ROP can observe a rise in number of ROP cases as the screening protocol improves ,availability of assisted ventilation increases and the sick and smaller neonates survive. This period is again followed by a gradual decrease in number[3].

The incidence of ROP is on the rise in India and is emerging as one of the leading cause of preventable blindness.

The question of interest here is why ROP in some preterm neonates progress on to severe grades while the most of the others regress spontaneously. Studies in the past have shown that African-American infants are less prone to severe ROP than whites, and Alaskan natives develop threshold ROP earlier than non natives. This racial variation suggests that genetic , socio-economic and dietary factors play an important role in determining the outcome of ROP[3]. Other risk factors for developing severe ROP are – poor post natal weight gain[3].

PATHOGENESIS

- NORMAL DEVELOPMENT OF THE RETINAL VASCULATURE

Beginning at 16 weeks of gestation[4], retinal elements including nerve fibers, ganglion cells, photoreceptors, migrate from the posterior pole towards the periphery[2]. They reach 80% of the distance at the ora serrata (resting place) by 28 weeks of gestation[2].Since sclera and choroid have already developed, the avascular retina receives its vascular supply by diffusion across the retina from the choroidal vessels ,before the retinal vessels develop[2].

The retinal vessels arise from the spindle cells in the adventitia of the hyaloid vessels at the optic disc[2].They start migrating outward by 16 weeks of gestation , and the migration is complete by 36 weeks on the nasal side and 40 weeks on the temporal side[2,4]. This process is aided normally by Vascular endothelial growth factor (VEGF).

- MECHANISMS OF INJURY

ROP begins to develop between 32 weeks and 34 weeks of conception[3].Onset of ROP consists of 2 stages:

- ACUTE/FIRST STAGE (Stage of hyperoxia): Initial insult at a critical period in retinal vascularisation, results in vasoconstriction and decreased blood flow to the developing retina[3]. This subsequently arrests the vascular development of the anterior retina[3]. The relative hyperoxia postnatally down-regulates the growth factors like VEGF, which are needed for the normal development of the retinal vasculature[2], perhaps mediated by free-radicals[4].
- CHRONIC/SECOND STAGE (Stage of hypoxia): Neovascularisation stage. The hypoxic avascular retina leads to increase in certain angiogenic growth factors like VEGF, leading to aberrant retinal vascular and glial cell growth[2]. These new vessels being immature, are easily permeable, leading on to hemorrhage, edema , extra-retinal fibrovascular proliferation and ultimately retinal detatchment[2]. Occasionally they involute or can lead on to arteriovenous shunt formation and permanent cicatricial changes[3.5].

POSTULATED RISK FACTORS

In 1942, Theodore L.Terry first described retrolental fibroplasia and postulated oxygen use as the causative agent. This led to severe curtailment of oxygen which led to increased mortality rates[6]. But today it is very well known that oxygen therapy is not the only risk factor for development of ROP.

Prematurity (<32 weeks) is the single most important risk factor for the development of ROP[2]. Studies have also shown a strong association of ROP with low birth weight (<1500g), prolonged oxygen exposure[2].

Some recent studies have shown association of ROP with other risk factors such as

- ✓ labilty in oxygen requirement
- ✓ systemic infections/sepsis
- ✓ apnea
- ✓ anemia needing blood transfusions[2]
- ✓ double volume exchange transfusion[6]
- ✓ bradycardia[4]
- ✓ Failure to use surfactant[6]
- ✓ Congenital heart disease[4]
- ✓ Intra-ventricular hemorrhage
- ✓ acidosis

- ✓ prolonged ventilatory support (especially when accompanied by episodes of hyperoxia and hypercapnea)[1]
- ✓ necrotizing enterocolitis[7]
- ✓ poor postnatal weight gain[2]
- ✓ male sex

An early preterm extremely low birth weight neonate can develop ROP even without the above risk factors.

Infants who are breast fed and those born to mothers with pregnancy induced hypertension (PIH) have a reduced incidence of ROP[1].

The risk factors for developing severe forms of ROP are low birth weight, prematurity , culture proven sepsis and blood transfusion[7].

CLASSIFICATION

ROP is classified using the INTERNATIONAL CLASSIFICATION OF RETINOPATHY OF PREMATURITY (ICROP)[8], for documentation of ROP deterioration or regression and to decide therapeutic interventions. According to it, location, zone and extent of ROP are classified as below:

- Location(Zones) : Based on how far the retinal vasculature has progressed.The retina is divided into 3 concentric zones/circles. (Fig-1)
    - Zone 1: optic nerve as the center of the circle , the radius being twice the distance between optic nerve and macula.

- Zone 2: extends from the edge of Zone 1 to the ora serrata on the nasal side , and half-way to the ora serrata on the temporal side.
- Zone 3: outer crescent extending outward from Zone 2 to the ora serrata temporally.

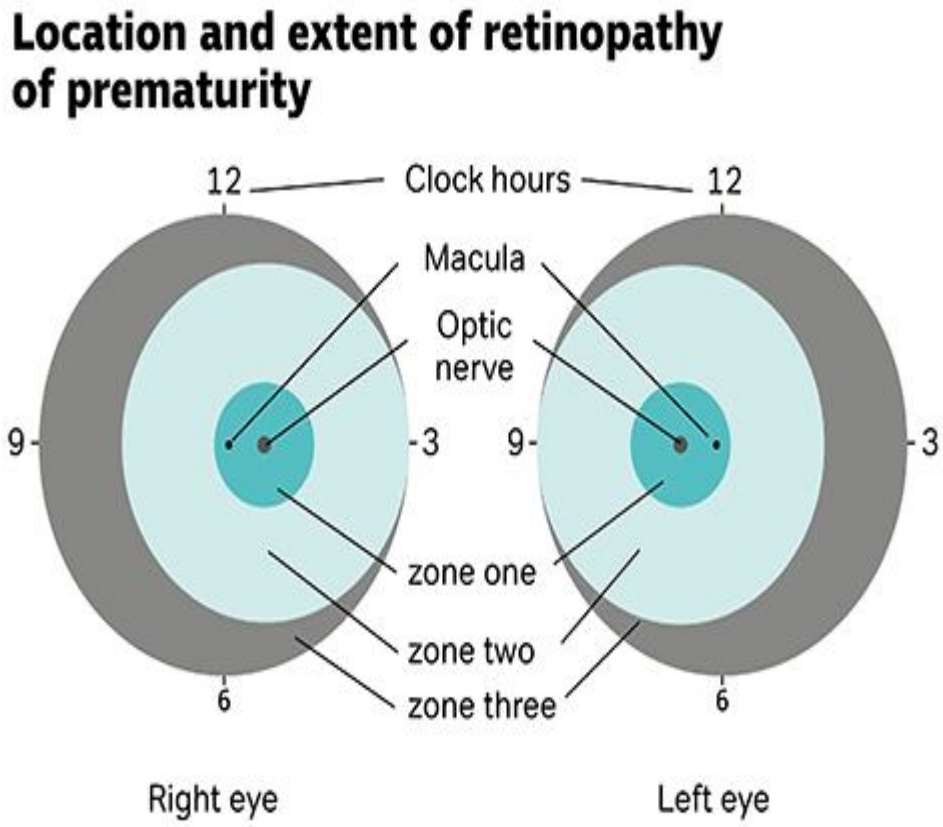


Figure 1- location and extent of ROP

- Stage (severity) : (Fig-2)
    - Stage 1 (demarcation line): A thin, flat, tortuous, grey-white line running parallel with ora serrata, separating the normal from the avascular retina. This line is within the retinal plane (appearing flat and white) and there is abnormal branching or arcading of the retinal vessels that lead on to the line[4].
    - Stage 2 : A fibro vascular ridge (mesenchymal and endothelial cells) with height and width extending inwards from the plane of retina replaces the stage of line [1]. Blood vessels enter the ridge and small isolated neovascular tufts may be seen posteriorly.[7]
    - Stage 3: The ridge has extra retinal fibro vascular proliferation , extending into the vitreous, causing scars and giving traction on the retina or disc. It is continuous with the ridge posteriorly, giving rise to a ragged appearance with extensive proliferation. The severity of this stage is further divided into mild, moderate and severe based on the extent of tissue infiltration. The highest incidence of this stage is around the post-conceptional age of 35 weeks[7].
    - Stage 4: Partial/subtotal retinal detachment sparing the macula(4A), when scar tissue pulls on the retina. Partial detachment involving the macula(4B) limits good vision. In

progressive cases the detachment increases in height as it contracts more and extends anteriorly and posteriorly.

- Stage 5: complete/total retinal detachment where the retina assumes a funnel shaped appearance, open or narrow in the anterior and posterior regions.

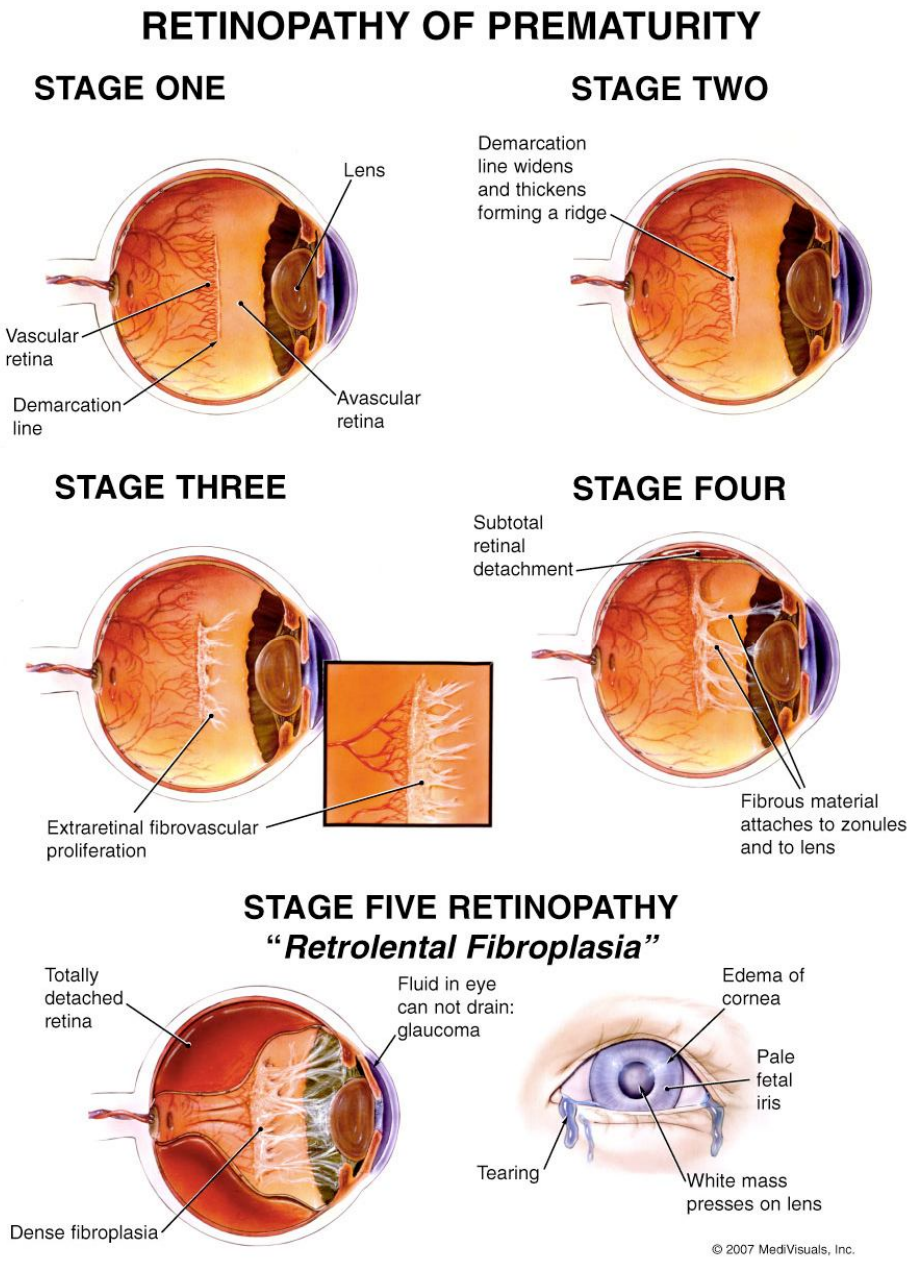


Figure 2- Stage/severity of ROP

- Extent(clock hours): (Fig-1)

  Refers to the circumferential location of the disease and is reported as clock hours in the appropriate zone (30 degree sectors).

- Plus disease: (Fig-3)

  This is a sign of progression as it signifies the presence of vascular dilatations and tortuosity of the posterior retinal vessels in at least 2 quadrants , indicating a more severe ROP and may also be associated with iris vascular engorgement , papillary rigidity, and vitreous haze.

Figure 3- Plus disease

- Pre-pulse disease: (Fig-4)

  Vascular abnormalities of posterior pole that don’t amount to plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal.

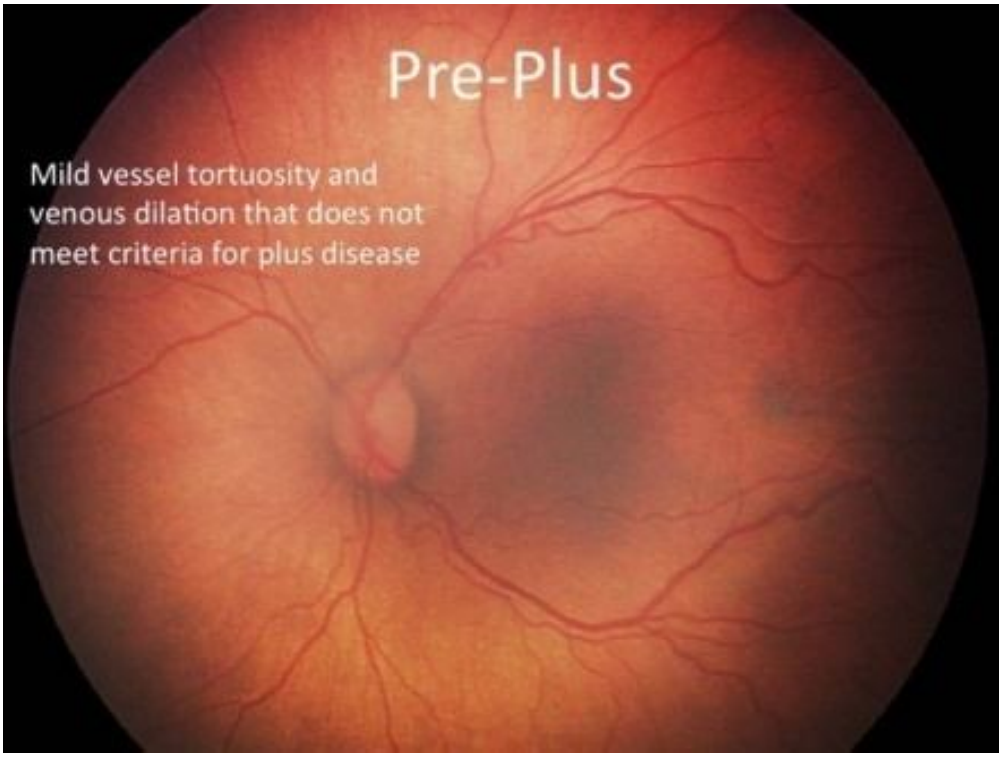


Figure 4- Pre-plus disease

CERTAIN DEFINITIONS:

- Aggressive posterior ROP(AP-ROP): (Fig-5)

  Previously called as “Type II ROP” or “Rush disease, is an uncommon rapidly progressing severe ROP. If untreated can progress rapidly to stage 5 ROP. It is characterized by abnormal closed loop vessels (instead of dichotomous branching pattern) with mild tortuosity that progresses to full blown picture in less than a week. It has posterior location (zone1) with prominence of plus disease out of proportion to the peripheral retinopathy. This may not have a classical ridge or extraretinal fibrovascular proliferation. Most commonly seen in zone 1, but may also occur in posterior zone 2.

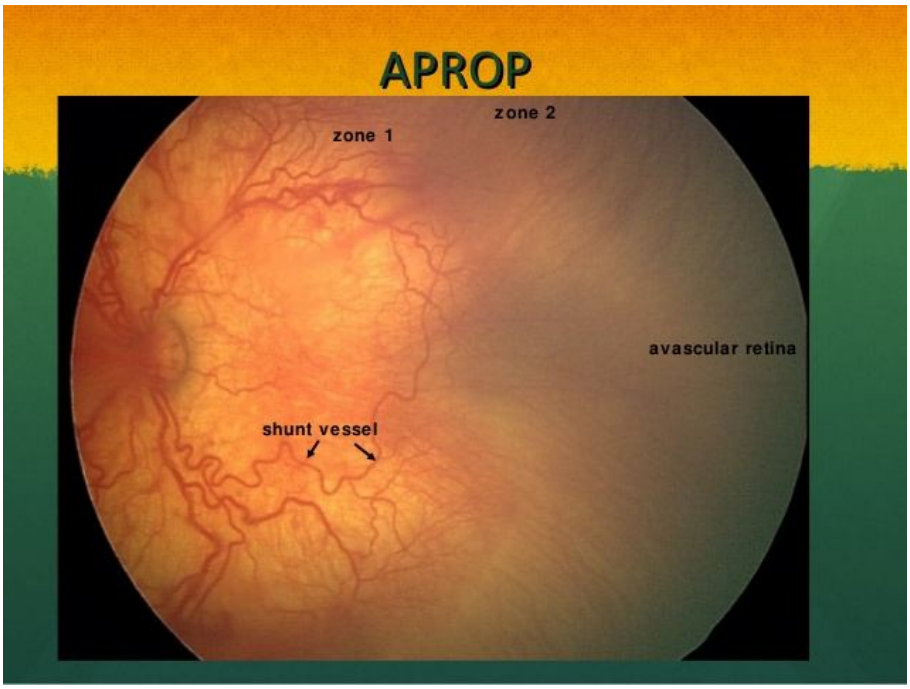


Figure 5 - Aggressive posterior ROP

- Threshold ROP:

  If 5 or more 8 contiguous or 8 cumulative clock hours of stage 3 with plus disease in either zone 1 or zone 2. Risk of blindness predicted is 50%[1,2].

- Pre-threshold ROP:

  Any ROP in zone 1 less than threshold ROP , and in zone 2 , stage 2 ROP with plus disease, stage 3 ROP without plus disease, or stage 3 ROP with plus disease but fewer than required clock hours for plus disease.

- This concept of threshold disease formerly taken as the criteria for treatment has been superseded, because it was found that outcomes improved when treatment was initiated much earlier. To decide about early treatment of ROP at the pre-threshold stage , a trial was conducted – ETROP (Early Treatment of ROP)[9] according to which 2 groups were introduced:
  - Type1 :
    - Zone 1: Any ROP and plus disease / stage 3 with or without plus disease.
    - Zone 2: Stage 2 or 3 ROP with plus disease[2]
  - Type2
    - Zone 1: Stage 1 or 2 ROP without plus disease
    - Zone 2: Stage 3 without plus disease[2]

DIAGNOSIS

A proper screening program is essential for early diagnosis and secondary prevention of visual loss in at risk infants. This can be done by early and regular opthalmological evaluation for all (new born intensive care unit) NICU graduates who meet the screening criteria.

Screening criteria includes:

- All Infants weighing <1500g[2,4]
- All Infants born before 32 weeks of gestation[2.3,4]
- Infants born after 32 weeks of gestation/ or those > 1500g , if they fall under high risk :
    - Newborns with RDS(Respiratory distress syndrome) or those needing prolonged oxygen requirement,
    - hypotension needing pressor ,
    - apnea of prematurity
    - anemia requiring blood transfusions
    - neonatal sepsis[3]
    - surgery in the first several weeks of life[2]

      This last criteria makes sure that not babies are missed , by bringing more babies under the screening criteria.

SCREENING WINDOW:

Progression of ROP usually follows a distinct time-table based on the post-menstrual age of the baby. ROP usually start developing only after 32 weeks of gestation and the median age for the detection of stage 1 ROP is 34 weeks, for pre-threshold disease is 36 weeks of post-menstrual age and threshold disease is 37 weeks[3]. The whole process of vascularization is completed by 40 weeks post-menstrual age and no ROP can be detected within 2 weeks of post natal age.. The main goal by early screening interventions is to identify ROP during their maximum period of progression , that is mainly between 34-35 weeks to 37-38 weeks of post-menstrual period[3].

Timing of screening : (Fig-6)

This depends on the postnatal age. Infants born <26 weeks of life to be screened 6 weeks postnatal , born at 27-28 weeks after 5 weeks of life , those born at 29-30 weeks of life after 4 weeks of life and those born beyond 30 weeks of life after 3 weeks of life[2].

Screening must be done 31 weeks postnatally or 4 weeks after birth, whichever is later. A regular follow up is mandatory to prevent the development of early and aggressive posterior ROP.

TIMING OF FIRST EYE EXAMINATION BASED ON GESTATIONAL AGE AT BIRTH

GESTATIONAL AGE AT BIRTH (wk)	AGE AT INITIAL EXAMINATION (wk)	
	Postmenstrual	Chronologic
22	31	9
23	31	8
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31	35	4
32	36	4

Figure 6- Timing of ROP screening based on gestational age at birth

FOLLOW UP EXAMINATIONS[3]:

- Newborns need follow up after 1 week if they have :
  - Stage 1 or 2 ROP : zone 1
  - Stage 3 ROP : zone 2
- Need follow up after 1-2 week if :
  - Immature vascularization : zone 1 – no ROP
  - Stage 2 ROP : zone 2
  - Regressing ROP : zone 1

- Follow up after 2 weeks if:
    - Stage 1 ROP :zone 2
    - Regressing ROP: zone 2
- Follow up after 2-3 week if :
    - Immature vascularization : zone 2 – no ROP
    - Stage 1 or 2 ROP : zone 3
    - Regressing ROP : zone 3
- Further examinations are not needed when:
    - Zone 3 retinal vascularization attained without prior zone 1 or 2 ROP
    - Full retinal vascularization attained
    - Postmenstrual age of 45 weeks and no prethreshold disease
    - Regression of ROP

THE NEONATAL OPTHALMOLOGICAL EXAMINATION:

- Place of choice:

  ROP screening can be done in the NICU itself under the supervision of the pediatrician. Never transport these smaller and sick neonates to opthalmology units as outpatients.

- Pupillay dilatation:

  The preferred choice is Phenylephrine 2.5% and Tropicamide 0.5% (or cyclopentolate 0.5%). The latter to be instilled one drop each, every 15 minutes, up to a maximum of 4 times , 1 hour prior to examination. One drop of Phenylephrine just before the examination is usually enough , since its repeated administration can lead on to increased systemic absorption leading to hypertension[3]. A non – dilated pupil is suggestive of tunica vasculosa lentis and it should be ruled out at to avoid excessive medication for dilatation of the pupils[1].

- Procedure: (Fig-7)

  Screening is done by a binocular indirect ophthalmoscopy using 20 D or 28/30 D condensing lens, or a 2.2 panfunduscopic Volk lens[5], by an experienced ophthalmologist. A topical anesthetist is usually instilled prior to examination. First, a wire speculum is used to keep the eye-lids apart and the anterior segment of the lens is looked for tunica vasculosa lentis, pupllary dilatation and lens / media

clarity. Next, the posterior pole is examined for presence of plus disease and sequential examination of all clock hours of retina peripherally[3]. This is done by scleral depressors that indent the eye externally, thus rotating and stabilizing the eye.

Figure 7-newborn ROP screening procedure

- Recording the findings:

  An experienced ophthalmologists should note down the zone, stage, extent of ROP and the presence of any plus or pre-plus disease in a record maintained by the NICU. This should also include the timing of next examination.

- Precautions:

  All examinations should strictly be done under sterile aseptic precautions. Some studies have shown that ROP examinations can raise blood pressures, and thus should be kept as short as possible in the NICU so that any emergency can be promptly managed[3]. Some studies have shown that swaddling the infant in a blanket and administration of oral sucrose (1.0 – 2.0 mL of 20% sucrose via syringe) prior to examination can alleviate the pain in newborns[3]. Avoiding feeding one hour before the examination can prevent aspiration in the babies[1].

- Use of wide field digital camera(RetCam) for screening[1.3]

  A mobile self contained RetCam system with a portable fundus camera as an alternative to routine indirect ophthalmoscopic examination can take pictures of retina that can be stored , transmitted to expert ,reviewed , analyzed and sequentially compared over time. Their cost and reduced accuracy have made them still lag behind standard indirect ophthalmoscopy.

TREATMENT

Indication:

Treat Type 1 prethreshold ROP (within 72 hours)

Closely monitor type 2 prethreshold ROP

Treatment options available:

- Laser therapy:

  Laser photo-coagulation is the preferred choice. Treatment must be done within 48 hours as it can rapidly progress to retinal detachment[3].It is delivered via an indirect ophthalmoscope, applied to the avascular retina anterior to the fibro-vascular proliferation ridge, for 360 degrees[2].An average 1000 shots applied to each eye , with burnt spacing of 0.5 – 1 burn-widths apart up to the ora serrata[3]. Both argon and infra-red diode laser have showed promising results[2]. The procedure can be performed in a newborn intensive care unit with local anesthesia and sedation[2]. There is a reduced risk of chemosis with better visual outcome with laser[1]. Complications include : development of cataracts , glaucoma , anterior segment ischemia[2].

  - Pre-requisites:
    - Consent for surgery
    - Proper papillary dilatation

- The babies are kept Nil per oral for 3 hours prior to surgery
- Start intravenous fluids and connect monitors and check warmers.
- Arrange necessary equipments

▪ Post-op follow up:

- First ophthalmological examination : 5-7 days after laser
- Continue weekly till regression noted
- Failure to regress: re-treatment after 10-14 days of the first laser.

❖ Cryotherapy:

A cryoprobe is applied on sclera and areas peripheral to the retinal ROP ridge. The area is frozen until the entire area treated. 35-75 applications in each eye are done under general anesthesia. Laser ablation is preferred more over cryoptherapy because of reduced post-operative complications, and better visualization of the areas ablated, such that no area is missed[3]. Thus it is needed only in special cases like poor papillary dilatation or vitreous hemorrhage – preventing adequate delivery of laser therapy[2].

- Anti-VEGF therapy:

  Intra-vitreal injections of VEGF inhibitors (bevacizumab) – considered as salvage treatment or together with vitrectomy surgery[2]. Zone I disease seemed to be more responsive than zone II[7]. The potential advantage here is that , it allows retinal development to proceed normally without destruction that is seen in laser therapy. But still out of scope of clinical trial.

- Retinal re-attachment:

  Once macula (stage 4B) or retinal detatchment(stage 5) , the surgery of choice is Vitrectomy with or without lensectomy ,membrane peeling , scleral buckling. Visual acuity is usually legal blindness[2]. Stage 4A has a success rate of 90% with pars plana vitrectomy[7].

- Systemic propranolol :

  Under trial.

- Visual rehabilitation :

  Should be offered to all visually challenged ROP babies[1].

PROGNOSIS:

Short term:

Most cases of stage 1 and 2 ROP completely regress , but still progression can be unpredictable till complete vascularisation. Risk factors for ROP that will eventually require treatment include posterior location , presence of ROP on the first examination, increasing severity of stage , circumferential involvement , plus disease and rapid disease progression. 31.5% of type 1 disease regress spontaneously[2]. Any zone 3 disease has excellent prognosis for complete recovery. The outcome in stages 4B(60%) and 5(20%) is very much unfavorable even with successful retinal re-attachment[7]. The prognosis for vision is hopeless when an infant presents with leukocoria (white pupillary reflex).

Some newborns with arrested or regressed ROP are left with demarcation lines, under-vascularisation of the peripheral retinal vessels, or abnormal branching, tortuosity and branching of retinal vessels.

Cicatricial complications arise in about 20% of the neonates with an advanced or posteriorly proliferative retinopathy at the time of involution. The usual findings are pigmentary changes of retina, moderate temporal vitreo-retinal fibrosis , straightened vascular arcades, dragging of retinal disc, ectopia of the macula, retinal folds/breaks[4]. Secondary angle closure glaucoma may develop due to progressive shallowing of the anterior chamber caused by the forward displacement of the iris, lens and diaphragm with anterior synechiae formation[7].

Long term:

Significant risk for developing

- myopia
- anisometropia and other refractive errors
- strabismus (stage 3 ROP)
- amblyopia
- astigmatism
- late retinal detachment and glaucoma(stage 4B and 5 ROP).
- CICATRICIAL DISEASE refers to retinal scarring and can later on lead to retinal detachment. This ultimately leads to a painful blind eye or a degenerated phthisical eye[4].

Visual acuity is maintained if the macula is spared. A routine follow up at 1 year of age is needed to look for sequel.

PREVENTION

No proven methods are available currently to prevent ROP. Some trials have used

- Prophylactic vitamin E therapy:

  Very low birth babies should receive 15-25IU of vitamin E as supplement, but this carries the risk of neonatal sepsis.

- Reduction in exposure to bright light[2] :

  This was considered to be a potential risk factor for ROP in past, but few recent studies, like The LIGHT-ROP study, found that ambient light reduction had no impact on ROP[4].

- Administration of penicillamine[2]

  Controversial and is associated with its own side effect (bleeding manifestation).

- Tightly regulated oxygen saturation:

  All NICU should have a written policy about the usage of oxygen. Each unit must have systems for delivering oxygen in various amounts (blenders) , measuring oxygen levels in blood (pulse oxymetre probes and monitors) and trained staff who understand the importance of controlling oxygen levels.

  The complication is mainly due to high oxygen tension and not the concentration of oxygen in the inspired air[1]. The oxygen requirement of all newborns needing resuscitation at birth, especially the preterm, should be titrated in such a way that there is a gradual

increase in oxygen saturation (70% at 3 minutes and 80% at 5 minutes after birth)[3] to prevent hyperoxia. It has been observed that ROP is more likely to develop when the PaO2 is maintained above 80mmHg, stating the need to maintain SaO2 between 85-93% to maintain PaO2 in the desirable range of 40-80mmHg[3].

It is still enigmatic as to how some Extremely low birth weight (ELBW) babies develop ROP even without prolonged oxygen therapy and strict oxygen regulatory policies, whereas some Low birth weight (LBW) preterms never develop ROP even with prolonged exposure to hyperoxia[1].

❖ Bevacizumab :

Intra-viteal injection of bevacizumab, a neutralizing anti-VEGF molecule has been demonstrated to diminish neovascular response significantly[1]. however due to uncertainties with respect to the dosing frequency, timing, and adjunct therapies to be used and potential side adverse effects, use of bevacizumab is not recommended outside the scope of clinical trial.

- Judicious use of blood transfusions:

The packed red blood cells used for transfusion are generally that of adult RBCs, which are rich in 2,3 DPG and adult Hemoglobin binds has low affinity to oxygen. This releases excess oxygen to the retinal tissues. Thus adhering to the strict protocol for blood transfusion is of at most importance.

- The use of antenatal steroids:

  Antenatal steroids are used to prevent Respiratory Distress Syndrome (surfactant deficiency) and Intra-Ventricular Hemorrhage, which are known risk factors for ROP.

  Thus their use must be encouraged in all preterm labors and the preferred drug is betamethasone – 2 doses 12mg each, given through intramuscular route , 24 hours apart[3].

- Prevent acidosis:

  By regular arterial blood gas monitoring.

- Early nutritional support

  Human breast milk has shown to be protective against ROP.

- Normalization of IGF-1 levels, and adequate physiological postnatal weight gain are associated with less severe ROP[2].

QUALITY IMPROVEMENT IN AN NICU[1]:

Roles and responsibilities:

- All new born units caring for at babies at risk of ROP should have a written protocol in relation to the screening for , and treatment of, ROP. This should include responsibilities for follow – up of babies transferred or discharged from the unit before screening is complete.
- If babies are transferred either before ROP screening is initiated or when it has been started but not completed, it is the responsibility of the consultant neonatologist to ensure that the neonatal team in the receiving unit is aware of the need to start or continue ROP screening.
- Whenever possible ROP screening should be completed prior to discharge. There should be a record of all the babies who require review and the arrangements for their follow-up.
- For babies discharged home before screening is complete, the first follow up out-patient appointment must be made before hospital discharge and the importance of attendance explained to the parents.

Auditing:

Following outcomes should be regularly audited in units with ROP screening and treatment program.

- Completeness of screening program: percentage of babies <32 weeks gestational age (GA) or <1500g birth weight who receive at least one ROP eye examination.
- Timing of first screening: percentage of babies <27 weeks GA, receiving a first ROP screening exam by 4 weeks of postnatal age.
- ROP treatment: percentage of babies with any zone 1 ROP who receive treatment.
- Timing of treatment: percentage of babies needing ROP treatment, and treated within 48 hours of the decision to treat being made.

“A STUDY ON FACTORS AFFECTING THE OUTCOME OF RETINOPATHY OF PREMATURITY – A CROSS SECTIONAL ANALYTICAL STUDY WITH INTERNAL COMPARISON, AT A TERTIARY CARE CENTER IN NORTH CHENNAI”

AIMS AND OBJECTIVES

- To determine the prevalence of ROP and severe (type 1) ROP in the newborns undergoing routine ROP screening.
- To be able to predict the risk factors associated with severe ROP requiring laser versus ROP undergoing spontaneous resolution.
- To be able to identify the preventable causes among these risk factors.

MATERIALS AND METHODS

Type of the study:

A Cross-sectional analytical study with internal comparison.

Study setting:

On newborns routinely screened for retinopathy of prematurity *in GOVT. RSRM Lying in Hospital and OUTBORN NICU, Institute Of Social Pediatrics.*

Study duration:

July 2017-September 2018 (15 months)

Sample size:

170 ($4pq/d^2$, p=30%)

Sampling technique:

Purposive sampling of all the newborns screened to be ROP positive.

Selection of study subjects:

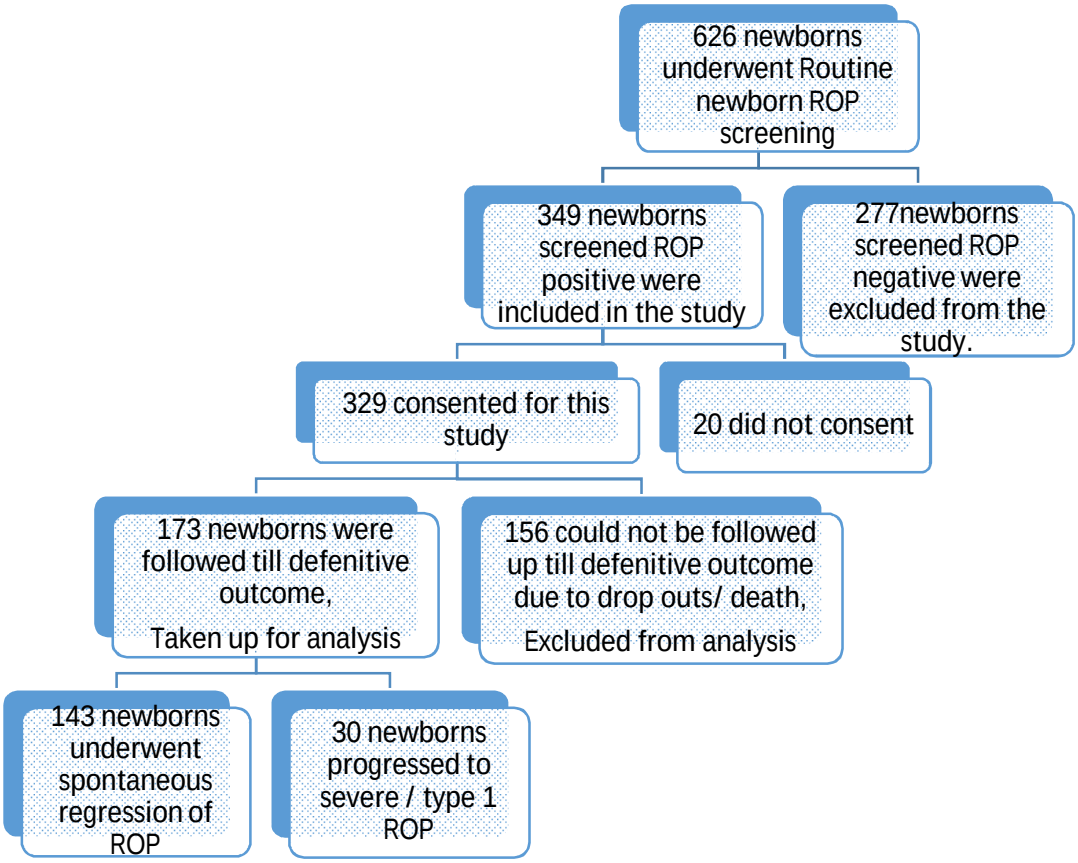
Inclusion criteria:

- All newborns who underwent routine newborn screeing for Retinopathy of prematurity and found to be positive.
- Newborns whose parents have given consent for the study.

Exclusion criteria:

- Newborns screened for Retinopathy of Prematurity who are found to be Negative.
- Parents who have not consented for the study.

Newborns who could not be followed up till a definitive outcome, due to premature death / insufficient clinical data's, were excluded from the analysis.



Study methodology:

THE ROP SCREENING

Routine newborn ROP screening protocol at our Newborn Unit included all newborns:

- born at <34 wks of gestation age
- with birth weight <1500g
- who received exchange transfusion
- who were on prolonged ventilation (>7days)

The first ophthalmological examination was carried out at 3wks of postnatal age, at the newborn unit.

Pupils were dilated using 2 drops of tropicamide 0.5% +5% phenylephrin at 10 minutes interval – to a maximum of three times until optimally dilated.

Examinations were done one hour after the last feed to reduce the risk of vomiting and aspiration.

After dilatation, ophthalmological examinations were done using a paediatric eye speculum and paediatric scleral depressors, with the help of neonatology nurse who restrains the baby.

Ophthalmological examinations were done by a single trained ophthalmologist for the entire study.

Indirect ophthalmoscopy was performed using binocular indirect ophthalmoscope .

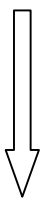
Newborns that were screened ROP positive were included in this study. Their individual risk factors were noted at the start of the study. The risk factors considered were:

MATERNAL RISK FACTORS:

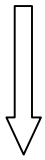
- Maternal age
- Pre-eclampsia
- GDM
- Use of antenatal steroids in the mother
- Type of pregnancy- singleton / multiple
- Premature rupture of membranes (PROM)

NEONATAL RISK FACTORS:

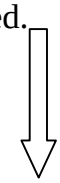
- Gender
- Birth weight
- Gestational age at birth
- Sepsis (culture positive / CRP positive)
- Neonatal hyperbilirubinemia requiring phototherapy
- Respiratory distress / conditions requiring Oxygen ($O_{2)}$.
- O_2 requirement for more than 7 days
- Use of surfactant in the neonate
- Seizures
- Congenital heart disease



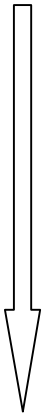
The ROP zones, stage and extent were recorded along with the presence or absence of plus or pre-plus disease.



Schedule for next visit was also recorded. They were followed up as per schedule till a definitive outcome reached.



The definitive outcome for this study included – spontaneous regression / severe ROP requiring treatment (type 1 ROP), thus classifying them into 2 groups. Treatment given at our NICU was laser therapy. Follow up was terminated at this stage.



Risk factors among each group were analyzed and data collection transferred into Excel sheet, which was then subjected to statistical analysis.

Statistical Analysis:

Analysis was done in IBM SPSS 23 and Excel 2013. Frequency and percentage was derived for categorical variables. Measures of dispersion and standard deviation was obtained for continuous variables. Chi square test was used for categorical variables and non-parametric test was used for comparison of two groups. P value of 0.05 was considered as significant.

Obtainment of consent:

Study group was recruited only after informed and written consent from parents of the babies was obtained , in presence of a witness.

Ethical considerations:

Prior to the commencement of the study, Ethical committee of Stanley medical college and hospital had approved the thesis protocol.

Definition of the risk factors for study purpose:

The factors analyzed in the study can be categorized into 2 groups, maternal and neonatal.

- Maternal factors included:
  - Maternal age

    Classified as those with age <30yrs and >30yrs at the time of conception.
  - Presence of Pre-eclampsia:

    Defined as hypertension with proteinuria, beyond 20 weeks' of gestation. Hypertension here was taken as elevated systolic blood pressure >140mmHg diastolic blood pressure >90mmHg , over 2 measurements at least 6 hours apart. All measurements were done during sitting position using proper cuff size.
  - Presence of GDM:

    Based on the results of Oral Glucose Tolerance test, where 75g glucose is given to mother. GDM was conformed if the 2^{nd} hour serum sample showed a glucose value > 140mg/dl.
  - The use of Antenatal steroids:

    The principle antenatal steroid used in the newborn unit of study is dexamethasone , given

as 4 doses 12 hours apart. Administration of even a single dose of dexamethasone was considered to have received steroids in this study.

- Singleton or multiple pregnancy

  All single live intra-uterine gestations were taken as singleton, and all other multiple gestations, either live born, or with single fetal intra-uterine demise or still born were included as multiple pregnancy.

- PROM

  Any Premature rupture of membranes >18 hours were included.

- The neonatal factors
  - Gender:

    Male and female babies

  - Birth weight

    Weighing of all the newborns were done by the same electronic weighing machine at the labor room. Birth weight was classified further into 3 groups as those weighing <1000g (Extremely low birth weight / ELBW), between 1000 and

1500g (VLBW) and those weighing >1500g (Low birth weight /LBW and the newborns with normal birth weight).

- Gestational age

  Calculated based on the Naegele's rule, which estimates the Expected date of deliver (40 weeks) by adding 9 months and 7 days to the Last Menstrual Cycle.

- Neonatal Sepsis:

  Both CRP and culture positive were taken into account. CRP positivity was taken as >5mg/dl. Investigations were done by a standardized laboratory attached to each newborn unit.

- Neonatal hyperbilirubinemia requiring phototherapy:

  For neonates born >35 weeks :Phototherapy was administered based on the Nomo gram (adapted from the AAP Subcommittee on hyperbilirubinemia) for assigning risk to newborns >35 weeks of gestation, based on hour-specific serum bilirubin value.

  For early and extreme preterm : phototherapy was given based on the birth weight of the newborns according to the institutional protocol.

- Respiratory distress / conditions requiring O_2

  This included any infant that required oxygen during NICU stay mainly due to:

  - Respiratory Distress Syndrome(RDS):

    Any premature newborn with signs of respiratory distress shortly after birth, with classical radiographic findings or those in whom improvement was noted with prophylactic surfactant therapy even before radiographic evidence, was taken as RDS.

  - Meconium Aspiration Syndrome(MAS):

    Respiratory distress in any term or near-term neonate, shortly after birth, with evidence of meconium staining liquor at birth, with or without classical radiographic evidence was taken as MAS.

  - Transient Tachypnea of Newborn:

    Milder forms of Respiratory distress in a term or late preterm neonate, presenting within 6 hours of life that usually recover

within 12-24 hours of life were taken as TTN.

- Birth asphyxia(BA):

  Any neonate with a 1 minute Apgar score <4 were considered to have birth asphyxia.

Majority of the neonates who require Oxygen in our unit fall under these 4 categories.

- Newborns who Required oxygen > 7 days:

  The cumulative use of oxygen for more than 7 days, through mechanical ventilation, nasal/Bubble CPAP, oxygen hood and nasal prongs were all taken into account.

- Surfactant administration:

  Both prophylactic and rescue (early for in-borns / late rescue for referrals) were taken into account.

- Neonatal Seizures:

  All forms of neonatal seizures – focal tonic, focal clonic, myoclonic, autonomic seizure that warranted administration of an anti-epileptic (phenobarbitone as the first line used in our unit) were taken into account. Those seizures

that were either proved to be due to hypoglycemia/hypocalcaemia or settled with intravenous dextrose or calcium administration were not included.

- Congenital heart disease:

  Any neonate with an ECHO proven congenital heart disease at the first screening were included.

RESULTS

A total of 626 newborn underwent routine ROP screening, out of which 349 were found to be ROP positive. This accounted for 55.7% of the total newborns screened.

329 consented to this study, out of which 156 could not be followed up due to drop outs or premature death.

A total of 173 newborns screened ROP positive were followed up till a definitive outcome was reached, that included 143 newborns who underwent spontaneous regression of ROP and 30 (17.3%) newborns progressed to severe stages.

Among the study group, maternal parameters showed – most of the mothers were under 30 years of age 86.7% (150), 27.1% (47) had pregnancy induced hypertension, 6.3% (11) had gestational diabetes mellitus, 16.7% (29) had PROM, 42.7%(74) were given antenatal steroids .84.9% (147) were singleton pregnancies and 15% (26) were multiple pregnancies.

Risk factor analysis for neonatal factors among the study group showed that 46.2% of the newborns were female (80) and 53.7% was male (93.7).

The birth weight distribution reveled 50% (87) to be weighing >1500g, 40% (69) between 1000 and 1500g, 10% (17) among <1500g.

The gestational age distribution showed 30% (52) to be born >34 weeks, 56% (97) born between 30 and 34 weeks, 14% (24) showed <30 weeks.

Among all neonates, 32.3% (56) had culture positive sepsis, 31.2% (54) had CRP positive sepsis.

67.6% (117) had respiratory distress or received oxygen therapy for RDS (36.4%), MAS (8%), TTN (13.8%), BA (9%) , out of which 15.6% (27) received oxygen for more than 7 days.

13% (23) of the neonates received surfactant, 54% (94) had neonatal hyperbilirubinemia requiring phototherapy, 13% (23) had seizures , 7% (10) were associated with congenital heart disease(PDA).

The study parameters have been summarized in Table-1 and 2.

Table 1 - Distribution of the maternal risk factors included in the study

Characteristics		n (%)
Maternal age	<30 years	150(86.7%)
	>30 years	23(13.2%)
Pre-eclampsia		47(27.1%)
GDM		11(6.3%)
AN steroid use		74(42.7%)
Pregnancies	Singleton	147(84.9%)
	Multiple	26(15%)
PROM		29(16.7%)

Table 2-Distribtion of the neonatal risk factors included in the study

Newborn characteristics		N (%)
Gender	Male	93(53.7%)
	Female	80(46.2%)
Birth Weight	>1.5 kg	87(50%)
	1-1.5kg	69(40%)
	<1kg	17(10%)
Gestational age	>34 weeks	52(30%)
	30-34 weeks	97(56%)
	<30 weeks	24(14%)
Sepsis	Culture proven	56(32.3%)
	CRP positive	54(31.2%)
Jaundice requiring phototherapy		94(54%)
Respiratory distress/ O2 requirement	Total	117(67.6%)
	ARDS	36.4%
	MAS	8%
	TTN	13.8%
	BA	9%
O2 requirement >7 days		27(15.6%)
Surfactant		23(13%)
Seizures		23(13%)
Congenital heart disease		10(7%)

Out of all the 173 neonates who were screened ROP positive, 17.3% (30) of the newborns progressed to type 1 ROP and 82.6% (143) underwent regression.

Analyzing the maternal risk factors 17% (26) of the infants born to mothers of <30 years and 17% (4) of infants born to mothers >30 years progressed to severe ROP (P=0.994).

17% (8) of infants born to mothers with pre-eclampsia and 23.5% (32) of infants born to mothers without pre-eclampsia progressed to type1 ROP (P=0.35).

45% (5) infants born to mothers with GDM progressed to type 1 ROP, which was a statistically significant risk factor for developing severe stages of ROP(P=0.011).

Antenatal steroids was administered in 9% (7) and 23% (23) neonates had not received steroids. The non-usage of antenatal steroids was found to be statistically significant risk factor for the development of severe type 1 ROP (P=0.018).

16% (24) of the newborn who were singletons and 23% (6) of newborn who were one among multiple pregnancies progressed to severe ROP (P=0.40).

17% (5) of the newborns whose mothers had PROM at delivery 17% (25) of them who did not have PROM progressed to laser which showed no statistical difference (P=0.98).

Analyzing the neonatal risk factors, 16% (13) male babes an 18% female babies(17) progressed to type 1 ROP , which showed no statistical significance(P=0.75).

14% (12) of the newborns weighing >1500g, 19% (13) weighing between 1000 and 1500g, 29% (5) weighing <1500g progressed to severe forms of ROP, which although shows a positive correlation, was not found to be statistically significant (P=0.27).

Similarly 13% (7) newborns born at >34 weeks of gestation, 18.5% (18) born between 30 and 34 weeks of gestation, 20% (5) born <30 weeks of gestation progressed to severe stages of ROP, showing that lower gestational age was associated with more severe ROP , but results were not statistically significant (P=0.65).

29% (16) out of 56 culture proven sepsis, 23% (13) of the CRP positive sepsis, progressed to severe ROP, that showed a major statistical significance with P value 0.000.

21% (20) of the newborns with Jaundice requiring phototherapy progressed to laser (P=0.042).

23.9% (28) of the newborns with respiratory distress/ that required oxygen progressed to severe ROP, which included 28.5% (18) of those having ARDS, 28.5% (4) with MAS, 4% (1) with TTN and 31% (5) of those with birth asphyxia, progressed to severe ROP. This showed a statistically significant association with a P value of 0.000.

40% (11) of the newborn who required O_2 / mechanically ventilated for more than 7 days and 13% (19) for those <7days, progressed to type 1 ROP (P=0.000).

43% (10) of the newborns who developed seizures and 13% (20) without seizures progressed to type 1 ROP with a statistically significant P value 0.000.

40% (4) of the newborns with congenital heart disease (PDA) and 16% (26) without a congenital heart disease had a statistically significant

association with progression of severe forms of ROP with a P value of 0.051.

18% (2) of the newborns administered surfactant and 18% (28) of the newborns not given surfactant progressed to ROP , showing no statistical significance (P=0.23)

Study parameters, among those who required laser and those who did not, are summarized in the tables below (Table-3 and 4)

Table 3-Maternal risk factors in association with severity of ROP

Characteristics		ROP outcome		
		Laser treated ROP n (%)	Regressed ROP n (%)	Chi square value (p value)
Maternal age	<30 years	26(17%)	124(83%)	0(0.994)
	>30 years	4(17%)	19(83%)	
Pre-eclampsia	Present	8(17%)	39(83%)	0.86(0.352)
	Not present	32(23.5%)	104(76.5%)	
GDM	Present	5(45%)	6(55%)	6.47(0.011)*
	Not present	25(15%)	137(85%)	
AN steroid	Used	7(9%)	67(91%)	5.6(0.018)*
	Not used	23(23%)	76(77%)	
Pregnancies	Singleton	24(16%)	123(84%)	0.702(0.402)
	Multiple	6(23%)	20(77%)	
PROM	Present	5(17%)	24(83%)	0(0.98)
	Not present	25(17%)	119(83%)	

* P considered significant at <0.005

Table 4- Neonatal risk factors in association with severity of ROP

Newborn characteristics		ROP outcome		
		Laser treated ROP n (%)	Regressed ROP N (%)	Chi square value (p value)
Gender	Male	13(16%)	67(84%)	0.12(0.725)
	Female	17(18%)	76(82%)	
Birth Weight	>1.5 kg	12(14%)	75(86%)	2.6(0.272)
	1-1.5kg	13(19%)	56(81%)	
	<1kg	5(29%)	12(71%)	
Gestational age	>34 weeks	7(13%)	45(87%)	0.85(0.653)
	30-34 weeks	18(18.5%)	79(81.5%)	
	<30 weeks	5(20%)	19(80%)	
Sepsis	Culture proven	16(29%)	38(71%)	17.94(0.000)*
	CRP positive	13(23%)	43(77%)	
	No sepsis	1(1.5%)	62(98.5%)	
Jaundice requiring phototherapy	Present	20(21%)	74(79%)	6.32(0.042)*
	Not present	8(10%)	67(90%)	
Respiratory distress/ O2 requirement	With distress	28(23.9%)	89(76%)	
	ARDS	18(28.5%)	45(71.4%)	
	MAS	4(28.5%)	10(71.5%)	
	TTN	1(4%)	23(96%)	
	BA	5(31%)	11(69%)	
	No distress	2(3.5%)	54(96.5%)	

O2 requirement	>7 days	11(40%)	16(60%)	12.22(0.000)*
	<7 days	19(13%)	127(87%)	
Surfactant	Administered	2(9%)	21(91%)	1.38(0.23)
	Not administered	28(18%)	122(82%)	
Seizures	Present	10(43%)	13(57%)	12.64(0.000)*
	Not present	20(13%)	130(87%)	
Congenital heart disease	Present	4(40%)	6(60%)	3.8(0.051)*
	Not present	26(16%)	137(84%)	

* P value significant at <0.005.

Age of the mothers of the babies under study

The following figure and table shows the association between maternal age of the babies under study and outcome of ROP. The mother age <30 had the maximum number of participants (86.7%) both in the regression and laser group. (Fig-8 and table-5)

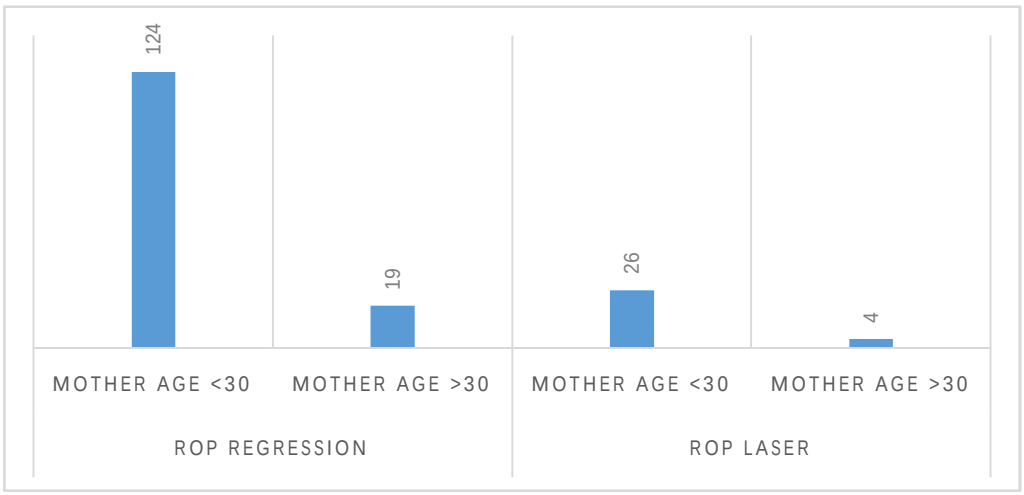


Figure 8- maternal age of the neonates in the study

Table 5- maternal age of the neonates under study and outcome of ROP

		ROP		Total
		Regression	Laser	
AGE	Mother age <30	124 (83%)	26 (17%)	150
	Mother age >30	19 (83%)	4 (17%)	23
Total		143	30	173

Gender of the babies

The following figure and table shows the significance of gender of the babies under study with ROP outcome. There was no statistical difference between the 2 groups.(Fig-9 and table-6)

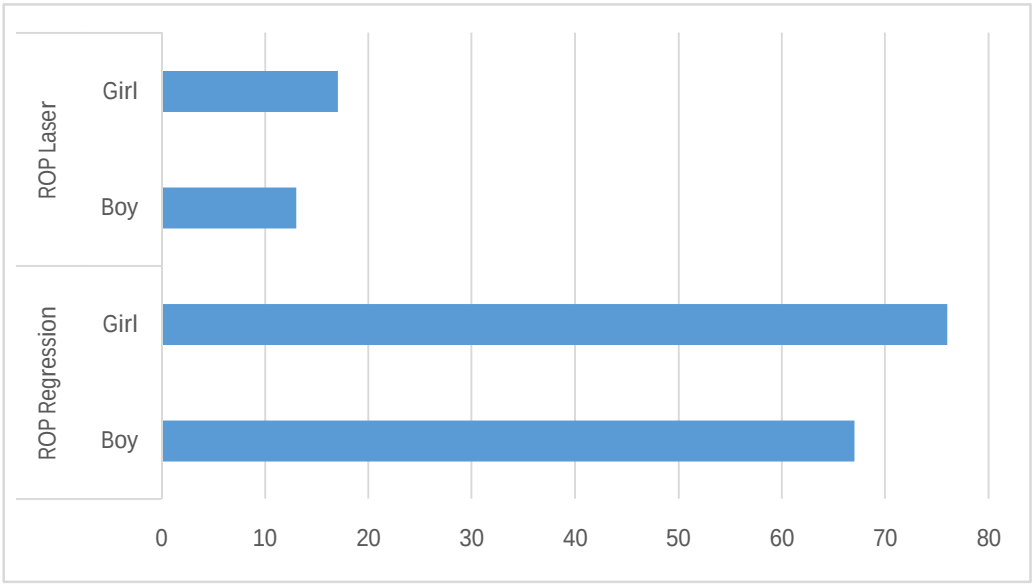


Figure 9- Gender of the babies under study and outcome of ROP

Table 6-Gender of the babies under study and outcome of ROP

		ROP		Total
		Regression	Laser	
SEX	Boy Baby	67 (84%)	13 (16%)	80
	Girl Baby	76 (82%)	17 (18%)	93
Total		143	30	173

Presence of pre-eclampsia

The following figure and table shows the presence of pre-eclampsia of the mothers under study. More number of mothers in regression group (27.3%) had pre-eclampsia than laser group (26.7%). (Fig-10 and table-7)

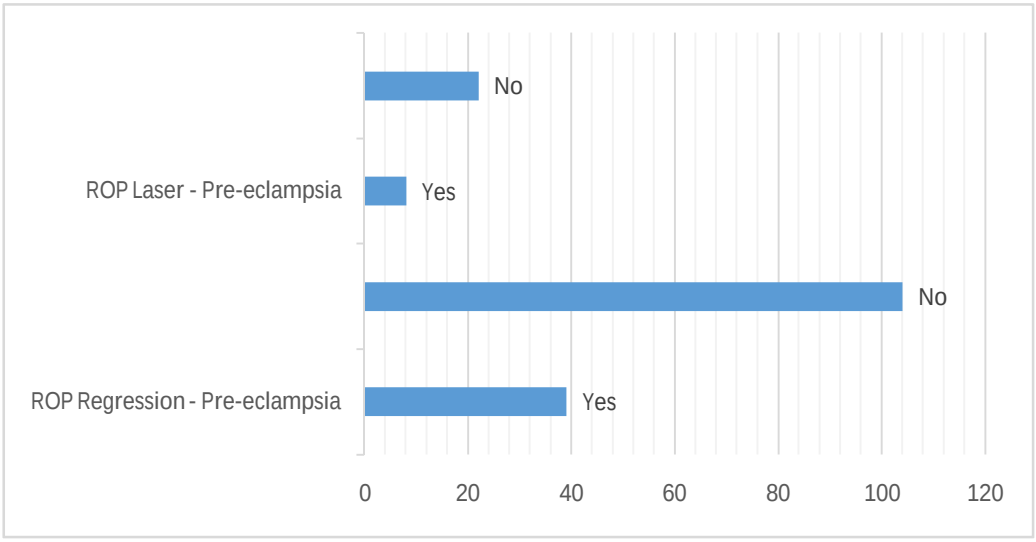


Figure 10- showoing distribution of maternal pre-eclampsia among the neonates under the study

Table 7- relation between maternal pre-eclampsia and ROP progression in their neonates.

		ROP		Total
		Regression	Laser	
PRE-ECLAMPSIA	Yes	39 (83%)	8 (17%)	47
	No	104 (76.5%)	22 (23.5%)	126
Total		143	30	173

Presence of gestational diabetes mellitus

The following figure and table shows the presence of GDM in the mothers of the neonates under study. More percentage of mothers in laser group (16.7%) had GDM than regression group (4.2%). Table 8 shows the chi-square test with a value of 6.477 with $p<0.05$. (Fig-11 and table-8)

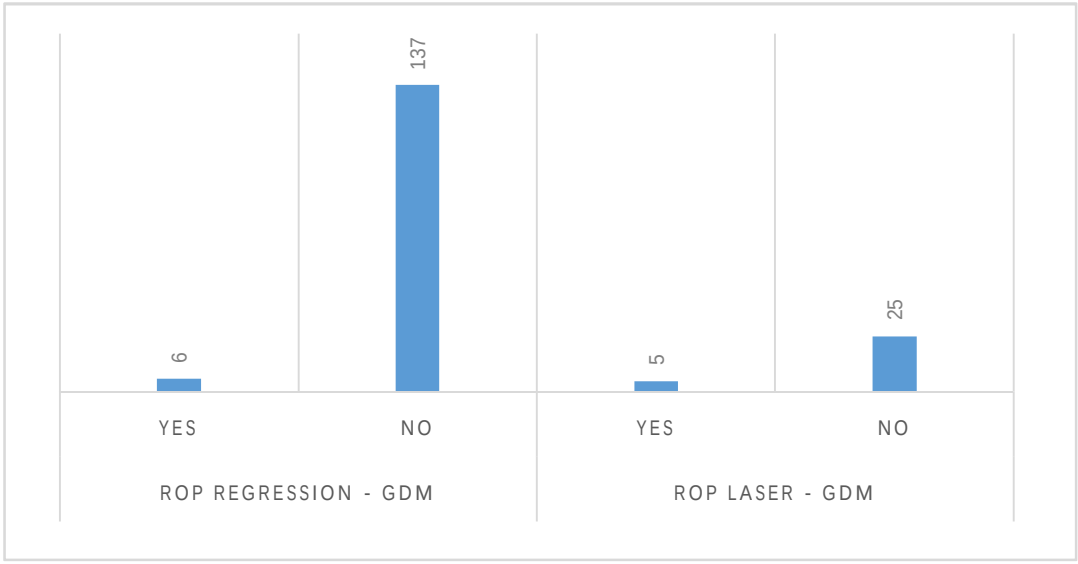


Figure 11- impact of maternal GDM on outcome of ROP

Table 8-impact of maternal GDM and outcome of ROP

		ROP		Total
		Regression	Laser	
GDM	Yes	6 (55%)	5 (45%)	11
	No	137 (85%)	25 (15%)	162
Total		143	30	173

Singleton Vs Multiple pregnancies

The following figure and table compares singleton and multiple pregnancies and the outcome of ROP. Fourteen percent babies in regression and twenty percent of babies in laser were multiple. (Fig-12 and table-9)

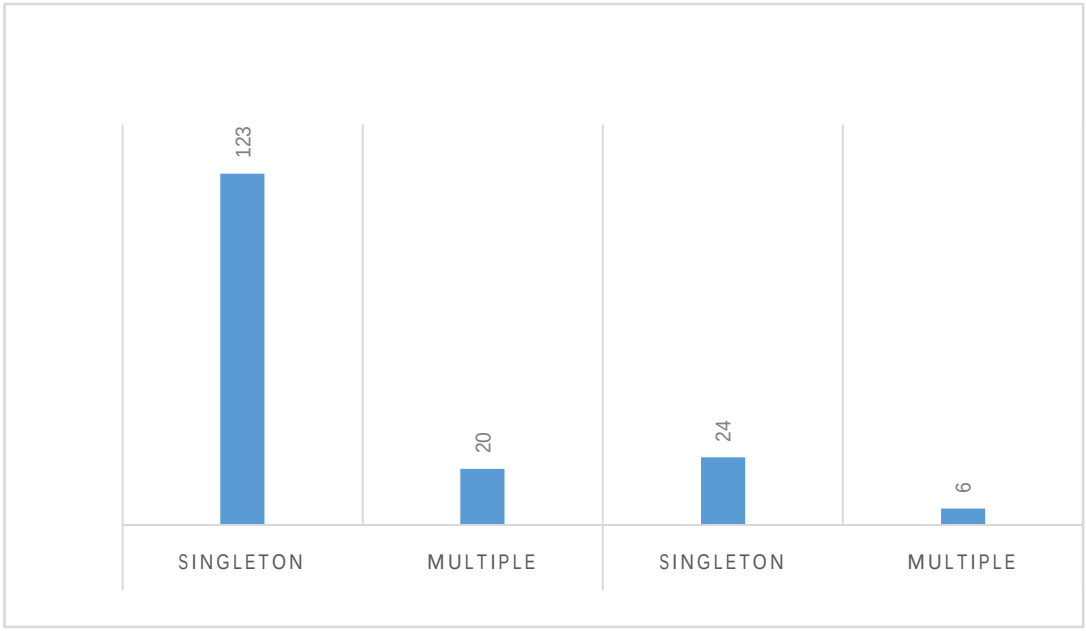


Figure 12-comparing type singleton / multiple pregnancies with outcome of ROP

Table 9- singleton/ multiple pregnancy Vs ROP outcome

		ROP		Total
		Regression	Laser	
PREGNANCY	Singleton	123 (84%)	24 (16%)	147
	Multiple	20 (77%)	6 (23%)	26
Total		143	30	173

Premature rupture of membranes

The following figure and table shows the relation of PROM in the mothers of the neonates under study with progression of ROP. Equal percentage of mothers in laser group (16.7%) and regression group (16.8%) had PROM. (Fig-13 and table-10)

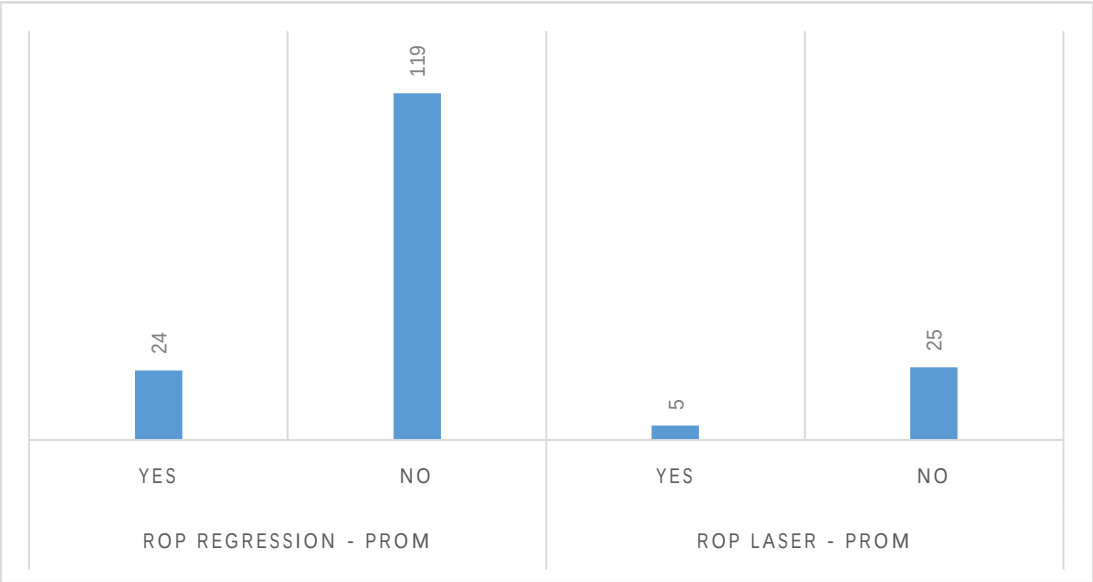


Figure 13- relation between PROM in mothers and ROP outcome

Table 10- PROM in mothers Vs ROP outcome

		ROP		Total
		Regression	Laser	
PROM	Yes	24 (83%)	5 (17%)	29
	No	119 (83%)	25 (17%)	144
Total		143	30	173

Use of Steroids

The following figure and table shows the impact of steroid usage antenatally and the outcome of ROP. Table 11 shows the chi-square test with a value of 5.604 with $p<0.05$.

(Fig 14 and table-11).

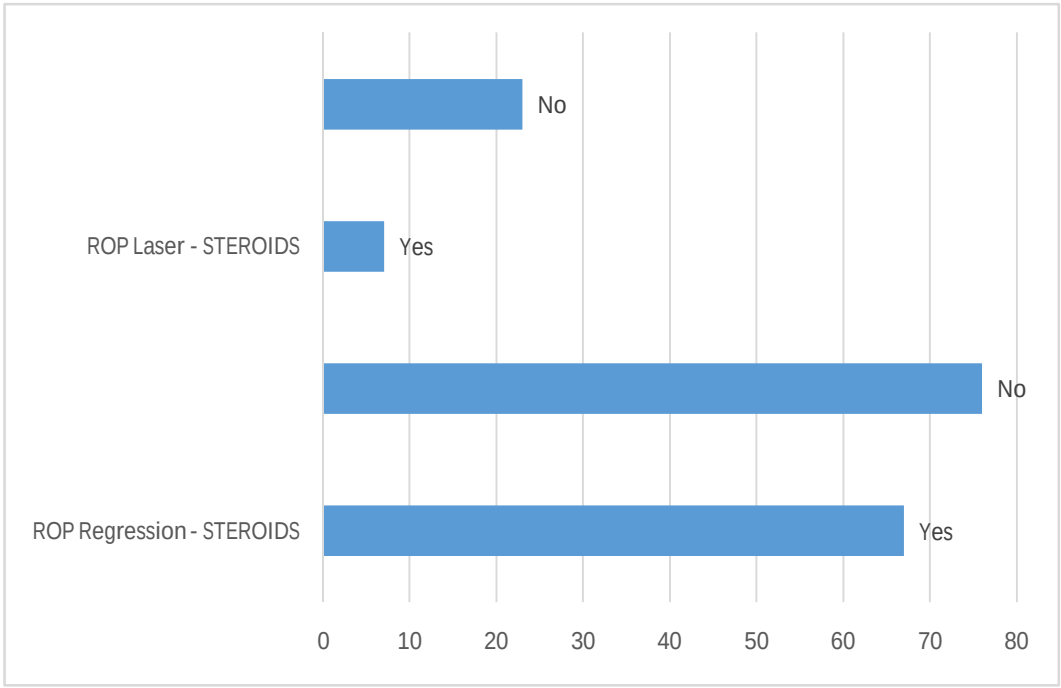


Figure 14-Impact of use on AN steroids and outcome of ROP

Table 11-Impact of use of AN steroids and outcome of ROP

		ROP		Total
		Regression	Laser	
STEROIDS	Yes	67 (91%)	7 (9%)	74
	No	76 (77%)	23 (23%)	99
Total		143	30	173

Birth weight of the babies

The following figure and table shows the relation between birth weight of the babies and their ROP outcome. Low birth weight had more chances of laser, though not statistically significant. (Fig 15 and table-12)

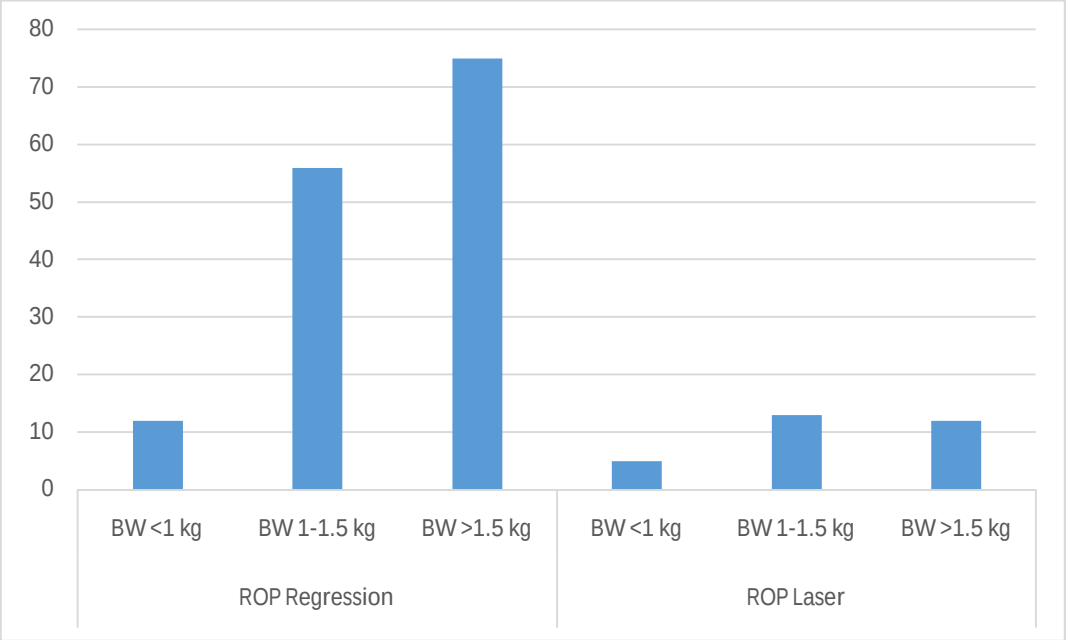


Figure 15- Birth weight of the babies and relation with ROP outcome

Table 12- relation between birth weight of babies and ROP outcomes

		ROP		Total
		Regression	Laser	
BW	<1 Kg	12 (71%)	5 (29%)	17
	1-1.5 Kg	56 (81%)	13 (19%)	69
	>1.5 kg	75 (86%)	12 (14%)	87
Total		143	30	173

Gestational Age

The following table shows the gestational age of the babies and their ROP outcomes. More babies among lower gestational age (<30 weeks) progressed to laser , though not statistically significant. (table-13)

Table 13- gestational age and progression of ROP

		ROP		Total
		Regression	Laser	
GA	<30 weeks	19 (80%)	5 (20%)	24
	30-34weeks	79 (81.5%)	18 (18.5%)	97
	>34 weeks	45 (87%)	7 (13%)	52
Total		143	30	173

Neonatal sepsis

The following figure and table shows relation between neonatal sepsis and the outcome of ROP. 30.1% of babies in regression had culture positive sepsis while 26.6% had CRP positive sepsis. 43.3% babies in laser had culture positive sepsis while 53.3% had CRP positive sepsis. Chi-square test revealed a value of 17.945 with p value <0.005. (Fig-16 and table-14)

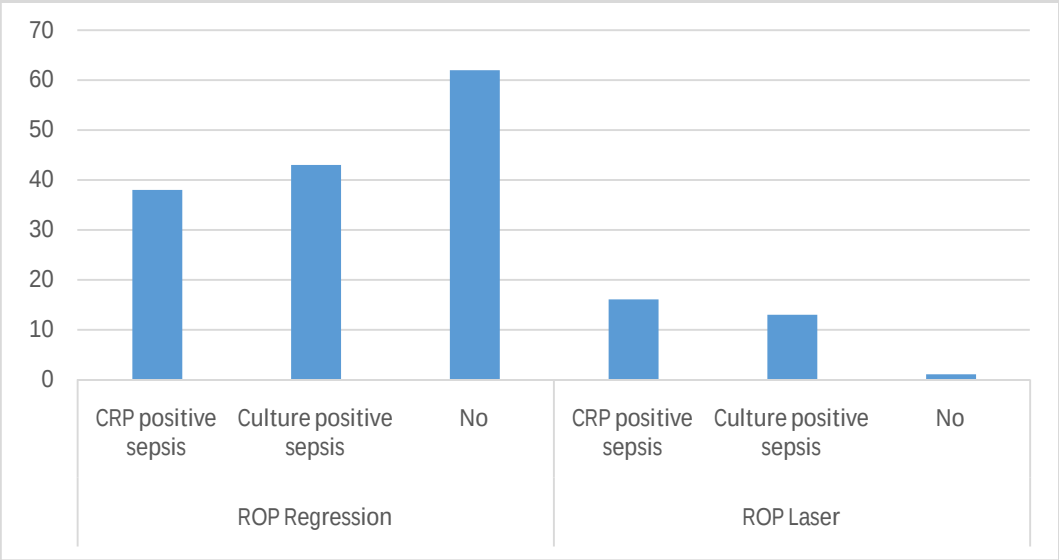


Figure 16- neonatal sepsis and ROP outcome

Table 14- neonatal sepsis Vs ROP outcome

		ROP		Total
		Regression	Laser	
SEPSIS	No	62 (98.5%)	1 (1.5%)	63
	Culture Positive Sepsis	43 (77%)	13 (23%)	56
	CRP positive sepsis	38 (71%)	16 (29%)	54
Total		143	30	173

Respiratory distress / Oxygen administration

The following figure and table shows the relation between respiratory distress / oxygen administration and outcome of ROP. Chi-square test shows a value of 19.248 with p<0.005. (Fig-17 and table-15)

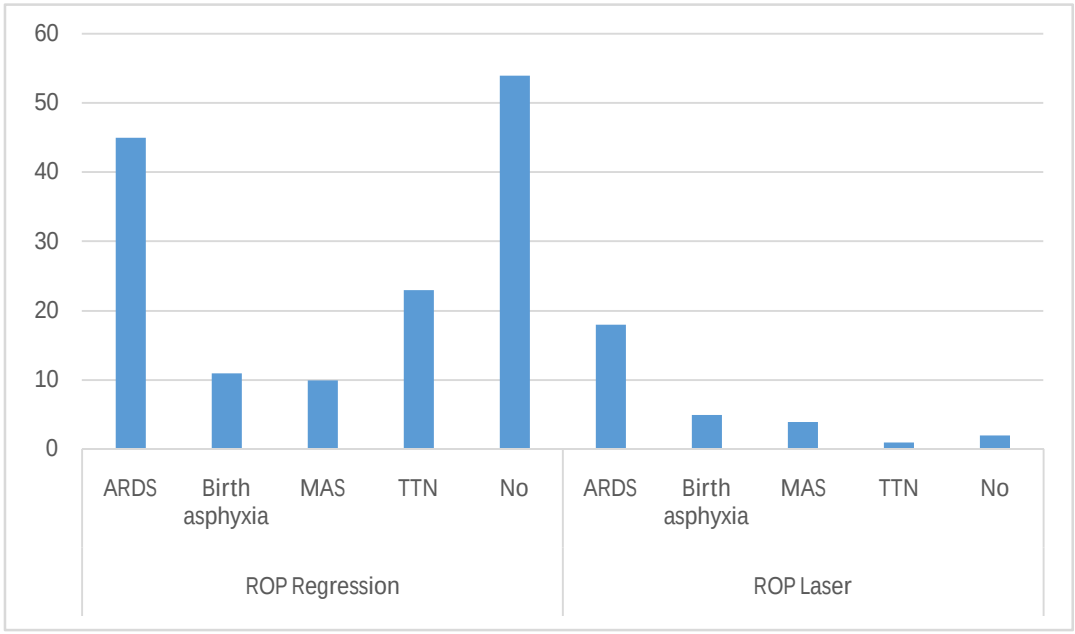


Figure 17- Respiratory distress/ oxygen administration and ROP outcome

Table 15- distress/ oxygen administration Vs ROP outcome

		ROP		Total
		Regression	Laser	
DISTRESS	Total cases with distress	28(23.9%)	89(76%)	117
	RDS	45 (71.4%)	18 (28.5%)	63
	MAS	10 (71.5%)	4 (28.5%)	14
	TTN	23 (96%)	1 (4%)	24
	Birth Asphyxia	11(69%)	5(31%)	16
	No distress	54(96.5%)	2(3.5%)	56
Total		143	30	173

Oxygen requirement greater 7 days

The following figure and tables shows the relation between newborns requiring oxygen for greater than 7 days and ROP outcome. This was more among laser group (36.7%). Chi-square tests shows a value of 12.221 with p<0.005. (Fig-18 and table-16)

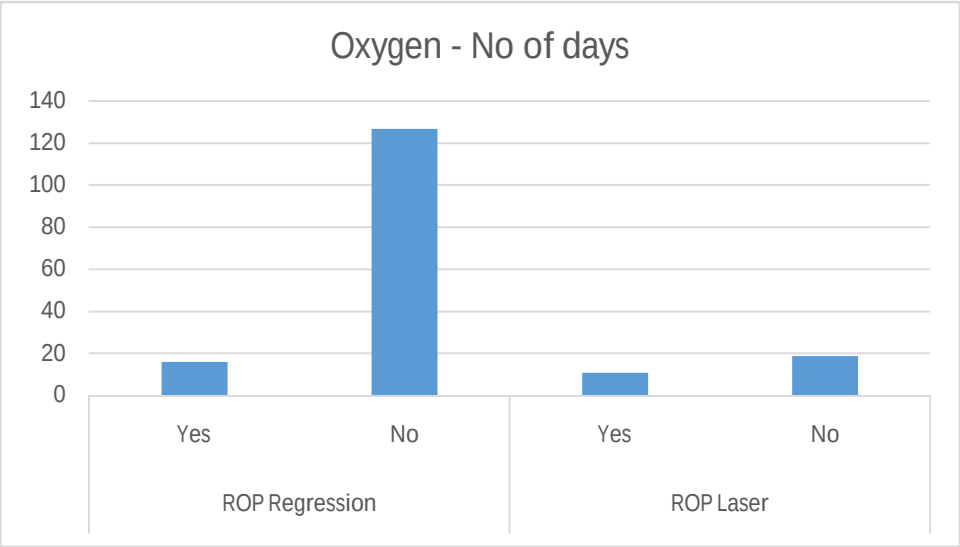


Figure 18-oxygen requirement > 7 days and ROP outcome

Table 16-oxygen requirement >7 days and ROP outcome

		ROP		Total
		Regression	Laser	
O2 > 7 DAYS	Yes	16 (60%)	11 (40%)	27
	No	127 (87%)	19 (13%)	146
Total		143	30	173

Surfactant use in babies

The following figure and table shows the relation between surfactant use in babies and their ROP outcome. The use of surfactant was higher among babies of regression group (14.7%) than laser (6.7%), though statistically not significant.(Fig-19 and table-17)

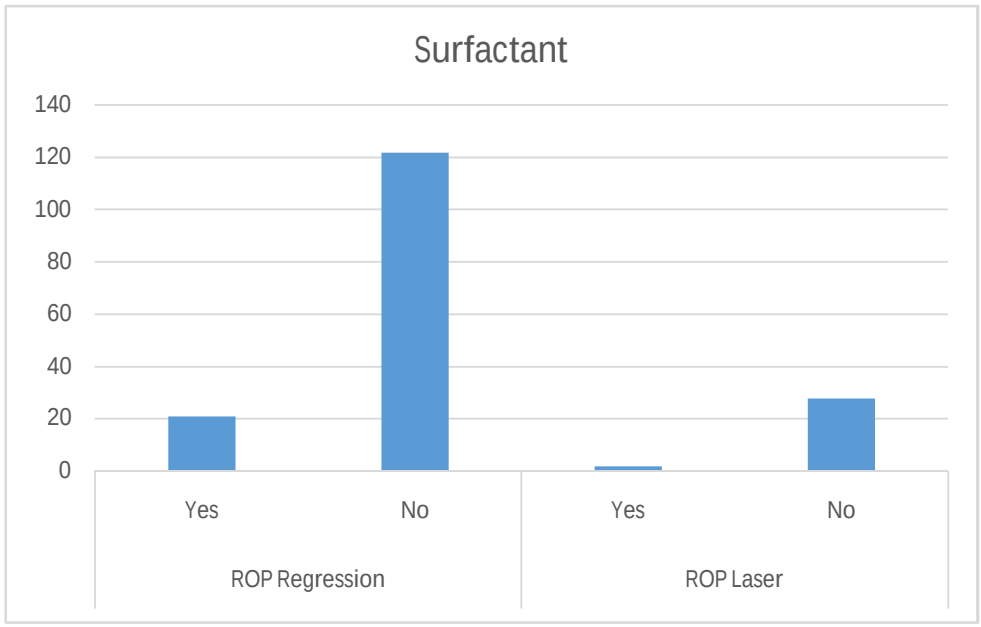


Figure 19- relation between use of surfactant in newborns and ROP progression

Table 17- relation between use of surfactant in newborn Vs outcome of ROP

		ROP		Total
		Regression	Laser	
SURFACTANT	Yes	21 (91%)	2 (9%)	23
	No	122 (82%)	28 (18%)	150
Total		143	30	173

Icterus

The following figure and table shows the association of icterus in the new born and the outcome of ROP. Since number of exchange transfusion was same among both the groups, only jaundice requiring phototherapy was taken into study.Chi-square test was 6.323 and significant with $p<0.05$. (Fig-20 and table-18)

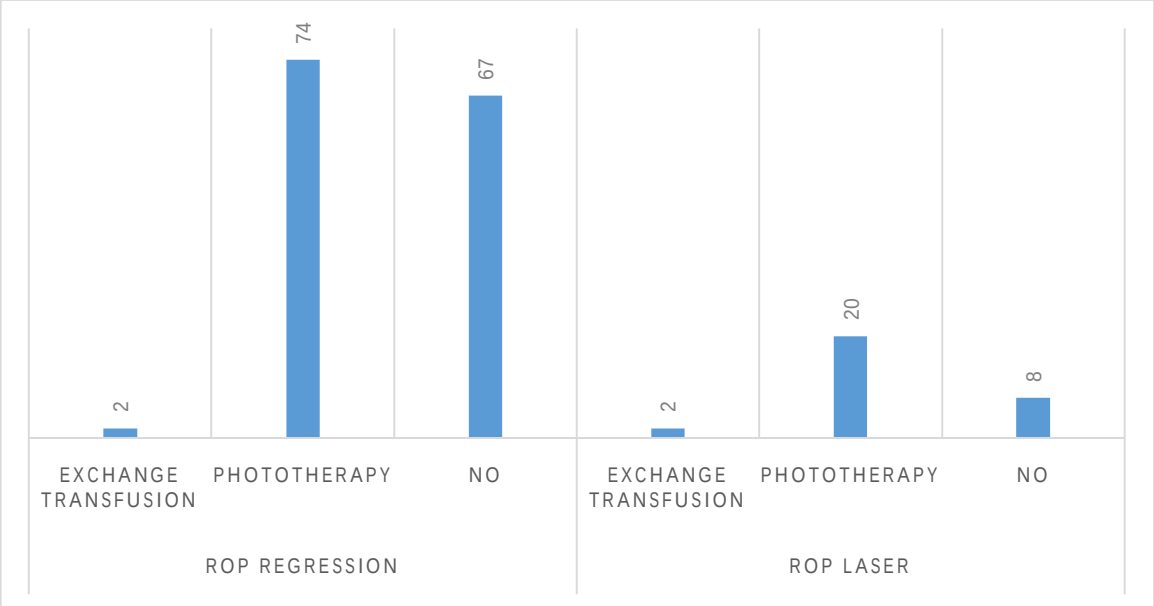


Figure 20 - relation between icterus and outcome of ROP

Table 18- relation between icterus and outcome of ROP

		ROP		Total
		Regression	Laser	
ICTERUS	No	67 (90%)	8 (10%)	75
	Phototherapy	74 (79%)	20 (21%)	94
	Exchange Transfusion	2 (50%)	2 (50%)	4
Total		143	30	173

Seizure in new born

The following figure and table shows the relation between seizures in new born and ROP outcome. Chi-square test shows a value of 12.643 with p <0.005. (Fig-21 and table-19)

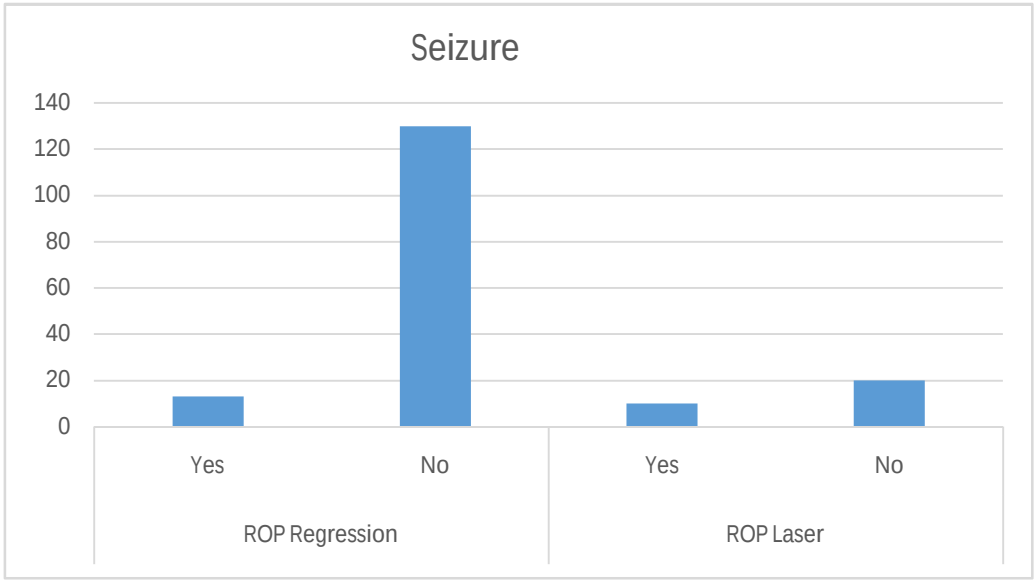


Figure 21- neonatal seizures and outcome of ROP

Table 19-neonatal seizures and ROP outcome

		ROP		Total
		Regression	Laser	
SEIZURE	Yes	13 (57%)	10 (43%)	23
	No	130 (87%)	20 (13%)	150
Total		143	30	173

Congenital Heart Disease

The following figure and tables show the presence of CHD in new born. The presence of CHD is higher in laser group (13.3%). Chi-square test shows a value of 3.802 with $p<0.05$. (Fig-22 and table-20)

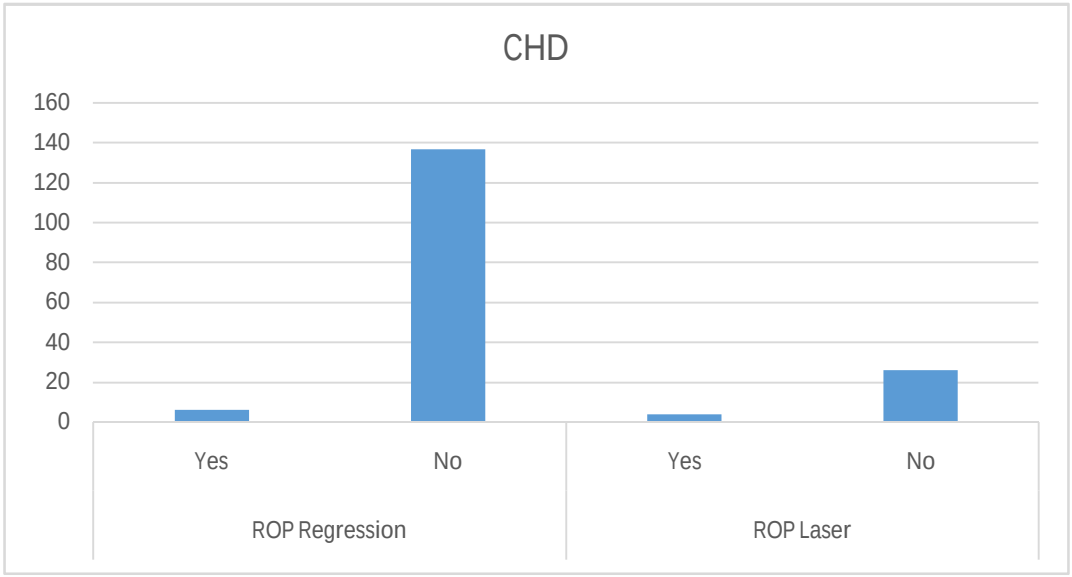


Figure 22- congenital heart disease in newborn and ROP outcome

Table 20- congenital heart disease in newborn an ROP outcome

		ROP		Total
		Regression	Laser	
CHD	Yes	6 (60%)	4 (40%)	10
	No	137 (84%)	26 (16%)	163
Total		143	30	173

Summarizing the results using univariate analysis (Chi square test):

An univariate analysis using Pearson Chi-Square and Fisher's Exact test was done which showed gestational diabetes mellitus(P=0.011) as the major maternal risk factors associated with severe of ROP. Among the neonatal risk factors that were taken, neonatal sepsis(culture proven)(P<0.001), respiratory distress (ARDS) (P=0.032), requirement of oxygen for more than 7 days duration (P<0.001), neonatal hyperbiluribinemia requiring phototherapy(P=0.001) , neonatal seizure (P<0.001) and congenital heart disease (weakly significant with P=0.051)were found to statistically significant.

Gestational age and birth weights of the neonates in the study group seemed to have an effect on the progression to severe grades of ROP, but were not statistically significant enough.

Use of antenatal steroids (P=0.025) showed a statistically significant association with ROP regression.

Pregnancy induced hypertension in the mother and the use of surfactant in the neonates , though statistically not significant, were associated with ROP regression in this study group.

Non-parametric tests to compare the two groups

Kruskal Wallis Test for the two groups shows that the two groups statistically vary in GDM, Steroid use, Sepsis, Distress, Oxygen >7 days, icterus and seizures with $p<0.05$. The following tables summarize the findings from the test. [1=ROP regression; 2=ROP Laser]. (Table 21)

Table 21-Chi square test in Kruskal wallis test

	GDM	AN steroid	Sepsis	Distress	O2 > 7 days	Icterus	Seizure
Chi-Square	6.440	5.572	16.539	4.576	12.151	5.029	12.570
df	1	1	1	1	1	1	1
Asymp. Sig.	.011	.018	.000	.032	.000	.025	.000

P value significant at <0.005

DISCUSSION

As discussed earlier, there has been a dramatic increase in the survival of extremely preterm, low birth weight and sick neonates with better newborn facilities and care. This has led to the increase in incidence of Retinopathy of Prematurity. Severe stage 1 ROP is associated with major visual handicaps and thus identifying risk factors for this stage 1 ROP earlier and promptly screening these neonates can help in improving their visual outcome.

PREVELENCE:

The rate of ROP positivity in this study is 55.7%, which was much lower than studies conducted by74.4% by Wani et al,[10] Ali Riza et al[7]. (75.5%). and higher than the study conducted by Murthy KR et al. in India,(24%)[11] , 29.2% in sinapore[12], 32.4% in Pakistan[13] and 19.2% in Africa[14].

The rate of type 1 ROP requiring laser treatment among those screened ROP positive in this study was 17.3%, which was much lower than studies by Ali et al.[7] (38.7%), Wani et al.(24.4%)[10], Abdel et al.(18.2%)[14].

RISK FACTORS:

There was no gender difference in this current study.

GDM in the mother was found to be associated with the development of severe ROP.

Maternal pre-eclampsia though not statistically significant, had a strong association with regression of ROP, which was also observed in studies by Weintraub et al[15].

Use of antenatal steroids in preterm births had a strong association with regression ROP, consistent with previous studies by Rosemary et.al[16]. Singleton and multiple pregnancies did not statistically affect the outcome of ROP in contrast to the CRYO-ROP study[17], which showed that severe ROP occurred 36% more in multiple pregnancies. This association was also seen with studies of Shaffer et al[18] and Bossi et al[19] and Riazi et al[20].

Lower Birth weight and gestational age was associated with severe forms of ROP, but there was no statistical significance in contrast to all previous studies by Ali Riza et al.[7], Jasmina et al.[21], Crystal Le et al.[23],Imren et al[24].,

Also some of the previous studies have shown an inverse relationship between birth weight gestational age and severity of ROP. In contrast studies by Weintraub et al[15]. and Araz et.al[25] showed that high BW and GA infants had severe ROP, indicating the need for larger screening criteria. According to the CRYO-ROP study, stage 1 ROP usually began at around 34 weeks post-conception age (up to 39 weeks).

Nevertheless this lack of association might have been because of lack of follow up of certain cases and premature death of many ELBW and extreme preterm that couldn't be included in the study.

Neonatal sepsis (culture proven) was found to have a strong association with severity of ROP in this study, which matched the outcome of Araz et al[25]., Jasmina et.al[21]., Crystal Le. Et.al[23] and also Weintraub et al[15]. explained that this could be probably because sepsis increases the oxygen demand, affects oxygen tension, thereby resulting in increased retinal ischemia. The study conducted by Iason et.al. and the ELGAN study[26] also proved the association between late culture proven bacteremia and threshold/ prethreshold disease and plus disease, stating that preterm neonates have a greater inflammatory response to infections , that accounts for development of severe stages of ROP.

Icterus requiring phototherapy and severe ROP's association was also found in the current study.

Having distress in the newborn period, especially RDS, had a strong association with the development of severe ROP. This is also similar to a study by Imren et.al.[24] and Akkoyun et.al[26].

Requirement of O_2>7 days (mechanically ventilated) is also a proven risk factor for severe ROP in a study of ROP conducted by Wani et.al.[10], Allegaert K, et al.[27] and Gordon, et al.[28]

Having neonatal seizures affected the outcome of ROP.

Congenital heart disease (PDA) affected the outcome of ROP, similar to the study by Crystal Le. Et.al.[23]

STUDY LIMITATIONS

There was slightly higher number of drop outs and parents who did not consent for this study. And also multivariate logistic regression could not be performed because all variables taken into consideration were discrete variables. Thus the individual cause effect relationship could not be analysed.

SUMMARY

- Incidence of ROP positivity in the newborn unit under study was 55.7% and incidence of severe ROP was 17.3%
- **Gestational diabetes mellitus and non-usage of antenatal steroids** were the maternal risk factors was associated with severe / type 1 ROP.
- **Neonatal sepsis (culture proven), neonatal hyperbilirubinemia requiring phototherapy, respiratory distress/conditions requiring oxygen (RDS), oxygen requirement >7 days, seizures and congenital heart disease in the newborns** were the neonatal risk factors associated with progression to severe ROP requiring laser treatment.
- Among the analyzed risk factors **non-usage of antenatal steroids , neonatal sepsis, neonatal hyperbilirubinemia, respiratory distress, oxygen requirement >7 days** are the preventable factors.

CONCLUSION

In this study, gestational diabetes mellitus was identified as a significant maternal risk factor for severe ROP and the use of antenatal steroid was associated with regression of ROP. Among the neonatal factors analyzed, culture proven sepsis, respiratory distress (majorly RDS), oxygen requirement > 7 days in mechanically ventilated newborns ,congenital heart disease (PDA), neonatal hyperbilirubinemia and neonatal seizures showed statistically significant association with the development of severe or type 1 ROP. In contrast to previous studies, VLBW and prematurity though associated with severe ROP, did not statistically affect the outcome of ROP.

Association between Gestational diabetes mellitus in the mother, neonatal hyperbilirubinemia requiring phototherapy ,neonatal seizures and the severity of retinopathy of prematurity, which was proved in this study, was not analyzed much in previous studies, implying the need for more similar studies.

Progression to severe stages of ROP can be prevented by prompt use of antenatal steroids whenever a preterm delivery is anticipated, preventing neonatal sepsis by strict asepsis, judicious use phototherapy in newborns, proper management of respiratory distress and restriction of oxygen administration / mechanical ventilation beyond 7 days.

The current study would like to highlight the fact to widen the screening criteria of ROP beyond just the VLBW and extreme prematurity, so as to include a larger proportion of sick neonates at risk of developing severe ROP. A study with a larger sample size and equal proportions in the 2 groups is required for better predictability of risk factors.

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APPENDICES

APPENDIX-I	:	PROFORMA
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APPENDIX-I

PROFORMA

Name: birth weight: gestational age:

gender:

Risk factors:

- Maternal age : <30 years / >30 years
- Pre-eclampsia: yes/no
- GDM: yes/no
- Gestation: singleton / multiple
- PROM >18hrs: yes/no
- Antenatal steroid use: yes/no
- Sepsis: yes(culture positive/CRP positive) / no
- Respiratory distress: yes (ARDS/MAS/TTN/BA/others) / no
- Requirement of oxygen: <7days / >7days
- Neonatal jaundice requiring phototherapy: yes / no
- Seizure : yes/no
- Congenital heart disease : yes / no
- Outcome : laser / regression

APPENDIX II

PATIENT CONSENT FORM

STUDY TITLE: "A study on factors affecting the outcome of retinopathy of prematurity – a cross sectional analytical study with internal comparison, at a tertiary care center in north Chennai"

STUDY CENTRE: INSTITUTE OF SOCIAL PAEDIATRICS, STANLEY MEDICAL COLLEGE

PARTICIPANT NAME: AGE: SEX:

O.P/I.P. NO:

I confirm that I have understood the purpose of the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the details of the study. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that the investigator, regulatory authorities and the ethical committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this study **“A study on factors affecting the outcome of retinopathy of prematurity – a cross sectional analytical study with internal comparison, at a tertiary care center in north Chennai”**

Date:

Place:

Patient’s name: Signature / thumb impression of patient

Signature of the Investigator:

Name of the investigator:

நோயாளி ஒப்புதல் படிவம்

நான் இந்த தகவல் சேகரிப்பு படிப்பிற்கான காரணங்களை உண்மையாக அறிந்து கொண்டேன். நான் எனக்கான இந்த வாய்ப்பை எனது எல்லா சந்தேகங்களையும் மற்றும் கேள்விகளையும் கேட்டு பதில் பெற்றுக் கொள்வதில் திருப்தி அடைக்கிறேன்.

எனக்கு இந்த ஆராய்ச்சி படிப்பிற்கான தகவல் விளக்கம் அளிக்கப்பட்டது. நான் அதை புரிந்து கொண்டு என்னுடைய பங்களிப்பினை நானாகவே அளிக்கிறேன் மற்றும் நான் எந்த முன்னறிப்பின்றி எந்த நேரத்திலும் ஆராய்ச்சியில் இருந்து செல்ல எனக்கு உரிமை உள்ளது என்பதை தெரிவித்துக் கொள்கிறேன்.

நான் எனது ஆராய்ச்சியாளர், ஒழுங்கு முறை விதியாளர் மற்றும் நெறிமுறையாளர் என்னுடைய உடல்நிலை பற்றிய தகவல் பதிவேடுகளை பார்க்க என்னுடைய அனுமதி தேவை இல்லை என்பதையும் தற்போதைய ஆராய்ச்சி மற்றும் பிற்காலத்தில் தொடர்ச்சியாக செய்ய நேரிடும் ஆராய்ச்சி தேவைப்படும் எனில், நான் இந்த தகவல் சேகரிப்பில் இருந்து வெளியே போனாலும் எனது அனுமதி தேவை இல்லை. என்னுடைய எந்த தகவலும் (உ.தி) என்னுடைய பெயர், உடல்நிலை பற்றிய தகவல் எதுவும் மூன்றாவது ஆட்களுக்கோ அல்லது பேப்பரில் போடவோ மாட்டார்கள் என்பதையும் சட்டத்திற்கு உட்பட்டு நடக்கும் என்பதையும் புரிந்து கொண்டேன். நான் இந்த தகவல் சேகரிப்புக்கு அல்லது ஆராய்ச்சி முடிவுக்கு எந்த கட்டுபாடுகளும் எழுப்ப மாட்டேன்.

நான் என்னுடைய ஒப்புதலை இந்த தகவல் சேகரிப்பான குறைமாதத்தில் பிறக்கும் விழித்திரை பாதிப்புகளால் தாக்கப்படுதல் பற்றிய ஆராய்ச்சிக்கு ஒப்புதல் அளிக்கிறேன்.

மேலும் இந்த படிவத்தில் கொடுக்கப்பட்டுள்ள விவரங்களை நன்கு படித்து உணர்ந்து கொண்டேன் என்றும் இந்த குறிப்பிட்ட சிகிச்சை முறையினையும் அதிலுள்ள ஆபத்துகளையும் நன்கு அறிந்து எனது முழு சுய உணர்வுடன் இந்த எழுத்து பூர்வமான ஒப்புதலை அளிக்கின்றேன்.

நோயாளியின் பெயர்/ பெருவிரல் ரேகை :

சாட்சி :

பெயர் : சாட்சியின் கையொப்பம் :

தேதி :

இடம் :

APPENDIX-III

INFORMATION SHEET

We are conducting a study on **"A study on factors affecting the outcome of retinopathy of prematurity – a cross sectional analytical study with internal comparison, at a tertiary care center in north Chennai"** in Institute of social Paediatrics, Stanley medical college, Chennai and for that your information is valuable to us.

The purpose of this study is to predict the risk factors associated with severe Retinopathy of prematurity.

We are selecting certain cases and if you are found eligible, we may be using your information which in any way does not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the Participant Signature of the Investigator

Date:

Place:

தகவல் படிவம்

நாங்கள் விழித்திரை பாதிப்புகளால் தாக்கப்பட்டுள்ள குழந்தைகளை பற்றி ஒரு ஆய்வை, அரசு ஸ்டான்லி மருத்துவமனையில் நடத்தி வருகிறோம். அதற்கு உங்கள் தகவல் தேவைப்படுகிறது.

அந்த கண் பிரச்சனையின் விளைவுகளுக்கு காரணமாக உள்ளவைகளை கண்டுப்பிடித்து கணிப்பதே இந்த ஆய்வுக்கான முக்கிய காரணமாகும்.

எங்களுடைய ஆராய்ச்சிக்கு உங்களது குழந்தை தகுதியுள்ளதாக இருந்தால் அதன் தகவல்களை எங்கள் தேவைக்கு பயன்படுத்தும் பட்சத்தில் உங்களுடைய குழந்தையின் சிகிச்சையை எவ்விதமும் பாதிக்காது.

உங்களது தனிப்பட்ட தகவல்களை இந்த ஆராய்ச்சி முழுவதுமாக இரகசியமாக பராமரிக்கப்படும் இந்த ஆராய்ச்சி பாதிப்பிடும் போதும் உங்களுடைய தனிப்பட்ட தகவல்கள் வெளியிடப்பட மாட்டாது.

உங்களது சுய விருப்பத்துக்குகேற்ப இந்த ஆய்வில் பங்கேற்கலாம். நீங்கள் எப்பொழுது வேண்டுமானாலும் இந்த ஆராய்ச்சியில் இருந்து வெளியேரலாம், அதனால் உங்களுக்கு எந்தவிதமானப் சிரமமும் ஏற்படாது.

இந்த ஆராய்ச்சியின் போது ஏதோனும் மருத்துவ பிரச்சனை இருந்தால் எப்பொழுது வேண்டுமானாலும் தெரிவிக்கப்படலாம். அது உங்கள் குழந்தையின் சிகிச்சைக்கு உதவும்.

APPENDIX-IV

MASTER CHART

	MATERNAL FACTORS							NEONATAL FACTORS										
	AGE	PRE-ECLAMPSIA	GDM	PREGNANCY	PROM	STEROIDS	ANEMIA	SEX	BW	GA	SEPSIS	DISTRESS	O2 > 7 DAYS	SURFACTANT	ICTERUS	SEIZURE	CHD	LASER
B/o Monisha Ismail	4	7	7	11	6	7	6	17	9	2	14	19	7	7	15	7	7	6
B/o ElakkiyaDevi Vijay	4	6	7	11	7	7	6	18	10	3	13	20	7	7	7	6	7	6
B/o Rekha Twin 2	4	7	7	12	7	6	6	17	9	1	13	19	6	7	15	7	7	6
B/o Saranya Twin2	4	7	7	12	7	6	7	18	10	2	13	19	7	7	15	7	7	6
B/o Nithya Prakash	4	7	7	11	7	6	7	18	9	2	13	7	7	7	15	7	7	6
B/o Ambiga Chelladurai	4	7	6	11	7	7	6	17	8	1	13	19	6	7	15	7	7	6
B/o Rehana Dominic	4	7	7	11	7	7	7	18	10	2	14	19	6	7	15	6	7	6
B/o Adukumalli Suresh	4	6	6	11	7	7	6	18	9	2	14	19	7	6	16	7	7	6
B/o Suganthi Vivekanandha	4	7	7	11	7	7	6	17	9	2	13	22	7	7	7	6	6	6
B/o Meena Senthil	5	6	7	11	7	6	7	18	9	2	13	19	7	7	7	7	7	6
B/o Hemavathy Mohan	4	7	7	11	7	7	6	17	9	2	14	19	7	7	15	7	7	6
B/o Hemavathy Sundar	5	7	6	11	7	7	6	18	8	2	14	19	6	7	15	6	7	6
B/o Rajakumari Raja	5	7	6	11	7	7	6	18	10	2	14	20	6	7	7	6	7	6
B/o Poongodi Mohan	4	7	7	11	7	7	7	18	10	3	14	20	6	7	7	7	7	6
B/o Sowmya	4	7	7	11	6	7	6	18	9	2	13	7	7	7	7	7	7	6
B/o Chandraleekha II	4	6	7	12	7	7	6	17	10	3	14	22	6	7	15	7	7	6
B/o Gayathri	4	7	7	11	7	7	6	18	8	2	14	19	7	7	15	6	7	6

B/o Kanaga	4	6	7	11	7	7	7	17	10	3	14	22	6	7	15	6	7	6
B/o Anushya Thangaraj II	4	7	7	12	7	7	6	17	10	1	13	19	7	7	15	7	7	6
B/o Anushya Thangaraj I	4	7	7	12	7	7	6	18	9	1	14	19	7	7	15	7	7	6
B/o Renitha Krishnakumar	4	6	7	11	7	6	7	17	10	3	13	20	7	6	15	6	6	6
B/o Nanthini Rajkumar	4	7	7	11	7	6	6	18	10	2	14	19	7	7	15	7	7	6
B/o Sundari Babu	4	7	7	11	6	7	6	18	8	2	14	19	7	7	15	7	6	6
B/o Ashwini Mohan	4	7	7	11	7	7	6	17	10	3	13	21	7	7	16	6	7	6
B/o Najumunisha Amarbasha	4	6	7	11	7	7	6	18	9	2	13	22	6	7	15	6	7	6
B/o Bhavani Mani	4	7	7	11	7	7	7	17	8	1	14	19	6	7	15	7	6	6
B/o Seethadevi II	5	6	7	12	6	6	6	18	9	2	13	19	7	7	7	7	7	6
B/o Krithiga Karthik	4	7	7	11	7	7	6	17	10	3	7	22	6	7	7	7	7	6
B/o Kaveri Anbusami	4	7	6	11	7	7	7	17	9	2	14	19	7	7	15	7	7	6
B/o Nirmala Vijaykumar	4	7	7	11	6	7	6	18	9	2	14	19	7	7	15	7	7	6

	MATERNAL FACTORS						NEONATAL FACTORS										
	AGE	PRE-ECLAMPSIA	GDM	PREGNANCY	PROM	STEROIDS	SEX	BW	GA	SEPSIS	DISTRESS	O2 > 7 DAYS	SURFACTANT	ICTERUS	SEIZURE	CHD	LASER
B/o Hajira Mohammad	4	7	7	11	6	7	17	9	1	14	21	7	7	15	7	7	7
B/o Arthi Twin 1	4	7	7	12	7	7	18	10	3	14	7	7	7	7	7	7	7
B/o Saranya Thambidurai	4	6	7	11	7	7	17	9	1	14	19	7	7	7	7	7	7
B/o Kalpana Ganesh	4	6	7	11	7	6	18	10	2	13	19	7	7	15	7	6	7
B/o Usharani	4	7	7	11	7	6	18	10	1	14	19	7	6	7	7	7	7
B/o Ambiga	4	7	7	11	7	7	17	8	2	14	19	7	7	15	7	7	7
B/o Kalpana	4	7	7	11	7	6	18	10	2	13	20	7	7	7	7	7	7
B/o Saranya Senthil	4	7	7	11	7	7	17	9	2	13	19	6	6	16	7	7	7
B/o Nithya Gopi	4	7	7	11	7	7	18	10	2	14	21	7	7	15	7	7	7
B/o Vijayalakshmi	4	7	7	11	7	6	18	10	2	14	21	7	7	15	7	7	7
B/o Anitha	4	7	7	11	6	7	18	10	2	7	7	7	7	15	7	7	7
B/o Deepa Lawrence	4	7	7	11	6	6	18	10	2	14	7	7	7	7	7	7	7
B/o Reshma Banu	4	6	7	11	7	7	17	10	2	7	21	7	7	7	7	7	7
B/o Gajalakshmi	4	7	7	11	7	6	17	9	1	7	19	7	7	7	7	7	7
B/o Iswarya	4	7	7	11	7	7	18	9	2	7	19	7	7	7	7	7	7
B/o Uma Tamilselvan	4	6	7	11	7	7	17	10	2	7	21	7	7	7	7	7	7
B/o Rajeshwari	5	7	7	11	7	6	18	9	2	14	21	7	7	15	7	7	7
B/o Renuka Siva	4	7	7	11	7	7	17	10	2	14	21	7	7	15	7	7	7
B/o Swarthammal	4	7	7	11	7	6	18	9	1	13	21	7	7	15	7	7	7
B/o Shamshath Begum	4	7	7	11	7	7	18	10	3	14	7	7	7	15	7	7	7
B/o Rajeswari Munnusamy	5	7	7	11	7	7	18	10	3	7	21	7	7	7	7	6	7
B/o Haseena Begum	4	7	7	11	7	7	18	10	3	7	20	7	7	7	6	7	7
B/o Saranya Sudhir	4	7	7	11	7	7	17	10	3	14	19	6	7	15	6	7	7
B/o Indumathi Sathya	4	7	7	11	6	7	17	10	2	14	7	7	7	15	7	7	7
B/o Farzana Hussain	4	7	7	11	7	6	17	10	3	7	7	7	7	7	7	7	7
B/o Durga Senthil Kumar	5	7	7	11	7	7	18	10	3	7	7	7	7	7	7	7	7
B/o Asmabegum Moham	4	7	6	11	7	6	18	10	1	7	7	7	7	7	7	7	7
B/o Indumathi Kuppusamy	4	6	7	11	7	6	17	10	2	7	7	7	7	15	7	7	7
B/o Ravali Anthony Raj	4	6	7	11	6	7	18	10	3	13	7	7	7	7	7	7	7
B/o Vinodhini Chandru	4	7	7	11	7	7	17	9	1	14	7	7	7	15	7	7	7
B/o Diana Naresh Twin2	4	7	7	12	7	7	18	9	2	7	19	7	7	7	7	7	7
B/o Sharmila Kanivelu	4	7	7	11	7	7	18	9	2	13	7	7	7	15	7	7	7
B/o Bhavani Twin1	4	7	7	12	7	6	17	10	3	7	7	7	7	15	7	7	7
B/o Bhavani Twin2	4	7	7	12	7	6	17	10	3	7	7	7	7	15	7	7	7
B/o Sivagamasundari	4	7	7	11	7	7	17	10	3	7	7	7	7	15	7	7	7
B/o Sindhu Arimuthu	4	7	7	11	7	7	18	10	3	13	22	6	7	7	7	7	7

B/o Dilliyammal Karthik	4	6	7	11	7	6	17	10	2	7	21	7	7	15	7	7	7
B/o Saranya Suresh Twin1	4	7	7	12	7	6	17	10	2	14	19	7	7	15	7	7	7
B/o Sumithra Sathish	4	7	7	11	7	6	18	9	1	14	7	7	7	7	7	7	7
B/o Nathiya Twin2	4	7	7	12	7	6	18	9	3	7	21	7	7	7	7	7	7
B/o Kareemanisha	4	7	7	11	7	7	18	10	3	7	7	7	7	15	7	7	7
B/o Gayathri Murali	4	7	7	11	7	7	18	10	3	13	7	7	7	7	7	7	7
B/o Kalaivani Girinath Twin1	4	6	7	12	7	6	17	9	3	7	19	7	7	7	7	7	7
B/o Kalaivani Girinath Twin2	4	6	7	12	7	6	17	9	3	7	19	7	7	7	7	7	7
B/o Prema	4	6	7	11	7	7	18	8	2	13	7	7	7	15	7	7	7
B/o Lakshmi Govinda	4	7	7	11	7	7	17	9	3	13	21	7	7	7	6	7	7
B/o Amala Dithyen	5	6	7	11	7	6	18	9	2	13	19	6	7	7	7	7	7
B/o Lavanya Chinnarasu	4	7	7	11	7	7	17	9	1	14	19	7	6	7	7	7	7
B/o Kalaivani Siva	4	7	6	11	7	7	17	9	2	14	19	7	6	15	7	7	7
B/o Usha Ramesh	4	7	7	11	7	7	18	10	2	7	21	7	7	15	7	7	7
B/o Jasmin Mary Twin 1	4	7	7	12	7	7	17	10	3	7	7	7	7	15	7	7	7
B/o Jasmin Mary Twin 2	4	7	7	12	7	7	18	10	2	7	7	7	7	15	7	7	7
B/o Mary	4	7	7	11	7	6	17	10	2	13	19	7	7	7	7	7	7
B/o Victoria Suresh	5	6	7	11	6	6	17	8	1	14	19	7	6	15	7	7	7
B/o Mohana Dhanasekaran	4	7	7	11	6	6	18	10	3	7	7	7	7	15	7	7	7
B/o Mythili Premkumar	4	7	7	11	7	6	18	10	3	7	7	7	7	7	7	7	7
B/o Subathra Balakrishnan	5	7	7	11	7	6	17	10	2	14	21	7	7	15	6	7	7
B/o Velankanni Kumar	4	7	7	11	7	6	18	10	2	7	19	7	7	15	7	7	7
B/o Kalaiarasi Chelladurai	4	6	7	11	7	7	17	9	2	13	21	6	7	7	7	7	7
B/o Jayapradha Twin1	4	7	7	12	7	7	17	10	2	13	7	7	7	15	7	7	7
B/o Jayapradha Twin2	4	7	7	12	7	7	18	10	2	13	7	7	7	15	7	7	7
B/o Yuvasri Rajini	4	7	7	11	7	6	17	8	2	13	19	7	7	7	7	7	7
B/o Jayapradha	4	7	7	11	7	7	17	9	2	13	21	6	7	15	7	7	7
B/o Ramya Suresh	4	6	7	11	7	7	18	8	1	14	19	7	6	15	7	7	7
B/o Ganga Renu	4	7	7	11	7	7	17	9	3	13	7	7	7	7	6	7	7
B/o Hemalatha Tamilarasu	4	7	7	11	7	7	17	10	2	7	7	7	7	7	7	7	7
B/o Shalini Shanmugam	4	7	7	11	7	7	18	9	2	7	19	7	7	7	7	7	7
B/o Deepa Nagappan	4	7	7	11	7	6	18	9	2	13	7	7	7	15	7	7	7
B/o Thilagavathy John	5	7	7	11	6	6	17	10	2	13	7	7	7	15	7	7	7
B/o Asha Pugazhendu	4	7	7	11	7	7	17	10	3	7	7	7	7	15	7	7	7
B/o praveena Gunasekaran	4	7	7	11	7	6	17	10	3	13	22	6	7	15	6	7	7
B/o Ramya Sureshkumar	4	6	7	11	7	7	17	8	1	13	22	6	6	15	6	6	7
B/o Sasikala Shankar	4	6	7	11	7	6	18	10	3	7	20	6	7	7	6	7	7
B/o Swetha Vivek	4	6	7	11	7	6	18	9	2	13	19	6	6	15	6	6	7
B/o Reena Nagaraj	4	7	6	11	7	6	18	9	2	7	19	7	7	15	7	7	7

B/o Devi Mani	4	7	7	11	7	6	17	8	1	14	7	7	6	15	7	7	7
B/o Sakkarakani Saravanan	4	7	7	11	7	7	18	8	1	14	22	6	6	15	7	7	7
B/o Thabeethal Justin	4	7	7	11	7	6	17	9	2	7	22	6	7	7	6	7	7
B/o Vishali Senthil	4	7	7	11	7	7	17	9	3	7	20	7	7	7	7	7	7
B/o Ponmani Venkatesh	4	7	7	11	7	6	18	8	1	7	22	7	7	15	7	7	7
B/o Kavitha	4	7	7	11	7	7	18	9	2	14	7	7	7	15	7	7	7
B/o Mythili	4	7	7	11	6	6	17	9	2	14	19	7	7	7	7	7	7
B/o Nasrin	4	7	6	11	7	6	17	9	2	14	19	7	6	7	7	7	7
B/o poonkodi	5	7	7	11	7	7	18	9	3	13	21	7	7	7	7	7	7
B/o Geethanjali	4	7	7	11	7	7	18	9	3	14	7	7	7	7	7	7	7
B/o Nagalakshmi Twin I	4	6	7	12	6	6	18	9	2	7	21	7	7	7	7	7	7
B/o Nagalakshmi Twin II	4	6	7	12	6	6	17	9	2	7	21	7	7	15	7	7	7
B/o Umamageshwari jayakumar	4	6	7	11	7	6	18	9	2	7	19	7	6	15	7	7	7
B/o Nasim Shahjahan	5	7	7	11	7	7	18	10	2	13	19	7	6	7	7	7	7
B/o Gayathri DeepanRaj	4	7	7	11	7	7	17	10	2	7	7	7	7	15	7	7	7
B/o Mythili Dhillibabu	5	7	7	11	6	6	18	10	2	7	7	7	7	7	7	7	7
B/o Muniyamma Aiyyappan	4	7	7	11	7	6	18	9	2	13	7	7	7	7	7	7	7
B/o Uma	4	7	7	11	6	7	18	10	3	7	22	7	7	7	7	7	7
B/o Kausalya Maheshkumar	4	6	7	11	7	7	18	9	2	13	20	7	6	15	7	7	7
B/o Bhuvaneshwari Dhineshkumar	4	7	7	11	7	7	18	10	3	14	20	6	7	7	7	7	7
B/o Kavitha Dineshkumar	4	7	7	11	7	7	17	8	1	7	7	7	7	7	7	7	7
B/o Asma Abdul Sabar	4	7	7	11	7	7	17	8	1	7	20	7	7	7	7	7	7
B/o Vijayalakshmi Dinesh	4	7	7	11	7	7	17	9	2	14	21	7	7	7	7	7	7
B/o Priya Arunkumar	4	7	7	11	7	7	17	9	2	14	7	7	7	15	6	7	7
B/o Shemi Rishikapoor	4	7	7	11	7	7	18	10	3	7	22	7	7	15	7	6	7
B/o Kousalya Maheshkumar	4	7	7	11	7	7	17	10	3	14	22	7	7	7	7	7	7
B/o Poongodi Mohan	4	7	7	11	7	7	18	10	3	7	20	6	7	7	7	7	7
B/o Kanniyammal	4	7	7	11	7	7	17	9	2	7	7	7	7	7	7	7	7
B/o Anitha Dharmalingam	4	7	7	11	7	7	18	10	3	13	19	7	7	15	7	7	7
B/o Narmadha	4	6	7	11	7	7	17	10	3	7	7	7	7	7	7	7	7
B/o Gayathri	4	7	7	11	7	6	18	10	3	13	19	7	6	7	7	7	7
B/o Baby	4	6	7	11	7	7	17	9	2	7	7	7	7	7	7	7	7
B/o Ashadhin	4	7	7	11	7	7	18	10	3	13	7	7	7	7	7	7	7
B/o Tharamani twin II	4	7	7	12	7	7	17	10	3	7	7	7	7	15	7	7	7
B/o Madhuri	4	7	7	11	7	7	18	8	1	14	19	7	6	15	7	7	7
B/o Christina	4	6	7	11	6	6	18	9	2	13	7	7	7	15	7	7	7
B/o Manjuladevi	4	7	7	11	6	6	17	9	2	14	19	7	7	7	7	7	7
B/o Nithya	4	7	7	11	7	6	17	9	2	14	22	7	7	15	7	7	7
B/o Sindhya	4	6	7	11	7	7	18	10	3	7	20	7	7	7	7	7	7
B/o Subha Murugan	4	7	7	11	7	6	18	9	2	14	7	7	7	7	7	7	7
B/o Rekha Srinivasan	4	7	7	11	7	7	18	10	3	13	21	7	7	15	7	7	7

B/o Nagajothi I	5	6	7	12	7	7	17	10	3	13	19	7	7	7	7	6	7
B/o Nagajothi II	5	6	7	12	7	7	18	10	3	7	19	7	7	15	7	7	7
B/o Amulu	4	6	7	11	7	6	18	10	2	13	19	7	6	15	7	7	7
B/o Kamatchi	4	7	7	11	7	7	17	10	3	13	7	7	7	7	6	7	7
B/o Rekha Siroman	4	6	7	11	7	7	18	10	2	7	7	7	7	15	7	7	7
B/o Akthar Nisha	4	7	7	11	7	6	18	10	2	7	19	7	7	15	7	7	7
B/o Anandhi Senthil	4	7	7	11	7	6	17	9	2	14	19	7	6	7	7	7	7
B/o Sridevi Velu	5	7	7	11	7	6	17	10	2	14	19	7	7	15	7	7	7
B/o Sangeetha Krishnarao	5	7	7	11	7	6	17	9	2	7	7	7	7	15	7	7	7
B/o Divya Raja	4	6	7	11	7	6	17	10	2	7	7	7	7	15	7	7	7
B/o Thenmozhi Prashanth	5	7	7	11	7	6	18	10	2	7	7	7	7	15	7	7	7
B/o Seethadevi I	5	6	7	12	6	6	18	10	2	7	7	7	7	15	7	7	7
B/o Sudha Seetharaman	4	6	7	11	6	6	18	10	2	13	19	7	7	7	7	7	7
B/o Shalini Senthil	4	7	7	11	6	6	17	9	2	14	19	7	6	15	6	7	7
B/o Vimala	4	6	7	11	6	6	18	9	2	7	7	7	7	7	7	7	7
B/o Vetriselvi I	5	6	7	12	6	6	18	9	2	7	19	7	7	15	7	7	7
B/o Vetrislevi II	5	6	7	12	6	6	17	10	2	7	19	7	7	15	7	7	7
B/o Kalaiselvi Raja	4	6	7	11	6	7	18	9	1	13	19	6	6	15	7	7	7
B/o Dharani Elango	4	7	7	11	7	6	18	9	2	13	21	7	7	7	7	7	7
B/o Nadhiya Devaraj	4	7	7	11	6	6	17	10	2	13	22	7	7	7	7	7	7
B/o Parameshwari Udhayakumar	4	7	7	11	7	6	18	9	2	13	7	7	7	15	7	7	7
B/o Ramya Santhoshkumar	4	7	7	11	7	6	17	10	3	7	7	7	7	16	7	7	7
B/o Shobana Ramesh	4	7	6	11	7	7	17	10	3	7	20	6	7	7	7	7	7
B/o Shakila Selvam	4	6	6	11	7	6	17	9	2	13	19	7	7	15	7	7	7
B/o Sudharshana Mohan	4	6	7	11	6	6	18	9	2	13	19	7	7	7	7	7	7
B/o Revathi Gandhi	4	6	7	11	7	7	18	9	2	13	19	7	6	15	7	7	7
B/o Sudha Kanniyappan	5	7	7	11	7	7	18	10	2	7	21	7	7	15	7	7	7

KEY TO MASTER CHART

1. Gestational age < 30 weeks

2. Gestational age 30 to 34 weeks

3. Gestational age > 34 weeks

4. Mother age < 30 years

5. Mother age > 30 years

6. Yes

7. No

8. BW < 1000 gms

9. BW 1000 to 1500 gms

10. BW > 1500 gms

11. Singleton Pregnancy

12. Multiple Pregnancy

13. Culture positive sepsis

14. CRP positive sepsis

15. Phototherapy

16. Exchange Transfusion

17. Boy baby

18. Girl baby

19. RDS

20. MAS

21. TTN

22. Birth asphyxia