"EFFECTIVENESS OF ANTENATAL CORTICOSTEROIDS IN REDUCING PERINATAL MORBIDITY AND MORTALITY IN LATE PRETERM BIRTHS-A RANDOMIZED CONTROL TRIAL"

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LIST OF ABBREVIATIONS USED

ACOG	-	American College of Obstetrics and Gynecology.
CI	-	Confidence Interval.
HIV	-	Human Immunodeficiency Virus.
HbsAg	-	Hepatitis b Surface Antigen.
HDP	-	Hypertensive disorders of pregnancy.
IVH	-	Intraventricular Haemorrhage.
IUGR	-	Intra Uterine Growth restriction.
LBW	-	Low Birth Weight.
LNMP	-	Last Normal Menstrual period.
NEC	-	Necrotizing Enterocolitis.
NICU	-	Neonatal Intensive Care Unit.
PDA	-	Patent Ductus Arteriosus
PPROM	-	Premature Prelabour Rupture of Membranes.
RDS	-	Respiratory Distress Syndrome.
RR	-	Relative Risk.
RCT	-	Randomized Controlled Trial.
RCOG	-	Royal College of Obstetrics and Gynaecology.
SNOSE	-	Sequentially Numbered Opaque Sealed Envelopes.
TTN	-	Transient Tachypnea of Newborn.
VLBW	-	Very Low Birth weight.
WHO	-	World Health Organization.

ABSTRACT

Introduction: Antenatal corticosteroids are simple,cheap,effective ,safe and an acceptable intervention whose efficacy is known since 1972 ,the time when Howie and Liggins demonstrated its effect on fetal lung maturity. In 1994 NIH concluded that antenatal corticosteroids should be used from 24-34 weeks of period of gestation in cases of preterm delivery to reduce the rate of respiratory distress.Currently there is no clear cut consensus regarding its use in late preterm. To find if a possible extension of its beneficial effects extends beyond 34 weeks is the aim of this study. Patients who do not have access to tertiary care centre and deliver in this period can benefit from this intervention thus reducing a considerable load on health care.

Objective: The objective of this prospective randomized trial is to determine the

effectiveness of antenatal corticosteroids in reducing perinatal morbidity and mortality in late preterm births(34-36 weeks of gestation with risk of imminent premature delivery).

Methodology:

Design: A Prospective Randomized Controlled Trial.

Setting: KLE University's Dr. Prabhakar Kore Hospital and Medical Research Center, Attached to Jawahar Lal Medical College, Belgavi.

Subjects: 200 patients who were consenting and fulfilling the inclusion criteria were randomized.105 patients were randomized in group A and 95 in group B.11 patients were excluded as 9 patients in group A delivered before 24 hours of administration of 1st dose of steroid,1 patient in group B had antepartum haemorrhage after

randomization and another 1 patient in group B went against medical advice..Finally,96 patients were analyzed in group A and 93 in group B.

Intervention: Cases were randomized into 2 groups by SNOSE method of Randomization. Those enrolled in Group A (n=96) were given Inj. Betamethasone 12mg i.m. 2 doses 24 hour apart. Those enrolled in Group B (n=93) were not given steroids. All the data pertaining to administration time and date of steroids, interval between administration and delivery, mode of delivery, intrapartum events and if a caesarean section was done then its indication, was documented and recorded . After delivery all neonates were assessed for the following outcomes-Perinatal mortality,Gestational age at birth,Birth weight in kgs,Apgar score At 1 and 5 minutes ,Admission to NICU and indication of NICU admission which included respiratory distress syndrome,transient tachypnoea of newborn,pneumonia,requirement of phototherapy,sepsis in the first 48 hours of life and duration of stay in NICU.

Results: The mean maternal age and gestational age at enrollment was comparable in both the groups.There was a significant difference p=0.023 in parity with 54.17% being primigravida and 45.83% being multigravida in steroid group as compared to 37.63% being primigravida and 62.37 % being multigravida in nonsteroid group.

There was no perinatal mortality in both the groups. The gestational age at delivery was comparable in both the groups with mean gestational age being 35.375±0.85 in steroid group vs 35.00±0.83 in nonsteroid group.p=0.363. Mean birth weight was 2.28 ±0.63 kg being in steroid group and 2.24±0.55kg in nonsteroid group(p=0.6888).Apgar score at 1 minute was comparable in both the groups with Apgar score<7 being in 59.38% in steroid group and in 61.29% in nonsteroid group.

(p=0.452). Apgar score <7 at 5 minutes was present in 26.04% of patients in steroid group and 33.33% in nonsteroid group.(p=0.272).

No statistically significant difference was found in rate of RDS with 8.33% being in steroid group and 7.53% being in nonsteroid group. (p=0.838).19.79% of patients had TTN when compared to 24.73% in nonsteroid grout(p=0.485).No cases of pneumonia were found in either group.The requirement of phototherapy was present in 34.38% of neonates in steroid group and 32.28% of neonates in nonsteroid group(p=0.875).Systemic infections in the first 48 hours were acquired by 12.50% of neonates in steroid group and 9.68% of neonates in nonsteroid group. (p=0.537) . Mean stay in NICU was 6.80±3.67 days in the steroid group as compared to 8.80±4.88 days in the nonsteroid group which was statistically significant with p=0.031

Conclusion: Antenatal corticosteroid administration are cost effective ,simple, acceptable ,safe intervention to prevent perinatal morbidity and mortality in preterm babies.But a possible extension of this benefit in late preterm was the objective of our study and was evaluated.

There is no significant difference between the gestational age at delivery, birth weight and Apgar score in the neonates who had received steroid than who did not receive steroid and delivered in late preterm.

Rate of NICU admission and indication of admission including respiratory distress syndrome, transient tachypnoea of newborn, pneumonia, requirement of phototherapy ,sepsis in first 48 hours and duration of stay in NICU were assessed and no statistical

significance was found between the group receiving steroid and the group not receiving steroid except in the duration of stay in NICU.

Thus it is concluded that antenatal corticosteroid administration ,did not reduce the rate of perinatal morbidity and mortality except the mean duration of stay in NICU,

in women admitted in late preterm gestation and at risk of imminent premature delivery

Key words: Late preterm neonates, Respiratory distress syndrome,Transient tachypnoea of newborn, phototherapy, neonatal outcome.

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

Preterm births account for 10-15% of all births globally. Preterm births refer to all the births occuring between 20 weeks to 37 weeks. This classification includes very preterm (<32 weeks),moderately preterm (32-0/7 to 33-6/7 weeks) and the late preterm births (34-0/7 to 36-6/7 weeks)[1]. Late preterm births are the fastest growing population among these accounting for 75% of all the preterm births and about 8% of the total births[2]. The 2005 workshop on "Optimizing Care and Outcome of the Near-term pregnancy and the Near –Term Newborn Infant " by National Institute of Health recommended that infants born at 34-0/7 through 36-6/7 weeks gestation after the onset of the mothers last menstrual period be referred to as late preterm to emphasize that these infants are preterm and at risk of immaturity related complications than being considered as safe as term infants[3]. Late preterm births have not been studied frequently, their developmental biology and functioning of systems are not yet understood completely. Management strategies for these babies are based on general principles , clinical experience and extrapolation from our knowledge of very preterm and term babies.

Preterm births have been on a drastic rise for many reasons including demographic changes, infertility treatment, increase in maternal age, increasing incidence of multiple pregnancies and increasing rate of caesarean delivery (30.3%), labour induction (22.3%). The late preterm births has risen 25-30% since 1990. [4]

The distribution of preterm births subtypes have been categorized into 2 groups.

1) Indicated or iatrogenic due to adverse maternal or fetal condition being 25%[5]. The most common etiology being pregnancy induced hypertension (40%), 4-6% in women with gestational hypertension and 10-11% in women with pre eclampsia, nonreassuring fetal testing(25%) ,IUGR(10%) ,antepartum haemorrhage (7%),and fetal death (7%)[7,8].
2) Spontaneous preterm births being 75%[5].Of these , 60% are the result of preterm labour and 40% are due to PPROM[6] .

The ACOG Committee on Obstetric Practice -The Society for Maternal-Fetal Medicine states that patients with placenta previa with suspected accreta, increta,or percreta should be delivered in the late preterm period as the risk of antepartum haemorrhage is 4.7% at 35 weeks, 15% at 36 weeks and 30% at 37 weeks. Patients with prior classical cesarean,Dichorionic-diamniotic twins with concurrent condition like abnormal Doppler and maternal comorbidities (chronic hypertension ,preeclampsia etc.) should also be delivered between 34 to 36 completed weeks. Monochorionic–Diamniotic twins with isolated fetal growth restriction also need to be delivered in late preterm, as chances of TTTS is 3-4% and fetal death rate rises by 1-2% per week after 32 weeks in monochorionic gestations.Patients with severe pre-eclampsia, pre-gestational well controlled diabetes and PPROM also need to be delivered between 34 to 36 completed weeks[9].

Contrary to our belief that late preterm babies fare well like term babies they are at very high risk of immaturity related complications. Rate of RDS varies between 15-25% in these neonates ,even with mature fetal lung indices, risk of RDS is as high as 10%[1]. A study done by David F. Lewis et al. in California states that risk of HMD during 34 weeks of gestation is 14.9% and demonstrated positive phosphatidylglcerol

rates of 22%, 35% and 43% at 34,35 and 36 weeks of gestation[10].A study done by Escobar et al . states that 8% of late preterm neonates requires supplemental oxygen support which was 3 times as compared to term infants, mortality rate being 0.8%[11]. Wang and Colleague found that 30% of late preterm had clinical evidence of respiratory distress and one third of them required prolonged hospital stay[12].The incidence of apnea in late preterm infants is reported to be 4-7% due to increased susceptibility to hypoxic respiratory depression, decreased central chemosensitivity to carbon dioxide, immature pulmonary irritant receptor, decreased upper airway dilator tone muscle[3].

At 34 weeks , the brain only weighs 65% of the term brain weight. Gray matter volume increases throughout gestation at a rate of 1.4% or 22ml/wk having a rapid growth between 36-40 weeks because of neuronal differentiation and gyral formation. 25% of the cerebellar volume develops after late preterm. In this period myelinated white matter to total brain volume increases exponentially. Thus the time period between 34 and 40 weeks is very critical. Infants born in late preterm are at 3 times more risk than term infants to develop cerebral palsy and cognitive delays. Periventricular leukomalacia, a predictor of adverse neurological outcome, affects approximately 3-4% of infants weighing less than 1500gm [13]. Gray and Associates reported a 19-20% prevelance of behaviour problems at age 8 in infants born between 35-37 weeks[14].There is 20% prevelance of hyperactivity,behavioural,or emotional problems in late preterm period[15,16].

Late preterm infants have a higher risk of developing hyperbilirubinemia and its sequelae than term infants due to immaturity of conjugation and enzymatic pathway, immature feeding pattern, age dependent susceptibility of developing

neurons and astrocytes to bilirubin induced injury. They have 2-5 fold increased risk of developing significant hyperbilirubinemia than term infants. Late preterm infants with total serum bilirubin greater than 25mg/dl at the time of readmission were more likely to have severe neurological sequelae compared with term infant (82.7% vs 70.8%) [17]

Infants born between 34 and 35 weeks of gestation have a 9 fold increased risk for having an outcome characterized by long term morbidity and persistent use of health care resources.[18]

Oligohydramnios is found in 2.3% of pregnancies at 34-36 weeks and is associated with 1.8 folds increase in fetal heart rate decelarations, 4.5 folds increase in stillbirths and 12 fold increase in meconium aspiration syndrome.[19]

Greater special education needs among moderate and late preterm infants suggest a need to start followup , anticipatory guidance and appropriate intervention in this group[20].

There is a 23% decrease in adverse outcome with each week of gestational age between 32 and 39 weeks (relative risk 0.77). It is demonstrated that infants born between 34 0/7-34-6/7 weeks have a 7 fold increase ($p<0.001$),whereas infants born between 35 0/7 and 35 -6/7 weeks have a 3 fold increased ($p=0.012$) risk of IVH,RDS ,NEC, witnessed seizures, hypoglycaemia, need for antibiotics for sepsis (longer than 48 hours), hyperbilirubinemia requiring phototherapy and hypothermia. Thus delivery at 35 weeks is associated with 56% reduction in the above outcome[21].

Late preterm infants discharged within 48 hours of birth are 1.8 times more likely to be readmitted than term infants[22].

Potentially avoidable low preterm births account for 17% of low preterm births and are associated with mostly prior caesarean delivery (OR,1.5;95%CI,1.0-2.1)[23].

Medical interventions that can potentially improve the outcome of late preterms include the use of tocolytics to delay the delivery and the administration of corticosteroid to promote fetal lung maturation. The use of corticosteroid at 34 weeks of gestation is not recommended according to American College of Obstetrics and Gynaecology, unless there is evidence of fetal pulmonary immaturity. Royal College of Obstetrics and Gynaecology advocates administration of corticosteroid from 24-34-6/7 weeks in those who are at risk of premature birth, and upto 35-6/7 weeks in pregnancies affected by intrauterine growth restriction[24]. Stutchfield et al have reported that exposure to antenatal corticosteroids before term elective caesarean delivery was associated with decreased rate of admission to NICU with respiratory distress[25]. Cochrane database of systematic reviews 2013 states that steroid reduce the rate of RDS, IVH,NEC and should be given from 24 to 34-6/7 weeks [26]. Another study by Porto et al in 2012 in Brazil has shown that phototherapy for jaundice was required less often in babies whose mother received corticosteroid during late preterm delivery.(RR 0.63, CI 0.44-0.91)[27].

Antenatal corticosteroids are simple, cheap, effective ,safe and an acceptable intervention whose efficacy is known since 1972 ,the time when Howie and Liggins demonstrated its effect on fetal lung maturity. To find if a possible extension of its beneficial effects extends beyond 34 weeks is the aim of this study. Patients who do not have access to tertiary care centre and deliver in this period can benefit from this intervention thus reducing a considerable load on health care.

Since nearly 2/3rd increase in preterm births is due to late preterm[28] ,extensive research is required on this subject and health care personnel at all levels need to be educated that seemingly healthy late preterm infants are physiologically immature and therefore need to be evaluated diligently and warrants an appropriate medical intervention, in form of antenatal corticosteroids, to reduce perinatal morbidity and mortality.

AIM AND OBJECTIVES

The objective of this prospective randomized trial is to determine the effectiveness of antenatal corticosteroids in reducing perinatal morbidity and mortality in late preterm births.(34-36 weeks of gestation with risk of imminent premature delivery).

REVIEW OF LITERATURE

Despite the increasing neonatal and long term morbidity and mortality that are associated with late preterm births , to date, no intervention has been shown to be valuable in improving neonatal outcome. It is against this background that treatment with corticosteroid therapy after 34 weeks was rekindled, though there is insufficient evidence to support the beneficial effect of antenatal corticosteroid in late preterm because of only few studies on the same.

Medical interventions that can potentially improve the outcome of late preterm infants include the use of tocolytics to delay delivery and administration of corticosteroid to promote fetal lung maturation.

In 1972, Liggins and Howie published a landmark article on the results of a randomized controlled trial using maternal administration of antenatal betamethasone to improve preterm neonatal lung function.[29] In this study, two 12-mg injections of betamethasone given 24 hours apart significantly reduced the incidence of RDS in preterm neonates, from 15.6% to 10.0%. In 1994 citing the results of metaanalysis of 15 randomized controlled trials, the NIH panel concluded that the use of antenatal corticosteroids significantly reduces neonatal mortality, RDS, and IVH with no proven risks to the infant[30]. The panel recommended that antenatal corticosteroids be administered to all women between 24 and 34 weeks' gestation at risk of preterm delivery. The American College of Obstetricians and Gynecologists (ACOG) advocated the NIH consensus statement on antenatal corticosteroids.

There are 3 key components to effective lung function which must occur immediately after birth to allow air breathing. First, alveoli must maintain inflation

during both inhalation and expiration to allow adequate gas exchange. This process is facilitated by the surface tension lowering effect of phopholipids that are secreted in utero by the type II alveolar cells as term approaches. Secondly, fetal lung fluid must be sufficiently cleared from the alveolar spaces. This process is also initiated in utero during late gestation. In the fetal lung, chloride secretion predominates and through this active transport, water is secreted into the lung lumen producing the lung liquid required for normal development[31]. During late gestation, the lung epithelium switches from active chloride secretion to active resorption of sodium and liquid allowing for rapid lung fluid removal at birth. Apically located epithelial sodium channels (ENaC) are essential for the clearance of alveolar fluid[32,33,34]. Thirdly, pulmonary vascular resistance must decrease sufficiently to allow the entire cardiac output of the heart to flow through the pulmonary circulation. This transition occurs at birth with the initiation of air breathing[35]. When ≥ 1 of these adaptations do not occur normally, disorders such as hyaline membrane disease, transient tachypnea of the newborn, or persistent pulmonary hypertension result.

Antenatal administration of corticosteroids accelerates the effect of endogenous corticosteroids. The most well-described biochemical effect is the induction of type II alveolar cells that increases surfactant production. Surfactant proteins A, B, C, and D are all increased, as are the enzymes necessary for phospholipid synthesis.

Corticosteroid treatment also stimulates lung structural development. Lungs of exposed fetuses have increased alveolar volume, closer alignment of alveoli to vessels and thinner alveolar walls compared with nonexposed fetuses of a similar gestational age. These maturational changes result in improved gas exchange and neonatal

respiratory function. Importantly, steroid-exposed fetuses also demonstrate enhanced response to postnatal surfactant treatment.

The beta-adrenergic system is also essential to normal fetal lung development and the neonatal transition. Release of surfactant and absorption of alveolar fluid can be stimulated by beta-adrenergic agonists. Pulmonary beta-adrenergic receptors increase during gestation, in parallel with the rise in endogenous glucocorticoids. Corticosteroids trigger additional biochemical effects critical to postnatal lung function. Among these is ENaC expression, which peaks in the alveolar epithelium at term, facilitating perinatal lung liquid clearance. Thus, corticosteroids likely enhance lung fluid clearance at birth in preterm infants by their effect on ENaC expression and function. This effect on fluid clearance may be especially beneficial to late preterm, or perhaps even term infants.

The mechanism of steroid action is complex and affects not only fetal lung maturation but also regulation of fetal growth, organ system maturation and the functions of the immune system and sympathetic nervous system. Steroids play important role in fetal brain development ,altering neuronal migration,synaptic plasticity and neurotransmitter activity[36].

Antenatal corticosteroid cause cerebral vasodilation and prevents intraventricular haemorrhage in babies in whom cerebral vasoconstriction occurs due to hypercapnoea and acidosis [37].

According to ACOG guidelines, both betamethasone and dexamethasone are acceptable agents for promotion of fetal. A number of studies, however, have attempted to determine the superior agent.

In 1999, Baud et al retrospectively analyzed a cohort of 883 infants born between 24 and 31 weeks. These authors found a higher rate of cystic periventricular leukomalacia (PVL) among neonates exposed to dexamethasone than those exposed to betamethasone[38]. Notably, neonates exposed to dexamethasone had a higher rate of PVL than infants who had not received a glucocorticoid. PVL is the most frequent cause of cerebral palsy in children born prematurely. Feldman et al retrospectively analyzed a cohort of 334 VLBW infants. These authors found significantly lower rates of RDS and bronchopulmonary dysplasia (BPD) in infants exposed to betamethasone compared with dexamethasone. Other neonatal outcomes were similar in both groups[39].

The management of patients whose infants deliver between 34 and 37 weeks of gestation is a controversial issue. In cases of preterm labour with intact membranes the risk of tocolytic therapy to the mother must be weighed against the risk of prematurity to the neonate. In group of patients with preterm premature rupture of membranes the risks of maternal and neonatal infections with expectant management must be weighed against the risk of prematurity.

The conservative approach (tocolytic use in preterm labour and expectant management of preterm premature rupture of membranes) that includes fetal pulmonary maturity testing is generally recommended.

Though antenatal corticosteroid use has many beneficial effects it has been studied to have both short and long term adverse outcomes also. A study by Barker et al. in 1998 stated that exposure to excess antenatal corticosteroids caused fetal origin of adult disease thus linking it to impaired glucose tolerance ,dyslipidemia, and hypertension[40].

A study by Rotmensch S et al. in 1999 showed that antenatal administration of betamethasone reduces the breathing episodes as well as total breathing time at 48 hours by 83%($p<0.01$) and 90.4% ($p<0.01$) respectively. Fetal limb and trunk movement decreased by 53.2% and 48.6%($p<0.01$).The total biophysical score was reduced. Pulsatility indices of umbilical and middle cerebral arteries remain unchanged at 48 hours and 96 hours[41].

A study by Helal KJ in Nebraska,USA in 2000 showed that antenatal betamethasone caused measurable adrenal suppression in women at risk of preterm delivery. The mean stimulated cortisol level decreased from 33.0 to 11.8 microgm/dl 1 week after the second dose of betamethasone ($p<0.001$).[42]

According to practice guidelines published by the ACOG, the management of PTL should involve the use of tocolysis and glucocorticoids up to 34 weeks gestation[43]. The management of PPROM remains controversial, but expert opinion generally recommends expectant management before 34 weeks[44]. However, beyond 34 weeks efforts are no longer directed at prolonging the pregnancy. These management strategies are based upon the fact that the survival rate of infants born at 34 weeks is within 1% of those born at term and prolongation of a pregnancy complicated by PTL or PPROM beyond 34 weeks may have unnecessary maternal and fetal risk[45].

Stutchfield et al. in 2005 conducted the Antenatal Steroid for Term Elective Caesarean Sections:a pragmatic randomized trial and found that antenatal corticosteroid prior to delivery by caesarean reduces the need for NICU admission upto 38+6 weeks of gestation compared with controls. The relative risk of RDS was 0.46(95%CI 0.23-0.93 P=0.02),RR for transient tachypnoea of newborn was 0.040 in

the control group and 0.021 in treatment group(RR 0.54,95% CI 0.26-1.12).The probability of admission to NICU at 37 weeks was 11.4% in control group and 5.2% in treatment group[25].

A study by Holland MG ,in 2009 shows that potentially avoidable latepreterm births accounted for 17% and were associated with later gestational age and prior caesarean delivery(OR 1.5;95%CI 1.0-2.1) .

A study by Anthony Shanks et al in 2010 assessed whether administration of steroids after 34 weeks of gestation enhances fetal lung maturity profiles in women with documented lung immaturity (TD_XFLM-II <45mg/g) discovered that women assigned to steroid group had a mean increase of TD_XFLM-II in one week of 28.37 mg/gm whereas women assigned to no treatment had an increase of 9.76 mg/gm ($p<0.002$)).This study also showed that despite having a lower initial mean TD_XFLM-II value,the group receiving steroids had both a higher increase of TD_XFLM-II in one week as well as a higher percentage of mature profiles (TD_XFLM II >45mg/gm)[46].

RCOG in 2010 issued guidelines on antenatal corticosteroids and their use in preterm birth. It advocates that clinicians should offer a single course of antenatal corticosteroids to women between 24+0 to 34+6 weeks of gestation who are at risk of preterm birth. In pregnancies affected by IUGR,antenatal corticosteroid should be given between 24+0 to 35+6 weeks who are at risk of preterm delivery[24].

The current ACOG Committee opinion is that elective delivery before 39 weeks of gestation should not be performed without documenting fetal lung maturity. It recommends administration of corticosteroid from 24-34+6 weeks if preterm

delivery is imminent. And administration after 34 weeks only if fetal lung immaturity is documented[47].

A retrospective cohort study done by Kamath-Rayne et al in 2011 in Ohio compared outcomes of 362 neonates born at 34 weeks of gestation or more after fetal lung maturity testing:102 with immature fetal lung indices were treated with antenatal corticosteroid followed by planned delivery within 1 week:76 with immature fetal lung indices were managed expectantly and 184 were delivered after mature amniocentesis. This study showed that compared with corticosteroid exposed neonates those born after mature amniocentesis had lower rates of adverse neonatal (26.5% compared with 14.1%,adjusted odds ratio 0.51,95% CI 0.27-0.96) and adverse respiratory outcome (9.8% compared with 3.3%,adjusted OR 0.33,95%CI 0.11-0.98); newborns born after expectant management had significantly less respiratory morbidity(1.3% compared with 9.8%, adjusted OR 0.11,95%CI 0.01-0.92)compared with corticosteroid exposed infants. In addition corticosteroid exposed neonates had twice the rate of hypoglycaemia ,need for intravenous fluid for hypoglycaemia ,sepsis evaluation and treatment with antibiotics[48].

A study done by Porto et al. in Brazil in 2011 randomized 320 women ,163 of whom were assigned to corticosteroid group and 157 to control group. Final analysis included 143 and 130 infants, respectively. The rate of respiratory distress syndrome was 1.4% in steroid group and 0.8% in placebo group with p value being 0.54. The rate of transient tachypnoea was high in both the groups 24% and 22% (p=0.77). There was no reduction in the risk of respiratory morbidity with corticosteroid use even after adjustment for subgroups of gestational age. The adjusted risk of respiratory morbidity was 1.12(95% CI 0.74-1.70). The need for ventilator support

was around 20% in both the groups. There was no difference in neonatal morbidity (62% in steroid group and 72% in placebo group p=0.87). Neonates who required phototherapy for hyperbilirubinemia was significantly reduced in the corticosteroid group 24% as compared to 38% in placebo group with p=0.01. Thus concluding that antenatal treatment with steroids at 34-36 weeks of pregnancy reduces the rate of requirement of phototherapy but does not reduce the rate of respiratory disorders[27].

A retrospective cohort study done by Yinon Y et al. in 2012 evaluated women who compared corticosteroid treated infants with the control group in late preterm, after immature fetal lung indices were documented, reported that the rate of the composite respiratory morbidity outcome was significantly higher in the nontreatment group compared with patients who received corticosteroid therapy (21% vs 8.4%, respectively; $P < .02$). Consistent with the aforementioned finding, significantly more infants in the nontreatment group required respiratory support (20%vs 8.4%, respectively;P=.03). In addition, the rate of admission to the special care unit was higher in the control than in the study group, although this difference did not reach statistical significance (29% vs 17% respectively; $P = .07$). The 2 groups did not differ significantly with regard to the rates of RDS, TTN, hypoglycemia, and hyperbilirubinemia. Multiple linear regression analysis was used to examine the contribution of treatment with antenatal corticosteroids to the composite respiratory morbidity outcome while adjustment was made for maternal age, TDx-FLM-II test result, the presence of gestational diabetes mellitus, mode of delivery, gestational age at delivery, birthweight, and sex .The final regression model revealed that corticosteroid administration (adjusted odds ratio [OR], 0.23;95% confidence interval [CI], 0.07–0.78) and TDx-FLM-II value (adjusted OR, 0.9; 95% CI, 0.86 – 0.99) and gestational age at delivery (adjusted OR, 0.33; 95% CI, 0.2– 0.55) were associated

independently with the composite morbidity outcome. Thus this study advocated the use of antenatal corticosteroid for late preterm births[49].

Cochrane database of systematic reviews 2013 advocated that neonatal death was not significantly reduced in corticosteroid treated infants born in late preterm (RR 2.62,95% CI 0.77- 8.96) .Combined fetal and neonatal death was significantly reduced in corticosteroid treated infants born before 36 weeks (RR 0.75,95%CI 0.61-0.94). RDS was not significantly reduced in corticosteroid treated infants born at a gestation of atleast 34 weeks (RR0.66,95% CI 0.38-1.16) and at a gestation of atleast 36 weeks (RR 0.30,95% CI 0.03-2.67). Cerebroventricular haemorrhage was also not significantly reduced in corticosteroid treated infants born at a gestation of atleast 34 weeks (RR 1.13,95%CI 0.07-17.92) and at a gestation of atleast 36 weeks . This review has not shown any benefits in primary outcome for infants delivered greater than 7 days after treatment with antenatal corticosteroids. Thus this review advocates benefit and administration of steroid across a range of 26-34+6 weeks[50].

Thus the clinical decision whether to deliver a premature baby is determined by the balance between the risk of death and morbidity associated with prematurity on one hand and the assessment of maternal and fetal well being by termination of pregnancy on the other. As there are no guidelines available for use of antenatal corticosteroids in late preterm population this study aims to evaluate the beneficial and adverse effects of antenatal betamethasone on late preterm population and determine its efficacy beyond 34 weeks.

METHODOLOGY

SOURCE OF DATA: All pregnant women attending and admitted in Obstetrics and Gynaecology department at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi and diagnosed with 34 to 36 weeks 6 days period of gestation with risk of imminent premature delivery either spontaneous or elective.

STUDY DESIGN: A hospital based prospective, Randomized Control Trial was proposed at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka; a tertiary hospital in India.

PERIOD OF STUDY: A one year prospective study.

SAMPLE SIZE: Sample size for the study is calculated as follows-

$$n=2(z\alpha+z\beta)^2\, p(1-p)/(p_0-p_1)^2$$

Taking the level of significance as 5% α error=0.05

β error=95%

Power of study=80%

p_0=28.9%

p_1=14.45

zα=1.96 and zβ=0.84

With an assumed 28.9% rate of respiratory disorder in late preterm births and 80% power to detect a reduction of 50% in the rate of respiratory disorder with the use of corticosteroid, the sample size is calculated to be 180(90 in each group). However to achieve a higher power total 696 patients were screened and 200 enrolled in the study.

STUDY AREA, ENROLMENT, AND STUDY POPULATION: All pregnant women attending and admitted in Obstetrics and Gynaecology department at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi and diagnosed with 34 to 36 weeks of period of gestation with risk of imminent premature delivery either spontaneous or elective were asked to participate in the trial. All the patients who were willing -their informed and written consent was taken and they were included in the study. All the neonates born were included in this study and their perinatal outcome was studied.

SELECTION CRITERIA:

Inclusion criteria

- Pregnant women receiving care at KLE'S hospital and MRC were included if they were at 34 to 36 weeks gestation and at risk of imminent premature delivery (either spontaneous or if early delivery is recommended as a result of high risk pregnancy endangering maternal or fetal outcome, or both)
- Gestational age is defined according to the date of the woman's last menstrual period, if known and reliable or by ultrasonography in first trimester.

Exclusion criteria-

- Major congenital malformations
- Multiple pregnancy
- Abruptio placenta.

- Clinical evidence of chorioamnionitis (maternal temperature of more than 100.4 degrees Fahrenheit ,maternal tachycardia, abdominal tenderness, foul smelling vaginal discharge, evidence of fetal distress on CTG).

- Previous use of corticosteroids in the present pregnancy.

- Need for immediate resolution of pregnancy for fetal or maternal indications (eg. Fetal distress, uncontrolled hypertension, antepartum haemorrhage, failed induction etc).

- Patients who delivered within 24 hours of receiving the 1st dose of steroid.

METHOD OF DATA COLLECTION (STUDY PROTOCOL)

The study got ethical approval by Institutional Review Board of Jawahar Lal Nehru Medical College, Belagavi, Karnataka, India vide a letter Ref.No. MCD/DOME/16 dated 30/11/2013. This was an academic study which was conducted in accordance with revised CONSORT guidelines.

We declare that we had no conflict of interest.

PERSONNEL: This trial was conducted at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka; a tertiary hospital.

INFORMED CONSENT: Women who presented to Obstetrics and Gynaecology department at KLE'S Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi diagnosed with 34 to 36 weeks of period of gestation with risk of imminent premature delivery either spontaneous or elective were screened for enrolment in the study using inclusion and exclusion criteria. Informed consent was obtained at the

time of enrolment. A signature or left hand thumb impression from the consented subject was obtained after reading the informed consent document . For iliterate participants, the consent document was read and written confirmation was obtained with the left hand thumb impression in the presence of women's relative, who would attest to be a witness. Adequate time was provided and the risks and benefits of participation in the study were equivocally described. No pressure was placed on the women to enrol for the trial.The lack of participation did not affect the usual and anticipated standard of care. No monetary benefit was offered to any patients to participate in the trial.

RANDOMIZATION:

Assignment of the participants to two groups was done using computer generated randomized number sequence list with block size of 2 into steroid group or no steroid group. The randomization list was concealed and placed in Opaque sealed envelopes. These envelopes were opened when a women fulfilled the inclusion criteria and was willing to participate in the study.

For allocation concealment, the randomization instructions were given in sequentially numbered, opaque, sealed, envelopes with unpredictable allocation code, which were only opened when a woman had consented to enrol. Randomization was done after admission .The nature of the intervention made it impossible to blind them. If an already randomized woman later became ineligible (eg, she developed antepartum haemorrhage during labour), the assignment code was not reused and such patients were excluded. The women were randomized into 2 groups Group A: steroid group and Group B: no steroid group.

PROCEDURE:

Informed and written consent was taken after fulfilment of eligibility criteria.

The proforma was completed for every pregnant women screened for enrolment in the study. A structured survey questionnaire was used to gather Obstetrical and medical details of the patient. Baseline maternal characteristics with regards to age, parity, gestational age at enrolment and detailed medical history was noted for all women. Detailed Obstetrical history was taken from all participants to recognize any high risk factor. Menstrual history was noted and confirmation of gestational age was done. A general physical and systemic examination including Obstetrical examination was done. The diagnosis was noted. If the patient was allocated in group A, she was given Inj. Betamethasone 12mg i.m. in buttock, 2 doses 24 hour apart. Those patients who received only 1 dose and delivered 24 hours or later after it, were also included in the above group. The patients who were allocated in Group B were not given Inj. Betamethasone.

The subject ID assigned to enrolled women identified all the data. All the data pertaining to administration time and date of steroid administration, interval between administration and delivery, mode of delivery, intrapartum events and if a caesarean section was done then its indication, were documented and recorded .

After delivery all neonates were assessed for the following outcome:

- Perinatal mortality.
- Gestational age at birth.
- Birth weight in kgs.

- APGAR score at 1 and 5 minutes.
- Admission to NICU.

✓ Indication for admission to NICU as follows: Respiratory distress syndrome as need for respiratory support for more than 24 hours, need for surfactant, need for CPAP/ventilator ,PaO2 <50 mm of Hg, x-ray film showing diffuse reticulogram.

✓ Transient tachypnoea of newborn as documented by respiratory distress which settled within 24 hours or chest x-ray film showing fluid in the interlobar fissure.

✓ Pneumonia as documented by evidence of consolidation in lungs on x-ray film.

✓ Requirement of phototherapy.

✓ Systemic infections in the first 48 hours of life .As blood culture could not be done for each neonate so complete blood count was used to document systemic infection and blood culture was sent for selected cases only.

✓ Duration of stay in hospital.

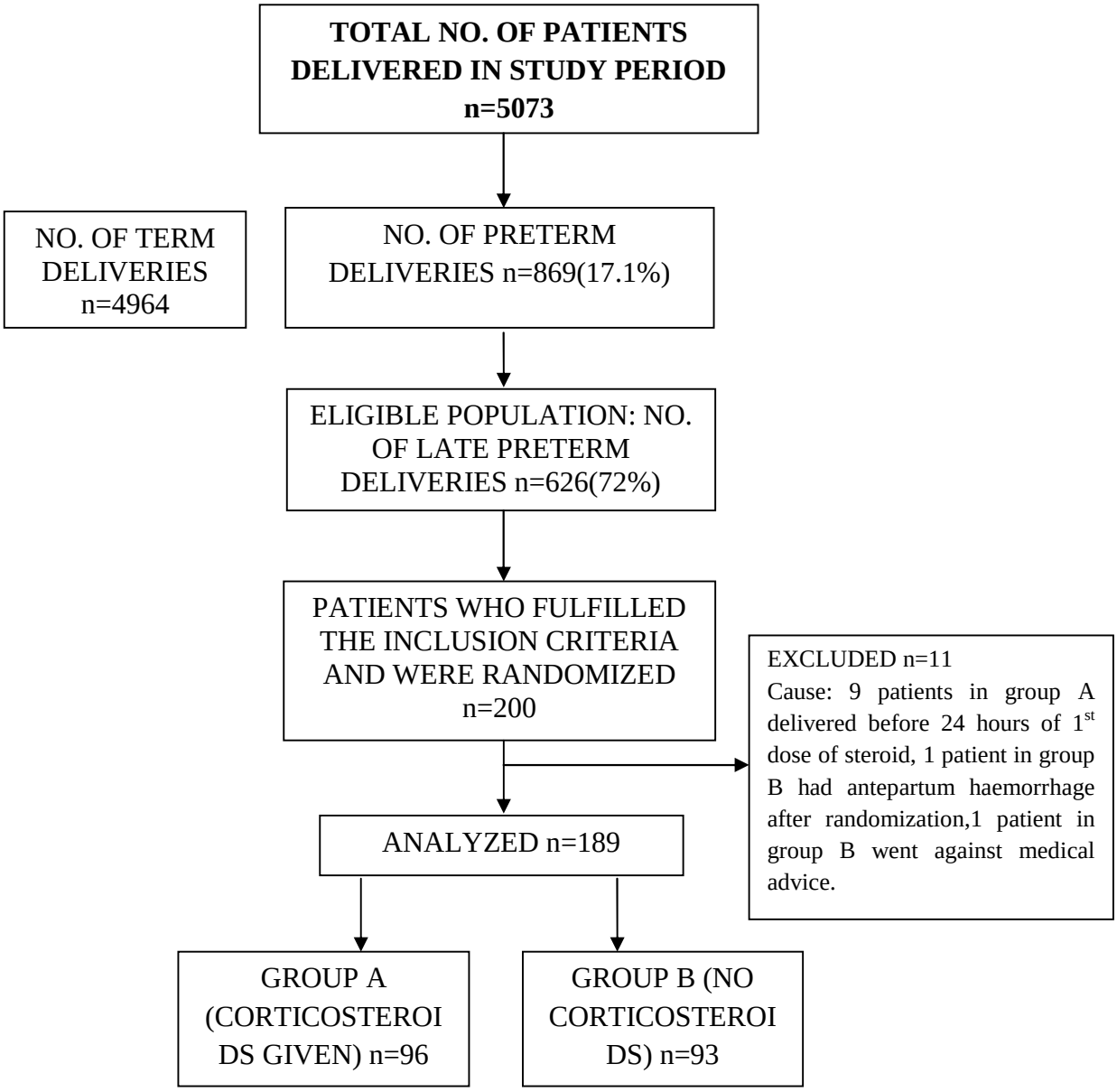
Care of the newborn was as per prevailing standard practices.

All maternal and neonatal details were entered in a master chart and evaluated.

STATISTICAL SIGNIFICANCE: Paired t test was used to evaluate pre and post interventional outcome. P value was calculated for each outcome to know the effectiveness of the intervention.

RESULTS

Out of 5073 patients who delivered in the study period- 869 (17.1%) patients had preterm delivery. In this 626 (72%) were late preterm deliveries i.e. between 34+0 to 36+6 weeks. 200 women among these who were consenting and fulfilling inclusion criteria were randomized. 105 patients were randomized in group A and 95 in group B. However, 11 patients were excluded from the study after randomization due to the following reasons-9 patients in group A delivered before 24 hours of administration of 1st dose of steroid, ,1 patient in group B had antepartum haemorrhage after randomization and 1 patient in group B went against medical advice .Finally,total 189 patients were analyzed in our study ,96 being in Group A and 93 in group B.

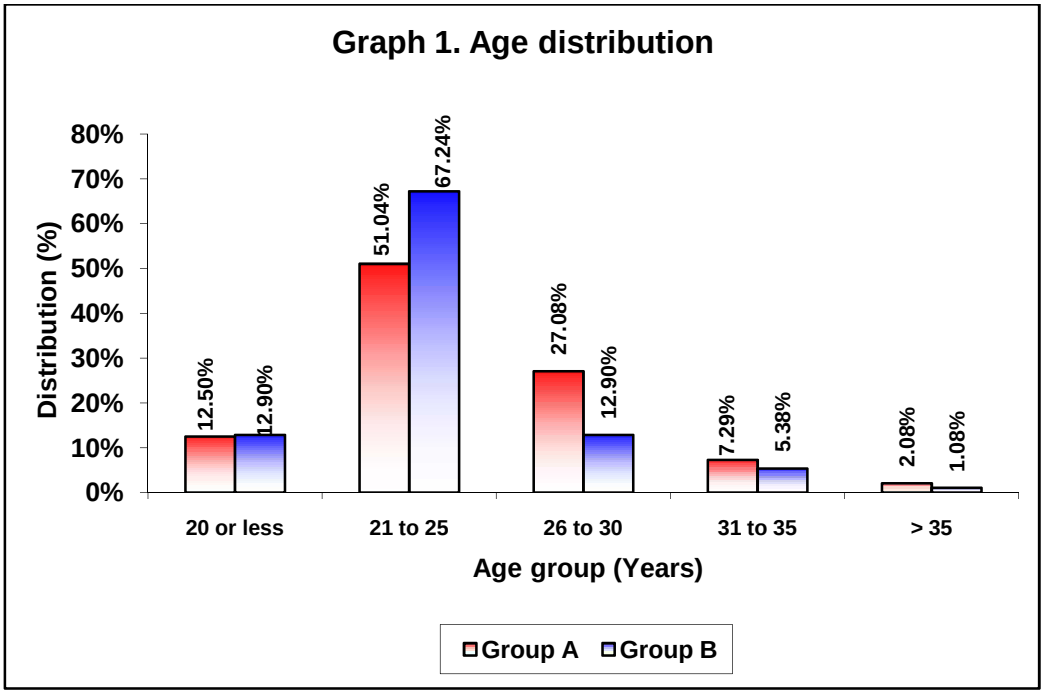

TOTAL NO. OF PATIENTS DELIVERED IN STUDY PERIOD n=5073
NO. OF TERM DELIVERIES n=4964
NO. OF PRETERM DELIVERIES n=869(17.1%)
ELIGIBLE POPULATION: NO. OF LATE PRETERM DELIVERIES n=626(72%)
PATIENTS WHO FULFILLED THE INCLUSION CRITERIA AND WERE RANDOMIZED n=200
EXCLUDED n=11
Cause: 9 patients in group A delivered before 24 hours of 1st dose of steroid, 1 patient in group B had antepartum haemorrhage after randomization,1 patient in group B went against medical advice.
ANALYZED n=189
GROUP A (CORTICOSTEROIDS GIVEN) n=96
GROUP B (NO CORTICOSTEROIDS) n=93

DEMOGRAPHIC CHARACTERISTICS:

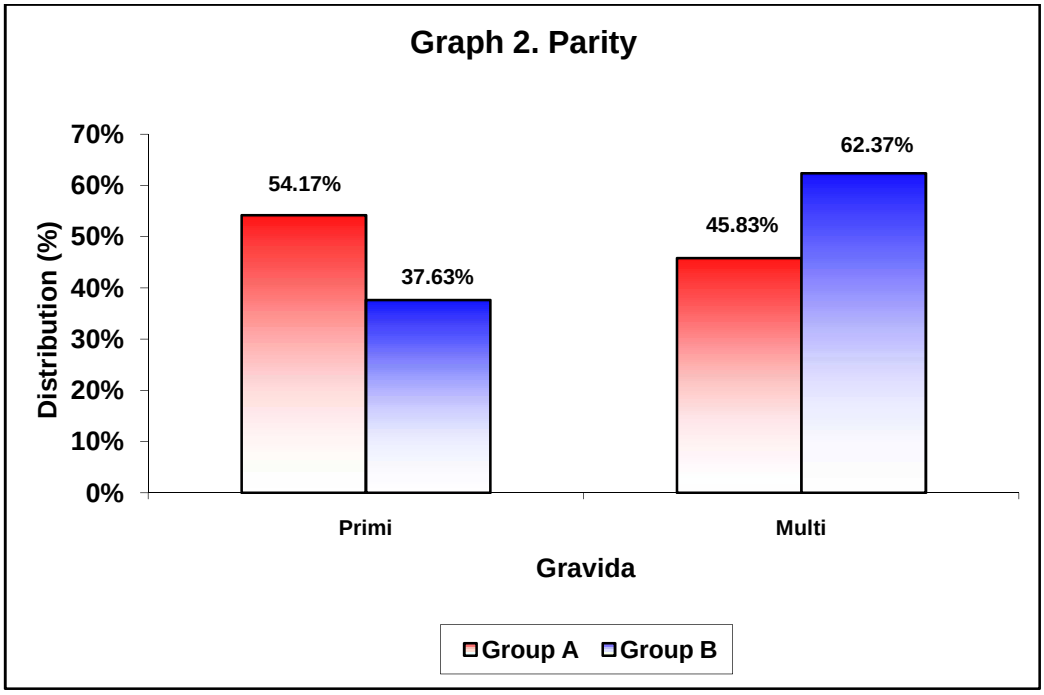
Table 1. Demographic Characteristics

Variables	Variables	Group A (n=96)		Group B (n=93)		p value
		No.	%	No.	%	
Age	20 or less	12	12.50	12	12.90	0.089
distribution	21 to 25	49	51.04	63	67.74	
(Years)	26 to 30	26	27.08	12	12.90	
	31 to 35	7	7.29	5	5.38	
	> 35	2	2.08	1	1.08	
	Total	**96**	**100.00**	**93**	**100.00**	
Mean age		**24.95±3.88**		**24.13±3.43**		0.127
Gravida	Primi	52	54.17	35	37.63	0.023
	Multi	44	45.83	58	62.37	
	Total	**96**	**100.00**	**93**	**100.00**	
Gestational age (weeks)at enrollment	34 to 34+6	24	25.00	20	21.51	0.638
	35 to 35+6	27	28.13	23	24.73	
	36 to 36+6	45	46.88	50	53.76	
	Total	**96**	**100.00**	**93**	**100.00**	
Mean GA	**Mean ± SD**	**35.66±0.86**		**35.75±0.87**		0.498

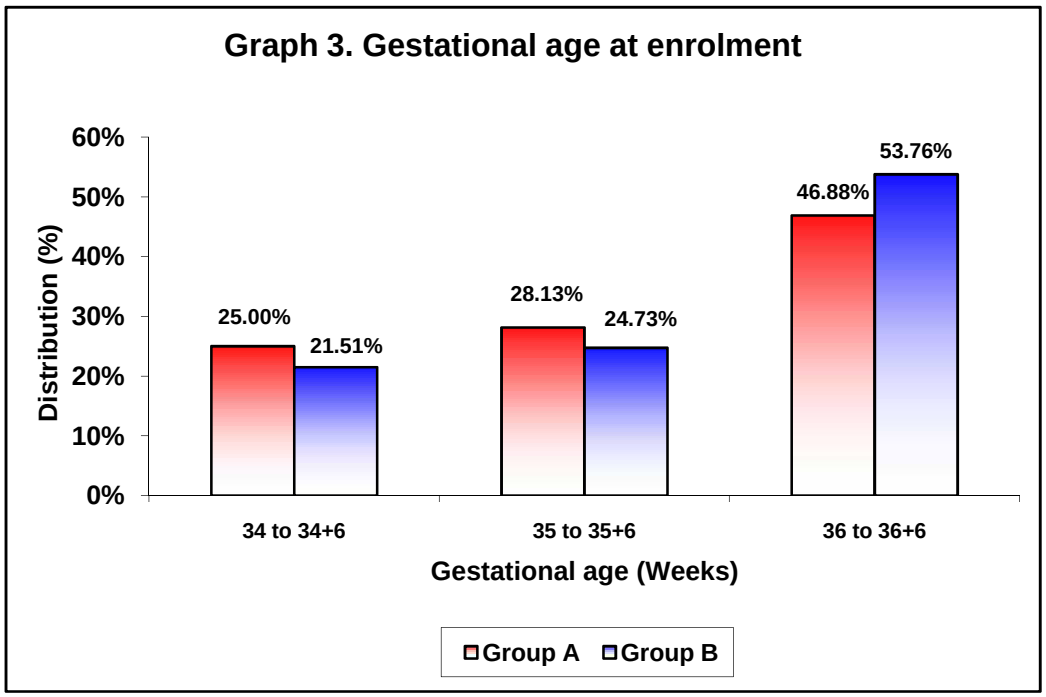
51.04% of women in steroid group and 67.74% in non-steroid group were between 21-25 years constituting the highest percentage in each group. The mean maternal age was comparable being 24.95±3.88 in steroid group as compared to 24.13±3.43 in non-steroid group.



There was a significant difference p=0.023 in parity with 54.17% being primigravida and 45.83% being multigravida in steroid group as compared to 37.63% being primigravida and 62.37 % being multigravida in non-steroid group.



Mean gestational age at enrolment was comparable in both groups being 35.66±0.86 in steroid group and 35.75±0.87 in non-steroid group with p=0.498.



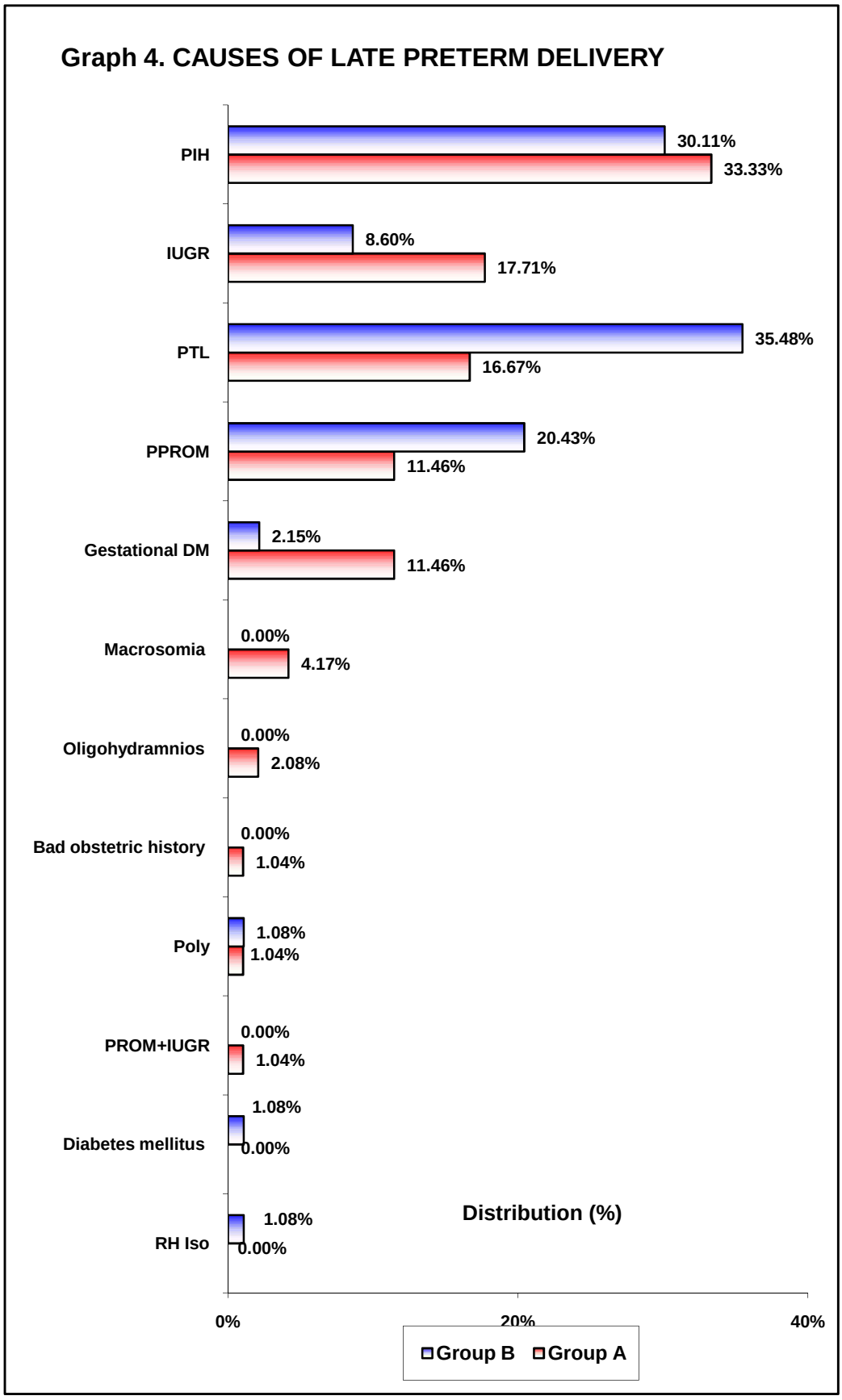
CAUSES OF LATE PRETERM DELIVERY:

The most common indication for late preterm delivery in our study was hypertensive disorder of pregnancy which constituted 33.33% in steroid group and 30.11% in non-steroid group. There was a significant difference in number of patients having gestational diabetes mellitus as it was 11.96% in steroid group as compared to 2.15% in non-steroid group. 16.67% of patients had spontaneous preterm delivery in steroid group and 35.48% had in non-steroid group. There was a significant difference in number of patients having IUGR as a cause of late preterm delivery which was present in 17.71% in steroid group and 8.60% in non-steroid group.

Table 2. Causes Of Preterm Delivery

CAUSES OF PRETERM DELIVERY	Group A (n=96)		Group B (n=93)	
	Number	**Percentage**	**Number**	**Percentage**
HDP	32	33.33	28	30.11
IUGR	17	17.71	8	8.60
PTL	16	16.67	33	35.48
PPROM	11	11.46	19	20.43
GDM	11	11.46	2	2.15
Macrosomia	4	4.17	0	0.00
Oligohydramnios	2	2.08	0	0.00
Bad obstetric history	1	1.04	0	0.00
Polyhydramnios	1	1.04	1	1.08
PROM with IUGR	1	1.04	0	0.00
Diabetes mellitus	0	0.00	1	1.08
RH isoimmunisation	0	0.00	1	1.08
Total	**96**	**100.00**	**93**	**100.00**

$p < 0.001$

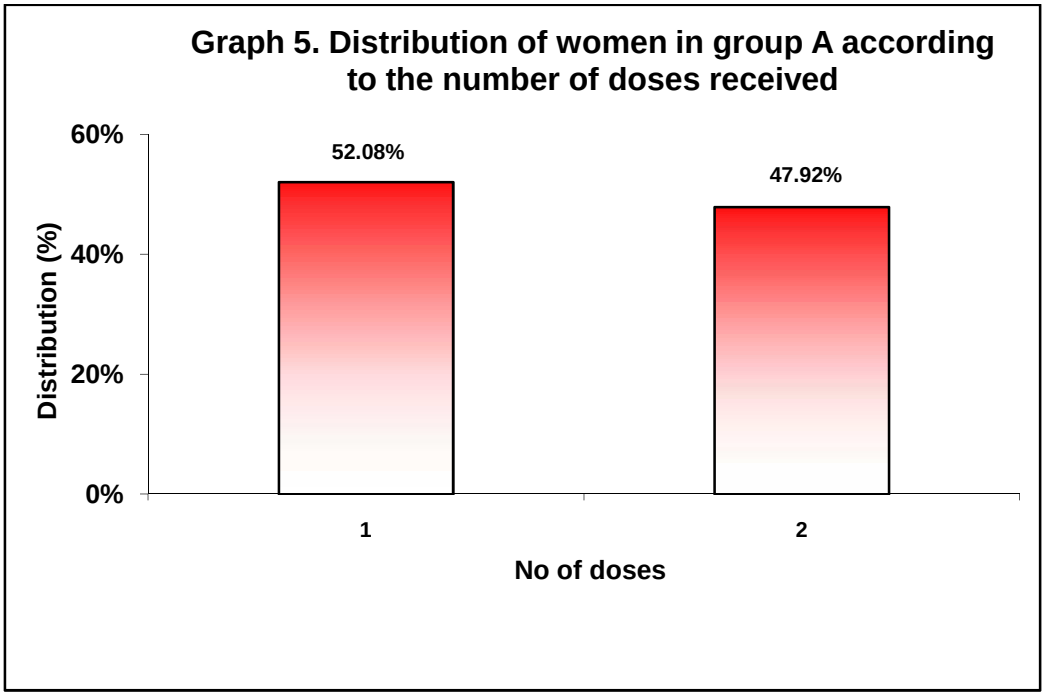

Graph 4. CAUSES OF LATE PRETERM DELIVERY
PIH
30.11%
33.33%
IUGR
8.60%
17.71%
PTL
35.48%
16.67%
PPROM
20.43%
11.46%
Gestational DM
2.15%
11.46%
Macrosomia
0.00%
4.17%
Oligohydramnios
0.00%
2.08%
Bad obstetric history
0.00%
1.04%
Poly
1.08%
1.04%
PROM+IUGR
0.00%
1.04%
Diabetes mellitus
1.08%
0.00%
RH Iso
1.08%
0.00%
Distribution (%)
0%
20%
40%
Group B
Group A

ADMINISTRATION TO DELIVERY INTERVAL:

Out of 189 patients who were randomized, total 96 patients were enrolled in group A . 50 patients received only 1 dose of Inj. Betamethasone i.m. and delivered 24 hours later whereas 46 patients received 2 doses of Inj. Betamethasone 12mg i.m. 24 hours apart and delivered 24 hours thereafter.

Table 3 . Distribution of women in group A according to the number of doses received

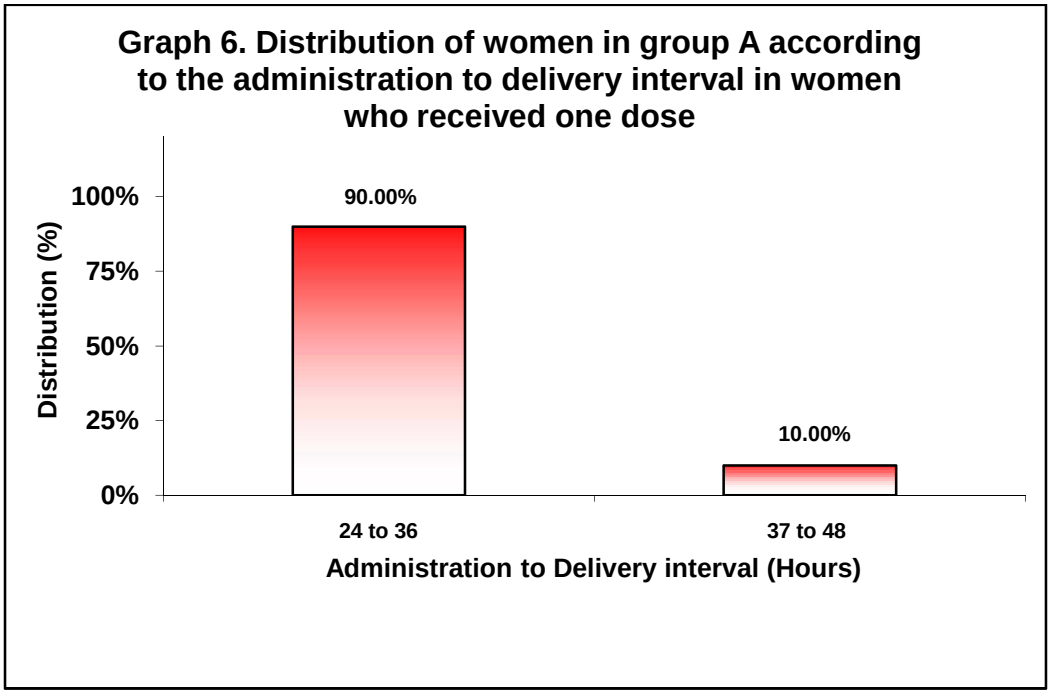
No. of doses	Distribution (n=96)	
	Number	Percentage
1	0	52.08
2	46	47.92
Total	**96**	**100.00**



Of the 50 patients who received 1 dose of steroid 45 patients delivered within 24-36 hours of administration and only 5 patients delivered between 36-48 hours of duration.

Table 4. Distribution of women in group A according to the administration to delivery interval in women who received one dose

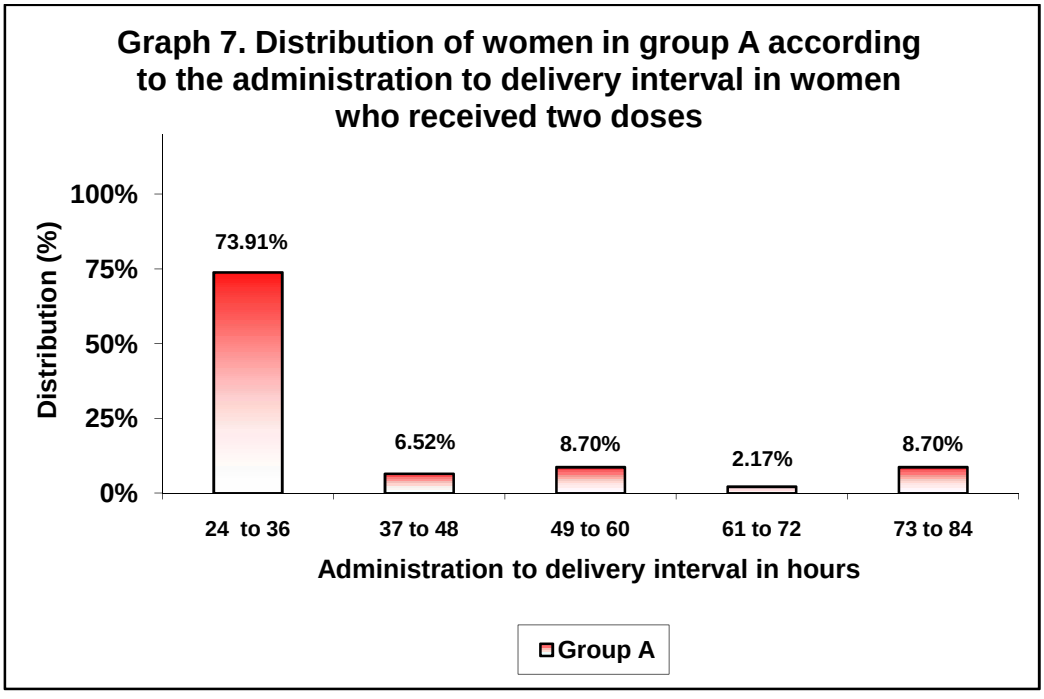
No. of doses	Distribution (n=96)	
	Number	Percentage
24 to 36	45	90.00
37 to 48	5	10.00
Total	**50**	**100.00**



Out of the 46 patients who received 2 doses of inj. Betamethasone 12 mg i.m. 24 hours apart 34 patients delivered within 24-36 hours of administration followed by 4 patients between 49-60 and 73-84 hours.

Table 5. Distribution of women in group A according to the administration to delivery interval in women who received two doses

No. of doses	Distribution (n=96)	
	Number	Percentage
24 to 36	34	73.91
37 to 48	3	6.52
49 to 60	4	8.70
61 to 72	1	2.17
73 to 84	4	8.70
Total	**46**	**100.00**



MODE OF DELIVERY:

LSCS was the main mode of delivery in both the groups being 59.38% in steroid group and 56.99% in non-steroid group. The difference thus being insignificant but the indication for LSCS in both the groups had significant variation (p=<0.01) with fetal distress being in 34.41% in non-steroid group as compared to 12.50% in steroid group. Failed induction was the main indication for LSCS in steroid group 33.33% and only 6.45% in non-steroid group.

Table 6. Mode of delivery

Mode of delivery	Group A (n=96)		Group B (n=93)	
	Number	Percentage	Number	Percentage
LSCS	57	59.38	53	56.99
Vaginal	39	40.63	40	43.01
Total	**96**	**100.00**	**93**	**100.00**

p = 0.740

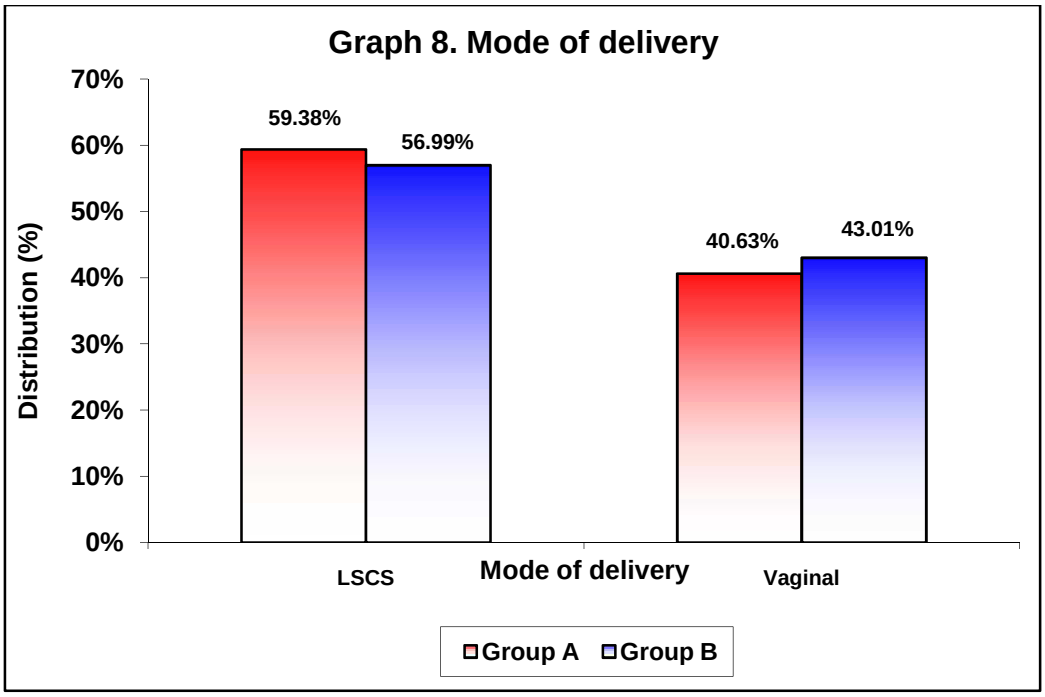
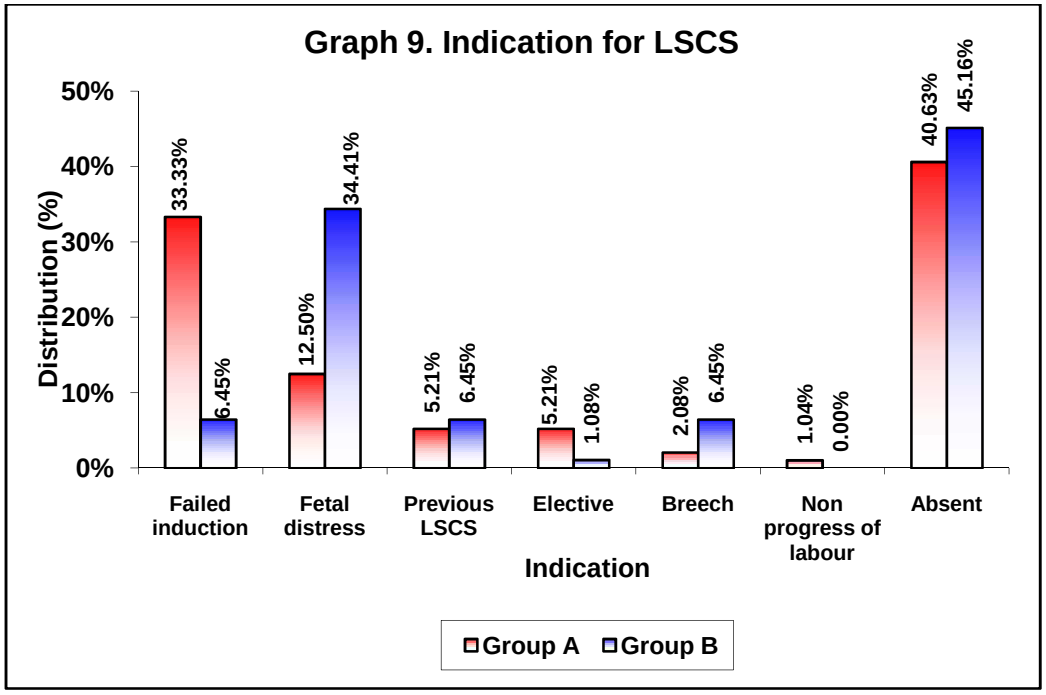


Table 7. Indication for LSCS

Diagnosis	Group A (n=96)		Group B (n=93)	
	Number	**Percentage**	**Number**	**Percentage**
Failed induction	32	33.33	6	6.45
Fetal distress	12	12.50	32	34.41
Previous LSCS	5	5.21	6	6.45
Elective	5	5.21	1	1.08
Breech	2	2.08	6	6.45
Non progress of labour	1	1.04	0	0.00
Absent	39	40.63	42	45.16
Total	**96**	**100.00**	**93**	**100.00**

$p < 0.001$



PERINATAL MORTALITY:

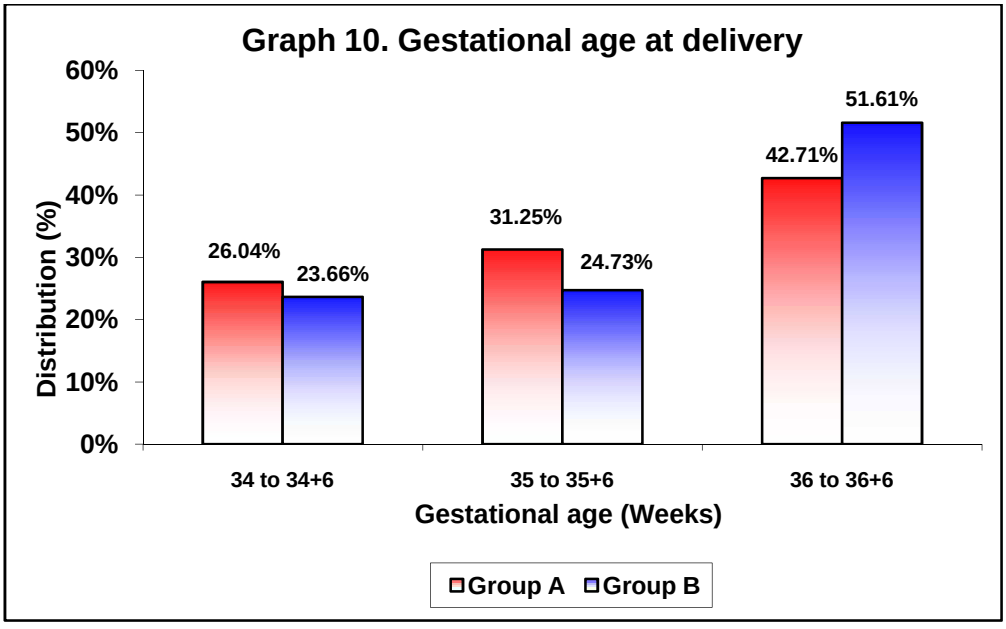
There was no perinatal mortality in both the groups. The gestational age at delivery was comparable in both the groups with mean gestational age being 35.63±0.85 in steroid group Vs 35.74±0.86 in non-steroid group(p=0.363).

GESTATIONAL AGE AT DELIVERY:

Table 8 . Gestational age at delivery

GA (weeks)	Group A (n=96)		Group B (n=93)	
	Number	Percentage	Number	Percentage
34 to 34+6	25	26.04	22	23.66
35 to 35+6	30	31.25	23	24.73
36 to 36+6	41	42.71	48	51.61
Total*	**96**	**100.00**	**93**	**100.00**
Mean ± SD**	**35.63±0.85**		**35.74±0.86**	

p = 0.445*; p=0.363**



The mean gestational age at delivery was comparable in both the groups being 35.63±0.85 in the steroid group as compared to 35.74±0.86 in the non-steroid group. The difference thus being statistically insignificant.

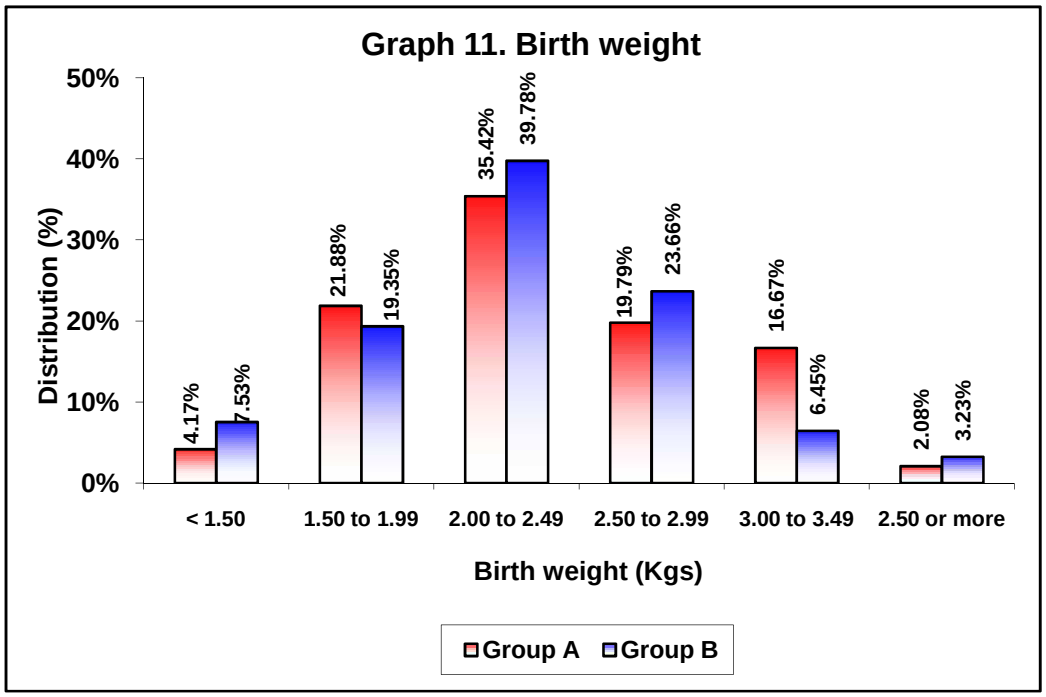
BIRTH WEIGHT:

Mean birth weight did not vary significantly in both the groups with 2.28 ±0.63 kg being in steroid group and 2.24±0.55kg in non-steroid group (p=0.6888). 35.42% of neonates in steroid group and 39.78% in non-steroid group had birth weight between 2 to 2.49kg.

Table 9 . Birth weight

Birth weight (Kgs)	Group A (n=96)		Group B (n=93)	
	Number	Percentage	Number	Percentage
<1.50	4	4.17	7	7.53
1.50 to 1.99	21	21.88	18	19.35
2.00 to 2.49	34	35.42	37	39.78
2.50 to 2.99	19	19.79	22	23.66
3.00 to 3.49	16	16.67	6	6.45
3.50 or more	2	2.08	3	3.23
Total*	**96**	**100.00**	**93**	**100.00**
Mean ± SD**	**2.28±0.63**		**2.24±0.55**	

p = 0.294*; p=0.688**

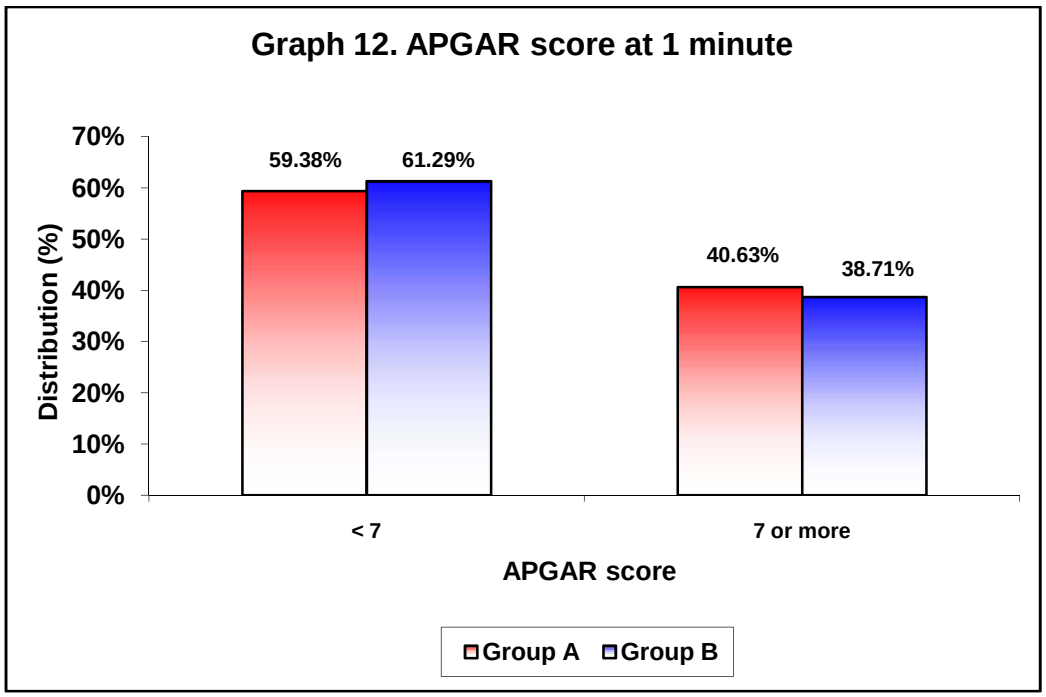

Graph 11. Birth weight
Distribution (%)
50%
40%
30%
20%
10%
0%
4.17%
7.53%
21.88%
19.35%
35.42%
39.78%
19.79%
23.66%
16.67%
6.45%
2.08%
3.23%
< 1.50
1.50 to 1.99
2.00 to 2.49
2.50 to 2.99
3.00 to 3.49
2.50 or more
Birth weight (Kgs)
Group A
Group B

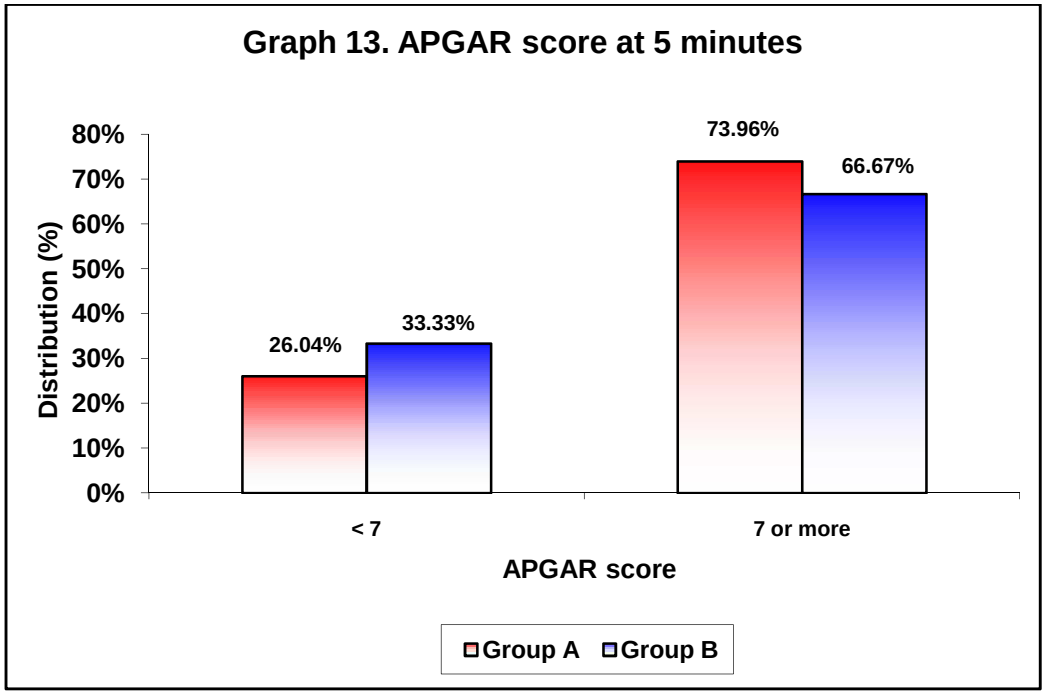
APGAR SCORE:

APGAR score at 1 minute was comparable in both the groups with APGAR score<7 being in 59.38% in steroid group and in 61.29% in non-steroid group. (p=0.452). APGAR score <7 at 5 minutes was present in 26.04% of patients in steroid group and 33.33% in non-steroid group(p=0.272).

Table 10. APGAR score at 1 minute and 5 minutes

Comparison	APGAR Score	Group A (n=96)		Group B (n=93)		p value
		No.	%	No.	%	
At 1 minute	< 7	57	59.38	57	61.29	**0.452**
	7 or more	39	40.63	36	38.71	
	Total	**96**	**100.00**	**93**	**100.00**	
At 5 minutes	< 7	25	26.04	31	33.33	**0.272**
	7 or more	71	73.96	62	66.67	
	Total	**96**	**100.00**	**93**	**100.00**	


Graph 12. APGAR score at 1 minute
70%
60%
50%
40%
30%
20%
10%
0%
Distribution (%)
59.38%
61.29%
40.63%
38.71%
< 7
7 or more
APGAR score
Group A
Group B

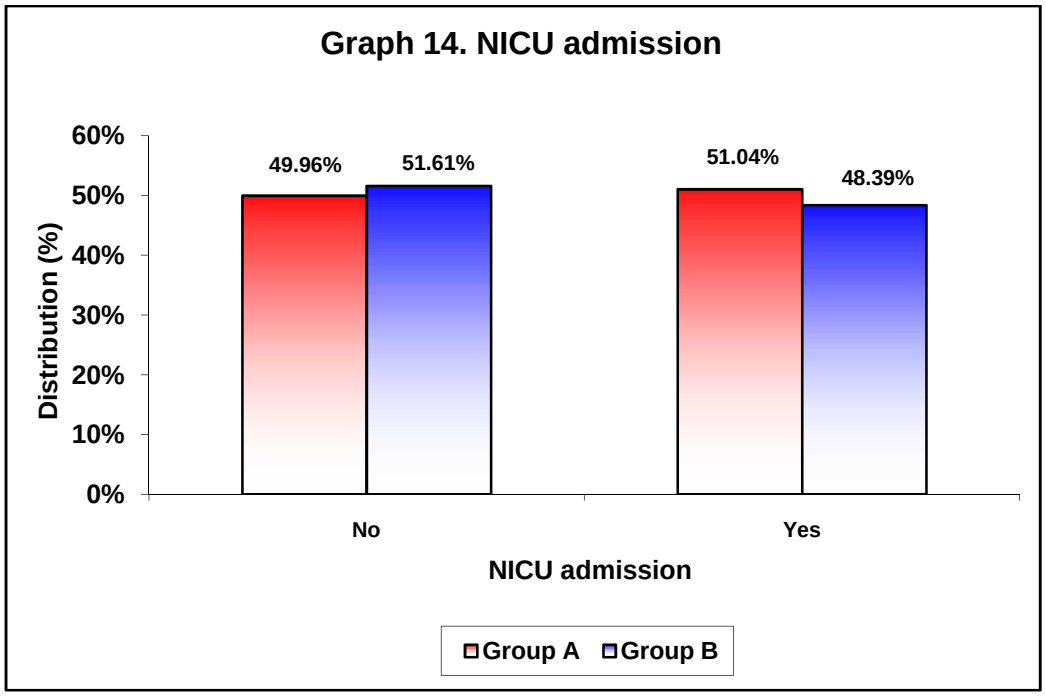

Graph 13. APGAR score at 5 minutes
80%
70%
60%
50%
40%
30%
20%
10%
0%
Distribution (%)
26.04%
33.33%
73.96%
66.67%
< 7
7 or more
APGAR score
Group A
Group B

NICU ADMISSION:

Table11. NICU admission

NICU admission	Group A (n=96)		Group B (n=93)	
	Number	Percentage	Number	Percentage
No	47	48.96	48	51.61
Yes	49	51.04	45	48.39
Total	**96**	**100.00**	**93**	**100.00**
Mean NICU Stay (Days)	**6.80±3.67**		**8.80±4.88**	

p = 0.715; p=0.031 (Mean NICU stay)



Of the 96 patients enrolled in steroid group 49(51.04%) neonates had NICU admission as compared to 45 (48.39%)neonates in the non-steroid group. The difference was statistically insignificant with p=0.715.

Evaluating the indication of NICU admission in the present study no statistically significant difference was found in rate of RDS with 8.33% being in steroid group and 7.53% being in non-steroid group. p=0.838.

In our study 19.79% of patients had TTN, the respiratory morbidity which is more common in late preterm than RDS, when compared to 24.73% in non-steroid group. The difference being insignificant (p=0.485).

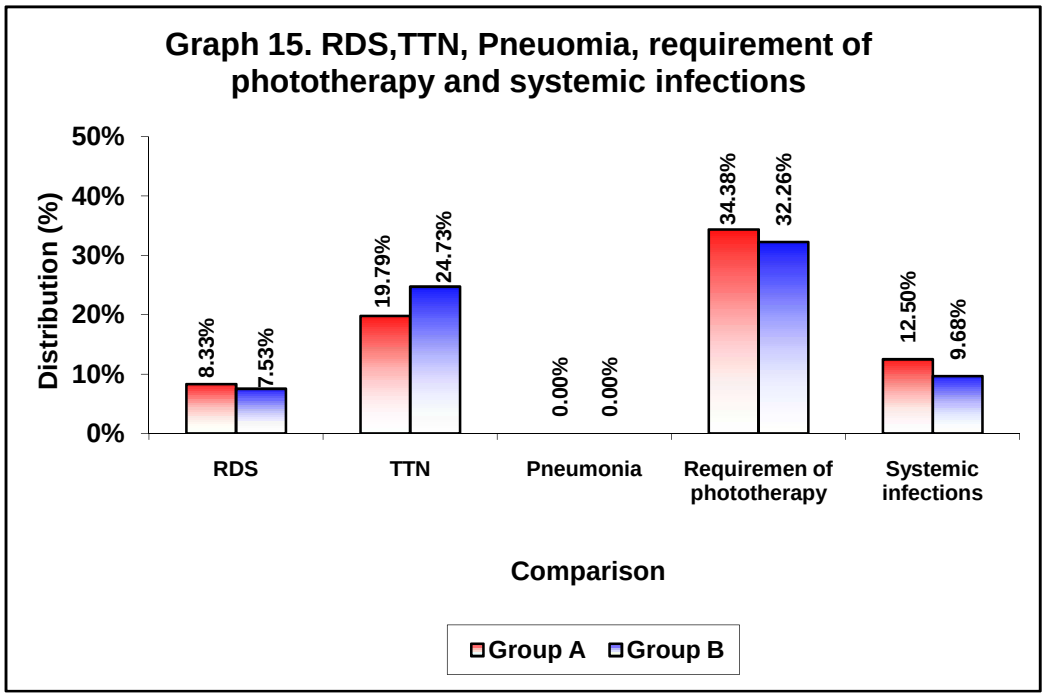
No cases of pneumonia were found in either group.

Another important consideration of this study, the requirement of phototherapy was present in 34.38% of neonates in steroid group and 32.28% of neonates in non-steroid group, thus implicating no beneficial role of steroid in reducing the requirement of phototherapy in late preterm (p=0.875).

In the present study systemic infections in the first 48 hours were acquired by 12.50% of neonates in steroid group and 9.68% of neonates in non-steroid group. But this difference could not reach a statistical significance (p=0.537).

Table12. RDS, TTN, pneumonia, requirement of phototherapy and systemic infections

Comparison of	Findings	Group A (n=96)		Group B (n=93)		p value
		No.	%	No.	%	
RDS	No	88	91.67	86	92.47	**0.838**
	Yes	8	8.33	7	7.53	
	Total	**96**	**100.00**	**93**	**100.00**	
TTN	No	77	80.21	70	75.27	**0.485**
	Yes	19	19.79	23	24.73	
	Total	**96**	**100.00**	**93**	**100.00**	
Pneumonia	No	96	100.00	93	100.00	**-**
	Yes	0	0.00	0	0.00	
	Total	**96**	**100.00**	**93**	**100.00**	
Requirement of phototherapy	No	63	65.63	63	67.74	**0.877**
	Yes	33	34.38	30	32.26	
	Total	**96**	**100.00**	**93**	**100.00**	
Systemic infections in the first 48 hours	No	84	87.50	84	90.32	**0.537**
	Yes	12	12.50	9	9.68	
	Total	**96**	**100.00**	**93**	**100.00**	



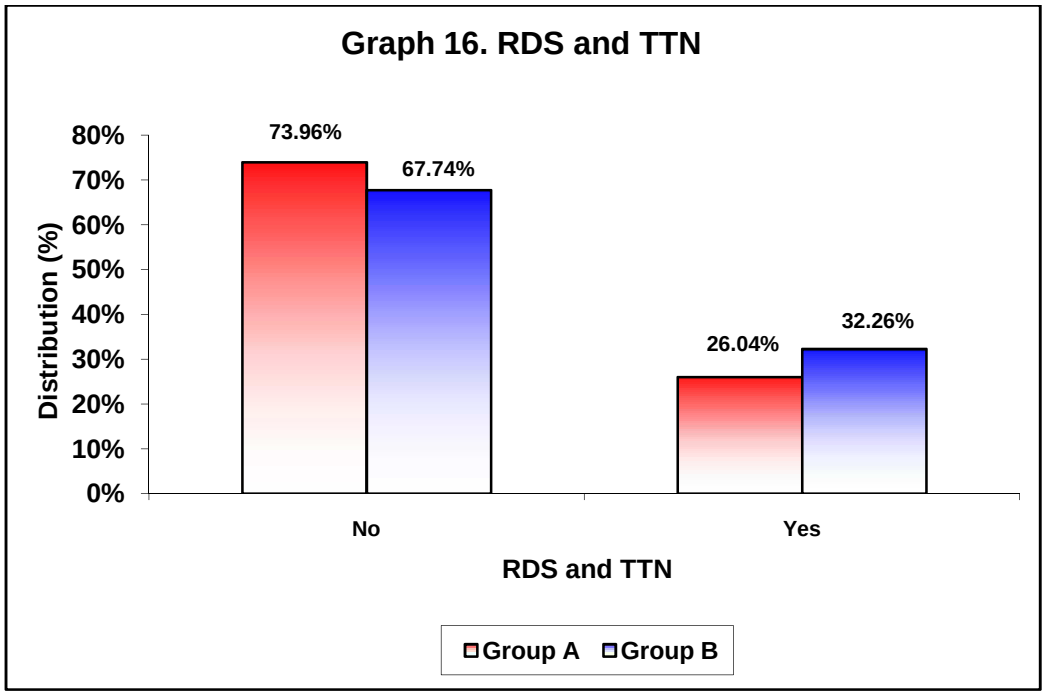
COMPOSITE RESPIRATORY MORBIDITY:

The composite respiratory morbidity also did not vary significantly in steroid group being 26.04% and 32.26% in non-steroid group with p=0.34. Risk ratio being 0.8073, 95%CI 0.5160-1.2631.

Table13. RDS and TTN

RDS and TTN	Group A (n=96)		Group B (n=93)	
	Number	Percentage	Number	Percentage
No	71	73.96	63	67.74
Yes	25	26.04	30	32.26
Total	**96**	**100.00**	**93**	**100.00**

RR=0.807; 95% CI=0.516 to 1.263; z=0.937; p = 0.347



DURATION OF STAY IN NICU:

In our study, mean stay in NICU was 6.80±3.67 days in the steroid group as compared to 8.80±4.88 days in the non-steroid group. The difference here was statistically significant with p=0.031

Thus it was found that administration of antenatal corticosteroid did not result in significant reduction in perinatal morbidity except in the mean duration of stay in NICU.

DISCUSSION

This prospective randomized control study evaluated the potential effects of antenatal corticosteroids (Inj. Betamethasone 12 mg) on perinatal morbidity and mortality in late preterms at risk of imminent premature delivery , in terms of , Perinatal mortality, Admission to NICU, Birth weight, APGAR score at 1 and 5 minutes ,Respiratory distress syndrome, Transient tachypnoea of newborn, Pneumonia, Need for phototherapy, Sepsis in first 48 hours of life, and Duration of stay in NICU .

AGE AND PARITY:

In our study as demonstrated in Table no.1, 51.04% of women in steroid group and 67.74% in non-steroid group respectively were between 21-25 years constituting the highest percentage in each group. The mean maternal age was comparable being 24.95±3.88 in steroid group as compared to 24.13±3.43 in non-steroid group.

There was a significant difference (p=0.023) in parity with 54.17% being primigravida and 45.83% being multigravida in steroid group as compared to 37.63% being primigravida and 62.37 % being multigravida in non-steroid group (p=0.023).

In a similar study done by Porto et al in Brazil over 320 women in 2012 the mean maternal age was 23.3 years in the steroid group and 22.9 years in the non-steroid group. 72 out of 143 (50%) of women were primigravida in the corticosteroid group and 65 of 130 (50%) women were primigravida in the non-steroid group[27].

Another retrospective study conducted by Yinon Y et al over 167 women in 2012 had a mean maternal age of 33 years in the steroid group and similar 33 years in the non-steroid group.[49]

CAUSE OF PRETERM DELIVERY:

The most common cause of late preterm delivery in our study, as shown in Table no 2., was hypertensive disorder of pregnancy which constituted 33.33% in steroid group and 30.11% in non-steroid group. There was a significant difference in number of patients having gestational diabetes mellitus as it was 11.96% in steroid group as compared to 2.15% in non-steroid group. 16.67% of patients had spontaneous delivery in steroid group and 35.48% had in non-steroid group. There was a significant difference in number of patients having IUGR as an indication of termination which was present in 17.71% in steroid group and 8.60% in non-steroid group.

In a prospective study by Porto et al in 2012 in Brazil the most common associated condition with prematurity was spontaneous preterm labour being in 68 of 143 women (68%) and 86 of 130 women (66%), followed by PPROM being in 54 of 143 women (38%) and 54 of 130 women (42%) in the steroid and non steroid group respectively[27]**.**

Another retrospective cohort study by Kamath-Rayne et al in 2012 in Ohio over 362 women states that spontaneous preterm labour was the most common condition associated with preterm delivery being 48 in 76(63.2%) and 43 in 102(42.6%) in patients who were managed expectantly and in whom steroids was given after immature lung indices were documented on amniocentesis respectively[48].

MODE OF DELIVERY:

In our study LSCS was the main mode of delivery in both the groups being 59.38% in steroid group and 56.99% in non-steroid group as depicted in Table no.6., the difference thus being insignificant but the indication for LSCS in both the groups had significant variation (p=<0.01) with fetal distress being in 34.41% in non-steroid group as compared to 12.50% in steroid group. Failed induction was the main indication for LSCS in steroid group being 33.33% and only 6.45% in non-steroid group.

In a prospective RCT by Porto et al in Brazil in 2012, 98 of 143 women delivered vaginally (69%) in the steroid group as compared to 90 of 130 women (69%) in the non steroid group[27].

In another retrospective study by Kamath-Rayne et al in Ohio in 2012 36 of 76 women (48%) and 72of 102 women (71.3%) delivered by caesarean section in patients who were managed expectantly and in whom steroids was given after immature lung indices were documented on amniocentesis, respectively[48].

BIRTH WEIGHT:

In the present study, as shown in Table no. 9,no significant difference (p=0.688) was found in the mean birth weight in group receiving steroid (2.28±0.63) and not receiving steroid(2.24±0.55). Similar results were obtained in the RCT done by Porto et al. where mean birth weight was 2.8 kg in steroid group as compared to 2.62 kg in placebo group thus showing no statistical significance (p=0.80).

A retrospective cohort study done by Kamath-Rayne et al in Ohio over 362 women in 2012 concluded that steroid administration and delivery ,after immature

lung indices were demonstrated by amniocentesis, resulted in mean birth weight of 2.7±0.5kg which was comparable to the group of patients who were managed expectantly being 2.7±0.8kg, a third group with documented mature fetal lung indices had mean birth weight of 2.8±0.5 kg, thus concluding that there was no statistical significance(p=0.25) and that steroid administration does not have an effect on mean birth weight in late preterm[48].

Another retrospective study done in 2012 by Yinon et al. over 167 women concluded that mean birth weight which was 2.79 kg in steroid group was comparable to 2.590 kg in non-steroid group and thus the difference was not statistically significant (p=0.17). Thus antenatal corticosteroid administration does not have a potential effect on birth weight in late pretems[49].

GESTATIONAL AGE AT DELIVERY:

The mean gestational age at delivery in our study,as shown in Table no. 8, was comparable in both the groups being 35.37±0.85 in the steroid group as compared to 35.00±0.83 in the non-steroid group. The difference thus being insignificant.

In a retrospective study by Yinon Y et al in 2012 over 167 women the gestational age at delivery was 37 weeks in the steroid group when compared to 36 weeks in non steroid group(p=0.4)[49]

In a prospective study by Porto et al in 2012 the mean gestational age at delivery was 35.6 weeks in the steroid group as compared to 35.5 weeks in the nonsteroid group[27].

APGAR SCORE:

Our study demonstrated that APGAR score ,the most important early demonstrable assessment of fetal wellbeing, was <7 at 1 minute in 59.38% of neonates in steroid group compared to 61.29% in non steroid group, as demonstrated in Table no.10. Though a difference was observed but it did not reach a statistical significance (p=0.452).

APGAR score at 5 minutes was <7 in 26.04% in steroid group as compared to 33.33% in non steroid group. The mode of delivery, a factor which can have significant impact on APGAR score, was comparable in both the groups with caesarean section percentage being more. Thus, no additional benefit of steroid was noticed in improving the APGAR score in late preterm births.

Consistent with the aforementioned findings, another RCT in Brazil by Porto et al in 2012 study showed that median number of neonates with APGAR score <7 at 1 minute to be 8 in steroid group with 8 also being in placebo group(p=0.20) and median no. of neonates with APGAR score <7 at 5 minutes to be 9 in both the groups with 1% and 2% of neonates in both the groups respectively[27].

Thus both the above studies conclude that antenatal corticosteroid administration did not improve APGAR score in late preterms.

ADMISSION TO NICU:

As shown in Table no. 11,out of 96 neonates analyzed in steroid group 49(51.04%) required NICU admission as compared to 45 of the 93 neonates analyzed in non-steroid group(48.39%) ,indicating no significant impact of antenatal corticosteroid (p=0.715) in reducing the rate of NICU admission.

A retrospective cohort study by Yinon et al. in 2012 over 167 women states that though the rate of admission to the special care unit was higher in the group not receiving steroid than the group receiving steroid ,but the difference did not reach a statistical significance (29% Vs 17%) with p=0.07. But the study still considered this as one of their impactful clinical outcome with regard to steroid administration[49].

Another retrospective cohort study in Ohio over 362 women by Kamath-Rayne et al stated that expectantly managed neonates were 40% less likely to have composite adverse neonatal outcome (adjusted OR 0.59, 95% CI 0.28-1.28,P=0.18) than the neonates who were given steroids and pregnancy terminated after documentation of immature fetal lung indices. The NICU admission rate being in 3 of 11 neonates (27.3%) as compared to 19 of 65 neonates(29.2%) ,though this figure could not reach a statistical significance(p=0.06). In the third group after adjustment with some covariates, neonates born after documented mature lung indices were 50% less likely to have the composite adverse neonatal outcome (14% as compared to 26.5% ,adjusted OR 0.51,95%CI 0.27-0.96,P=0.04) when compared to the steroid administered group, thus reaching a statistical significance . The study thus states that once immature lung indices are documented, expectant management as long as maternal and fetal wellbeing persists should be opted rather than steroid administration and immediate delivery[48].

Another RCT study enrolling 320 late preterm concluded that steroid administration did not decrease the rate of admission to NICU .Their results showed that 33% of neonates were admitted in NICU in steroid group and 33% were admitted in non steroid group with p=0.97[27].

RESPIRATORY DISTRESS SYNDROME:

The most important outcome studied in this trial was respiratory distress syndrome which has the most significant impact on neonates and healthcare system. It was defined by presence of respiratory distress for more than 2 hours after birth and characterized by tachypnoea, expiratory grunting ,chest wall retraction , flaring of nostrils , cyanosis, having need for oxygen, CPAP, need for mechanical ventilation or surfactant or X-ray demonstrating diffuse reticulogranular infiltrate.

In our study, as shown in Table no.12, RDS was present in 8 neonates (8.33%) in steroid group as compared to 7 neonates (7.53%) in non steroid group. Thus it indicates that steroid administration did not significantly lower the rate of RDS in late preterm births (p=0.838). In a stratified sub analysis to detect any difference in the effect of corticosteroid by gestational age, the rate of respiratory distress was 1.04% in 34 to 34+6 weeks, 5.21% in 35 to 35+6 weeks and 2.08% in 36 to 36+ 6 weeks as compared to 3.23%, 4.30% and 0% respectively in non-steroid group ,thus indicating no statistical significance.

Another similar RCT BY Porto et al. in Brazil over 320 women also consented stating that steroid administration in late preterm failed to reduce the risk of respiratory distress in late preterms. Rate of RDS being 1.4% in steroid group and 0.8% in placebo group (p= 0.54) ,with one baby in steroid group requiring exogenous surfactant. Necessity for ventilator support was also similar being 20% in steroid group and 19% in placebo group[27].

A retrospective cohort study by Kamath-Rayne et al. in 2012 in Ohio demonstrated that composite adverse respiratory outcome was significantly less

(p=0.01) in late preterms subjected to expectant management being 0% as compared to 9% neonates terminated after steroid administration, once amniocentesis showed immature fetal lung indices. The need for oxygen supplementation was 0% Vs 13.9%, need for continuous positive airway pressure 0% Vs 6.2% and time on respiratory support 0% Vs 4.7% in both the groups respectively. Thus the statistical significance reached p=0.01 for oxygen supplementation, 0.08 for CPAP, and 0.11 for time on respiratory support. These results thus concluded that if fetal lung indices are immature, expectant management should be opted than steroid and immediate delivery[48].

On the contrary another retrospective cohort study by Yinon et al in 2012 states that rate of RDS was 2.4% in their study as compared to 8.3% in no steroid group . Though this difference was impactful but it failed to reach a statistical significance (p=0.16). But it also states that need for respiratory support was 8.4% Vs 20% and composite respiratory morbidity was 7% Vs 18% in steroid group and non steroid group respectively , both of which reached a statistical significance with p=0.03 for need for respiratory support and p= 0.036 for composite respiratory morbidity. Patients who received steroid therapy had a significantly lower TD_XFLMII value compared to patients who were not treated with steroids (29 Vs 32.7mg/dl with p=0.036). However multiple linear regression analysis was used and adjustment was made for TD_XFLMII test results. The final regression revealed that corticosteroid administered were independently associated with reduced composite respiratory morbidity outcome (adjusted odds ratio 0.23 95 CI 0.07-0.78). But the limitation of this study was that it was a retrospective cohort study although they had performed multiple linear regression analysis[49].

Thus in our study steroid administration failed to reduce the rate of RDS. Further large Randomized control trials are needed to substantiate on the same.

TRANSIENT TACHYPNOEA OF NEWBORN:

In our study, as depicted in Table no. 12, TTN was more common than RDS, being present in 19 of 96(19.79%) in the group receiving steroid as compared to 23 of 93(27.73%) in the group not receiving steroid. Though steroid administration reduced the rate of TTN but the difference failed to reach a statistical significance (p=0.485). Subsequent stratified analysis showed that rate of TTN was 8.33% Vs 6.45% in 34 to 34+6 weeks, 6.25% Vs 6.45% in 35 to 35+6 weeks and 5.21% Vs 11.83% in 36 to 36+6 weeks. But the differences failed to reach any statistical significance.

Another RCT in Brazil by Porto et al in 2012 over 320 women showed that rate of TTN was higher than RDS in late preterm yet a statistical significance was not reached when steroid were administered antenatally . The rate being 24% in steroid group and 22% in placebo group. (p=0.77).It also stated that treatment with corticosteroid failed to reduce the risk of any respiratory morbidity in late preterms. (Risk ratio 1.09, 95%CI 0.72-1.66)[27]

Similar results were noted in another retrospective cohort study by Yinon et al in 2012 over 167 women which claims that rate of TTN was 6% Vs 12% in steroid and non-steroid group respectively. Though a statistical significance could not be reached with p=0.28[49].

REQUIREMENT OF PHOTOTHERAPY:

One of the current debatable aspects regarding benefit of steroid in preventing neonatal hyperbilirubinemia was also assessed in our study. As shown in Table no. 12,33 of 96 (34.38%) neonates required phototherapy in the steroid group as compared to 30 of 93 (32.26%) of neonates in non-steroid group thus clearly ruling out any beneficial role of antenatal corticosteroid in reducing requirement of phototherapy in late preterm.

On contrary ,in the study done by Porto et al. over 320 in 2012 women who delivered in late preterm, it was found that the rate of requirement of phototherapy in neonates suffering from hyperbilirubinemia was 24% as compared to 38% in placebo group thus reaching a statistical significance of p= 0.01 with risk ratio of 0.63(0.44 to 0.92). The rate of hyperbilirubinemia was 53% in steroid group as compared to 57% in placebo group (p= 0.57). The possible mechanism that they stated was that similar to lung maturation, liver maturation could also be accelerated with corticosteroid, the details of which are still unknown. One of the major limitation of this study was that 43 patients were loss to follow up and study was not powered sufficiently [27].

Kamath-Rayne et al. in 2012 in a retrospective cohort study over 362 women found that phototherapy was required in 2 of 11 neonates (18.2%) as compared to 3 of 65 (4.6%) neonates who were managed expectantly Vs who were given steroid after documentation of immature fetal lung index and pregnancy was terminated thereafter, respectively. Whereas in third group who delivered in late preterm but amniocentesis had documented mature lung indices, 4 of 70 neonates(5.7%) required phototherapy. Thus this result could not reach statistical significance.[48]

Though the retrospective nature of the study may introduce bias based on inherent differences among pregnancies in which one approach was chosen over the other, the difference in reason for amniocentesis testing may influence the frequency of morbidities.

In another retrospective cohort study, rate of hyperbilirubinemia was 23% in steroid group as compared to 29% in non-steroid group. The result thus being insignificant (p=0.4), but requirement of phototherapy was analyzed subsequently.

Thus due to various conflicting results regarding rate of hyperbilirubinemia and requirement of phototherapy in late preterms and regarding the potential benefit of steroids in reducing the same, further randomized control trials having a large sample size are needed to draw a conclusive result.

SEPSIS IN THE FIRST 48 HOURS:

One of the most dreaded complication of steroid use especially in cases of preterm labour and prelabour rupture of membrane, is neonatal sepsis and warrants a thorough research. This important morbidity was analyzed in our study. Since blood culture could not be done for all patients in our study complete blood count was done for documenting systemic infection and blood culture was done for selected patients only. Our study, as shown in Table no. 12, showed that the rate of systemic infections was 12.50% with 12 in 96 neonates being affected in steroid group as compared to 9 in 93 neonates (9.68%) in non-steroid group. Though a difference was noted but it failed to reach a statistical significance. The stratified analysis also showed 3.13% of neonates developing systemic infection in steroid group as compared to 3.23% in

non-steroid group in patients delivering between 34-34+6 weeks, 4.17% Vs 3.23% in 35-35+6 weeks and 5.21% Vs 3.2% in 36-36+6 weeks, respectively.

Porto et al. in 2012 demonstrated that neonatal sepsis was present in 4% in steroid group as compared to 7 % in non-steroid group with difference being nonsignificant (p=0.6), risk ratio of 0.32 and 95%CI being 0.22-1.64[27].

In a retrospective cohort study done in Ohio by Kamath-Rayne et al, rate of sepsis was 9.1 % in patients managed expectantly as compared to 26.2% who were known to have immature lung index and thus were given steroid as they were at risk of imminent preterm delivery. This result reached a statistical significance of p=0.02. ,further emphasizing on the fact that once immature fetal lung indices are documented, expectant management should be the line of treatment as long as fetal and maternal wellbeing permits. Treatment with antibiotics was 0% in expectantly managed neonates as compared to 13.9% in steroid group. Thus the difference reached a statistical significance of p=0.01. However since this was a retrospective study, bias of administering steroid in high risk pregnancy could not be excluded and is thus a limitation[48].

Another retrospective cohort study by Yinon et al. in 2012 over 167 women demonstrated 0% rate of sepsis in steroid group as compared to 3% in non-steroid group, the result not reaching a statistical significance[49].

Thus steroids have been demonstrated to have neither a beneficial nor harmful role in perinatal outcome in late preterms but still it warrants further studies.

DURATION OF STAY IN NICU:

Mean stay in NICU in our study, as shown in Table no. 11, was 6.80±3.67 days in the steroid group as compared to 8.80±4.88 days in the non-steroid group. The difference here was statistically significant with p=0.031

The study of Porto et al. in 2012 in Brazil demonstrated mean duration of stay in NICU to be 2.2 days in steroid group as compared to 2.8 days in placebo group thus not achieving any statistical significance p=0.65.[27]

Another retrospective cohort study done in 2012 by Yinon et al also consented with above findings stating that in their study median duration of stay was 4 days in steroid group as compared to 5 days in the group who had not received steroid ,thus having no statistical significance with p=0.18[49].

Thus , our study demonstrates no significant reduction in perinatal morbidity and mortality by corticosteroid administration in antenatal period in women who are risk of imminent late preterm delivery except reduction in the mean duration of stay in NICU(p=0.031).

CONCLUSION

With the increasing incidence of preterm deliveries, and 70-80% of which fall in late preterm group(34-36+6), a considerable issue on health care is to reduce the perinatal mortality and morbidity in late preterm. Though lung maturity is attained at 34 weeks but 28.9% of neonates still suffer from respiratory morbidity in late preterms. Antenatal corticosteroid are cost effective, simple, acceptable, safe intervention to prevent perinatal morbidity and mortality in preterm births. But a possible extension of this benefit in late preterm was the objective of our study and was evaluated.

There is no significant difference between the gestational age at delivery, birth weight and APGAR score in the neonates who had received steroid than who did not receive steroid and delivered in late preterm. No statistically significant difference was found in rate of RDS with 8.33% being in steroid group and 7.53% being in non-steroid group(p=0.838). 19.79% of patients had TTN when compared to 24.73% in non-steroid group,the difference being insignificant(p=0.485). The requirement of phototherapy was present in 34.38% of neonates in steroid group and 32.28% of neonates in non-steroid group(p=0.875). Systemic infections in the first 48 hours were acquired by 12.50% of neonates in steroid group and 9.68% of neonates in non-steroid group (p=0.537)**.** In our study, mean stay in NICU was 6.80±3.67 days in the steroid group as compared to 8.80±4.88 days in the non-steroid group. The difference here was statistically significant with p=0.031.

Thus, our study demonstrates no significant reduction in perinatal morbidity and mortality by corticosteroid administration in antenatal period in women who are

risk of imminent late preterm delivery except reduction in the mean duration of stay in NICU(p=0.031).

Further research with longer follow up of infants and also evaluation maternal outcome are essential to substantiate on effect of antenatal corticosteroid in late preterm births.

SUMMARY

There is no formulated guideline on the administration of corticosteroid in women who are at risk of imminent premature delivery in late preterm (34+0 to 34+6). Evidence published data has not clearly established the impact of antenatal corticosteroid in late preterm births thus necessitating further research.

This is a prospective randomized controlled study the objective of which is to assess the effect of antenatal corticosteroid in reducing the perinatal morbidity and mortality in late preterm births.

Out of 5073 patients who delivered in the study period 869 (17.1%) patients had preterm delivery. In this 626 (72%) patients delivered in the late preterm i.e. between 34+0 to 36+6 weeks. 200 of women among these who were fulfilling inclusion criteria and were consenting were randomized,105 being in group A and 95 in group B. 11 patients were excluded from the study after recruitment as 9 patients in group A delivered before 24 hours of 1st dose of steroid, ,1 patient in group B had antepartum haemorrhage after randomization and 1 patient in group B went against medical advice.

Finally 189 patients were analyzed in our study of which 96 women were randomized in group A i.e. group receiving steroid and 93 in group B i.e. group not receiving steroid.

The perinatal outcome which were studied were - Gestational age at delivery, Birth weight , APGAR score at 1 and 5 minute, NICU admission and Indication for NICU admission.

The mean maternal age was comparable being 24.95±3.88 in steroid group as compared to 24.13±3.43 in non-steroid group.

There was a significant difference (p=0.023) in parity with 54.17% being primigravida and 45.83% being multigravida in steroid group as compared to 37.63% being primigravida and 62.37 % being multigravida in non-steroid group.

Mean gestational age at enrolment was comparable in both groups being 35.66±0.86 in steroid group and 35.75±0.87 in non-steroid group with p=0.498.

The most common cause for late preterm delivery in our study was hypertensive disorder of pregnancy which constituted 33.33% in steroid group and 30.11% in non-steroid group. There was a significant difference in number of patients having gestational diabetes mellitus being 11.96% in steroid group as compared to 2.15% in non-steroid group. 16.67% of patients had preterm labour in steroid group and 35.48% in non-steroid group. There was a significant difference in number of patients having IUGR which was present in 17.71% in steroid group and 8.60% in non-steroid group.

The indication for LSCS in both the groups had significant variation (p=<0.01) with fetal distress being in 34.41% in non-steroid group as compared to 12.50% in steroid group. Failed induction was the main indication for LSCS in steroid group 33.33% and only 6.45% in non-steroid group

There was no perinatal mortality in both the groups. The gestational age at delivery was comparable in both the groups with mean gestational age being 35.37±0.85 in steroid group Vs 35.00±0.83 in non-steroid group(p=0.363).

Mean birth weight did not vary significantly in both the groups with 2.28 ±0.63 kg being in steroid group and 2.24±0.55kg in non-steroid group(p=0.6888).

APGAR score at 1 minute was comparable in both the groups with APGAR score<7 being in 59.38% in steroid group and in 61.29% in non-steroid group(p=0.452). APGAR score <7 at 5 minutes was present in 26.04% of patients in steroid group and 33.33% in non-steroid group(p=0.272).

No statistically significant difference was found in rate of RDS with 8.33% being in steroid group and 7.53% being in non-steroid group. (p=0.838).

In our study 19.79% of patients had TTN , the respiratory morbidity which is more common in late preterm than RDS ,when compared to 24.73% in non-steroid group. The difference being insignificant (p=0.485)

No cases of pneumonia were found in either group.

Another important consideration of this study, the requirement of phototherapy was present in 34.38% of neonates in steroid group and 32.28% of neonates in non-steroid group (p=0.875)

Systemic infections in the first 48 hours were acquired by 12.50% of neonates in steroid group and 9.68% of neonates in non-steroid group (p=0.537) **.**In our study ,mean stay in NICU was 6.80±3.67 days in the steroid group as compared to 8.80±4.88 days in the non-steroid group. The difference here was statistically significant with p=0.031.

Cochrane Database of Systemic Reviews 2013 advocates administration of steroid till 34+6 weeks. And RCOG guidelines 2010 states that corticosteroid should

be administered between 24 to 34+6 weeks. Few studies have been done to assess the possible benefit of steroid after 34 weeks.

Our study demonstrates no significant reduction in perinatal morbidity and mortality by corticosteroid administration in antenatal period in women who are risk of imminent preterm delivery except reduction in the mean duration of stay in NICU. But nonetheless further Randomized control trials with large sample size are required to substantiate on the same.

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ANNEXURE-I

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Ms _____

You are invited to participate in our research study titled **"EFFECTIVENESS OF ANTENATAL CORTICOSTEROIDS IN REDUCING PERINATAL MORBIDITY AND MORTALITY IN LATE PRETERM BIRTH- A RANDOMIZED CONTROL TRIAL"**

Respected Sir/Ma'am we request you to enroll yourself in our study as you are eligible for participation. Your participation in research is voluntary. If you decide to participate you are free to withdraw at any time.

Purpose of the Study: The purpose of research is to determine the effectiveness of antenatal corticosteroids in reducing perinatal morbidity and mortality in late preterm births..

Procedure Involved: If you agree to enroll yourself in this study, you will be asked your present, past and family history. You will be clinically examined and relevant investigations will be done. You will be asked to undergo an intervention in which either you will be given injection betamethasone 12 mg ,2 doses 24 hour apart or no intervention will be done and progress and outcome of labour will be monitored.and documented.

Risks and Benefits: There are no major risks involved, however some complications may occur primarily due to the risks of prematurity itself . Your participation may

benefit you and others with the same condition in future, by helping us learn more about the late preterm births and effect of steroids on it. No financial incentives are promised for being a part of the study.

Alternatives: If you are not willing to participate you will be treated according to the existing protocol & it will not affect your relationship with this hospital.

Costs for participating in this research: There will not be any extra cost incurred by you. There is no commitment for any reimbursement or any other compensation.

Privacy and Confidentiality: Your privacy is guaranteed. However, your medical records can be directly accessed and reviewed by authorized individuals or by the ethics committee. Records, which could reveal your identity, will be kept confidential. Personal data will remain anonymous if data is being published or written as a dissertation.

Authorization to Publish Results: When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity.

Compensation: In the event of injury related to the study, treatment will be made available through KLES Dr.Prabhakar Kore Hospital & MRC, Belgaum. There is no compensation or payment for such medical treatment by law. The doctors and the staff will provide facilities and medical attention to you.

Questions

If you have any questions about the research you may please contact:

1. Dr. A.S. GODHI , Principal, JNMC, Belgaum and Chairman, Institutional Ethics Committee. Contact No. (0831) 2471350

ಸಂಶೋಧನೆ ಪ್ರಯೋಗದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಸಮ್ಮತಿ

ನಾನು ಶ್ರೀ//ಶ್ರೀ/ಶ್ರೀ ಮತಿ _____ ಸ್ವಯಂ ಪ್ರೇರಣೆಯಿಂದ ಈ ಅಧ್ಯಯನದ ವಿಷಯವಾಗಿ ಭಾಗವಗಿಸಲು ಒಪ್ಪುತ್ತೇನೆ. ಈ ಸಮ್ಮತಿ ಪತ್ರವನ್ನು ಸಹಿ ಮಾಡುವುದರಿಂದ ನನ್ನ ಯಾವುದೇ ಹಕ್ಕುಗಳನ್ನು ಕಳೆದುಕೋಳ್ಳುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸುವಿಕೆಯನ್ನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಹಿಂತೆಗೆದುಕೊಳ್ಳಹುದು. ನಾನು ಸಮ್ಮತಿ ಪತ್ರವನ್ನು ಓದಿದ ನಂತರ, ನನ್ನ ಸ್ವಂತ ದೇಶಿಯ ಭಾಷೆಯಲ್ಲಿ ಓದಿದ ನಂತರ ಅಥವಾ ಅಪಾಯ ಮತ್ತು ಲಾಭಗಳನ್ನು ತಿಳಿದ ನಂತರ ನಾನು ಒಪ್ಪಿಗೆ ಪತ್ರಕ್ಕೆ ಸಹಿ ಮಾಡಲಾಗಿದೆ.

ವಿಷಯದ ಹೆಸರು: _____

ವಿಷಯದ ಸಹಿ ಅಥವಾ ಹೆಬ್ಬೆರಳು ಮುದ್ರಣ: _____

ಸಂಶೋಧಕಿಯ ಹೆಸರು: _____

ಸಂಶೋಧಕಿಯ ಸಹಿ: _____

ದಿನಾಂಕ: _____

ಮಾರ್ಗದರ್ಶಿಯ ಹೆಸರು: _____

ಮಾರ್ಗದರ್ಶಿಯ ಸಹಿ: _____

ಗೌಪ್ಯವಾಗಿ ಇಡಲಾಗುತ್ತದೆ. ಒಂದು ವೇಳೆ ಸುದ್ದಿಯನ್ನು ಪ್ರಕಟಿಸುವಾಗ ಅಥವಾ ಪ್ರೌಢಪ್ರಬಂದ ಬರೆಯುವಾಗ ವೈಯಕ್ತಿಕ ವಿಷಯವನ್ನು ಗೌಪ್ಯವಾಗಿ ಇಡಲಾಗುವುದು.

ರಿಸುಟ್ ಪ್ರಕಟಣೆಗೆ ಅಧಿಕಾರ: ಸಂಶೋಧನೆಯ ಫಲಾಂಶಗಳು ಪ್ರಕಟವಾದ ಅಥವಾ ಕುರಿತು ಚರ್ಚಿಸುವಾಗ, ಯಾವುದೇ ನಿಮ್ಮ ಮಾಹಿತಿ ಗುರುತನ್ನು ಬಹಿರಂಗಪಡಿಸಬಹುದು ಎಂದು ತೋರಿಸಲ್ಪಡುತ್ತದೆ.

ಪರಿಹಾರ: ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಯಾವುದೇ ಗಾಯಗಳಾದರೆ, ಕೆ ಎಲ್ ಇ ಡಾ ಪ್ರಭಾಕರ ಕೋರೆ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಎಂಆರ್ಸಿ, ಬೆಳಗಾವಿ ಅವರಿಂದ ಚಿಕಿತ್ಸೆ ಕೊಡಲಾಗುವುದು. ಕಾನೂನು ವ್ಯಾಪ್ತಿಯಲ್ಲಿ ವೈದ್ಯಕೀಯ ಚಿಕಿತ್ಸೆಗಾಗಿ ಯಾವುದೇ ಪರಿಹಾರ ಅಥವಾ ಪಾವತಿ ಇಲ್ಲ. ವೈದ್ಯರು ಮತ್ತು ಸಿಬ್ಬಂದಿ ನಿಮಗೆ ಸೌಲಭ್ಯಗಳನ್ನು ಮತ್ತು ವೈದ್ಯಕೀಯ ಗಮನ ಒದಗಿಸುತ್ತದೆ.

ಪ್ರಶ್ನೆಗಳು

ಸಂಶೋಧನೆ ಬಗ್ಗೆ ಯಾವುದೇ ಪ್ರಶ್ನೆಗಳಿದ್ದಲ್ಲಿ, ದಯವಿಟ್ಟು ಈ ಕೆಳಗಿನ ಕೊಟ್ಟ ದೂರವಾಣಿ ಸಂಖೆಯನ್ನು ಸಂಪರ್ಕಿಸಿ.

3. ಮಾರ್ಗದರ್ಶಿ, ಎ. ಎಸ್. ಗೋದಿ, ಪ್ರಾಂಶುಪಾಲರಾದ ಜೆಎನ್ಎಮ್ಸಿ, ಬೆಳಗಾವಿ ಹಾಗೂ ನೈತಿಕ ಸಮಿತಿಯ ಅಧ್ಯಕ್ಷರು, **ದೂರವಾಣಿ ಸಂಖೆ: (0831) 2471350**

ಸಂಶೋಧನಾ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಗೆ

ಶ್ರೀ//ಶ್ರೀ/ಶ್ರೀ ಮತಿ _____

, ಇವರ ಮಾರ್ಗದರ್ಶನದಲ್ಲಿ ನಡೆಸುತ್ತಿರುವ "ಪ್ರಸವಪೂರ್ವ ಜನ್ಮ ಪರಿನಾಟಲ್ ಮತ್ತು ಸಾವಿಗೆ ತಗ್ಗಿಸುವಲ್ಲಿ ಪ್ರಸವಪೂರ್ವ ಕೋರ್ಟಿಕೋಸ್ಟೆರಾಯ್ಡ್ಗಳ ಪರಿಣಾಮಕಾರಿತ್ವವನ್ನು ಒಂದು ಯಾದೃಚ್ಛಿಕ ನಿಯಂತ್ರಣಾ ಪ್ರಯೋಗ" ಎಂಬ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಿಮ್ಮನ್ನು ಆಮಂತ್ರಿಸಲಾಗಿದೆ.

ಗೌರವಾನ್ವಿತ ಸರ್/ಮ್ಯಾಡಮ ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಅರ್ಹರಾಗಿರುವುದರಿಂದ ನಾವು ನಿಮಗೆ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಮನವಿ ಮಾಡುತ್ತೇವೆ. ಸಂಶೋಧನೆಯಲ್ಲಿ ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆ ವೈಯಕ್ತಿಕವಾಗಿರುತ್ತದೆ. ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನಿರ್ಧರಿಸಿದರೆ ನೀವು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಹಿಂದಕ್ಕೆ ತೆಗೆದುಕೊಳ್ಳಬಹುದು. ಹಸ್ತಕ್ಷೇಪಕ್ಕೆ ಒಳಗಾಗಲು ಕೇಳಲಾಗುತ್ತದೆ ಅಥವಾ ಯಾವುದೇ ಹಸ್ತಕ್ಷೇಪ ಮಾಡಲಾಗುತ್ತದೆ. ಪ್ರಗತಿ ಮತ್ತು ಕಾರ್ಮಿಕ ಫಲಿತಾಂಶದ ಮೇಲ್ವಿಚಾರಣೆ ದಾಖಲಾತಿ ಮಾಡಲಾಗುತ್ತದೆ.

ಅಧ್ಯಯನದ ಉದ್ದೇಶ: ಕೋರ್ಟಿಕೋಸ್ಟೆರಾಯ್ಡ್ಗಳ ಮೂಲಕ "ಪ್ರಸವಪೂರ್ವ ಜನನ ಮತ್ತು ಅದರಿಂದಾಗುವ ಸಾವಿನ ಸಂಖ್ಯೆ ಕಡಿಮೆ ಮಾಡುವುದು" ಈ ಅಧ್ಯಯನದ ಮುಖ್ಯ ಉದ್ದೇಶ.

ಒಳಗೊಂಡ ವಿಧಾನ: ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನಿಮ್ಮನ್ನು ದಾಖಲಾಗಲು ಒಪ್ಪಿದ್ದಲ್ಲಿ, ನಿಮ್ಮ ವರ್ತಮಾನ, ಭೂತ ಮತ್ತು ಕುಟುಂಬದ ಇತಿಹಾಸವನ್ನು ಕೇಳಲಾಗುತ್ತದೆ. ನಿಮ್ಮನ್ನು ಪ್ರಾಯೋಗಿಕವಾಗಿ ವಿಚಾರಣೆ ಮಾಡಲಾಗುವುದು ಮತ್ತು ಸೂಕ್ತವಾದ ತನಿಕೆ ಮಾಡಲಾಗುವುದು. 24 ಗಂಟೆ ಹೊರತುಪಡಿಸಿ ನಿಮಗೆ ಬೆಟಾಮೆತಾಸಾನ್ 12ಎಮಜಿ 2 ಪ್ರಮಾಣ ಇಂಜೆಕ್ಷನ್ ನೀಡಲಾಗುವುದು.

ಅಪಾಯ ಮತ್ತು ಲಾಭಗಳು: ಪ್ರಮುಖವಾಗಿ ಯಾವುದೇ ಅಪಾಯಗಳನ್ನು ಒಳಗೊಂಡಿಲ್ಲ. ಅದಾಗ್ಯೂ ಪ್ರಿಮ್ಯಾಚುರಿಟಿಯಿಂದ ಕೆಲವು ತೊಡಕುಗಳು ಸಂಭವಿಸಬಹುದು. ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆ ನಮಗೆ ಪ್ರಸವಪೂರ್ವ ಜನನ ಮತ್ತು ಅದರ ಮೇಲೆ ಸ್ಟರಾಯ್ಡಗಳ ಪರಿಣಾಮ ಬಗ್ಗೆ ಹೆಚ್ಚು ತಿಳಿಯಲು ಸಹಾಯ ಮಾಡುತ್ತದೆ. ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಿದ್ದಕ್ಕೆ ಯಾವುದೇ ಹಣಕಾಸಿನ ಪ್ರೋತ್ಸಾಹ ನೀಡಲಾಗುವುದಿಲ್ಲ.

ಪರ್ಯಾಯ: ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪದಿದ್ದಲ್ಲಿ, ನೀವು ಆಸ್ಪತ್ರೆಯಲ್ಲಿರುವ ಪ್ರೋಟೋಕಾಲ್ ಪ್ರಕಾರ ಪರಿಗಣಿಸಲಾಗುತ್ತದೆ. ಇದು ನಿಮ್ಮ ಸಂಭಂದ ಮತು ಆಸ್ಪತ್ರೆಯ ಮೇಲೆ ಯಾವುದೇ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ.

ಈ ಸಂಶೋಧನೆಯಲ್ಲಿ ಭಾಗವಹಿಸವ ವೆಚ್ಚ: ನಿಮಗೆ ಯಾವುದೇ ಹೆಚ್ಚುವರಿ ವೆಚ್ಚ ಉಂಟಾಗುವುದಿಲ್ಲ. ಯಾವುದೇ ಮರುಪಾವತಿ, ಯಾವುದೇ ಪರಿಹಾರ ಅಥವಾ ಯಾವುದೇ ಬದ್ಧತೆ ಇಲ್ಲ.

ಗೌಪ್ಯತೆ ಮತ್ತು ರಹಸ್ಯ: ನಿಮ್ಮ ಗೌಪ್ಯತೆಯ ಭರವಸೆ ಇದೆ. ನಿಮ್ಮ ವೈದ್ಯಕೀಯ ದಾಖಲೆಗಳನ್ನು ನೇರವಾಗಿ ಅಧಿಕಾರ ವ್ಯಕ್ತಿಗಳು ಅಥವಾ ನೈತಿಕತೆಯ ಸಮಿತಿಯವರು ವಿಮರ್ಶ ಮಾಡಬಹುದು. ನಿಮ್ಮ ಗುರುತನ್ನು, ದಾಖಲೆಗಳನ್ನು ಬಹಿರಂಗವಾಗಿ,

ANNEXURE-II

PROFORMA

EFFECTIVENESS OF ANTENATAL CORTICOSTEROIDS IN REDUCING PERINATAL MORBIDITY AND MORTALITY IN LATE PRETERM BIRTH - A RANDOMIZED CONTROL TRIAL

S.I.No. Date: Time:

OP/IP No.

Registered/Unregistered

Patients Name:

Age:

Address:

Contact number:

Obstetric History:

G: P: L: A: D:

Menstrual History:

LMP

EDD

Period of Gestation:

USG PARAMETERS	1st TRIMESTER	2nd TRIMESTER	3rd TRIMESTER
BIPARIETAL DIAMETER			
HEAD CIRCUMFERENCE			
ABDOMINAL CIRCUMFERENCE			
FEMUR LENGTH			
EXPECTED DATE OF DELIVERY			

DIAGNOSIS:

INTERVENTION A OR INTERVENTION B:

1st Dose: DATE: TIME:

2nd Dose: DATE: TIME:

Delivery details:

Date: Time: AM/PM

Duration between the administration of drug and delivery:

NEONATAL DETAILS:

Perinatal mortality: YES/NO

Gestatonal age: 34-35wk ☐ 35-36wk ☐ 36-37wk ☐

Birth weight: 1.5-1.9kg ☐ 2.0-2.4kg ☐ 2.5-2.9kg ☐ 3.0-3.5kg ☐

Apgar score:

1 min-

5 min-

Admission to NICU: YES/NO

Indication for NICU admission:

Respiratory Distress Syndrome: YES/NO

Transient tachypnoea of newborn: YES/NO.

Pneumonia: YES/NO.

Requirement of Phototherapy: YES/NO

Sepsis in the first 48 hours of life: YES/NO

Duration of stay in NICU:

KEY TO MASTER CHART

D.M.	-	Diabetes Mellitus.
GDM	-	Gestational diabetes mellitus.
G.HTN	-	Gestational Hypertension.
IUGR	-	Intrauterine growth restriction.
PTL	-	Preterm labour.
PPROM	-	Premature prelabour rupture of membrane.
PIH	-	Pregnancy induced hypertension.
POLY	-	Polyhydramnios.
Rh ISO	-	Rh isoimmunisation.