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The Effect of Antenatal Magnesium Sulphate for Fetal Neuroprotection in Threatened Preterm Labour: A Prospective Cohort Study

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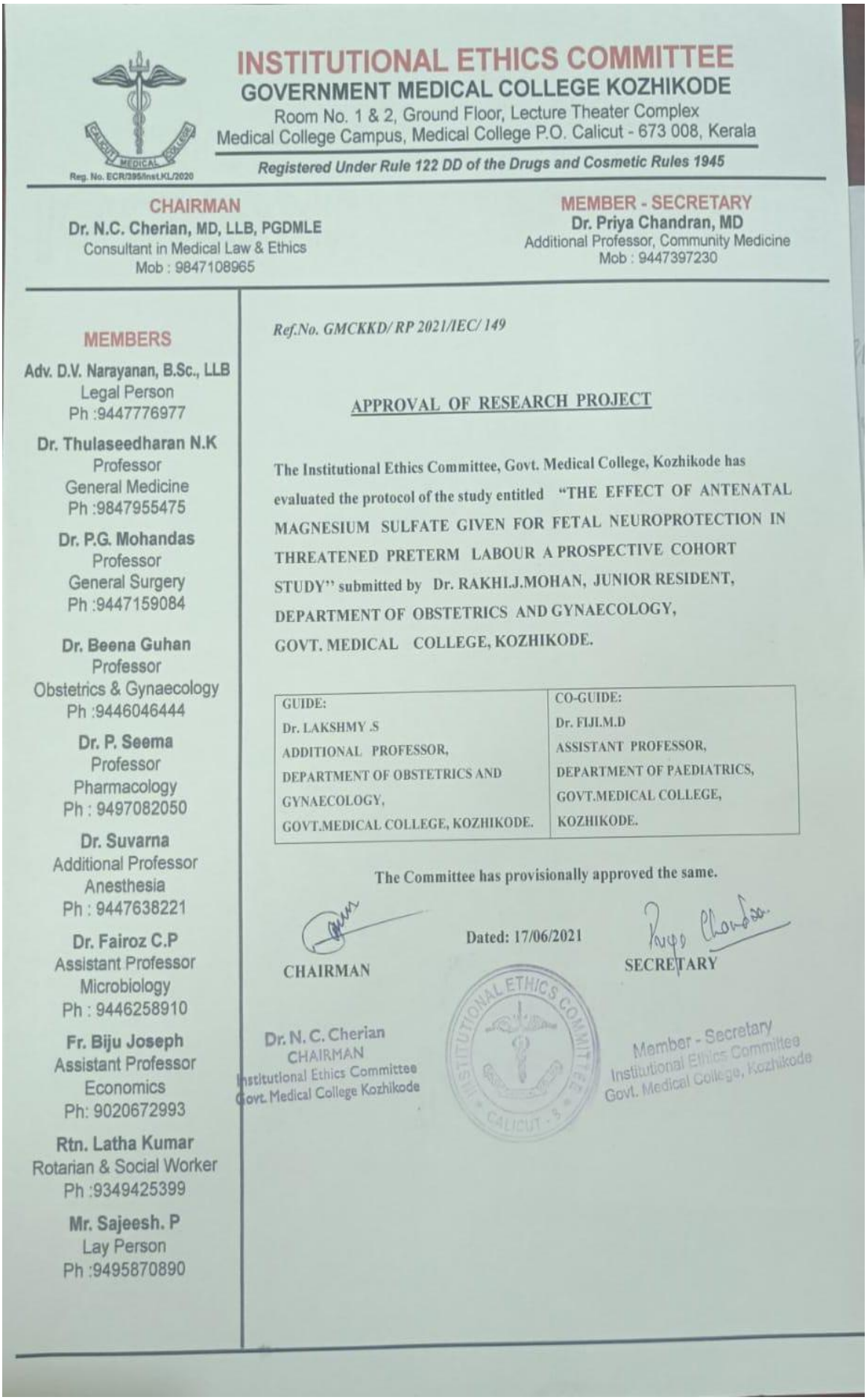

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APPROVAL OF RESEARCH PROJECT

The Institutional Ethics Committee, Govt. Medical College, Kozhikode has evaluated the protocol of the study entitled "THE EFFECT OF ANTENATAL MAGNESIUM SULFATE GIVEN FOR FETAL NEUROPROTECTION IN THREATENED PRETERM LABOUR A PROSPECTIVE COHORT STUDY" submitted by Dr. RAKHI.J.MOHAN, JUNIOR RESIDENT, DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY, GOVT. MEDICAL COLLEGE, KOZHIKODE.

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The Committee has provisionally approved the same.

Dated: 17/06/2021

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STRUCTURED ABSTRACT

Introduction: The prevalence of preterm birth is increasing. In India, out of the 27 million babies born every year [2010 data], 3.5 million babies born are premature. Preterm births account for 75% of perinatal mortality and more than half of the long term morbidity. Due to the advances in perinatal care, the survival rate of premature babies is also increasing. This lead to the increase in the learning disabilities, medical disabilities, behavioral and psychological problems among these surviving premature babies. The risk of neurological impairments such as cerebral palsy, blindness, deafness, and cognitive dysfunction are high in preterm babies. Magnesium sulphate used as the seizure prophylaxis in severe pre-eclamptic women and as a tocolytic found to have neuroprotective action in the preterm babies. Several studies concluded that exposure to both antenatal corticosteroids and magnesium sulphate was associated with lower rates of severe neurodevelopmental impairment or mortality.

Objectives: To determine the role of magnesium sulphate given for fetal neuro protection to women at risk of preterm birth in preventing neonatal mortality and neuro developmental morbidity.

Method:
STUDY DESIGN-Prospective cohort study
STUDY SETTING-Department of Obstetrics and Gynaecology and Department of Paediatrics, IMCH Calicut
SAMPLE SIZE-All the patients satisfying the inclusion criteria who came to Government Medical College Kozhikode during the study period were included as cases (75 patients), and equal number of controls were studied.
DURATION OF STUDY-1.5 years JUNE 2021- DEC 2022

INCLUSION CRITERIA
1]Women were eligible for the study if they are at risk of preterm birth
[spontaneous/induced] between 28-32 weeks of gestation where birth is planned or definitely expected within 24 hours were included.
2]Women with singleton pregnancy or twin pregnancy were included.
3]Severe preeclampsia, eclampsia, induced preterm for maternal or fetal indications were also included

EXCLUSION CRITERIA
1]Multifetal gestation more than 2 fetuses were excluded.
2]Women with preterm labour induced from outside hospitals were not included.
3]Preterm delivery from outside hospitals are not included in the study.

During the period of study, pregnant women with preterm labour with gestational age 28 to 32 weeks were enrolled in the study as cases [Group A]. Women with preterm labour who deliver before magnesium sulphate regime started were taken as controls[Group B].

Women with preterm birth, who are given antenatal magnesium sulphate for fetal neuroprotection, administered as a 4g IV loading dose, over 20 minutes, followed by a 1g/hr maintenance infusion for 24 hours using an infusion pump were observed. [Routinely practiced in our hospital as a standard protocol of management of threatened preterm labour].

Delivery was not delayed in order to administer antenatal magnesium sulphate for fetal neuroprotection if there were maternal and/or fetal indications for emergency delivery.

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When magnesium sulphate was given for fetal neuroprotection, used existing protocols to monitor women who received magnesium sulphate for preeclampsia/ eclampsia. Corticosteroids (Injection Dexamethasone 6mg 4 doses 12 hrs apart) for fetal lung maturation was administered (if not already given). Continuous fetal heart surveillance was provided.

Maternal obstetric outcome and fetal outcome were observed. Infant was followed up until corrected age of 1 year of age. Participants were called to Institute of Maternal and Child Health [IMCH], Kozhikode at corrected age of 1year. They were examined at Regional Early Intervention Centre [REIC], IMCH to assess any infant morbidity and neurosensory disabilities like blindness, deafness or developmental delay. Trivandrum developmental screening chart was used to screen the infants.

OUTCOME MEASUREMENT: The outcome measured are the maternal obstetric outcome and incidence of neonatal outcomes including intraventricular haemorrhage[all grades], periventricular leukomalacia, neonatal seizures , respiratory distress syndrome , need for supplemental oxygen at 36 weeks , bronchopulmonary dysplasia, need for mechanical ventilation, necrotising enterocolitis, neonatal death, infant neuro developmental outcomes upto 1 year including substantial gross motor dysfunction, major neurological disability, blindness, deafness and incidence of infant death.

DATA ANALYSIS: Data will be entered in excel sheet and analysed using SPSS. P value less than 0.05 will be considered significant.

Results: The neonatal mortality(6% versus 12.5%; relative risk [RR],0.48; 95% confidence interval [CI], 0.17-1.3), residual neonatal morbidity(3.8% v/s 11.6%;RR, 0.32;95% CI, 0.09-1.16) , the neurological disabilities like cerebral palsy(1.3% v/s 2.18%; RR,0.47;95% CI, 0.04-5.17) and the combined death or cerebral palsy(8.1% v/s 18.3%; RR,0.44;95% CI, 0.17-1.10) were less frequent in the Group A who received magnesium for neuroprotection, but the differences are not significant statistically.Respiratory distress (78.4% v/s 55.4%; RR,0.72; 95% CI, 0.5-0.9) and necrotizing enterocolitis(3.6% v/s14.7%;RR,0.24; 95% CI, 0.07-0.82) were significantly reduced in the Group A.

Conclusion: Magnesium sulphate for fetal neuroprotection is found to reduce the incidence of neonatal mortality,total neonatal morbidity and neurological disabilities but there is no statistical significance. However, significant reduction is seen in the respiratory distress and necrotizing enterocolitis in the neuroprotection group.Thus concluding there is definitely a role of magnesium sulphate clinically, in having a favourable neonatal outcome, although statistically insignificant.

Keywords:- *Preterm labour, Magnesium sulphate, Fetal neuroprotection.*

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CHAPTER ONE

INTRODUCTION

Preterm birth is defined as being born before 37 weeks of gestational age or before 259 days, according to World Health Organization [1].

They are further classified into
1] Late preterm- 34 weeks to <37 weeks
2] Moderate preterm- 32 weeks to <34 weeks
3] Very preterm- <32 weeks
4] extremely preterm- <28 weeks

Three main conditions explain preterm birth:
1] Medically indicated (iatrogenic) preterm birth [18.5%-35.2%]
2] Preterm premature rupture of membranes (PPROM) [7.1%- 51.2%]
3] Spontaneous preterm birth [23.2%- 64.1%][2]

The risk factors of preterm birth includes prior preterm labor, multiple pregnancy, polyhydramnios causing overdistension of uterus, infections like malaria, other genital tract infections by Mycoplasma hominis, Ureaplasma urealyticum, and, bacterial vaginosis, periodontal diseases, short cervix, prior ablative or excisional procedures on the cervix, uterine abnormalities, pregnancy following assisted reproductive techniques, maternal medical disorders like hypertension, diabetes and fetal factors like fetal growth retardation, abnormal Doppler studies which necessitate the early delivery etc.

The prevalence of preterm birth is increasing. In India, out of the 27 million babies born every year [2010 data], 3.5 million babies born are premature. Preterm births account for 75% of perinatal mortality and more than half of the long term morbidity [3].

Complications of prematurity can be classified into
1]Short term complications in the neonatal period
2]Long term sequelae in the survivors

Short term complications include respiratory abnormalities, cardiovascular problems, Intraventricular hemorrhage, hypothermia, necrotizing enterocolitis, neonatal sepsis, Retinopathy of prematurity etc.

Long term complications are mainly the neurodevelopmental disabilities such as cerebral palsy, learning disabilities, behavioral and psychological problems and also infant mortality.

Due to the advances in perinatal care, the survival rate of premature babies is also increasing. This lead to the increase in the learning disabilities, medical disabilities, behavioral and psychological problems among these surviving premature babies. The risk of neurological impairments such as cerebral palsy, blindness, deafness, and cognitive dysfunction are high in preterm babies. Numerous studies have found that extremely preterm children perform significantly worse than term-born controls in a number of fundamental cognitive abilities, including short-term memory, processing speed, visual-perceptual skills, sensorimotor integration, and attention[4].

The prevalence of cerebral palsy decreases significantly with increasing gestational age.14.6% at 22-27 weeks' gestation, 6.2% at 28 to 31 weeks' gestation, 0.7% at 32 to 36 weeks of gestation, and 0.1% in term infants. Interestingly, a significant decrease in prevalence of cerebral palsy starts only from 27 weeks onwards[5].

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Magnesium sulphate used as the seizure prophylaxis in severe pre-eclamptic women and as a tocolytic found to have neuroprotective action in the preterm babies. Several mechanisms of actions of magnesium sulphate has been postulated, but still the exact cause is unknown. The most common pathologic lesion associated with cerebral palsy in preterm infants is periventricular white matter injury. Oligodendrocytes constitute a major glial population in the white matter. N-Methyl-D-aspartic acid [NMDA] receptors on the oligodendrocytes are important in the glial injury process. NMDA receptor antagonists which prevents excitotoxic calcium -induced injury, are potent neuroprotective agents in severe animal models of perinatal brain injury.

Magnesium sulphate also found to have anti-inflammatory properties. It reduces oxidative stress and reduces the production of pro-inflammatory cytokines interleukin-6 and tumor necrosis factor alpha [6].

Several randomized controlled trials were conducted shown to have improved perinatal outcomes in the preterm infants who received antenatal magnesium sulphate for neuroprotection.

According to the ACTOMgSO4 trial [1996-2000], the combined rate of death or substantial motor dysfunction at a corrected age of 2 years was significantly lower in the magnesium group compared with the placebo group [17% v/s 22.7%][7].

In the BEAM trial conducted by Rouse et al 2008, 2241 women at imminent risk for preterm birth between 24 and 31 weeks of gestation were assigned to magnesium sulphate or placebo. A 2-year assessment was available for 95.6% of the children in the BEAM trial. The rate of the primary outcome was not significantly different in the two groups [11.3% and 11.7%, Relative risk, 0.97; 95% CI,0.77-1.23]. But in a prespecified secondary analysis, moderate or severe cerebral palsy occurred significantly less frequently in the magnesium sulphate group [1.9% v/s 3.5%; Relative risk,0.55;95% CI, 0.32-0.95]. The risk of death did not differ significantly between the two groups [9.5% v/s8.5%; Relative risk, 1.12; 95%CI 0.85-1.47][8].

A prospective observational study by Gentle et al [2020], of infants between 22 weeks to 27 weeks of gestational age based on the exposure to antenatal corticosteroids and magnesium sulphate or antenatal corticosteroids alone concluded that exposure to both antenatal corticosteroids and magnesium sulphate was associated with lower rates of severe neurodevelopmental impairment or death and death compared to infants exposed to antenatal corticosteroids alone[9].

A. Objectives Of The Study

To determine the role of magnesium sulphate given for fetal neuro protection to women at risk of preterm birth in preventing neonatal mortality and neuro developmental morbidity.

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CHAPTER TWO

REVIEW OF LITERATURE AND BACKGROUND

A. Definition of preterm birth

Preterm birth, also known as premature birth is defined as the birth of the baby at fewer than 37 completed weeks of gestational age or before 259 days, according to World Health Organization[1].

B. Clinical subtypes

Preterm births are classified into subtypes based on the clinical presentations:

- Spontaneous onset of labour
- Following premature rupture of membranes
- Medically indicated preterm birth2.

Savitz et al[10] have suggested that in these clinical subtypes. aetiological factors, prevention strategies, and possibly consequences of infants might vary.

C. Risk factors

The aetiology of preterm birth can be multifactorial.

➢ *Previous preterm labour*

Prior history of preterm labour is the most common risk factor of preterm birth. Also the risk of preterm birth occurs around the same gestational age in following pregnancies[11, 12, 13]. The risk of preterm birth was three times after one previous preterm birth, and six-fold increase is seen after two previous preterm births[11].

➢ *Low body mass index*

Low body mass and poor weight gain is associated with preterm labour. Pre-pregnancy body mass index less than 20 is considered to be linked with the spontaneous onset of preterm labour[14].

➢ *Demographic factors*

Maternal age is one the factors that is related to preterm birth. Extremes of maternal age, that is age less than 18 years[2] and age more than 40 years[15] are associated with risk of preterm birth. Low socioeconomic status is also a risk factor for preterm birth[2,14].

➢ *Uterine distension*

Uterine distension usually caused by multiple pregnancy or polyhydramnios can lead to preterm labour. Prevalence of preterm birth is high in multiple pregnancies[2, 16, 17]. It increases with the order of gestation. Onset of parturition is related to the physiological stimuli including stretch, which initiates various endocrine cascades, is stronger in multiple pregnancies and polyhydramnios. Also placental corticotrophin releasing hormone is high in the multiple gestations[18]. Placental corticotrophin release hormones control the myometrial contractility by modulating the signalling systems, hence involved in onset of labour[19].

➢ *Uterine anomalies*

Uterine anomalies like bicornuate uterus, septate uterus, uterine didelphys, unicornuate uterus can precipitate preterm labour[2, 20]. Fibroid uterus is also associated with preterm birth[21]. Surgical corrections of these anomalies and fibroid uterus can reduce the risk of preterm birth.

➢ *Short cervix*

The risk of preterm birth is high in women with ultra-sonogram showing cervical length less than 2.5cm. The risk increases with further shortening of cervix[22].

- *Previous cervical surgeries*

Wittmack et al[23] concluded that the risk of preterm delivery is high in women with history of cervical conization and loop electrosurgical excision procedure.

- *Psychosocial stress*

Due to psychological stress, there is increase in corticotrophin releasing hormones and cytokines. Preterm labour can occur due to increase in cytokine production. The susceptibility of infections will also increase with increase in cytokines, which can lead to preterm labour[24].

- *Lifestyle issues*

Obesity can increase spontaneous preterm labour risk as well as the medically indicated preterm birth risk. Obese women are at risk of medical illnesses, gestational hypertension, diabetes mellitus etc. which may necessitate the need for preterm birth[11]. Smoking leads to preterm birth by increasing the spontaneous onset of labour and also preterm premature rupture of membranes[25].

- *Drug abuse*

Baer et al [26] found out that the incidence of preterm labour in cannabis users were 11.6% and cocaine users were 24.31%, compared to those women without any drug abuse which was 6.7%. Preterm birth before 32 weeks is common in women using cocaine and polysubstance.

- *Infections*

Agarwal et al[27] in their study says that the main factor causing infection-related preterm labour is thought to be intrauterine bacterial infections. In less than 1% of women who are not in labour at term, the amniotic cavity is contaminated with germs. Therefore, microbial invasion of the amniotic cavity(MIAC)[28], a pathologic finding defined as the isolation of bacteria in the amniotic fluid, is a consequence of this. Without an examination of the amniotic fluid, most of this colonisation goes undetected since it is subclinical. The rate of positive amniotic fluid cultures in patients with preterm labour and intact membranes is 12.8%. However, the frequency is almost twice as high (22%) among individuals who have preterm labour with intact membranes and deliver a preterm infant.

Genital Mycoplasmas, particularly Ureaplasma urealyticum, are the most frequent microbes discovered in the amniotic cavity. The amniotic cavity also contains Mycoplasma hominis, Streptococcus agalactiae, E. coli, Fusobacterium species, and Gardnerella vaginalis, among other microbes[28].

Intra-amniotic infection pathways include ascending infections from the cervix and vagina, hematogenous dissemination through the placenta (transplacental infection), retrograde seeding from the peritoneal cavity through the fallopian tubes, and unintentional introduction during invasive procedures like amniocentesis, percutaneous foetal blood sampling, and chrorionoscopy. The ascending route is the most typical intrauterine infection route[28].

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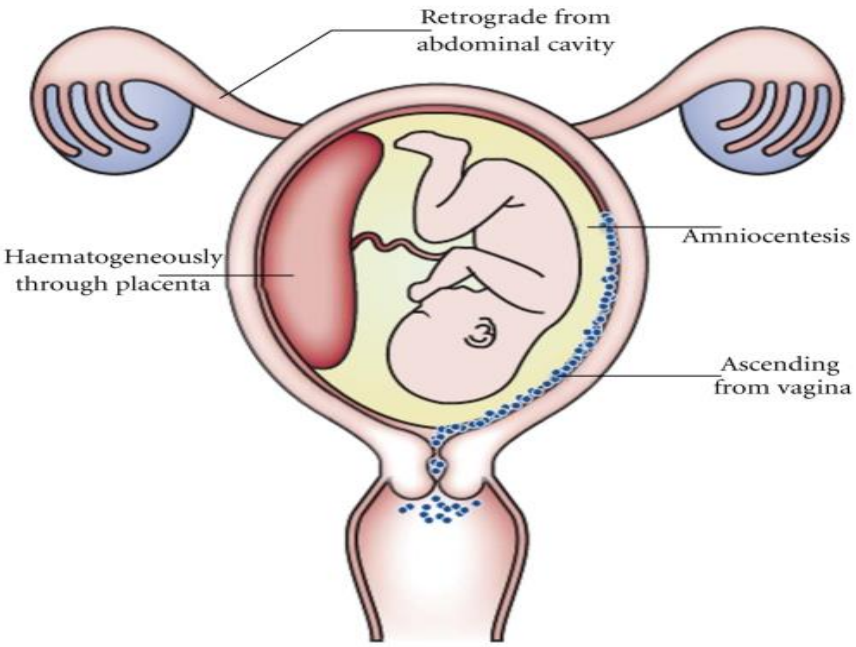

Fig. 1: Pathways of intrauterine infections,source:Goldenberg et al[29].

The significance of toll like receptors[TLR] in preterm birth: Because TLRs are essential for the recognition of microbes, it is expected that impaired signalling through this pattern recognition receptor will impede preterm labour brought on by bacteria. TLR-2 and TLR-4 are expressed in the amniotic epithelium of pregnant women[30]. Furthermore, regardless of the membrane status (intact or ruptured), spontaneous labour at term and preterm delivery with histologic chorioamnionitis are linked to an elevated mRNA expression of TLR-2 and TLR-4 in the chorioamniotic membranes. These findings imply that, whether or not there is observable intra-amniotic infection or inflammation, the innate immune system contributes to parturition[28].

- *Fetal anomaly*

The risk of preterm delivery varies by fetal anomalies and occurs in less than one-third of women with fetal anomalies. Sacrococcygeal teratoma and gastrointestinal anomalies were linked to higher risks of spontaneous preterm birth[31].

- *Preterm premature rupture of membranes*

Preterm premature rupture of membranes [PPROM] is the spontaneous rupture of the foetal membranes before 37completed weeks of pregnancy, before the commencement of labour, and can lead to preterm birth[32]. PPROM has been linked to a number of variables, including infections, placental haemorrhage, uterine overdistension (twins), prior preterm birth and abortion, hypertension, black race, pre-existing diabetes, age between 20 and 35, and smoking during pregnancy[32,33,34]. In microbial infections, vaginal bacteria ascend into the uterus from the lower genital tract. Fetal membranes made of collagen start to break down once they reach the choriodecidua, either directly through proteolysis or indirectly through the activation of matrix metalloproteinases (MMPs). MMPs are a collection of enzymes that are triggered by infections or PPROM[33]. Alternatively, downregulation of tensile strength-related genes may cause infection-associated PPROM[35].

- *Fetal growth restriction*

Fetal growth restriction often necessitates medically induced preterm birth.

- *Gestational hypertension*

Hypertensive disorders of pregnancy can cause both fetal and maternal complications if pregnancy is continued. Hence preterm delivery of fetus may be necessary in case of severe preeclampsia, antepartum eclampsia.

- *Obstetrical complications*

Obstetrical complications such as antepartum haemorrhage either due to abruptio placenta or placenta previa often leads to preterm birth.

- *Pregnancy following assisted reproductive techniques*

There has long been speculation that preterm birth and assisted reproduction are linked. According to Blickstein I, this association has been linked to factors like iatrogenic preterm birth , fertility history, past obstetric performance, and the female partner's underlying medical conditions . Two different meta-analyses conducted recently revealed that compared to naturally occurring pregnancies, singleton pregnancies resulting from in vitro fertilisation (IVF) had a higher rate of preterm birth at 33 weeks of gestation (OR 2.99; 95% CI 1.54-5.80), at 37 weeks of gestation (OR 1.93; 95% CI 1.36-2.74), and a relative risk of 1.98 (95% CI 1.77-2.22) for preterm birth. All pregnancies following assisted reproduction may be wise to be thought of as being at risk as there is no way to determine which pregnant woman is more likely to give birth preterm[36].

- *Periodontal disease*

Even while not all of the actual data support this idea, there is growing evidence that maternal periodontal disorders may be a risk factor for unfavourable pregnancy outcomes, such as preterm birth and low birth weight. The causes and/or correlations between pathologic oral diseases and unfavourable pregnancy outcomes definitely call for more research. From a clinical perspective, it appears that assessing a pregnant woman's periodontal health in the early stages of her pregnancy may be helpful in identifying her risk for future obstetric difficulties[37].

- *Maternal medical disorders*

Women with maternal medical disorders like hypertensive disorders, diabetes, antiphospholipid antibody syndrome may need early induction of labor. Also other medical conditions such as asthma and seizure disorders may necessitates preterm birth[38].

- *Africo-American ethnicity*

In comparison to non-Hispanic white women, non-Hispanic black women had a 2-fold higher risk of premature birth. The causes of this disparity are poorly understood and cannot be fully accounted for by sociodemographic parameters alone. The disparities between racial groups are likely caused by underlying causes such as a complicated interaction between maternal, paternal, and foetal genetics, epigenetics, the microbiome, and sociodemographic risk factors, although these linkages are now poorly understood[39].

D. Screening of cervical length

Cervicometry is regarded as a helpful tool for treating and monitoring preterm delivery because of its high specificity (98%) and sensitivity (71%) for properly predicting preterm birth. It also has positive and negative predictive values (91% and 94%, respectively)[40].

Transvaginal ultrasound cervical length is a screening procedure that is risk-free, tolerable, repeatable, and accurate. Given its viability, it may be widely available. In order for this screening to be successful, the ultrasounds must be performed using the correct transvaginal ultrasound technique and with ongoing quality assurance. Clinicians should refrain from screening various populations, at various gestational ages, and from expanding the criteria of short cervical length to include measures above 25 mm.

For all singleton gestations, a single transvaginal ultrasound cervical length measurement can be given between 18 and 24 6/7 weeks. Vaginal progesterone should be given to the 2% to 5% of these women who exhibit a transvaginal ultrasound cervical length of 20 mm or less.

To singleton gestations with a prior spontaneous preterm birth, serial cervical length measurements, roughly every two weeks and weekly if cervical length is 25 to 29 mm, can be given between 16 and 23 6/7 weeks.

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Cerclage should be offered to the 40% of these women who are expected to have a short cervical length of less than 25 mm because it is linked to a significant 30% reduction in the probability of PTB occurring before 35 weeks and a 36% reduction in composite perinatal mortality and morbidity. Transabdominal cervical length screening has not been adequately investigated, hence it cannot be advised[41].

The benefit with cervical encerclage in multiple pregnancies is seen from less than 1.5 cm cervical length.

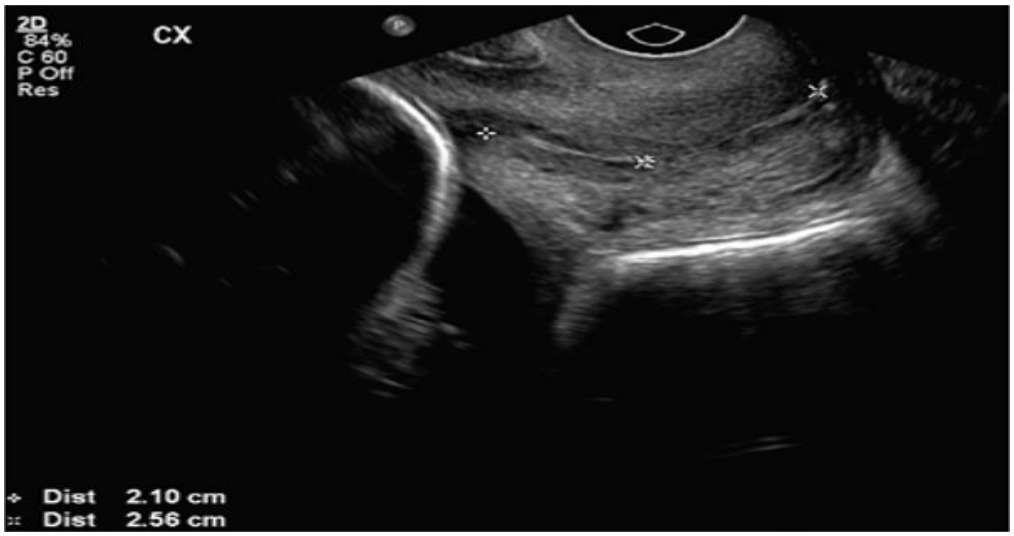

Fig. 2: Transvaginal ultrasound showing cervical length measured with calipers (*Courtesy*: Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine).

E. Diagnosis of preterm labour

Frequent contractions (more than four per hour), cramping, pelvic pressure, excessive vaginal discharge, backache, and low back discomfort are among the signs and symptoms that seem to indicate preterm labour. Preterm labour symptoms may not always be recognisable.

When uterine contractions happen four times every 20 minutes or eight times every 60 minutes, a patient between 20 weeks and 36 weeks, six days of gestation, and are accompanied by any of the following: PROM, cervical dilatation greater than 2 cm, effacement greater than 50%, or a change in either cervical dilation or effacement found by repeated exam, it should be diagnosed as preterm labour[42].

- *Role of fetal fibronectin*

Fetal fibronectin (FFN) is a glycoprotein found in the extracellular matrix that is mostly located at the maternal-fetal junction of the amniotic membranes, between the chorion and decidua, and between the decidua and trophoblast. In cervico-vaginal secretions under typical circumstances, fetal fibronectin is present at incredibly low quantities. An increased risk of spontaneous preterm birth has been linked to levels of 50 ng/mL or higher at or after 22 weeks. In fact, fetal fibronectin is one of the most accurate indicators of preterm delivery in all populations examined thus far, and it can be used to identify the women who are most at risk[43].

As the test is expensive, it is not routinely done. It is collected by taking swab from the posterior vaginal fornix.

- *Role of insulin like growth factor binding protein-1[IGFBP-1]*

The insulin growth factor (IGF) system includes the IGFBP-1 protein, which binds to insulin-like growth factor. The capacity of various IGFBP-1 isoforms to influence IGF function varies. Amniotic fluid, fetal serum, decidua, and the conditioned media from various cell types have all been found to include phosphorylated IGFBP-1 (pIGFBP-1) variations as well as the original peptide. The growth and differentiation of both maternal and foetal tissues depend on IGFs and the proteins that bind to them throughout pregnancy.

Almost all fetal organs create these peptides from the beginning of development and exhibit the corresponding receptors[44,45].

Prior to ultrasound evaluation or digital examination, cervical fluid from the external cervical os was collected with a Dacron swab for the purpose of pIGFBP-1 determination. Following collection, the swab was immediately placed in a specimen extraction solution (0.5 ml of phosphate solution, bovine albumin, and protease inhibitors), and the sample was extracted by shaking for 10 seconds. Five minutes in the solution with an immunochromatography dipstick was followed by an analysis of the results. The least detectable dosage was 10 g/ml, while a positive result—shown as two blue lines on the test dipstick—required a concentration of 30 g/ml. A single blue line denoted negative result[44].

F. Complications of preterm birth in neonates

Complications of preterm birth includes :

- Short term complications in the neonatal period
- Long term sequelae in the survivors

Short term complications include respiratory abnormalities, cardiovascular problems, Intraventricular hemorrhage, hypothermia, necrotizing enterocolitis, neonatal sepsis, Retinopathy of prematurity etc.

Long term complications are mainly the neurodevelopmental disabilities such as cerebral palsy, blindness, deafness, learning disabilities, behavioral and psychological problems and also infant mortality.

The pathogenesis of chronic lung disease, necrotizing enterocolitis, retinopathy of prematurity (ROP), and brain white matter injury in the preterm infant have also been linked to the intricate interplay of the mechanisms involved in preterm delivery, including inflammation and cytokine injury[46].

➢ *Short term complications*

- Respiratory abnormalities

The lungs begin to produce surfactant, a substance that aids in keeping the alveoli open, around about 30 to 32 weeks of gestation. Before 28 to 30 weeks of pregnancy, they lack alveoli and breathes through their terminal bronchioles and primitive air sacs. The respiratory rhythm usually improves after delivery and becomes more consistent, but immature regulating systems might cause brief episodes of apnea[46].

✓ Respiratory distress syndrome

Surfactant deficiency leads to neonatal respiratory distress syndrome, especially when the lungs are immature. The small airways and alveoli's surface tension rises due to a surfactant shortage, which lowers the immature lung's compliance. To avoid the alveolus collapsing or filling with fluid, a delicate balance of pressures at the air-fluid interface is necessary.

With the use of LaPlace law, the pathophysiology of RDS can be explained as follows: P=2T/R, where R is the radius, T the surface tension, and P the pressure. The link between the form of the surface and the pressure difference across the interface of two static fluids is described by Laplace's law. The amount of pressure needed to keep alveolar form increases as surface tension at the alveolar level rises. Reduced gas exchange results from atelectasis, which happens throughout the lung as a result of decreased surfactant production. Atelectasis that is widespread and persistent eventually destroys the respiratory epithelium and results in an inflammatory reaction driven by cytokines[47,48]. As the inflammatory reaction causes pulmonary edema, more and more protein-rich fluid from the vascular space leaks into the alveoli, further inactivating surfactant.

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The neonate may exhibit lowered peripheral pulses and weakened breath sounds. Such newborns exhibit cyanosis, decreased peripheral perfusion, tachypnea, expiratory grunting, nasal flaring, retractions (subcostal, subxiphoid, intercostal, and suprasternal), and use of accessory muscles. Air entry will be decreased uniformly. In untreated RDS, the newborn may become lethargic and apneic as the symptoms deteriorate over the course of 48 to 72 hours, eventually leading to respiratory failure[46].

✓ Bronchopulmonary dysplasia[BPD]

A persistent complication of respiratory distress syndrome is bronchopulmonary dysplasia. In addition to lung damage and inflammation, BPD's pathophysiology also includes arrested lung development. In addition to lacking surfactants, the premature infant's lung also has immature vascular development, decreased compliance, and decreased fluid clearance, all of which increase the risk of lung injury and inflammation and interfere with the normal growth of the alveoli and pulmonary vasculature. A third cause of lung damage is the increased production of TGF-1 and other pro-inflammatory cytokines brought on by oxidative stress caused by hyperoxia due to mechanical breathing and the premature lung's lower antioxidant capacity[49].

- Intracranial haemorrhage

A significant complication of premature birth is intraventricular haemorrhage (IVH). The germinal matrix, a densely vascularized cluster of neuronal-glial precursor cells in the developing brain, is where IVH typically occurs. The intrinsic brittleness of the germinal matrix vasculature and the change in cerebral blood flow are the main causes of IVH, which has a complex aetiology. The number of angiogenic blood vessels that show a lack of pericytes, immaturity of the basal lamina, and a lack of glial fibrillary acidic protein (GFAP) in the endfeet of astrocytes render the microvasculature of the germinal matrix fragile. Rapid angiogenesis is triggered in the germinal matrix by high VEGF and angiopoietin-2 levels. The relative hypoxia of the germinal matrix, possibly brought on by the increased metabolic activity and oxygen consumption of the neural progenitor cells, may be responsible for the elevation of these growth factors[50].

The risk of certain neurologic sequelae increases with IVH and it lowers the survival rate of premature newborns. Premature newborns with severe IVH have been shown to have a greater mortality rate than those without IVH[51]. Newborns with mild IVH (grade 1-2) are at risk for developmental problems, while premature infants with moderate-to-severe IVH (grade 3-4) are at high risk of post hemorrhagic hydrocephalus, cerebral palsy, and mental retardation [52,53].

Premature children with moderate-to-severe IVH suffer significant cognitive abnormalities in 45–85% of cases, and roughly 75% of these infants require special instruction in schools [54].

- Cardiovascular abnormalities

Tanner et al in their study revealed that 16% of all newborns with cardiovascular malformations are preterm and that preterm infants have more than twice as many cardiovascular defects as infants born at term. It also revealed, not surprisingly, that infants born preterm with a cardiovascular abnormality have a higher mortality risk. Tetralogy of Fallot, a full atrioventricular septal defect, a hypoplastic left heart, ventricular septal defect etc. are seen in preterm babies.

- Necrotizing enterocolitis[NEC]

The pathogenesis of necrotizing enterocolitis is not fully understood[56].

NEC is most likely the result of a complex interaction of factors that result in mucosal damage when the following pathologic events co-occur: intestinal ischemia, immaturity of the gastrointestinal tract, an excess of protein substrate in the intestinal lumen,[57,58] and bacterial colonisation of the intestine. Preterm newborns acquire these colonising gastrointestinal bacteria from the neonatal intensive care environment[58]. It has been hypothesised that some children may have a genetic tendency with less mucin-producing goblet cells given that the majority of premature infants do not develop NEC[59].

Stage 1 and 2 can be treated conservatively. However, surgical intervention is taken into consideration in the event of intestinal perforation or clinical worsening[60].

- Retinopathy of prematurity

Retinopathy of prematurity is caused by insults that affect the development of the neurovascular system in the underdeveloped retinas of preterm newborns. Retinal vascularization is stopped as a result of maternal-fetal interaction being lost and growth hormones being suppressed by hyperoxia (phase 1). The subsequent hypoxic state of the retina, which is becoming more metabolically active but is still minimally vascularized, promotes growth factor-induced vasoproliferation (phase 2), which might result in retinal detachment. Controlled oxygen treatment lessens but does not completely eradicate retinopathy of prematurity in very preterm newborns. To stop retinopathy of prematurity from progressing to a severe, sight-threatening condition and to reduce comorbidities with which the illness has modifiable risk factors, it is crucial to identify and control these factors. Optimizing oxygen saturation, diet, and maintaining normal concentrations of vital substances like insulin-like growth factor 1 and -3 polyunsaturated fatty acids are all important components of prevention strategies for retinopathy of prematurity. Additionally, reducing the effects of infection and inflammation will help to promote normal growth and prevent excessive suppression of neurovascular development.[61].

- Neonatal sepsis

Glazer et al[62] says that while Coagulase-negative staphylococci make up the bulk of cases in late-onset sepsis, Group B streptococcus and Escherichia coli are the most frequent pathogens in early-onset sepsis. Due to traits such as lower cellular activity, immature complement systems, selective anti-inflammatory responses, and limited pathogenic memory, the newborn immune system is susceptible[62].

- Periventricular leukomalacia

The most common neurologic morbidity seen in premature birth survivors is periventricular leukomalacia (PVL).

Three interacting components are related to the aetiology of periventricular leukomalacia. A susceptibility for ischemia injury to cerebral white matter is caused by the first two of these factors:

- ✓ an inadequate state of development of the vascular supply to the cerebral white matter.
- ✓ maturation-dependent defect in regulation of cerebral blood flow.
- ✓ The third important pathogenetic element is the oligodendroglial (OL) precursor cell's maturation-dependent susceptibility, which serves as the primary cellular target in PVL.

Recent neurobiologic research demonstrates that these cells are incredibly susceptible to damage from free radicals, which are known to be produced in large quantities during ischemia-reperfusion[63]. The brain tissue doesn’t regenerate in preterm neonates, the irreversibly damaged areas seems as echolucent cysts in imaging studies[64].

- Hypothermia

Hypothermia, is a frequent and potentially dangerous condition in preterm neonates. Because their bodies are still developing and less able to regulate their body temperature, preterm neonates are more likely to develop hypothermia.

Additionally, preterm newborns are more likely to lose heat because of their increased body surface area in comparison to their size.

Hypothermia in preterm newborns can have major repercussions, including higher morbidity and mortality rates as well as lengthier hospital stay. Complications from hypothermia can affect the brain and other organs by causing hypoglycemia, respiratory distress, and hypoxia. Additionally, it can weaken the immune system and increase the risk of infections.

- Hypogylcemia

One of the most frequent illnesses seen in the newborn critical care unit is hypoglycemia. Due to their limited glycogen and fat reserves, inability to produce new glucose through gluconeogenesis pathways, higher metabolic demands because of a relatively larger brain size, and inability to mount a counter-regulatory response to hypoglycaemia, preterm neonates are particularly vulnerable to developing, hypoglycaemia and its associated complications[65].

➢ *Long term complications*

Long term sequelae of preterm birth include neurodevelopmental disabilities like cerebral palsy, blindness, deafness, learning disabilities, behavioural and psychological problems and also infant mortality.

One of the main causes of neurological disability in children is cerebral palsy (CP). An important risk factor for the development of CP is preterm delivery. Impairment of gross motor function and cognitive ability, visual impairment, and epilepsy are the clinical outcomes[67].

Drljan et al[67] studied 145 children with CP , more than half (54.4%) of them were born premature. More specifically, 30.3% of babies were delivered between 32 and 36 weeks gestation, 17.2% between 28 and 31, and 6.9% of births occurred at less than 28 weeks. Bilateral spastic CP type and higher gross motor function classification system [GMFSC] degree of functional limitation were more common among the prematurely born kids included in this study. The largest prevalence of related disorders and more severe cognitive and visual impairment were found in children born before 28 weeks of gestation.

G. Management of preterm labour

➢ *Corticosteroids*

The most effective intervention for the prevention of RDS, minimising early newborn death and morbidity, is antenatal steroid therapy for women who are at risk of preterm delivery[68].The majority of glucocorticoid hormones, both synthetic and natural, have the ability to cross the placenta and initiate the maturational process that results in the creation and release of surfactant into the fetal lung's alveoli[69,70,71]. The first clinical experiment with betamethasone was done by Liggins[72] in 1969.

In the meta-analysis by Kambwafile et al[73] reviewed the available data globally and estimate the effect of antenatal steroid administration to women prior to an anticipated preterm labour, compared with placebo or no treatment, on neonatal mortality due to complications from preterm birth, with a focus on variation in the effect size in low- and middle-income countries.

Dexamethasone is given in four doses of 6 mg each, spaced 12 hours apart, whereas betamethasone is given in two doses of 12 mg each, spaced 24 hours apart[74].

Newnham et al, concluded that repeated rounds of prenatal corticosteroids may improve the respiratory function of the preterm newborn, albeit at the expense of slower fetal growth. Although birth head circumference reductions are generally minor, the significance may be increased by worries about possible impacts on brain development, especially myelination[75].

➢ *Tocolysis*

Tocolytic drugs includes calcium channel blockers: Nifedipine,beta agonists, cyclooxygenase inhibitors, nitric oxide donors, oxytocin receptor antagonists.

They are used to subside the premature uterine contractions, so as to allow antenatal corticosteroids for the respiratory maturity of preterm baby.

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- Calcium channel blockers: Nifedipine

Hawkins et al in their randomised, double-blind, placebo-controlled research discovered that nifedipine administration was not significantly linked to pregnancy lengthening comparing nifedipine for acute tocolysis to placebo. They found no differences in perinatal outcomes, and despite nifedipine's tendency to raise maternal heart rates, there were no negative consequences or unfavourable changes in mother's blood pressure[76].Nifedipine is the commonly used tocolytic.

- Cyclooxygenase inhibitors: Indomethacin

Kashanian et al concluded that in comparison to nifedipine, indomethacin was less successful at treating premature labour quickly. However, the delay in delivery caused by indomethacin was comparable to the delay caused by nifedipine for women who responded to treatment within 2 hours[77].

- Beta agonists

Ritodrine and terbutaline are the commonly used drugs.

In the systematic review conducted by Yaju et al, they concluded that perinatal mortality, the percentage of RDS, preterm birth, and low birth weight newborns did not significantly decline with use of ritodrine. Patients taking ritodrine experienced considerably more adverse maternal effects than those taking a placebo. Short-range gestational prolongation is the only way parenteral ritodrine hydrochloride is beneficial for tocolysis in preterm labour. Oral ritodrine hydrochloride maintenance tocolytic therapy's efficacy was not demonstrated[78].

- Nitric oxide donors

Transdermal glyceryl trinitrate is one example.

In systematic review conducted by Duckitt et al Nitric oxide donors did not significantly outperform other tocolytics in terms of pregnancy prolongation, despite the fact that they did seem to be linked to a decrease in the majority of side effects, with the exception of headache. With regard to newborn morbidity or death, there was no significant difference between the groups[79].

- Oxytocin receptor antagonists

Atosiban is the commonly used drug in this category**.** In the clinical trial conducted by Romero et al, they found out that atosiban treatment of patients in preterm labour in this experiment resulted in a pregnancy extension for those with a gestational age > or =28 weeks for up to 7 days, and this occurred with a low rate of maternal-fetal side effects. The infant morbidity and mortality of atosiban-initiated standard care were also comparable to those of placebo-initiated standard care at a gestational age > or =28 weeks[80].

- Magnesium sulphate

The American College of Obstetricians and Gynecologists continues to advise MgSO4,despite its weak evidence, for short-term pregnancy extension (up to 48 hours) so that corticosteroids can be administered[81].

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Table 1: Commonly used tocolytics.

Type of Agent	Dosage	Mechanism of Action	Side Effects (Maternal)	Side Effects (Fetal-Neonatal)	Contraindications	Interactions with Anesthesia
β_2 Agonist (terbutaline)	0.25 mg SQ q20min	Decreases myometrial contractions	Tachycardia, dysrhythmia, hypotension, myocardial infarction, hyperglycemia, pulmonary edema, nausea/vomiting, hyperinsulinemia	Hypoinsulinemia, hypoglycemia, intravascular hemorrhage, hyperbilirubinemia	Dysrhythmia, uncontrolled diabetes, uncontrolled thyroid disease	Need to monitor blood pressure, heart rate, and rhythm closely
Calcium channel blockers (nifedipine)	20-30 mg SL/PO, then 10-20 mg PO q4-6h	Decreases calcium uptake into cells and decreases calcium release from sarcoplasmic reticulum, thus decreasing myometrial contractions	Hypotension, flushing, headache, nausea, vomiting, pulmonary edema, dyspnea	Nonreassuring fetal status due to maternal hypotension	Cardiac disease, renal disease, hepatic disease, hypotension, magnesium	Increased risk of hypotension and reflex tachycardia
Cyclooxygenase inhibitors (indomethacin)	50-100 mg PO or PR, then 25-50 mg q4h	Inhibiting prostaglandin production thereby reduces intracellular calcium, thus decreasing myometrial contractions	Heartburn, nausea	Closure of ductus arteriosus, pulmonary hypertension, oligohydramnios, hyperbilirubinemia	Thrombocytopenia, coagulation disorders, renal disease, gastritis, nonsteroidal anti-inflammatory drug sensitivities	Neuraxial blockade can be performed safely[5]
Magnesium (magnesium sulfate)	4-6 g IV loading dose, then 1-2 g/h IV infusion	Competitor of calcium at the receptor, decreasing calcium uptake into the myometrium	Muscle weakness, diplopia, flushing, lethargy, headache, pulmonary edema, cardiac arrest	Hypotonia, respiratory depression, lethargy	Maternal neuromuscular disorders	Hypotension due to neuraxial blockade may be accentuated May prolong action of nondepolarizing muscle relaxant

- *Magnesium sulphate for fetal neuroprotection*

Chollat et al[82] says that the neuroprotective effects of magnesium could be attributed to a number of processes. Multiple mechanisms that may be implicated in premature brain damage are impacted by magnesium. Magnesium is a non-competitive NMDA receptor antagonist, it protects against excitotoxic calcium-induced damage (Nowak et al)[83]. Under ischemic conditions, magnesium reduces extracellular glutamate, perhaps lowering excitotoxicity (Kang et al)[84]. Calcium influx through voltage-gated channels is restricted by magnesium, which may lessen the activation of apoptosis (Türkyilmaz et al)[85].

Due to its ability to lower oxidative stress and the generation of the pro-inflammatory cytokines interleukin-6 and tumour necrosis factor, magnesium also possesses anti-inflammatory effects (Mazur et al, Aryana et al, Rayssiguier et al, Burd et al)[86,87,88,89]. Lack of magnesium causes an increase in the generation of endothelial nitric oxide, which can lead to endothelial dysfunction (Cho et al, Zheltova et al)[90,91]. Neurotransmitter release inhibition, inhibition of nuclear factor kappa B, decreased calcium influx and activation of phagocytic cells, and other possible mechanisms could all contribute to this.

H. Randomized controlled trials for magnesium sulphate as neuroprotection

- *Magnesium and Neurological Endpoints Trial [MagNET]*

The MagNET included 1,049 women who underwent treatment at a single US facility between October 1995 and January 1997 for preterm labour at 25-33 weeks of gestation (165 fetuses). Women in active labour with cervical dilation of at least 4 cm who were in the tocolytic arm were randomly assigned to receive either MgSO4 (4 g bolus followed by 2-3 g/h maintenance dosage) or another tocolytic drug. Women with cervical dilatation of more than 4 cm were randomly assigned to receive MgSO4 (4 g bolus alone) or 0.9% saline placebo in the neuroprotection group.

The MgSO4 group's mortality rate (11%) was in line with earlier reports of premature newborns, but the placebo group's (1.4%) was surprisingly low. Furthermore, it was challenging to ascribe the deaths primarily to the MgSO4 treatment because the causes of death were comparable to those seen in preterm children. Additionally, because more twin neonates were assigned to the treatment group than the control group, the confounding effect of multiple births was not taken into consideration. Finally, the results of observational studies did not support the increased mortality rate[82].

- *Australian Collaborative Trial of Magnesium Sulphate [ACTOMgSO4 Trial]*

The Australaian Collaborative Trial of Magnesium Sulfate [7](ACTOMgSO4) comprised 1,062 women in preterm labour before 30 weeks of gestation from 16 locations during February 1996 and September 2000. 535 women (629 live foetuses) got MgSO4 (4 g bolus followed by 1 g/h maintenance for 24 h or till birth), while 527 women (626 live foetuses) received placebo. The rate of motor dysfunction was significantly lower in the MgSO4 group (2.9 versus 5.4% in the control group; RR, 0.53; 95% CI, 0.30-0.92), even though the rate of cerebral palsy at 2 years was similar in both groups (5.7% in the MgSO4 group versus 6.7% in the control group; RR, 0.85; 95% CI, 0.55-1.31). Mortality among neonates and paediatric mortality rates were also similar.

- *Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG Trial*

In the PREMAG Trial[92] by S Marret, 573 women were treated at 18 French facilities between July 1997 and July 2003. Of these, 286 women (354 fetuses) received a 4-g bolus of MgSO4 by randomization, while 278 women (341 fetuses) received a placebo. After 6 years of enrollment, the experiment was terminated. The key outcomes (rates of death and white matter injury) were comparable between the groups (mortality, 9.4 against 10.4%; OR, 0.79; 95% CI, 0.44-1.44; white matter injury, 10% versus 11.7%). At two years, the MgSO4 group had a reduced combined mortality or gross motor dysfunction rate (25.6 versus 30.8%; OR, 0.62; 95% CI, 0.41-0.93), although cerebral palsy rates were not different.

- *Beneficial Effects of Antenatal Magnesium Sulphate [BEAM Trial]*

2241 women in preterm labour before 32 weeks of gestation participated in the BEAM experiment by Rouse et al[93] between December 1997 and May 2004 at 20 locations. MgSO4 was given to women either as a 6-g bolus followed by a 2-g/h maintenance dosage for 12 hours (1,096 women and 1,188 foetuses) or as a placebo (1,145 women, 1256 fetuses). The mortality of children was not affected by antenatal MgSO4 treatment. Although the two groups' major outcomes-stillbirth, death at one year, or cerebral palsy at two years, were identical, the MgSO4 group saw a markedly lower rate of moderate or severe cerebral palsy (1.9 versus 3.5%; RR, 0.55; 95% CI, 032-0.95).

- *Magnesium sulphate for prevention of eclampsia, MAGPIE Trial*

Between July 1998 and November 2001, 10,141 women with preeclampsia participated in the MAGPIE trial[94], a significant international study to assess the effectiveness of antenatal MgSO4 administration in the prevention of eclampsia. Of these, 1,544 women (1,593 foetuses) were pregnant before 37 weeks gestation. MgSO4 (4 g bolus followed by 1 g/h maintenance dose for 24 hours) or a placebo was randomly given to the women. A paediatric follow-up study with 4,483 children (2,254 in the MgSO4 group and 2,229 in the placebo

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group, respectively) found no differences in mortality or neurological outcomes at 18 months (as measured by the Ages and Stages questionnaire). Notably, just 19% of the kids who were raised after were born prior to 33 weeks of gestation.

I. Ongoing trials

- Magnesium Sulphate for Preterm birth [MASP study]
- Magnesium sulphate at 30 to 34 weeks of gestational age: Neuroprotection Trial [MAGENTA Trial]

J. Trivandrum developmental screening chart

In order to create the Trivandrum Developmental Screening Chart (TDSC),Nair et al used 17 test items from the Bayley Scale of Infant Development (Baroda Norms). It was tested against the Denver developmental screening test[DDST] benchmark at both the hospital and community levels. With a sensitivity and specificity of 66.7% and 78.8%, respectively, the TDSC is a suitable straightforward screening tool even for community level workers.

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CHAPTER THREE

RELEVANCE

Despite improvements in perinatal care, preterm birth is still occurs regularly and the associated brain injury and adverse neurological outcomes remain a persistent challenge. Antenatal magnesium sulphate administration is an intervention with demonstrated neuroprotective effects for preterm births before 32 weeks of gestation to reduce the fetal /infant death, cerebral palsy and gross motor disabilities.

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CHAPTER FOUR

METHODOLOGY

A. Research Question

What is the therapeutic benefit of antenatal magnesium sulphate used for fetal neuroprotection in preterm labour in the neonatal mortality and neuro- developmental morbidity?

B. Objectives Of The Study

To determine the role of magnesium sulphate given for fetal neuroprotection to women at risk of preterm birth in preventing neonatal mortality and neuro- developmental morbidity.

C. Hypothesis

The hypothesis is that magnesium sulphate given for fetal neuroprotection to women at risk of preterm birth between 28-32 weeks will reduce the risk of mortality and neonatal morbidity including IVH and other neuro sensory disabilities like blindness, deafness or developmental delay

D. Study Design

Prospective cohort study

E. Study Setting

Department of Obstetrics and Gynaecology and Department of Paediatrics, IMCH Calicut

F. Sample Size

All the patients satisfying the inclusion criteria who came to Government Medical College Kozhikode during the study period are included as cases (75 patients), and equal number of controls were studied.

G. Duration Of Study

1.5 years JUNE 2021- DEC 2022

H. Inclusion Criteria

- Women were eligible for the study if they are at risk of preterm birth [spontaneous/induced] between 28-32 weeks of gestation where birth is planned or definitely expected within 24 hours were included.
- Women with singleton pregnancy or twin pregnancy were included.
- Severe preeclampsia, eclampsia, induced preterm for maternal or fetal indications were also included

I. Exclusion Criteria

- Multifetal gestation more than 2 fetuses were excluded
- Women with preterm labour induced from outside hospitals were not included
- Preterm delivery from outside hospitals were not included in the study

J. Method

During the period of study, pregnant women with preterm labour with gestational age 28 to 32 weeks were enrolled in the study as cases.

Women with preterm labour who deliver before magnesium sulphate regime started were taken as controls

Women with preterm birth, who were given antenatal magnesium sulphate for fetal neuroprotection, administered as a 4g IV loading dose, over 20 minutes, followed by a 1g/hr maintenance infusion for 24 hours using an infusion pump were observed. [Routinely practiced in our hospital as a standard protocol of management of threatened preterm labour]

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Delivery was not delayed in order to administer antenatal magnesium sulphate for fetal neuroprotection if there were maternal and/or fetal indications for emergency delivery.

When magnesium sulphate was given for fetal neuroprotection, used existing protocols to monitor women who received magnesium sulphate for preeclampsia/ eclampsia. Corticosteroids (Injection Dexamethasone 6mg 4 doses 12 hrs apart) for fetal lung maturation was administered (if not already given). Continuous fetal heart surveillance was provided

Maternal obstetric outcome and fetal outcome was observed.

Infant was followed up until corrected age of 1 year of age. Participants were called to Institute of Maternal and Child Health,Kozhikode[IMCH] at corrected age of 1year. They were examined at Regional Early Intervention Centre [REIC], IMCH to assess any infant morbidity and neurosensory disabilities like blindness, deafness or developmental delay. Trivandrum developmental screening chart was used to screen the infants.

K. Outcome Measurement

The outcomes measured were the maternal obstetric outcome and incidence of neonatal outcomes including intraventricular haemorrhage[all grades], periventricular leukomalacia, neonatal seizures, respiratory distress syndrome, need for supplemental oxygen at 36 weeks, bronchopulmonary dysplasia, need for mechanical ventilation, necrotising enterocolitis, neonatal death, infant neuro developmental outcomes upto 1 year including substantial gross motor dysfunction, major neurological disability, blindness, deafness and incidence of infant death.

L. Data Analysis

Data will be entered in excel sheet and analysed using SPSS software

P value less than 0.05 is considered as statistically significant.

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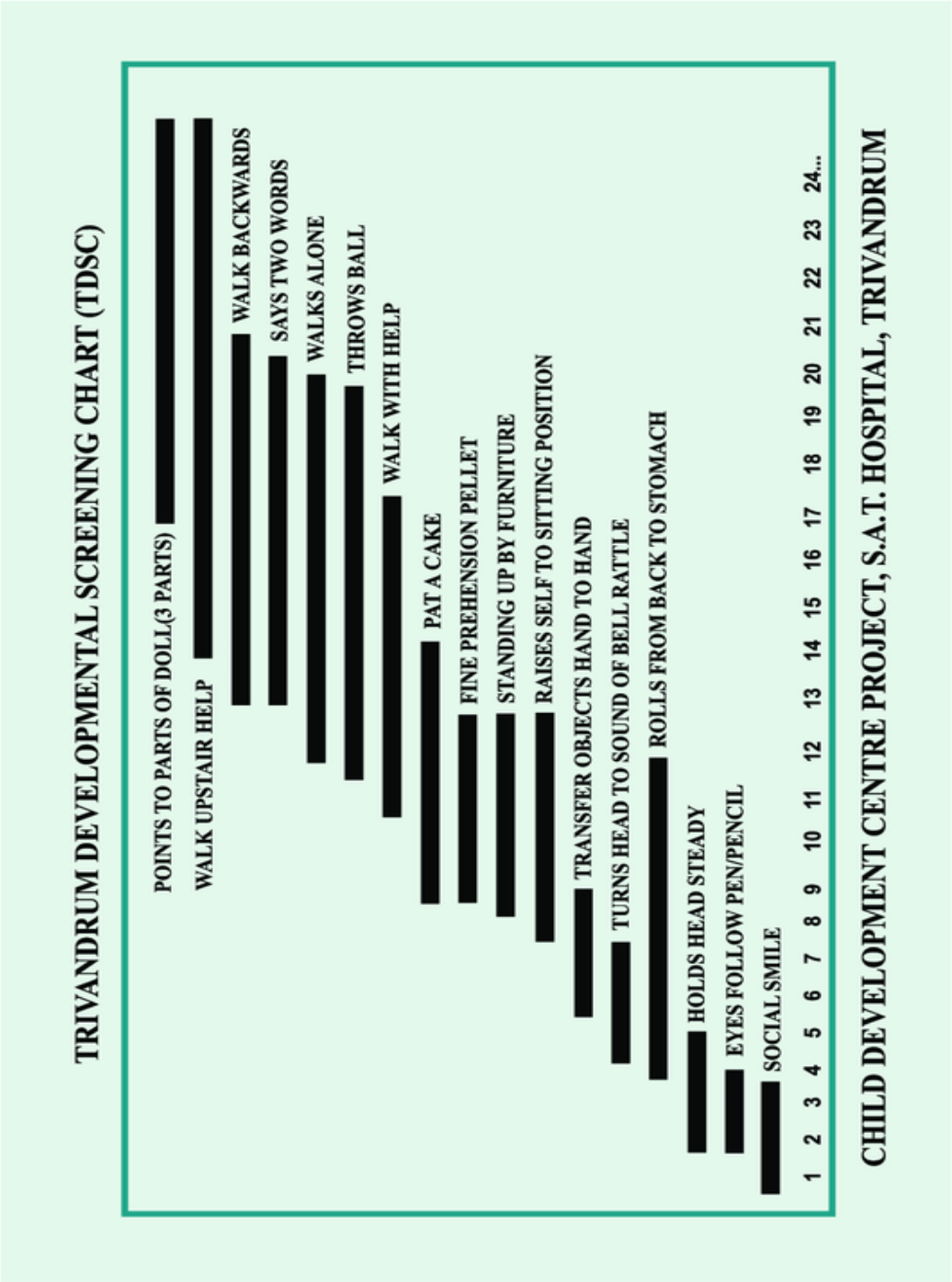

Fig. 3: Trivandrum Developmental Screening Chart

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CHAPTER FIVE

RESULTS

The study was conducted among 75 cases who received antenatal magnesium sulphate for fetal neuroprotection [GROUP A] and same number of controls who delivered before administration of magnesium sulphate [GROUP B]. SPSS software was used for data analysis. Bar diagrams, pie charts and multiple bar diagrams were used to illustrate the data.

A. Age distribution

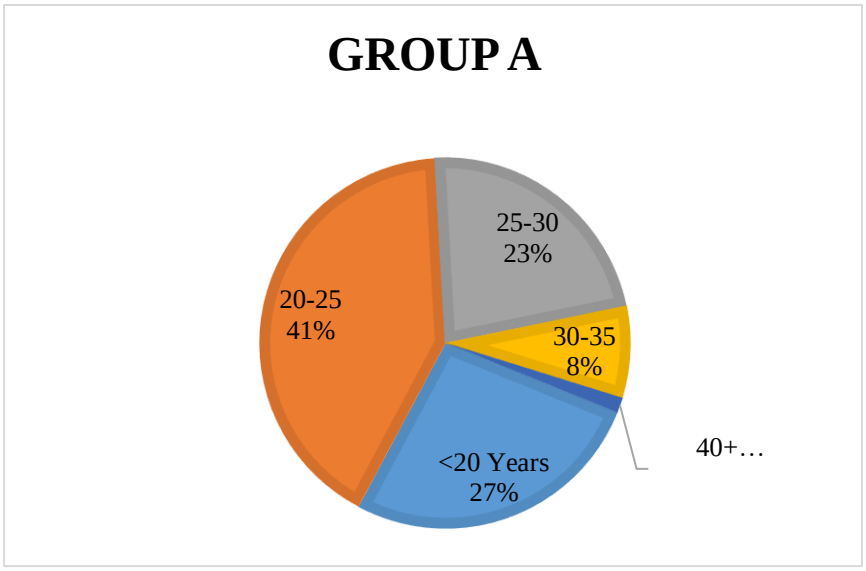

Fig. 4: Age distribution in Group A

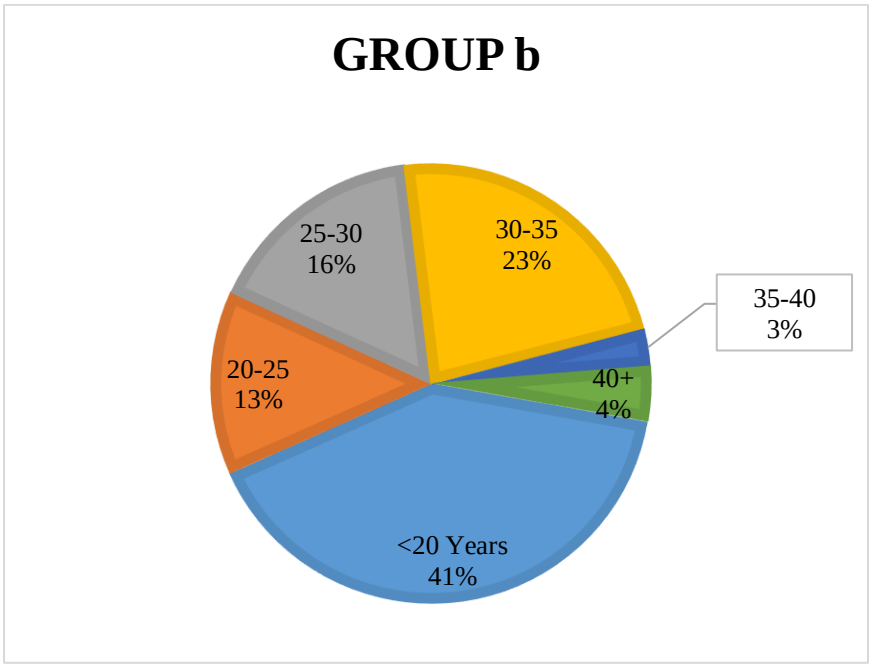

Fig. 5: Age distribution in Group B

Majority of the patients in group A belong to age group 20-25 years.
Majority of the patients in Group B belong to <20 years.
Age distribution was almost similar between both groups.

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B. Obstetric score

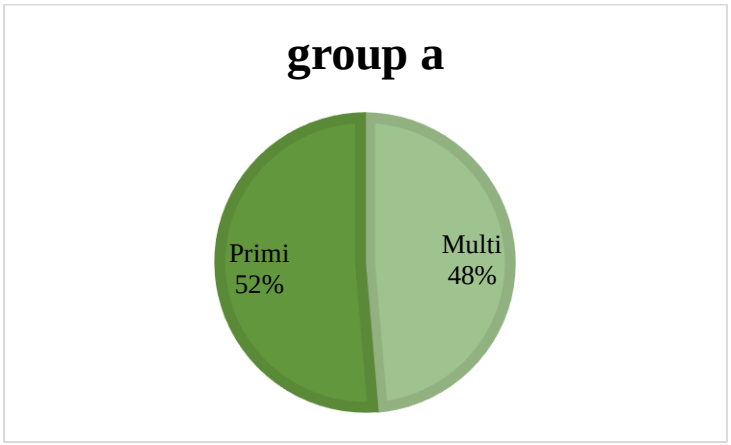

Fig. 6: Obstetric score in Group A

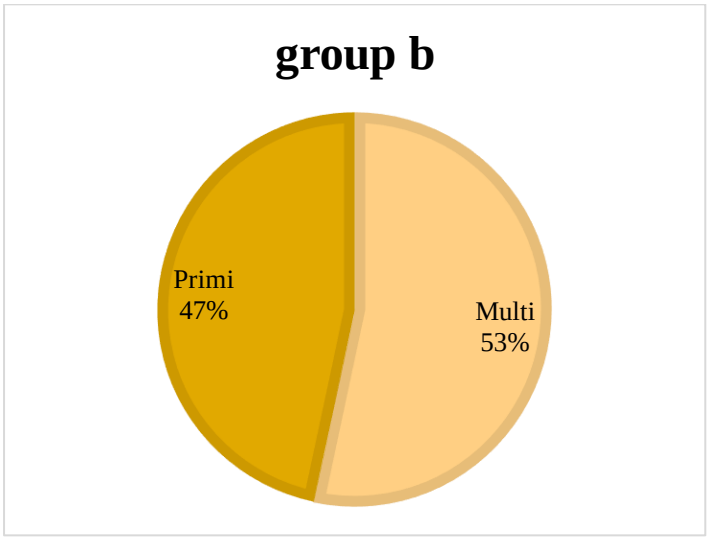

Fig. 7: Obstetric score in Group B

52% of patients were primi gravida in Group A
47% of patients were primi gravida in Group B

C. Singleton/Multiple pregnancy

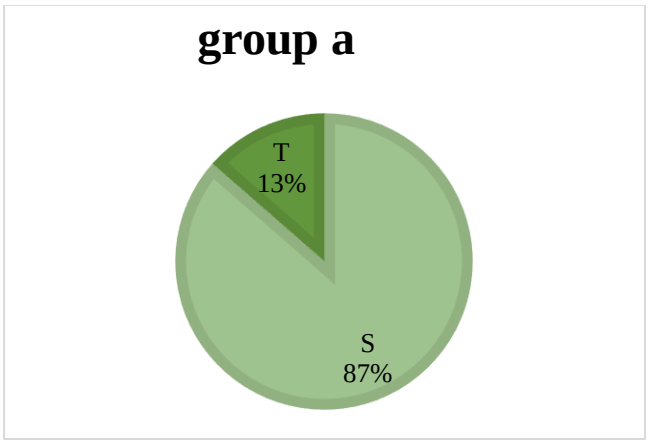

Fig. 8: Singleton/twins in Group A

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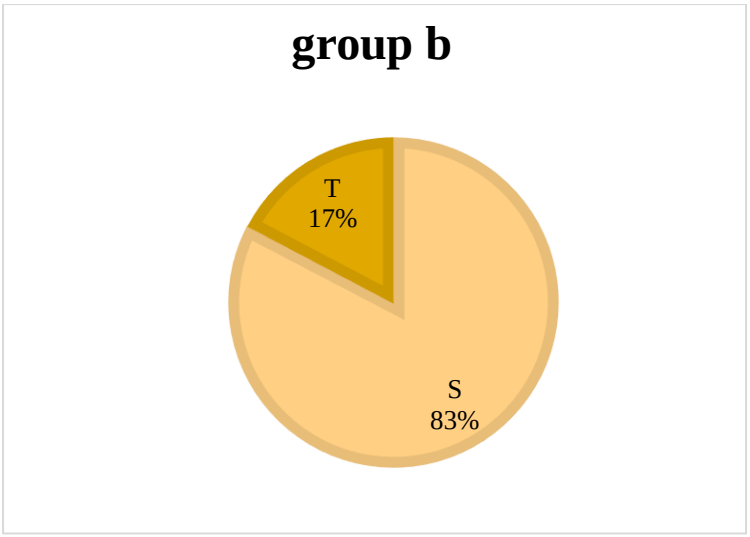

Fig. 9: Singleton/twins in Group B

87% were singleton pregnancies in Group A
83% were singleton pregnancies in Group B

D. History of preterm birth

Table 2: History of preterm birth

	Group A		Group B	
	Frequency	**Percent**	**Frequency**	**Percent**
No history	63	84	67	89.3
H/o prior preterm birth	12	16	8	10.7
Total	75	100	75	100

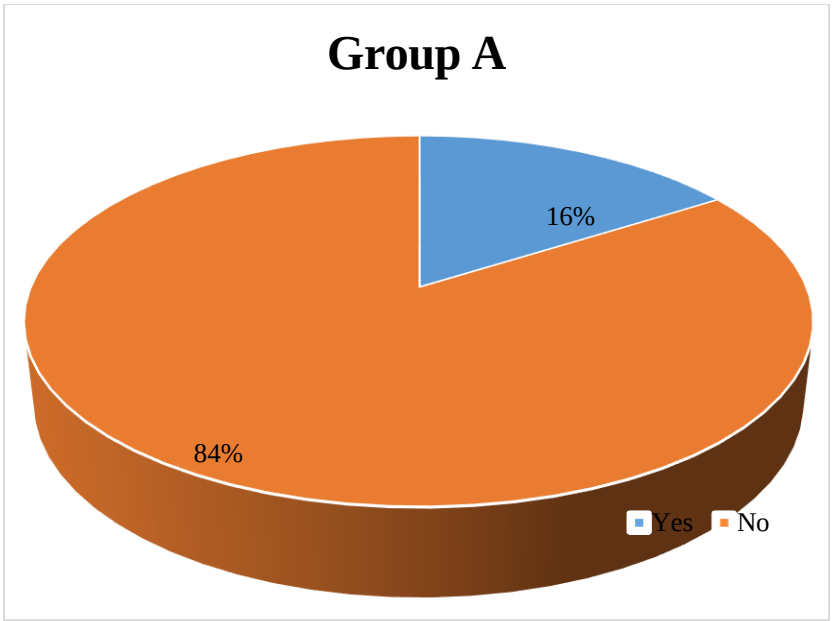

Fig. 10: History of preterm birth in Group A

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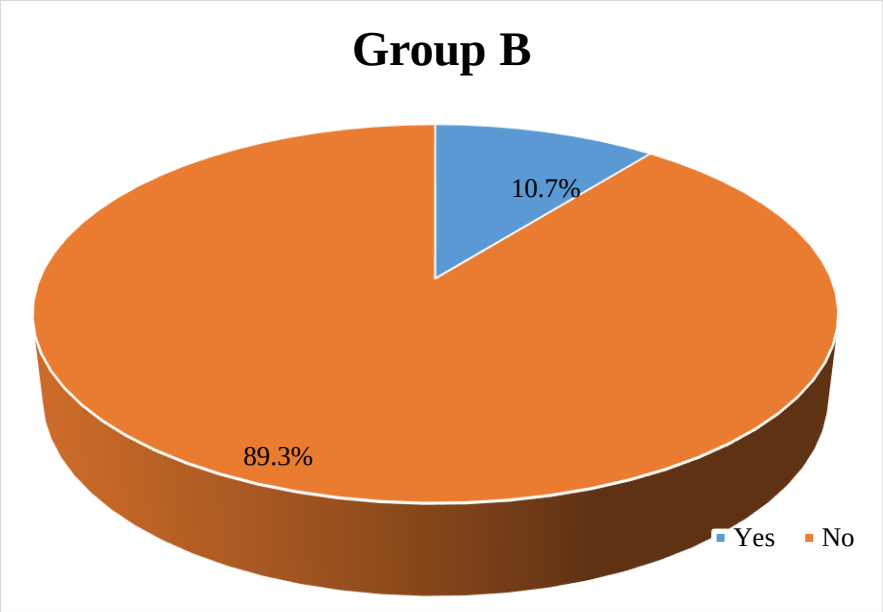

Fig. 11: History of preterm birth in Group B

16% of patients had the history of prior preterm birth in Group A
10.7% of patients had the history of preterm birth in Group B

E. Maternal comorbidities

In Group A, 12% of the mothers had severe preeclampsia, and in Group B, 8% of mothers had severe preeclampsia. The incidence of severe preclampsia in this study is 9.33%.

17.3% were diabetic in Group A and same percentage were diabetic in Group B.

F. Magnesium sulphate regime completed/not

Table 3: Magnesium sulphate regime completed /not

Magnesium Sulphate completed /not	Frequency	Percent
Not completed(N)	22	29.3
Completed(Y)	53	70.7
Total	75	100

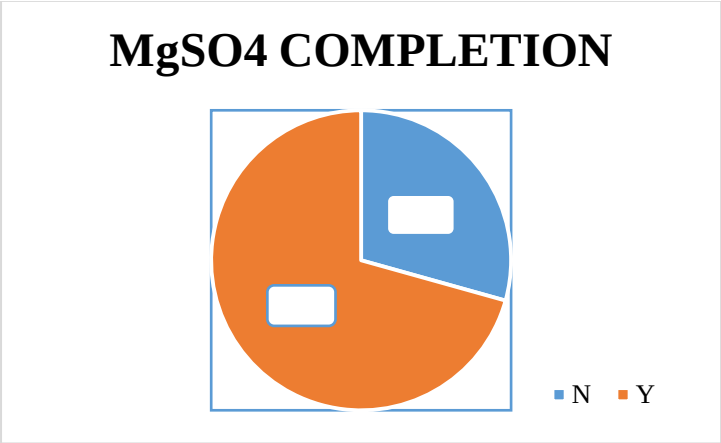

Fig. 12: Magnesium sulphate regime completed /not

70.7% of Group A patients completed the magnesium sulphate regimen

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G. Time interval between completion of regime and delivery in hours (n= 53)

Table 4: Time interval between completion of regime and delivery in hours

Mean	63.34
Median	**40**
Mode	**72**
Std. Deviation	70.636
Minimum	4
Maximum	312

Out of the 53 patients who completed the magnesium sulphate regime, 40 hours is the median duration between the time of completion and delivery. Mode is 72 hours.

H. Hours of MgSO4 regime given in those whom did not completed regime(n=22)

Table 5: Hours of MgSO4 regime given in those whom did not completed regime

Mean	10.95
Median	11.5
Mode	12
Std. Deviation	4.715
Minimum	5
Maximum	19

In 22 patients,magnesium sulphate regime could not be completed as they delivered while regime was ongoing. A mean of 10.95 hours of regime is obtained in them.

I. Mode of delivery

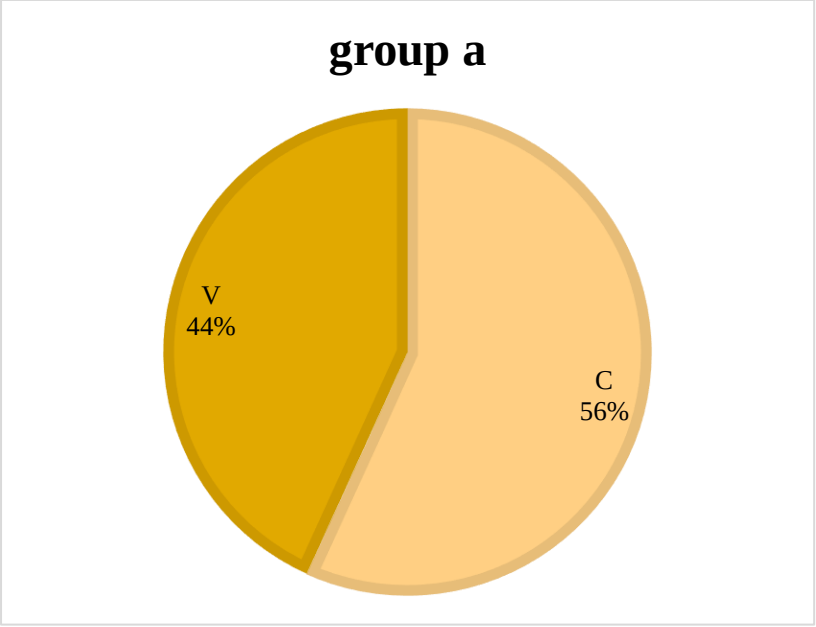

Fig. 13: Mode of delivery in group A

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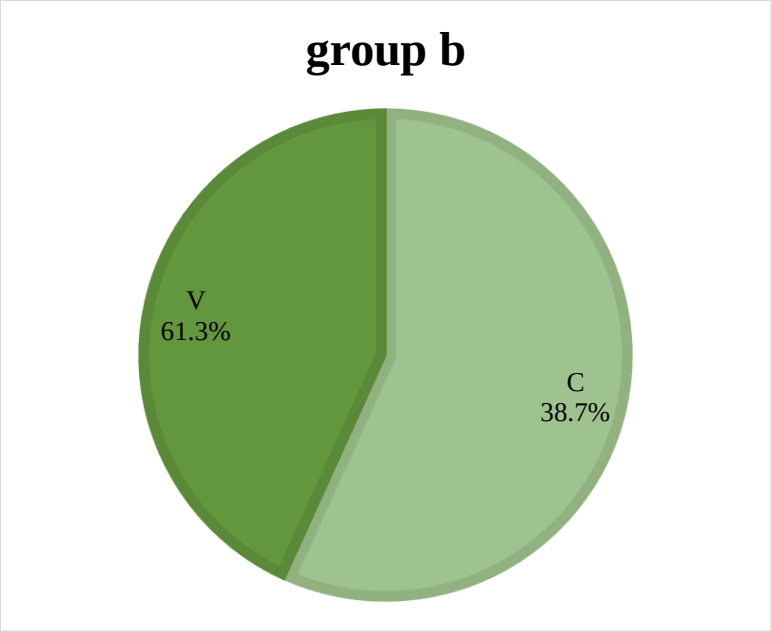

Fig. 14: Mode of delivery in group B

In group A 44% delivered vaginally and 56% delivered by caesarean section.
In group B 61.3% delivered vaginally and 38.7% delivered by caesarean section

J. Induction among cases and controls

Table 6: Induction among cases and controls

	Group A		Group B	
Induced/not	**Frequency**	**Percent**	**Frequency**	**Percent**
NO	65	86.7	72	96
YES	10	13.3	3	4
Total	75	100	75	100

In group A 13.3% were induced and in Group B only 4% were induced.

K. Indication of cs among cases and controls

Table 7: Indication of cs among cases and controls

		GROUPS		Total
		Group A	Group B	
INDICATIONS	Abruptio placenta	0	4	4
	Anhydramnios	1	0	1
	Antepartum eclampsia	1	0	1
	Breech, oligamnios	3	0	3
	Category C covid pneumonia	0	1	1
	Cord prolapse	2	0	2
	Dcda twins,1st twin breech	5	0	5
	Eisenmengers syndrome	1	0	1
	Elderly primi, type 2 placenta previa	2	0	2
	HELLP syndrome	1	2	3
	Placenta previa	3	4	7
	Previous cs	8	17	25

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	Severe pre-eclampsia	7	0	7
	Impending eclampsia	1	0	1
	Partial HELLP	1	0	1
	FGR,Abnormal doppler	4	1	5
	FGR, Chronic kidney disease	1	0	0
	Long period of infertility, FGR	1	0	1
Total		42	29	71
		59.20%	40.80%	100.00%

Maximum number of preterm CS was done in previous CS patients(35.2% of total 71 caesarean sections)

L. Gestational age at birth among both groups

Table 8: Comparison of gestational age at birth

		GROUPS		Total
		Group A	Group B	
GA	28-29 WEEKS 6 DAYS	12	24	36
		33.3%	66.7%	100.0%
	30-32 WEEKS	63	51	114
		55.3%	44.7%	100.0%
Total		75	75	150
		50.0%	50.0%	100.0%

55.3% of patients in Group A belongs to the gestational age 30-32 weeks.
44.7% of patients in Group B belongs to the gestational age 30-32 weeks

M.Sex of baby

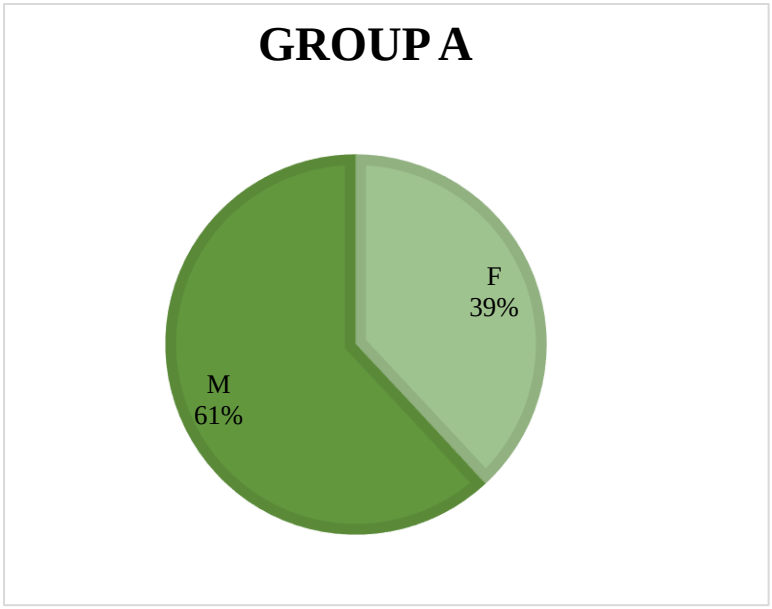

Fig. 15: Sex of baby in Group A

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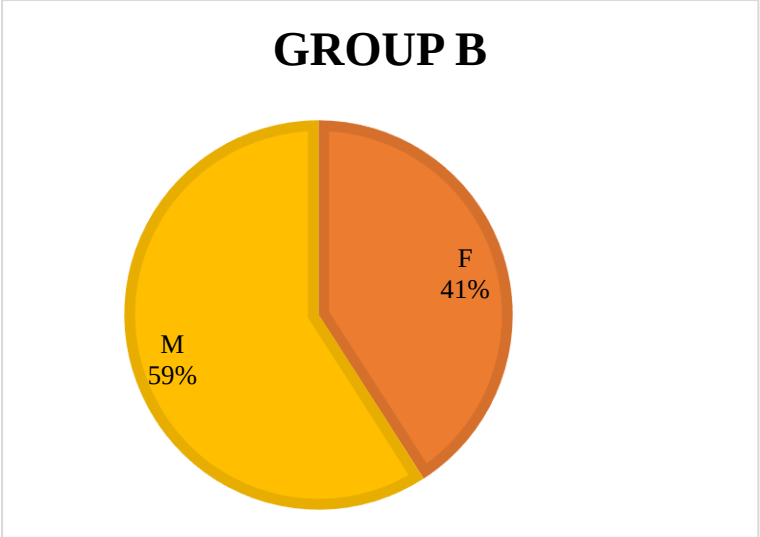

Fig. 16: Sex of baby in Group B

62% were male babies in Group A and 59% were male babies in Group B.

N. Type of birth

Table 9: Type of birth

		Type of birth		Total	P value- 0.2864 Not sgnificant
		IUD FSB	Live birth		
Groups	Group A	2	83	85	
	Group B	0	88	88	
Total		2	171	173	

2 cases of Intrauterine fetal demise were seen in Group A. The differences are not statistically significant.

O. Birth weight of baby

Table 10: Birth weight

	Groups	Less than 1000g	1000-1500g	1500-2000g	More than 2000g
Birth Weight	Group A	12	43	24	6
	Group B	10	44	39	5

Majority of babies in both groups belongs to 1500-2000grams.

P. Appropriate/Small/Large for gestational age

Table 11: Appropriate/Small/Large for gestational age

		AGA	LGA	SGA	Total
Groups	Group A	62	5	16	83
	Group B	67	8	13	88
Total		129	13	29	171

Majority of the baby weights were appropriate for gestational age in both groups.
5 babies(6%) in group A and 8 babies(9%) in group B were large for gestational age.
19% in Group A and 14% in Group B were small for gestational age.

Q. APGAR SCORE

Table 12: Comparison of APGAR score in both groups

	GROUP A	GROUP B
APGAR 1' <7	35	43
APGAR 1' >7	48	45
APGAR 5' <7	5	11
APGAR 5' >7	78	77

In Group A, 6.02% babies had APGAR <7 at 5 minutes and in Group B,12.5% babies had APGAR <7 at 5 minutes.
P Value=0.1581

R. NICU admission

Table 13: Comparison of NICU admissions in both groups

		NICU Admission		Total
		NIL	YES	
Groups	Group A	0	83	83
	Group B	0	88	88
Total		0	171	171

All patients were admitted to our NICU, since all babies were under 32 weeks of gestational age.

S. Duration of stay in NICU

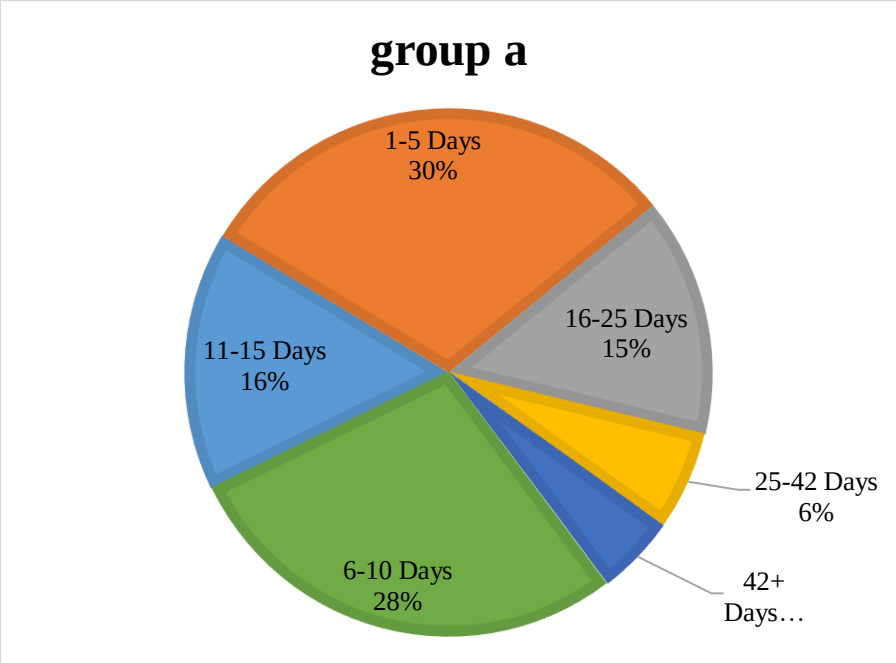

Fig. 17: Duration of stay in NICU in Group A

Mean duration of NICU stay in group A= 14.1 days

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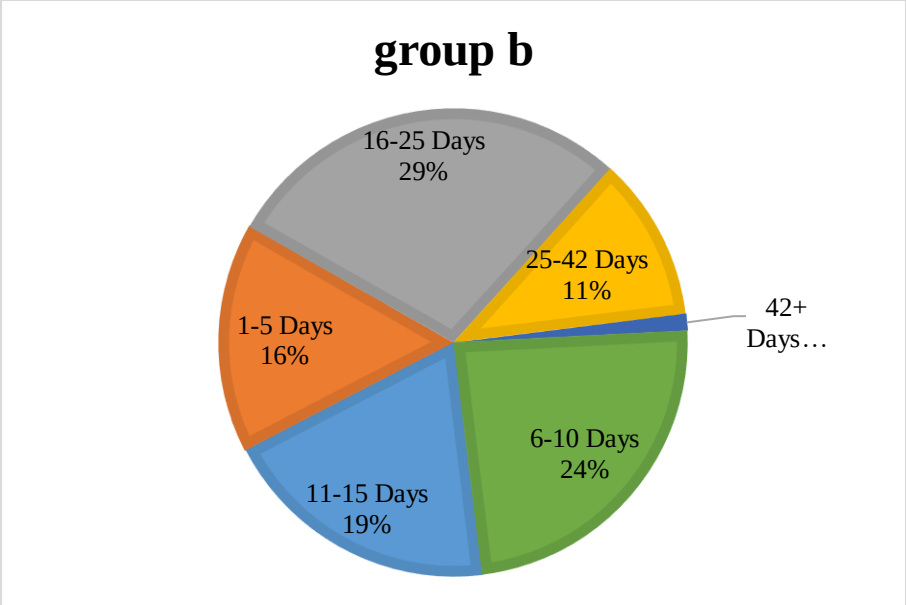

Fig. 18: Duration of stay in NICU in Group B

Mean duration of NICU stay in group B=14.9 days
The NICU stay is same in both groups

T. Neonatal morbidity

The intrauterine fetal demise cases were excluded.

Table 14: Comparison of total neonatal morbidity

		NEONATAL MORBIDITY		Total		
		PRESENT	NIL		P value	Relative risk
Groups	Group A	68	15	83		
	Group B	83	5	88	0.014	0.86
Total		151	20	171		

The group B had higher incidence of neonatal morbidity compared to the group A. The Relative risk among Group A [MgSO4 group] to have neonatal morbidity was found to be 0.86 times [reduced] than that of Group B. p value is 0.014,which is statistically significant.

Table 15: Comparison of neonatal morbidity and significance

Neonatal morbidity	Group A	Group B	P value
Respiratory distress needed ventillator	6	18	0.04 [significant]
Respiratory distress needed CPAP	40	51	0.2
Neonatal seizures	1	4	0.2
Neonatal sepsis	6	7	0.8
Necrotizing enterocolitis	3	13	0.02 (significant)
IVH	3	4	0.7
Moderate HIE	1	0	0.4
Severe HIE	0	1	0.5
ASD	0	3	0.2
PDA	1	4	0.22

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DIC	1	1	0.9
Neonatal shock	1	2	0.6
Neonatal depression	1	0	0.4
Intrinsic AKI	1	0	0.4
Prerenal AKI	0	2	0.3
Neonatal hyperbilirubinemia	20	22	0.8
Brain abscess communicating hydrocephalus	0	1	0.5
Transient tachypnea of newborn	0	4	0.14
Pneumothorax	1	6	0.1
Anemia of prematurity	1	0	0.4

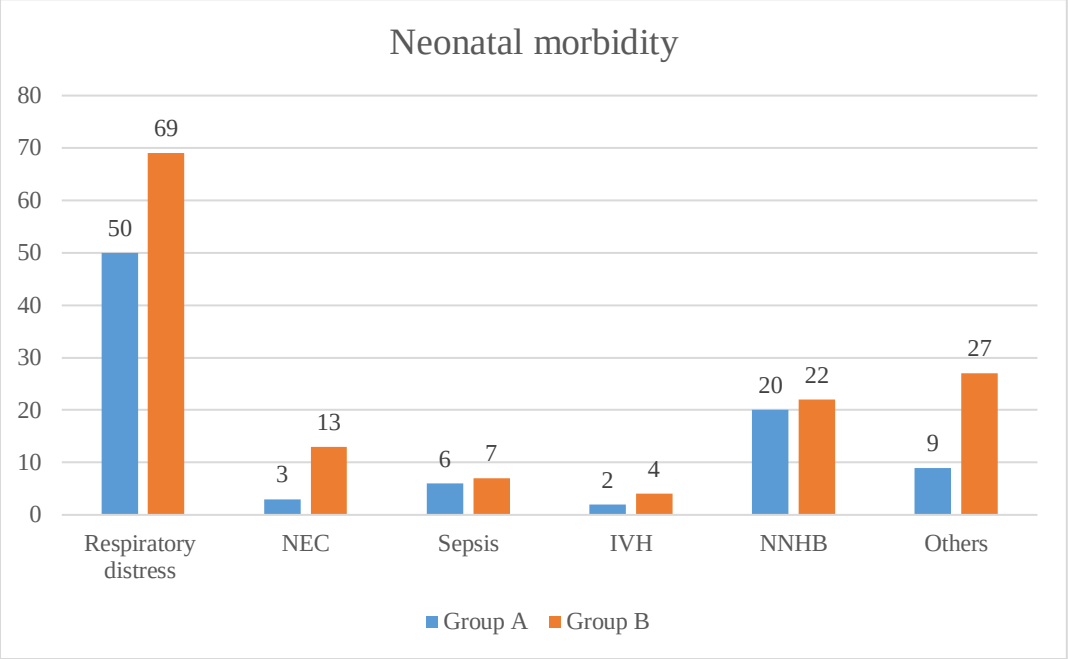

Fig. 19: Comparison of neonatal morbidity

The incidence of respiratory distress needing mechanical ventillation is decreased significantly in Group A while compared with Group B.

The incidence of necrotizing enterocolitis, is significantly decreased in Group A while compared with Group B.

The incidence of IVH is reduced in Group A(3.6%) when compared to group B(4.5%), but not significant statistically.

U. Cause of neonatal death

5 neonatal deaths occurred in Group A.

Table 16: Cause of neonatal death in group A

Cause of neonatal death in group A	
IVH	1
Neonatal depression, IVH, RDS	1
Neonatal sepsis, RDS	1
Neonatal shock,Pulmonary hemorrhage,DIC, RDS	1
Pneumothorax	1

11 neonatal deaths occurred in Group B

Table 17: Cause of neonatal death in group B

Cause of death of NND in group B	
IVH,RDS	2
Severe HIE,RDS	3
Neonatal shock	1
Pneumothorax, RDS	2
Pulmonary hemorrhage,RDS	3

V. Residual neonatal morbidity

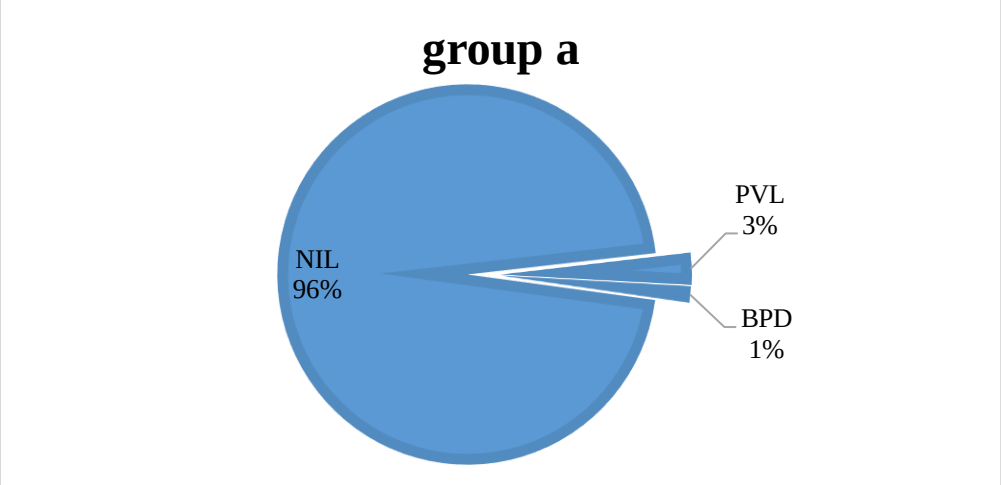

Fig. 20: Residual neonatal morbidity in Group A

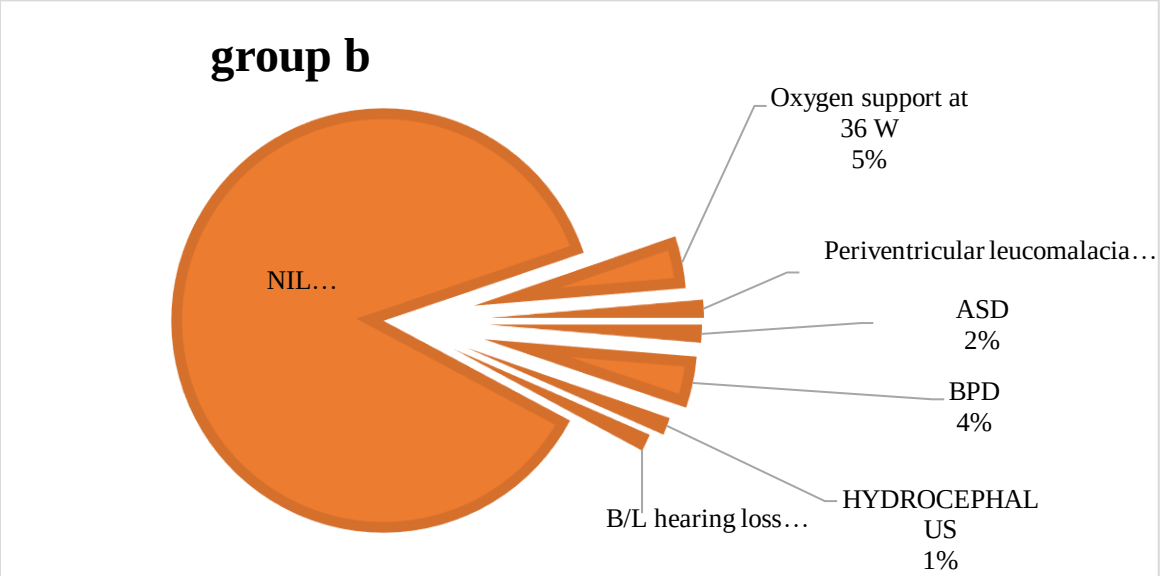

Fig. 21: Residual neonatal morbidity in Group B

75 babies in Group A (Total 78) did not had any residual neonatal morbidity compared to 68 in Group B(Total 77).

Relative risk of residual neonatal morbidity in Group A is 0.3291times [reduced] that of Group B, p value = 0.08(not statistically significant).

Number needed to be treated to benefit 1 baby= 12

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W.Screening based on Trivandrum Developmental Screening Chart at 6 weeks

Table 18: Comparison of screening at 6weeks

		TDSC at 6weeks		Total	p-value-0.4
		Negative	Positive		
Groups	Group A	78	0	78	
	Group B	76	1	77	
Total		154	1	155	

Table 19: Comparison of type of developmental delay at 6 weeks

		Developmental delay at 6 weeks		
		NIL	Bilateral Hearing loss	Total
Groups	Group A	78	0	78
	Group B	76	1	77
Total		154	1	155

The control group had 1child screened positive for developmental delay compared to none in the MgSO4 group,but not statistically significant. [P value=0.4]

Relative risk is 0.3291 , Number Needed to Treat to benefit 1 baby is 77.

X. Screening based on Trivandrum Developmental Screening Chart at 6 months

All the children were followed up at 6 months and screened.

Table 20: Comparison of screening at 6 months

		TDSC at 6months		Total	P value-0.070
		Developmental delay-positive	NIL		
	Group A	2	76	78	
Groups	Group B	8	69	77	
Total		10	145	155	

Table 21: Comparison of type of developmental delay at 6 months

		Type of developmental delay at 6 months				
			Bilateral hearing loss	Gross Motor Delay	Neurological Disability [Hypotonia]	**Total**
	Group A	76	0	1	1	78
Groups	Group B	69	1	5	2	77
Total		145	1	6	3	155

Group B had higher number of children screened positive for developmental delay than Group A by TDSC at 6 months. Relative Risk is 0.2468 ,p value is 0.070[not significant statistically]

Number Needed to Treat = 12.7 for one infant to benefit

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Y. Screening based on Trivandrum Developmental Screening Chart at corrected age of 1 year

4 babies in Group A were lost to follow up, 6 babies from Group B lost to follow up.

Table 22: Comparison of screening at corrected age of 1 year

		TDSC at corrected age of 1 year		**Total**	p value-0.0699
		Developmental delay-positive	NIL		
	Group A	2	70	74	
Groups	Group B	8	63	71	
Total		10	138	145	

Table 23: Comparison of type of developmental delay at 1 year

		Developmental delay at 1 year				**Total**
		Nil	Bilateral Hearing loss	Gross Motor Delay	Cerebral palsy	
Groups	Group A	72	0	1	1	74
	Group B	63	1	5	2	71
Total		135	1	6	3	145

Group B had 8 children screened positive for developmental delay while Group A had 2 children screened positive by TDSC at corrected age of 1 year.p value-0.0647, which is not significant statistically.

Relative Risk is 0.2399 , Number Needed to Treat [NNT] for 1 baby to benefit = 11.6

The incidence of cerebral palsy in Group A is 1.3% and in Group B is 2.8%. However the difference is not statistically significant(P value=0.55)

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CHAPTER SIX

DISCUSSION

A. Age distribution

In Group A majority [41%] of the mothers belonged to the age group of 20-25 years. But in Group B majority[41%] of the mothers belonged to the age group of less than 20 years. 1% of the mothers were above the age of 40 in Group A and 4% were above 40 years in Group B.

Compared to women in their mid-twenties to early forties, preterm birth rates are higher among teenagers and older mothers, according to previous studies [96]. Although low socioeconomic position, extreme body mass index, and may be common preterm birth risk factors for both teen and older moms, physiologic immaturity is a risk factor for teen mothers, and the prevalence of preexisting chronic disease is higher among older mothers[97].

B. Obstetric score

52% of the mothers were primi gravidas and 48% were multi gravidas in Group A. 47% of the mothers were primi gravidas and 53% were multi gravidas in Group B.

Koullali et al (2020)[98] found an increased risk of preterm birth in nulliparous women and also in fifth gravidas compared to second gravidas.

C. Singleton/Multiple pregnancy

13% of the women had multiple pregnancy in Group A and 17% of the women in Group B had multiple pregnancy.

According to Kurdi et al [99] preterm labour in multiple pregnancy was 7 times greater than singletons[42% versus 6.4%]

D. History of preterm birth

16% of patients had the history of prior preterm birth in Group A

10.7% of patients had the history of preterm birth in Group B.

The incidence of history prior preterm birth in this study is 13.33%.

According to Iams et al[100], women having a history of preterm delivery were more likely to give birth prematurely, although the gestational age at the time of the most recent preterm birth had no impact on this risk.

E. Interval between completion of magnesium sulphate and delivery

Among the 53 patients who completed the magnesium sulphate regime, 40 hours was the median duration between the time of completion and delivery. In the PREMAG trial by Marret et al, no significant difference obtained between interval from infusion to delivery in MgSO4 and placebo group.(P=0.21)

F. Gestational age at birth

The gestational age at birth in this study is between 28-32 weeks.

In Group A, 33.3% belongs to 28-29weeks and 6 days and 55.3% belongs to 30-32 weeks. In Group B,66.7% belongs to 28-29 weeks and 6 days and 44.7% belongs to 30-32 weeks. There is almost twice the number of babies born in geststional age less than 30 weeks in the Group B compared to Group A,which may result in more unfavourable outcomes in the Group B compared to Group A.

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In PREMAG trial, gestational age at birth ranged from 24 weeks 1 day to 32 weeks 6 days in MgSO4 group and 23 weeks 4 days to 32 weeks 6 days in the placebo group.

The difference is not statistically significant.

G. Mode of delivery

In group A 44% delivered vaginally and 56% delivered by caesarean section. In group B 61.3% delivered vaginally and 38.7% delivered by caesarean section.

Among the 71 caesarean sections done in this study, 59.2% were in Group A and 40.8% were in Group B.

Incidence of vaginal delivery is 52.6% and incidence of caesarean section is 47.33% in this study.

In PREMAG trial, 40.6% caesarean section in magnesium sulphate group and 34.7% caesarean sections in the placebo group.

H. Inductions

13.3% of the cases were induced in Group A and 4% cases were induced in Group B.Incidence of induction in this study is 8.66%. the incidence of severe preeclampsia in this study is 9.33% which contributed to the medically induced preterm births and also cause unfavourable intrauterine environment for the fetus in terms of placental insufficiency, which results in the adverse fetal outcome.

I. Indication for preterm caesarean section

In Group A, 24 caesarean sections were done for maternal indications and 17 caesarean sections were done for fetal indications.

In group B, 18 caesarean sections were done for maternal indications and 7 cases were done for fetal indications.

In the study done by Hogberg et al[101], in extremely preterm to describe the indications for caesarean section for extremely preterm delivery, six out of ten caesarean sections were performed on fetal indication.

J. Sex of baby

62% were male babies in Group A and 59% were male babies in Group B.

Incidence of male babies in this study is 60.11%.

In PREMAG trial, 55.4% were male babies in the MgSO4 group and 58.9% male babies in the placebo group. P value was 0.46.

Astolfi and Zonta [102] observed an excess of males among preterm compared to term babies in their study.

K. Intrauterine death

2 babies in Group A died intrauterine, which may be due to the severe fetal growth restriction in first case(birth weight 850g) and chorioamnionitis in the second case.

The differences are not statistically significant. P value is 0.2864.

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L. Birth weight of baby

Mean birth weight of babies in Group A is 1393.6 grams and in Group B it is 1429.17 grams with standard deviations 376.898 and 369.184 in Group A and Group B respectively.

In PREMAG trial the average birth weight in MgSO4 group was 1350grams and in placebo group it was 1415 grams.P value-0.45

M.APGAR score

In Group A, 6.02% babies had APGAR <7 at 5 minutes and in Group B,12.5% babies had APGAR <7 at 5 minutes,but not significant statistically.

In PREMAG trial, APGAR <7 in 12.8% in MgSO4 group and 9.2% in the placebo group.

According to meta-analysis by Crowther et al, no statistically significant differences seen in APGAR score at 5 minutes < 7.

N. NICU admission

All babies in our study were admitted in NICU,as our institutional guidelines suggests admission for all babies less than 32 weeks.

De Silva et al, in their study found that in Canada before the national guidelines to implement magnesium sulphate for neuroprotection, the admission to NICU was 82% and after the implementation of the guidelines it reduced to 77.2%, P value was <0.001

O. NICU stay

Both groups had similar mean duration of stay in this study.

P. Neonatal morbidity

55.4% of the live babies had respiratory distress in Group A and 78.4% had respiratory distress among Group B. Relative risk is 0.7068 and p value is 0.0022, which is statistically significant.

In PREMAG trial, 42% had respiratory distress among the MgSO4 group and 37.8% in the placebo group.P value=0.43.

In this study,3 babies had necrotizing enterocolitis [NEC] among the Group A, but 13 babies had NEC in the Group B. Relative risk is 0.0383 and P value is 0.02, which is statistically significant.

In PREMAG trial 2.6% had necrotizing enterocolitis in MgSO4 group and 1.9% in the placebo group.P value=0.50.

In this study, neonatal seizures seen in 1 case in Group A and 4 cases in Group B. P value 0.2, not significant.

In PREMAG trial, 2.1% in the MgSO4 group and 2.9% in the placebo group had neonatal seizures .P value=0.50.

According to metaanalysis conducted by Crowther et al, no statistically significant differences or any significant heterogeneity were seen in any of the analyses for the other neonatal morbidity outcomes reported or defined by the trialists, including use of ongoing respiratory support after birth, any intraventricular haemorrhage (IVH), severe IVH (grade 3 or 4), cystic periventricular leucomalacia (PVL), neonatal convulsions, neonatal encephalopathy, chronic lung disease/bronchopulmonary dysplasia (BPD), post haemorrhagic hydrocephalus or ventriculomegaly, proven systemic infection, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA) requiring treatment, any retinopathy of prematurity (ROP)

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Q. Neonatal death

5 neonatal deaths occurred in Group A.11 neonatal death happened among Group B. Neonatal mortality in this study is 6% in Group A and 12.5% in Group B.

Relative risk of 0.48 is obtained in the study.Number needed to treat=15.

P value=0.1581.Hence no statistically significant difference in mortality between the 2 groups.

Out of the total 11 neonatal deaths in Group B, 27% of the babies belongs to less than 30 weeks gestational age.In Group A , out of the total 5 neonatal deaths,40% belongs to less than 30 weeks gestational age.

In the meta analysis performed by Crowther et al, there was a statistically significant decrease in the risk of mortality or cerebral palsy in the prespecified sensitivity analysis of the four trials[ACTOMgSO4, PREMAG, MAGNET, BEAM trials] with fetal neuroprotective purpose, with no significant heterogeneity (p = 0.28). In order to prevent 1 infant from either dying or developing cerebral palsy, 41 women and babies were required for the treatment to be beneficial.

R. Residual neonatal morbidity

In this study,none of the cases in Group A needed oxygen support at 36 weeks,but in Group B, 3 cases (3.8%) needed oxygen support at 36 weeks.

P value=0.19,hence not significant statistically.

The incidence of periventricular leucomalacia in Group A was 1.2% and the incidence in Group B was 2.5%. P value =0.5, not statistically significant.

In PREMAG trial , 8.4% needed Oxygen support at 36 weeks among MgSO4 group and 10% among the placebo group.

In this study, the total residual neonatal morbidity is 3.8% in Group A and 11.6% in Group B.P value=0.08. Hence statistically not significant.

S. Total mortality

In this study,in utero 2 babies died in Group A, P value=0.2.

Postnatal mortality in this study is 6% in Group A and 12.5% in Group B.P value=0.1581.

Hence no statistically significant difference in mortality between the 2 groups.

In PREMAG trial also there was no significant difference in mortality in the two groups.

T. Screening based on Trivandrum Developmental Screening Chart at 6 weeks

Group B had 1 child screened positive for developmental delay using the TDSC at 6weeks compared to none in Group A.

Relative risk is 0.3291. Number needed to treat is 77.

But P value is 0.4.

Hence it is not statistically significant.

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U. Screening based on Trivandrum Developmental Screening Chart at 6 months

Group B had higher number of children screened positive for developmental delay than Group A by TDSC at 6 months.

Relative Risk is 0.2468 , Number Needed to Treat = 12.7 for one infant to benefit.

P value is 0.07. Hence statistically not significant.

Gross motor delay in Group A was seen in a baby born at 29 weeks of gestational age. Hypotonia was detected in a baby who had neonatal seizures,moderate HIE and periventricular leucomalacia, in Group A

V. Screening based on Trivandrum Developmental Screening Chart at 6 months at corrected age of 1 year

4 babies in Group A were lost to follow up, 6 babies from Group B lost to follow up.. Group B had 8 children screened positive for developmental delay while Group A had 2 children screened positive by TDSC at corrected age of 1 year(p value-0.0647), which is not significant statistically.

The incidence of gross motor delay is 1.3% in group A and 7% in Group B, P value is 0.12.

The incidence of cerebral palsy in Group A is 1.3% and in Group B is 2.8%. However the difference is not statistically significant(P value=0.55).

Gross motor delay in Group A was seen in a baby born at 29 weeks of gestational age. Cerebral palsy was detected in a baby who had neonatal seizures, moderate HIE and periventricular leucomalacia, in Group A, who had hypotonia at the 6 months screening.

In Group B ,2 babies had cerebral palsy,both of them were born after 30 completed weeks of gestation.One of them had intraventricular hemorrhage and seizures in the neonatal period.Other baby had prerenal AKI.

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CHAPTER SEVEN

SUMMARY

- 12.5% babies in Group B and 6.02% babies in Group A had APGAR <7 at 5 minutes, but the difference is not statistically significant. P value=0.581
- 78.4% had respiratory distress among Group B while only 55.4% of the live babies had respiratory distress in Group A ,which is statistically significant.P value=0.43
- 3.6% of the babies had necrotizing enterocolitis [NEC] among the Group A, but 14.7% of cases had NEC in the Group B. The difference is statistically significant.P value=0.02
- Neonatal seizures seen in 1.2% in Group A and 4.5% in Group B,which is not statistically significant.P value=0.2
- None of the cases in Group A needed oxygen support at 36 weeks,but in Group B, 3.8% needed oxygen support at 36 weeks, but not significant statistically P value=.0.19
- The incidence of periventricular leucomalacia[PVL] is 1.2% in Group A and 2.5% in Group B, but the differences are not statistically significant.P value=0.5
- The incidence of IVH is reduced in Group A(3.6%) when compared to group B(4.5%), but not significant statistically.P value=0.7
- The incidence of bronchopulmonary dysplasia is reduced in Group A (1.2%) compared to Group B(3.8%), but no statistical significance.P value=0.3
- The total residual neonatal morbidity is 3.8% in Group A and 11.6% in Group B, but statistically not significant.P value=0.08
- 2 babies in Group A died intrauterine, which may be due to the severe fetal growth restriction in first case (birth weight 850g) and chorioamnionitis in the second case. The differences are not statistically significant.P value=0.2
- Out of the total 11 neonatal deaths in Group B, 27% of the babies belongs to less than 30 weeks gestational age.In Group A , out of the total 5 neonatal deaths,40% belongs to less than 30 weeks gestational age.
- Neonatal mortality in this study is 6% in Group A and 12.5% in Group B,but not significant statistically.P value=0.1581
- 31.25% of the neonatal deaths were seen in babies under the gestational age at birth less than 30 weeks.
- Group B had 1 child screened positive for developmental delay using the TDSC at 6weeks compared to Group A, but not statistically significant.P value=0.4
- Group B had higher number of children screened positive for developmental delay than Group A by TDSC at 6 months but statistically not significant.P value=0.07
- Group B had higher number of children screened positive for developmental delay than Group A by TDSC at corrected age of 1 year but statistically not significant.P value=0.06
- The incidence of deafness is 1.4% in Group B while compared to no cases in Group A,but the differences are not statistically significant.P value=0.4
- The incidence of cerebral palsy is 1.3% in Group A and 2.8% in Group B, vut the differences are not significant statistically.P value=0.55
- The 3 children in this study who had cerebral palsy were born after 30 completed weeks of gestational age.
- The combined death or cerebral palsy is reduced in the Group A(8.1%) ,while compared to Group B(18.3%) ,but the differences are not significant statistically.P value=0.1
- The incidence of gross motor delay is 1.3% in group A and 7% in Group B,but the differences are not statistically significant.P value=0.12.

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CHAPTER EIGHT

LIMITATIONS

The limitations of this study includes smaller size of population.with increasing size of study population, statistical significance of the outcomes could have been analysed to accuracy.

However the study benefited our study population, by having a comparatively better neonatal outcome.

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CHAPTER NINE

CONCLUSION

Magnesium sulphate for fetal neuroprotection is found to reduce the incidence of neonatal mortality,total neonatal morbidity and neurological disabilities but there is no statistical significance. However, significant reduction is seen in the respiratory distress and necrotizing enterocolitis in the neuroprotection group. Thus concluding there is definitely a role of magnesium sulphate clinically, in having a favourable neonatal outcome, although statistically insignificant.

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CHAPTER TEN

FUTURE RECOMMENDATIONS

The incidence severe preeclampsia in this study was 9.33 %, which contributed to the medically induced preterm births. Hence there is a role in the early severe preeclampsia screening in our population and the use of prophylactic use of aspirin.

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ANNEXURES

CONSENT

I confirm that I have freely agreed to participate in the observational study conducted by Dr. Rakhi J Mohan, Junior Resident, Department of Obstetrics and Gynaecology, Calicut Medical College entitled "THE EFFECT OF ANTENATAL MAGNESIUM SULPHATE FOR FETAL NEUROPROTECTION IN PRETERM LABOUR- A PROSPECTIVE COHORT STUDY"

I agree to cooperate with the study and provide necessary informations and investigations for the same under the following conditions.

The details disclosed by me for the study will not be misused and not used in ways which can be detrimental to me.

I don't have any financial burden in participating in the study. I may withdraw and discontinue participation at any stage of the study without penalty.

Participation in the study will not affect the services entitled to me. Study does not include any procedures harmful to my health. I have read and understood the above information. I consent to participate in the study.

Signature:
Name of the patient:
Signature
Name of the relative :
Address:

Principal Investigator: Dr. Rakhi J Mohan
Department of Obstetrics and Gynaecology, Calicut Medical College.
Signature:

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LIST OF ABBREVIATIONS

MgSO4	- Magnesium sulphate
PPROM	-Preterm premature rupture of membranes
CP	- Cerebral Palsy
RDS	- Respiratory Distress Syndrome
NMDA receptor	- N-Methyl D -Aspartic acid receptor
E. coli	-Escherichia Coli
TLR	-Toll like receptors
mRNA	-microsomal RNA
MMP	-Matrix Metallo Proteinases
IVF	-In Vitro Fertilization
PROM	-Premature rupture of membranes
FFN	-Fetal Fibronectin
IGFBP-1	-Insulin like Growth Factor Receptor Binding Protein-1
BPD	-Broncho pulmonary Dysplasia
TGF	-Transforming Growth Factor
IVH	-Intra ventricular hemorrhage
VEGF	-Vasculo endothelial Growth Factor
NEC	-Necrotizing Enterocolitis
PVL	-Periventricular leukomalacia
OL	-Oligodendroglial
TDSC	-Trivandrum Developmental Sreening Chart
HIE	-Hypoxic ischemic encephalopathy
ASD	-Atrial septal defect
PDA	-Patent ductus arteriosus
DIC	-Disseminated intravascular coagulation
AKI	-Acute kidney injury
NNT	-Number needed to treat
NICU	-Neonatal Intensive Care Unit