“THE ROLE OF PROGESTERONE IN MAINTENANCE THERAPY FOLLOWING ARRESTED PRETERM LABOUR : A RANDOMIZED CONTROLLED TRIAL”

REG.NO. BJ0110004

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

MASTER OF SURGERY
in
OBSTETRICS AND GYNAECOLOGY

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"THE ROLE OF PROGESTERONE IN MAINTENANCE THERAPY FOLLOWING ARRESTED PRETERM LABOUR : A RANDOMIZED CONTROLLED TRIAL"** is a bonafide research work done by **THE CANDIDATE REG NO. BJ0110004**.

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LIST OF ABBREVIATIONS USED

‘p’ value	- Probability value
cAMP	- Cyclic adenoside monophosphate
cGMP	- Cyclic guanosine monophosphate
Cms	- Centimeters
DF	- Degree of freedom
Kg	- Kilogram
LMP	- Last menstrual period
mg	- Milligram
Mins	- Minutes
NICU	- Neonatal intensive care unit
No	- Number
PNMR	- Perinatal mortality rate
PTL	- Preterm labour
RCT	- Randomized controlled trial
SD	- Standard deviation
vs	- Versus

ABSTRACT

Background and objective

Progesterone has long been considered as an important agent in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of preterm delivery. The present study was aimed to determine the role of vaginal micronized progesterone (400 mg) in prolonging the latency period upto 37 weeks of gestation in patients with arrested preterm labour.

Methodology

This study was a randomized controlled trial conducted in the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum. A total of 98 pregnant women fulfilling the inclusion criteria were included in this study. Based on computer generated random numbers, these women were randomized into two groups of 49 each, namely study group (Group S) which received 400 mg of vaginal micronized progesterone and control group (Group C) which did not receive any drug.

Results

Of the 98 patients, four from group C and one from group S were lost to follow up. The mean age of the women in group S was 22.73±3.47 years and in group C it was 24.55±4.14 years. The mean period of gestation at delivery was significantly high in group S (37.25±2.51 weeks). The recurrence of preterm labour was significantly high in the group C as 71.11% of the women delivered before 37 weeks of gestation compared to only 41.66% in group S. Majority of

women (25%) had a latency period between 36 to 42 days in group S. In group C 57.78% had latency period of < 7 days ($p<0.001$). The mean latency period in group S was significantly higher in group C (28.77±15.95 days; $p<0.001$).

Conclusion

Maintenance tocolytic therapy with vaginal micronized progesterone (400 mg) in patients with arrested preterm labour significantly prolonged the latency period and reduced the recurrence of preterm labour.

Keywords:

Arrested preterm labour; Latency period; Progesterone; Preterm labour;

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Chapter 1

Introduction

INTRODUCTION

Preterm birth is the most frequent cause of fetal and neonatal morbidity and mortality.[1] The incidence of preterm birth is variably reported between 5% and 11% of all births,[2,3] Preterm labour is defined as the occurrence of regular uterine contractions (four or more in 20 minutes or eight or more in one hour) and cervical changes (effacement equal to or greater than 80% and dilatation equal to or greater than 1 cm) in women with gestational age between 20 – 37 weeks.[4] Preterm delivery continues to provide an enormous challenge in the delivery of perinatal health care, which is estimated to affect approximately 13 million births annually worldwide.[5]

Infants born preterm are over 40 times more likely to die during the neonatal period than are term infants.[6,7] Though preterm birth contributes to a relatively small proportion of total births, it is associated with an excess of 70% of the total perinatal mortality in developed countries, excluding deaths related to congenital anomalies.[8,9,10]

The incidence of PNMR in India varies from 40 to 50 per 1000 births in contrast to 10-20 in developed countries. Prematurity contributes to 75% of all perinatal and 85% of neonatal deaths.[11]

Threatened preterm is defined as presence of regular, frequent uterine contractions, with digital examination showing cervical dilatation less than 1 cm and the effacement less than 80%.[12]

Use of tocolytics in such patients with threatened preterm labour, may help in prolonging pregnancy by increasing latency period and thereby reduce the incidence of preterm labour and perinatal morbidity. Latency period is the number of days of pregnancy gained after arresting threatened preterm labour till delivery.

The chance to improve neonatal survival increases by 2% for each day prolonged in-utero. Hence, though the patients with arrested preterm labour are at an increased risk for recurrence, the increase in the latency period by even 1 day is of significance. This emphasizes on efforts to maximize gestational age as much as possible.

The effectiveness of tocolytics in patients with preterm labour, to stop uterine contractions (acute tocolysis) or maintain quiescence (maintenance therapy) has been reviewed in the past. The primary therapeutic goal of acute tocolysis is to delay preterm delivery upto 48 hours from the initiation of steroid prophylaxis. Many drugs have been used for this purpose viz. nifedepine, magnesium sulphate, beta-mimetics, indomethacin, atosiban, etc. These drugs have been further tested for maintenance tocolysis. However, long term use of these drugs was observed to have less efficacy and also adverse effects, due to which they are not recommended for maintenance tocolysis.[13]

Nifedepine when used for tocolysis, was seen to be associated with side effects like dyspnoea, pulmonary oedema, myocardial infarction, severe hypotension, hypoxia and elevated liver enzymes.[14]

Maintenance of magnesium sulfate therapy requires strict monitoring and careful assessment of maternal urine output, respiratory rate and deep tendon reflexes, with discontinuation whenever evidence of toxicity exists. In addition, magnesium sulfate readily crosses the placenta and may lead to respiratory and motor depression in the neonate. It is also seen to have adverse effects in the mother.[1]

Ritodrine, a betamimetic, when used for tocolysis, was seen to be associated with maternal adverse effects like chest pain, dyspnoea, tachycardia, palpitations, tremor, headache, pulmonary oedema, hypokalemia, hyperglycaemia, nausea and vomiting, and nasal stuffiness. Also, it did not play any role in the reduction of incidence of neonatal morbidities such as respiratory distress syndrome, cerebral palsy, and necrotising enterocolitis.[1]

Antenatal indomethacin, when used for tocolysis, was associated with an increased risk of periventricular leukomalacia, necrotising enterocolitis and premature closure of ductus arteriosus.[1]

Atosiban, another tocolytic, has been shown to have similar efficacy in preventing preterm labour when compared to betamimetics but with reduced maternal side effects. However, it is very expensive and not available in India.[1] The various studies done, analysing the effectiveness of the above mentioned drugs in maintenance tocolysis, did not recommend these drugs for the same.[1]

On the other hand, progesterone has long been considered an important agent in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of preterm delivery. Progesterone helps in allowing pregnancy to reach its physiologic term because at sufficient levels in the myometrium, it blocks the oxytocic effect of prostaglandin F2 α.[15]

Progestins in women at risk of preterm labour, is seen to improve the latency period and reduce its occurrence by 43%.[16] Women who received progesterone were statistically significantly less likely to give birth before 37 weeks, to have an infant with birth weight of <2.5kg, or to have an infant diagnosed with intraventricular hemorrhage. The use of progesterone contributes to a significant reduction in low birth weight and intraventricular hemorrhage, thus contributing to better neonatal outcome.

Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. However, this is not true for certain artificial progestins. A vaginal pessary of micronized natural progesterone was preferred over intramuscular synthetic 17-hydroxyprogesterone because of enhanced bioavailability and the absence of undesirable side effects such as fatigue, drowsiness and headache. We, therefore, chose this pharmacological agent as the active drug for our study.[15]

Continued tocolytic treatment with any agent after arrest of acute preterm labour has been of questionable value in extending gestation or improving outcome. The efficacy of maintenance tocolytic therapy after successful arrest of

preterm labour, hence, remains controversial.[17] More number of studies are there by required in this front, analysing the need and effectiveness of maintenance tocolytic therapy in prolonging gestation.

Chapter 2

Objectives

OBJECTIVES

The objective of this study was to determine whether maintenance tocolytic therapy with micronized progesterone (400 mg) in patients with arrested preterm labour, prolongs the latency period.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

PRETERM BIRTH

In 1907, Simpson referred to a birth on December 25, 1642 when a widow gave birth prematurely to a male child who was "so small that he could have been put into a quart mug". The infant survived and grew up to be Sir Isaac Newton, who subsequently described gravity. Indeed, this is one of the earliest descriptions of preterm labour.[18]

One hundred years ago, preterm birth was considered an unfortunate event that occurred for unknown reasons and led to loss of the child. Presently, preterm delivery is the major cause of perinatal mortality, and complicates approximately 5-10% of all deliveries. Severe neonatal morbidity, especially respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary dysplasia and necrotising enterocolitis are far more common in preterm infants than in term infants. Long-term impairments such as cerebral palsy, visual impairment and hearing loss are also more common in preterm infants.[1,2]

Unfortunately, the incidence of premature birth has not decreased during the past 40 years. In the United States, preterm delivery affects approximately one in 10 births and is the cause of at least 75% of neonatal deaths, excluding those related to congenital malformations. The incidence of PNMR in India varies from 40 to 50 per 1000 births in contrast to 10-20 in developed countries.[2,11]

Preterm delivery is responsible for 40-75% of neonatal deaths in the developing countries. However, due to continued innovation in neonatal intensive care facilities and obstetric interventions, fetal survival is now possible even at 20 weeks gestation in developed countries. However, even with the best setups in developing countries, salvage is rare below 28 weeks of gestation.[19]

The main burden of preterm birth exists in developing countries. There are no accurate recent worldwide data, but estimates of preterm birth rates range from 5% in developed countries to 25% in developing countries.[2] A study stated that incidence of first time hospitalization for preterm labor is 9% with only 38% delivering in their first episode. Incidence of preterm labor is showing an increasing trend due to assisted reproduction leading to an increase in multiple births, early and late procreation, and better obstetrical intervention.[19]

It is important to appreciate the 'haziness' of the transition between babies who need supportive care in special care baby units, and those that can stay with their mothers. In the North West Thames database consisting of 517,381 births (1988–2000 inclusive), the proportion of babies transferred to a special care baby unit was more than 90% for those born before 33 completed weeks of gestation, but this number fell steadily to below 5% by 39 weeks (83% at 34 completed weeks, 58% at 35 weeks, 31% at 36 weeks, 14% at 37 weeks and 7% at 38 weeks). Approximately, over 40% of babies at 35 weeks of gestation will show signs of lung maturity. Studies have observed that the chance to improve neonatal survival increases by 2%, for each day prolonged in-utero.[20]

Preterm labor is the presence of uterine contractions of sufficient frequency and intensity (4 contractions in 20 mins or 8 in 60 mins) to effect progressive effacement and dilation of the cervix (effacement more than 80% and dilatation > 1cm), prior to term gestation (between 20 and 37 wk).[21,22] A preterm delivery, as defined by the World Health Organization, is one that occurs at less than 37 and more than 20 weeks' gestational age.[4]

Threatened preterm is defined as presence of uterine contractions with the cervical dilatation being less than 1 cm and the effacement less than 80%. Use of tocolytics in such patients with threatened preterm labour, may help in arresting preterm labour and prolonging pregnancy, and thereby reduce the incidence of preterm delivery and perinatal morbidity and mortality.[12]

Tocolytics are drugs used to inhibit or delay contractions during the labor process. Several tocolytics are available to prevent preterm birth. These agents may be administered as primary therapy to control acute episodes of preterm labor or as maintenance therapy to prevent subsequent episodes. Maintenance tocolysis is usually provided for prolonged periods after arrest of acute preterm labor to inhibit the process of parturition until term.[23]

The effectiveness of tocolytics in patients with preterm labour, to stop uterine contractions (acute tocolysis) or maintain quiescence (maintenance therapy) has been reviewed in the past. The primary therapeutic goal of acute tocolysis is to delay preterm delivery upto 48 hours from the initiation of steroids. Many drugs have been used for this purpose viz. nifedepine, magnesium sulphate, beta-mimetics, indomethacin, atosiban, etc. These drugs have been

further tested for maintenance tocolysis. However, long term use of these drugs was not proven to be efficacious in prolonging the latency period and was observed to have various adverse effects, due to which they are not recommended for maintenance tocolysis.[24]

Nifedepine tocolysis, when used over a period of time, was associated with maternal side effects like dyspnoea, pulmonary oedema, myocardial infarction, severe hypotension, hypoxia and elevated liver enzymes and fetal complications.[14]

Maintenance tocolysis with magnesium sulfate therapy requires strict monitoring and careful assessment of maternal urine output, respiratory rate and deep tendon reflexes, with discontinuation whenever evidence of toxicity exists. In addition, magnesium sulfate readily crosses the placenta and may lead to respiratory and motor depression of the neonate.[13]

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Atosiban, another tocolytic, has been shown to have similar efficacy in preventing preterm labour when compared to betamimetics but with reduced maternal side effects.[13] However, it is very expensive and not available in India.

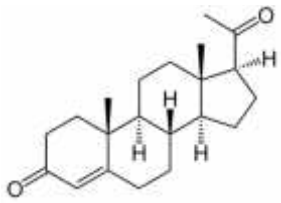
Indomethacin, when used for tocolysis is associated with an increased risk of periventricular leukomalacia, necrotising enterocolitis and premature closure of ductus arteriosus in the neonate.[13]

Hence the above mentioned drugs are not recommended in maintenance tocolysis.

On the other hand, progesterone has long been considered an important agent in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of preterm delivery. Progesterone is useful in allowing pregnancy to reach its physiologic term because at sufficient levels in the myometrium, it blocks the oxytocin effect of prostaglandin F2 α and α-adrenergic stimulation and therefore increases the α-adrenergic tocolytic response. Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. This is not true for certain artificial progestins and β-mimetics.[15]

PROGESTERONE

Progesterone also known as P4 (pregn-4-ene-3,20-dione) is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy (supports gestation) and embryogenesis of humans and other species.



Chemical structure of progesterone

Progesterone was independently discovered by four research groups. Willard Myron Allen co-discovered progesterone with his anatomy professor George Washington Corner at the University of Rochester Medical School in 1933. Allen first determined its melting point, molecular weight, and partial molecular structure. He also gave it the name Progesterone derived from Progestational Steroidal ketone.[25-29]

Like other steroids, progesterone consists of four interconnected cyclic hydrocarbons. Progesterone contains ketone and oxygenated functional groups, as well as two methyl branches. Like all steroid hormones, it is hydrophobic.

Progesterone, which is present in high concentrations during pregnancy, increases cAMP production. cAMP and cGMP maintain uterine quiescence by promoting the uptake of intracellular calcium into the sarcoplasmic reticulum and thereby reducing intracellular calcium concentrations and reducing contractility. They also lower the amount of phosphorylated myosin and promote myometrial relaxation. Progesterone therefore exerts a relaxant effect on the uterus, and has been used in the treatment of preterm labour.[13]

Mechanism of action

The exact mechanism of the onset of both term and preterm labor in humans is a complex interaction of many different hormonal pathways, culminating in co-ordinated uterine contractile activity, mediated by the production of prostaglandins. Before birth, coordinated uterine activity is associated with connective tissue changes resulting in cervical ripening and dilatation. Progesterone has an essential role in maintaining pregnancy, primarily

through establishing uterine quiescence. This is achieved through suppression of the calcium-calmodulin-myosin light chain kinase system, reducing calcium flux and altering the resting potential of smooth muscle.[5]

There is considerable debate about the relationship between progesterone withdrawal and the onset of labor. In humans, the progesterone receptor (PR) has two major subtypes PR-A and PR-B. Binding of progesterone to PR-A is not found to be associated with intra-cellular pathway mechanisms, prevents the actions of progesterone mediated by PR-B. An increase in the myometrial PR-A to PR-B expression ratio occurs at the onset of labor at term, resulting in an increase in myometrial PR-A, and in effect a functional withdrawal of progesterone, with increasing sensitivity to contractile stimuli.[5]

Prostaglandins produced prior to the onset of labor, also act to increase the PR-A/PR-B expression ratio, and therefore the potential to initiate a functional withdrawal of progesterone. In many animals the onset of labor is associated with a decrease in progesterone concentrations, but this has not been shown to occur in women before term or preterm birth, with no apparently detectable changes in circulating steroid hormone levels.[5]

In both term and preterm labor, there is evidence of an increase in inflammatory markers tumor necrosis factor (TNF) -alpha, interleukin-1 (IL-1) and interleukin-6 (IL-6), and down-regulation of the anti-inflammatory interleukin-10 (IL-10). Inflammatory cytokines may alter enzyme expression, increasing prostaglandin production prior to the onset of labor. These maternal inflammatory mediators may then interact at the feto-placental unit, precipitating

preterm birth.80 In particular, inflammatory cytokines interleukin-1 and TNF-alpha act to increase prostaglandin production, while both IL-10 and progesterone have a negative effect on prostaglandin production.[5]

It is in this context that progesterone may exert its anti-inflammatory properties, raising a possible link between inflammatory process, alterations in progesterone receptor expression and the onset of preterm labor.[30] While it has been postulated that the effect of progesterone on preterm birth is related to its anti-inflammatory properties, the specific mechanism of action remains unclear.

Elovitz and colleagues have developed a mouse model of intra-uterine inflammation with intrauterine injection of lipopolysaccharide (LPS).[31-32] In these experiments, pre-treatment with progesterone was associated with suppression of activation of contraction-associated genes and inflammatory mediators, as well as prevention of the cervical ripening response to intrauterine inflammation.[31]

Toll-like receptors are involved in both the initiation and modulation of the inflammatory response, and regulation of these receptors may be one mechanism whereby intrauterine inflammation mediates the onset of labor, and therefore modifiable by the administration of progesterone.[31-32]

Other investigators[33-34] have evaluated the anti-inflammatory effect of progesterone at the feto-placental unit. Placental chorionic plate arteries were exposed to either lipopolysaccharide alone or in combination with progesterone. Exposure to LPS alone was associated with an increase in the production of the inflammatory cytokine IL-6. Pre-treatment of the arteries with progesterone was associated with reduced production of IL-6 after LPS exposure, although there

was no demonstrable effect on the concentrations of TNF-alpha or IL-10. Similarly, exposure to progesterone was associated with a reduction in both fetal and maternal mononuclear cell expression of IL-6 after exposure to LPS, again suggesting these cell populations as possible targets for the anti-inflammatory effects of progesterone, and a potential mechanism for the observed reduction in preterm birth following progesterone.

Pharmacokinetics of progesterone by route of administration

There are few data available regarding the optimal route of administration of progesterone in women in later pregnancy. Vaginal progesterone is found to have better bioavailability as compared to intramuscular route of administration. Also, vaginal route of administration is preferred due to absence of undesirable side effects such as fatigue, drowsiness and headache. For 100 mg vaginal progesterone pessaries the peak blood concentrations are obtained 3 to 8 hours after vaginal administration, due to avoidance of first pass hepatic metabolism. In blood, progesterone is 96% to 99% protein bound, mainly to albumin. While there may be advantages in the use of intramuscular progesterone in terms of increased blood concentrations, such preparations are not available in many countries world-wide.[5]

Safety of progesterone

Natural progesterone has been used in pregnancy without demonstrated effect on fetal development or on the risk of congenital anomalies.[36,37] Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects.[38] However, this is not true for certain artificial progestins. Recognized

maternal side-effects related to progesterone therapy include headache, nausea, breast tenderness, and cough, which are however found to be rare.

The administration of progesterone as a therapeutic agent for the prevention of preterm birth dates to the early 1960s, with considerable renewed interest in its use following recent reports of randomized controlled trials.[5]

Interest in the use of progesterone as a therapeutic agent to reduce the risk of preterm birth dates back to the 1960s.[39] Recent randomized controlled trial reports have re-ignited the interest in progesterone for this indication. Evidence from randomized controlled trials and systematic reviews indicates a potential beneficial effect in the use of progesterone for some women considered to be at increased risk of preterm birth, primarily in the reduction in the risk of preterm birth before 34 weeks gestation. However, it remains unclear if the observed prolongation of pregnancy translates into improved health outcomes for the infant, as there is limited information available about neonatal and long-term infant health.[5]

While there is information available from randomized trials suggesting that progesterone therapy may be beneficial for some women considered to be at increased risk of preterm birth, for some pregnancy outcomes, there is limited information available relating to neonatal and infant health outcomes. In particular, there is little information about the benefits and harms of progesterone in relation to long-term infant outcomes.

Maternal outcomes after antenatal progesterone therapy have to date been poorly reported, including treatment, side-effects, preferences of mode of

administration and satisfaction with their pregnancy care. Further information is required on these important issues.

The role of maintenance tocolysis following arrested preterm labour is still controversial. Patients with arrested preterm labour are at increased risk for recurrence. Hence it is essential to assess if maintenance tocolysis is beneficial once a patient with threatened preterm labour has been acutely tocolysed and labour has been arrested.

Patients with arrested PTL are at increased risk for PTL recurrence; but to this point, continued tocolytic treatment with any agent after arrest of acute preterm labor is of questionable value in prolongation of pregnancy or improving outcome.

Progesterone is useful in allowing pregnancy to reach its physiologic term because at sufficient levels in the myometrium, it blocks the oxytocin effect of prostaglandin F2 α and α-adrenergic stimulation and therefore increases the α-adrenergic tocolytic response. Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects. Though this is not true for certain artificial progestins and β-mimetics.[15]

There is considerable variation in the dose of progesterone administered in the treatment of preterm labour, ranging from 90 mg daily to 400 mg daily when administered vaginally, and from 250 mg weekly to 250 mg every 3 days, every 4 days, 133 up to 1000 mg weekly. The optimal time to commence therapy also varies considerably across studies, as does the duration of treatment. While the majority of studies commenced therapy in the mid-late second trimester at 24

to 28 weeks gestation, others commenced in the first trimester at the time of antenatal "booking", and some others from 16 weeks gestation.[5]

There are numerous controversies regarding progesterone administration for the prevention of PTL. The ideal progesterone formulation, dosage, duration and route of administration are still unclear.

Vaginal pessaries of micronized natural progesterone was preferred over intramuscular synthetic 17-hydroxyprogesterone because of enhanced bioavailability and the absence of undesirable side effects such as fatigue, sleepiness and headaches in most of the studies. We, therefore, chose this pharmacological agent as the active drug for our study.

Progestins in women at risk of preterm labour, is seen to improve the latency period and reduce the occurrence of preterm labour by 43%. Women who received progesterone were statistically significantly less likely to give birth before 37 weeks, to have an infant with birth weight of < 2.5 kg, or to have an infant diagnosed with intraventricular hemorrhage. The use of progesterone is seen to contribute to a significant reduction in low birth weight and intraventricular hemorrhage, thus contributing to better neonatal outcome.[16]

A randomized controlled trial[15] in 2008, evaluated the efficacy and safety of vaginal progesterone in prevention of recurrent preterm labor in 70 patients with preterm labor treated with intravenous magnesium sulfate in perinatology department of Valiasr hospital. Treatment group after inhibition of preterm labor with magnesium sulfate received progesterone suppository (400 mg) daily until delivery and control group received no treatment. Latency until delivery,

recurrence of preterm labor and neonatal outcomes were studied. Categorical data were tested for significance with the χ^2 and Fisher exact tests. Comparison of Bishop score and cervical dilatation were made with Cochran–Mantel–Haenszel test. Latency period were tested for significance with the Mann–Whitney *U*-test. Continuous data were evaluated for normal distribution and tested for significance with the Student's *t*-test. Statistical significance was defined as $P < 0.05$. All patients were included in the analysis. The Mean latency until delivery ($p< 0.05$), low birth weight ($p< 0.05$), birth weight ($p< 0.01$) were significantly different between the two groups. Recurrence of preterm labor was not significantly different between the groups. Authors concluded that, the use of vaginal progesterone suppository after successful parenteral tocolysis was associated with a longer latency preceding delivery but failed to reduce the incidence of recurrent preterm labor.

A placebo-controlled, double-blinded randomized clinical trial[40] was conducted at Alzahra Hospital, Guilan University of Medical Sciences between June 2007 and May 2009, to evaluate the efficacy of 200 mg vaginal progesterone in order to prevent preterm birth in women with episodes of threatened preterm labour. The study included women with singleton pregnancies between 28-36 weeks of gestation, who were hospitalized for labour. A total of 173 pregnant patients were randomly allocated to receive 200 mg vaginal progesterone suppositories (n=86) or placebo (n=87) daily until the 36th gestational week. The two groups were compared relative to demographic characteristics for incidence of preterm birth before 34 and 37 weeks, maternal and neonatal complications. Data was analyzed using $\chi 2$ or Fisher exact test and

student's t-test. Kaplan-Meier survival analysis was performed to determine the relationship between vaginal progesterone and time to delivery. The log-rank $\chi 2$ test was used to compare the latency period in the two study groups. Statistical analysis was performed using SPSS version 14. P-value <0.05 was considered statistically significant. The results showed that, mean latency until delivery in the cases was longer than the control group (23.88 ± 18.01 vs. 16.67 ± 12.9; p=0.004).Treatment with progesterone was not associated with a reduction in the rate of preterm birth before 34 weeks [cases: 9 (10.8%) vs. controls: 8 (10%)] and 37 weeks [cases: 45 (54.2%) vs. controls: 33 (41.2%)]. Log rank analysis revealed a significant difference for mean latency until delivery between the two groups (p=0.028). There were no significant differences for neonatal and maternal complications in the two groups. Overall, the study concluded that, prophylactic administration of 200 mg vaginal progesterone suppositories after successful tocolysis in patients with threatened idiopathic labour is associated with a longer latency to delivery, but failed to reduce the rate of preterm birth.

A meta-analysis[38] in 2000, to analyze published randomized trials assessing the efficacy of maintenance tocolytic therapy after short-term tocolysis in patients with acute preterm labor, supplemented a search of entries in electronic databases with references cited in original studies and review articles to identify randomized trials assessing the efficacy of maintenance tocolytic therapy after resolution of the acute preterm labor episode. Two masked investigators performed independent trial quality evaluation and data abstraction of each trial. Of 17 studies identified, 12 met criteria for meta-analysis. These 12 trials included 1590 patients, including 855 who received maintenance tocolysis

and 735 comparison patients who received placebo or no maintenance treatment. Compared with placebo or no treatment, the pooled odds ratio for preventing preterm delivery was 0.95 (95% confidence interval, 0.77-1.17), and the odds ratio for preventing recurrent preterm labor was 0.81 (95% confidence interval, 0.64-1.03). In addition, use of maintenance tocolytic therapy was not associated with decreased rates of neonatal respiratory distress syndrome, perinatal deaths, or differences in birth weight. Although no difference was noted in mean gestational age at delivery, those receiving tocolytic agents had a longer latency period. Authors concluded that, maintenance tocolytic therapy after successful treatment of an acute episode of preterm labor does not reduce the incidence of recurrent preterm labor or preterm delivery and does not improve perinatal outcome. Accordingly, the results of this meta-analysis do not support the use of maintenance tocolytic therapy after successful treatment of preterm labor.

In Cochrane Database of Systematic Reviews,[41] a few authors assessed the effects of oral betamimetic maintenance therapy after threatened preterm labour for preventing preterm birth. Data was obtained from the Cochrane Pregnancy and Childbirth Group's Trials Register (June 2005) and MEDLINE (from 1966 to August 2003). Data was updated on 1 October 2009 and the results were added to the awaiting classification section. The selected studies included randomised controlled trials comparing oral betamimetic with alternative tocolytic therapy, placebo or no therapy, for maintenance of pregnancy following treatment of threatened preterm labour. Two review authors independently applied the selection criteria and carried out data extraction and quality assessment of studies. For dichotomous data, results were presented as summary

risk ratio with 95% confidence intervals and for continuous data, the mean difference if outcomes were measured in the same way between trials. Study used the standardised mean difference to combine trials that measure the same outcome, but use different methods. A total of 13 RCTs with a total of 1551 women were considered. There were no differences for admission to the neonatal intensive care unit when betamimetics were compared with placebo (risk ratio (RR) 1.28, 95% confidence interval (CI) 0.68 to 2.41; two RCTs of terbutaline with 2600 women) or with magnesium (RR 0.80, 95% CI 0.43 to 1.46; one RCT of 137 women). The rate of preterm birth (less than 37 weeks) showed no significant difference in six RCTs, four comparing ritodrine with placebo/no treatment and two comparing terbutaline with placebo/no treatment (RR 1.11, 95% CI 0.91 to 1.35; 644 women). The authors observed no differences between betamimetics and placebo, no treatment or other tocolytics for perinatal mortality and morbidity outcomes. Some maternal adverse effects such as tachycardia were more frequent in the betamimetics groups than the groups allocated to placebo, no treatment or another type of tocolytic. The analysis concluded that, available evidence does not support the use of oral betamimetics for maintenance therapy after arrested preterm labour.

Another study[42] in 2004, aimed to evaluate the efficacy of maintenance oral nifedipine in pregnant women initially treated with intravenous ritodrine and verapamil for threatened preterm labor. It included 73 patients with threatened preterm labor with intact membranes. Patients were randomized to receive either maintenance oral nifedipine therapy (n=37) administered 20 mg every six hours or no treatment (controls, n=36) after discontinuation of acute intravenous

tocolysis. Compared to the control group, the mean ± SD time gained from initiation of maintenance therapy to delivery (26.65 +/- 18.89 vs. 16.14 +/- 12.91 days, p=0.007) and the gestational age at delivery (37.03 +/- 2.06 vs. 35.1 +/- 3 weeks, p=0.003) were higher in the nifedipine maintenance therapy group. The proportion of patients who required one or more courses of subsequent intravenous therapy and perinatal outcome was similar in the maintenance therapy and control groups. The study concluded that, the gestational age and time gained from initiation of maintenance therapy to delivery was longer in women receiving oral maintenance tocolysis with nifedipine. However, maintenance therapy did not decrease the recurrence of preterm labor episodes or improve perinatal outcome.

Studies[15,16,38,40,41,42] carried on so far, have still not reached a consensus regarding the efficacy of maintenance tocolysis. More number of studies, involving larger number of patients are required to analyse the role of maintenance tocolysis in patients with arrested preterm labour and reach a conclusion.

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum.

Study design

A randomized controlled trial.

Source of data

Pregnant women admitted in Labour Room at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, with arrested preterm labour were included in this study.

Place

The present study was conducted at the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

This study was conducted in a total of 98 women, divided into two groups, study and control, comprising of 49 patients each.

Sampling technique

The sample size was calculated based on the formula.

$$n = \frac{(Z_\alpha + Z_\beta)^2 \, 2s^2}{d^2}$$

Where,

Z_α = 1.65 at 5% level of significance, one sided for power of test at 80%,

Z_β = 0.84

The rest of the values have been taken as per results obtained in a randomized controlled trial conducted by Sedigheh BORNA and Noshin SAHABI, where the latency (day, mean ± SD) in the control and study groups, were (24.5 ± 27.2) and (36.1 ± 17.9) respectively.

d^2 = Difference of means square, that is, $(36.1 - 24.5)^2 = 134.56$

s^2 = Mean of the $(SD)^2$ of the two groups i.e.

$$\frac{SD_1^2 + SD_2^2}{2}$$

i.e. $$\frac{(27.2)^2 + (17.9)^2}{2} = 530.1$$

Hence, $(1.65 + 0.84)^2(2)(530.1) / 134.56 = 49$

Hence a minimum sample size of 98 patients that is, minimum of 49 in each group were included in this study.

Selection criteria

Inclusion criteria

- Singleton pregnancy.

- Gestational age between 28 to 36 completed weeks.
- Patients with confirmed gestational age by LMP and/or first or second trimester ultrasound scan.
- Threatened preterm labour arrested with depin tocolytic regimen.

Exclusion criteria

- Preterm premature rupture of membranes.
- Cervical encerclage.
- Chorioamnionitis

Ethical clearance

Prior to the commencement, the study was approved by the Institutional Ethics and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

Pregnant women who presented with signs and symptoms of threatened preterm labour following arrest of uterine activity with oral depin tocolytic therapy, fulfilling the selection criteria were explained about the nature of the study and a written informed consent was obtained from all the participants before enrollment (Annexure I).

Randomization

After obtaining the written informed consent, patients were randomized into two groups of 49 each, based on computer generated randomization namely.

Study group (Group S): Received 400 mg of vaginal micronized progesterone.

Control group (Group C): Did not received any drug.

Method of collection of data

After the enrollment, demographic data such as age, obstetric history, menstrual history, details of 1st and 2nd trimester scans done were recorded on a predesigned and pretested proforma (Annexure II).

Study design

Pregnant women with arrested preterm labour following acute tocolysis (acute tocolysis - C. Depin 30 mg stat f/b C. depin 20 mg eighth hourly, for 3days) for threatened preterm labour were randomized into study and control groups.

Threatened preterm labour was defined as presence of regular, frequent uterine contractions, along with digital examination showing cervix < 80% effaced and dilated < 1 cm.

Arrested preterm labour was defined as a 12 hour contraction free period after the completion of depin tocolytic regimen.

The study group received 400 mg of vaginal micronized progesterone, while the control group did not receive any drug. The patients were followed up till 37 completed weeks. The latency periods (the time period from arrest of preterm labour upto delivery) alongwith the birth weight of the babies, following

maintenance therapy with progesterone and without any maintenance therapy, was determined and the results were compared in both the groups.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical data was expressed as rates, ratios and proportions and comparison was done using test of proportions or chi-square test. The continuous data was expressed as mean ± standard deviation (SD) and the comparison was done using unpaired 't' test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

This randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum.

A total of 98 pregnant women, fulfilling the inclusion criteria, were included in the present study. The eligible women were then randomized into two groups of 49 each based on computer generated random numbers.

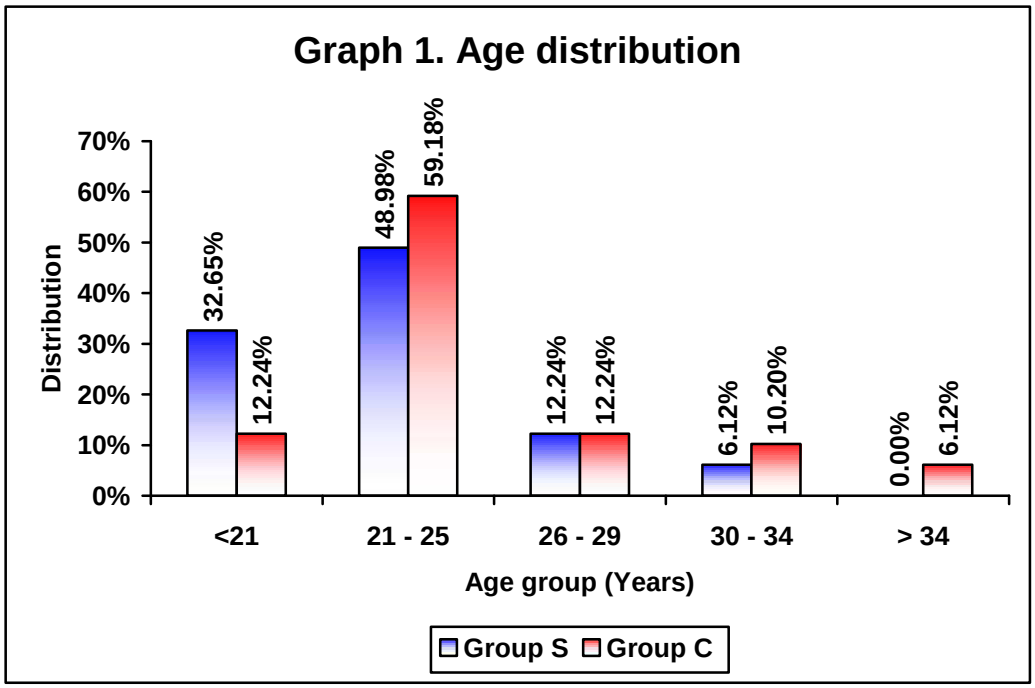
Study group (Group S): Received 400 mg of vaginal micronized progesterone.

Control group (Group C): Did not receive any drug.

The data obtained was coded and entered into Microsoft Excel Worksheet. The data was analysed and tabulated as below.

Table 1. Age distribution

Age group (Years)	Group S (n=49)		Group C (n=49)	
	No.	**%**	**No.**	**%**
< 21	16	32.65	6	12.24
21 - 25	24	48.98	29	59.18
26 - 29	6	12.24	6	12.24
30 - 34	3	6.12	5	10.20
> 34	0	0.00	3	6.12
Total	**49**	**100.00**	**49**	**100.00**

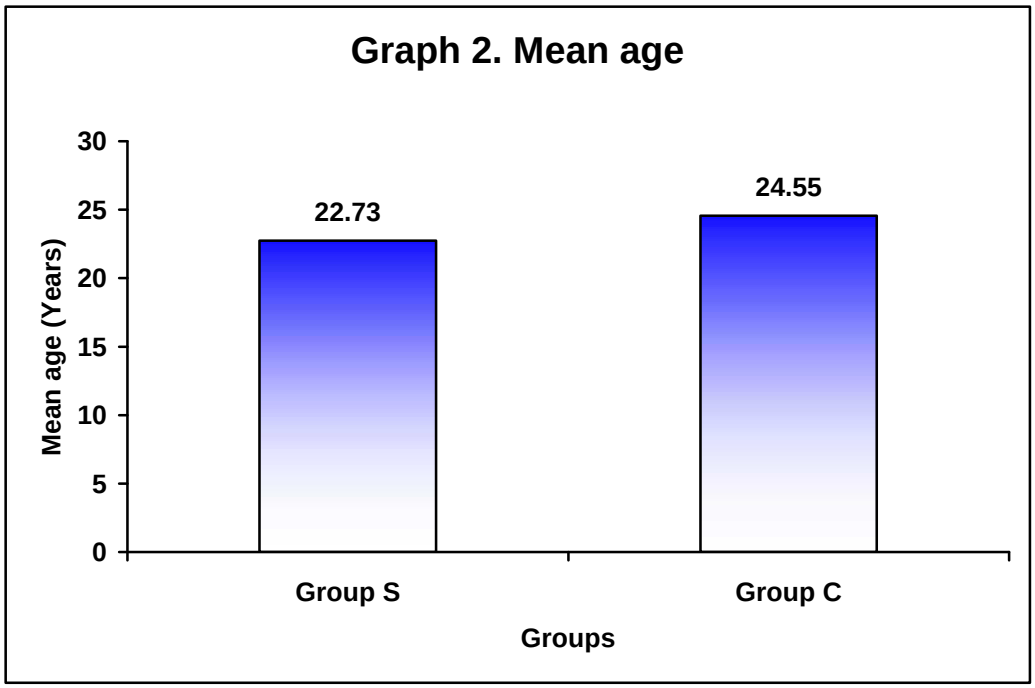


In the present study, majority of the patients were in the age group of 21 to 25 years, and the distribution was comparable in both the study and control groups (48.98% vs 59.18%).

Table 2. Mean age

	Group S	Group C
Mean	22.73	24.55
SD	3.47	4.14
Median	22	24
Maximum	34	37
Minimum	17	19

t = 2.358 **DF = 96** **p = 0.020**

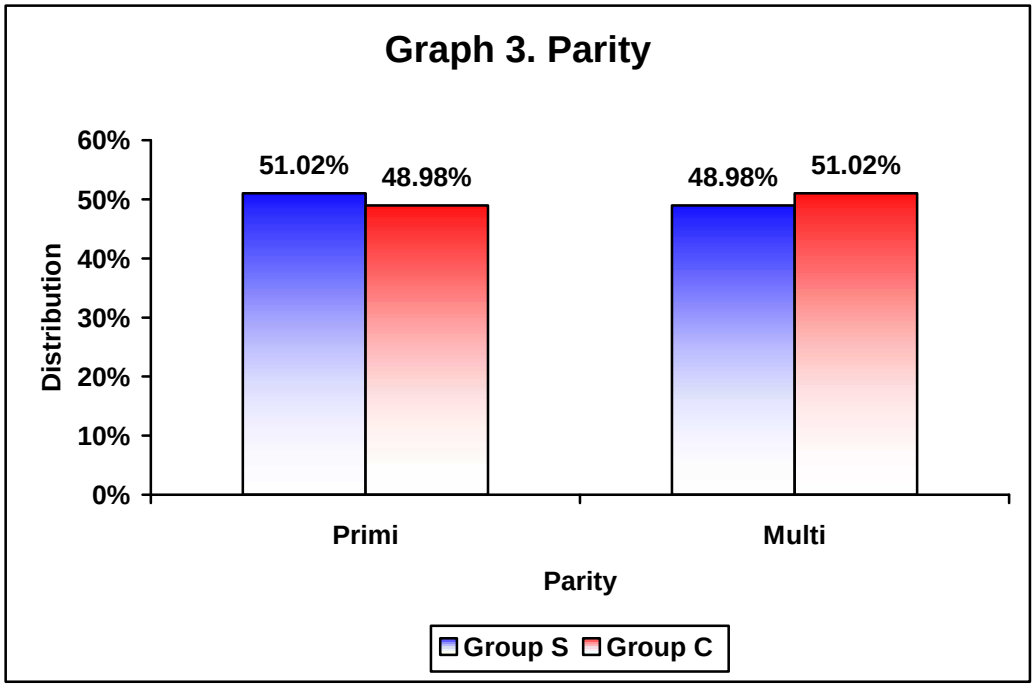


In the present study the mean age in Group S was 22.73 ± 3.47 years whereas, in Group C it was 24.55 ± 4.14 years, which was comparable.

Table 3. Parity

Parity	Group S (n=49)		Group C (n=49)	
	No.	**%**	**No.**	**%**
Primi	25	51.02	24	48.98
Multi	24	48.98	25	51.02
Total	**49**	**100.00**	**49**	**100.00**

x^2_1 = 0.0008 **p = 0.977**



In the present study, the number of primigravidae and muligravidae were almost equal in both the groups and thus they were both comparable.

Table 4. Period of gestation at enrollment

Period of gestation (Weeks)	Group S (n=48)		Group C (n=45)	
	No.	**%**	**No.**	**%**
28 - 31.6	16	33.33	9	20.00
32 - 33.6	16	33.33	14	31.11
34 - 36.6	16	33.33	22	48.89
Total	**48**	**100.00**	**45**	**100.00**

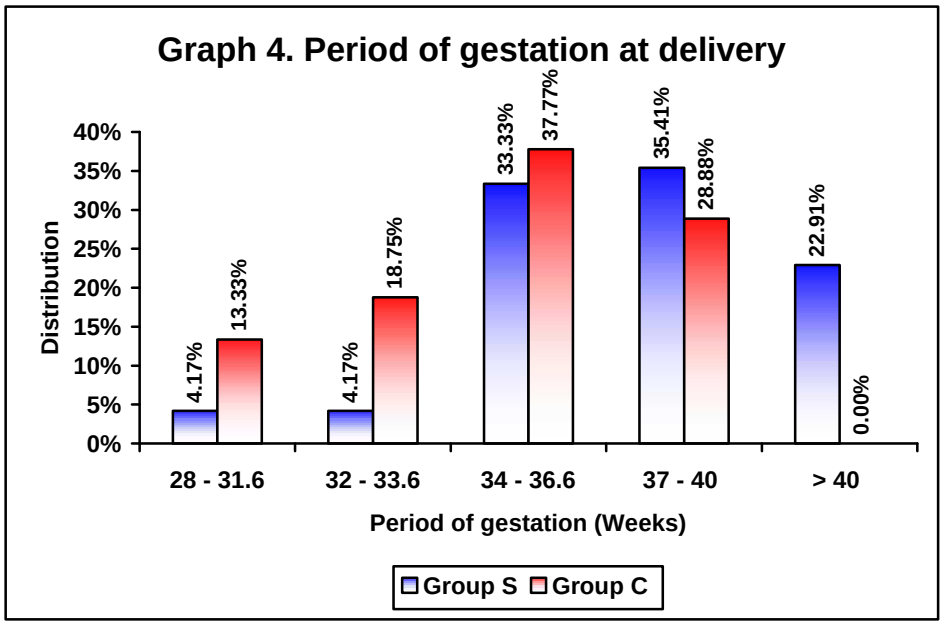
t = 1.173 **DF = 96** **p = 0.243**

In the present study, equal number of women (33.33%) were enrolled at 28 to 31.6 weeks, 32 to 33.6 weeks and 34 to 36.6 weeks each in the study group. In the control group, maximum number of women (48.89%) were enrolled at 34 to 36.6 weeks, followed by 31.11% at 32 to 33.6 weeks followed by 20% at 28 to 31.6 weeks. The gestational age of the eligible women, at enrollment was comparable in both the groups (p=0.243).

Table 5. Period of gestation at delivery

Period of gestation (Weeks)	Group S (n=48)		Group C (n=45)	
	No.	%	No.	%
28 - 31.6	2	4.17	6	13.33
32 - 33.6	2	4.17	9	18.75
34 - 36.6	16	33.33	17	37.77
37 - 40	17	35.41	13	28.88
> 40	11	22.91	0	0.00
Total	**48**	**100.00**	**45**	**100.00**

x^2=17.9 **DF =4** **p = 0.001**

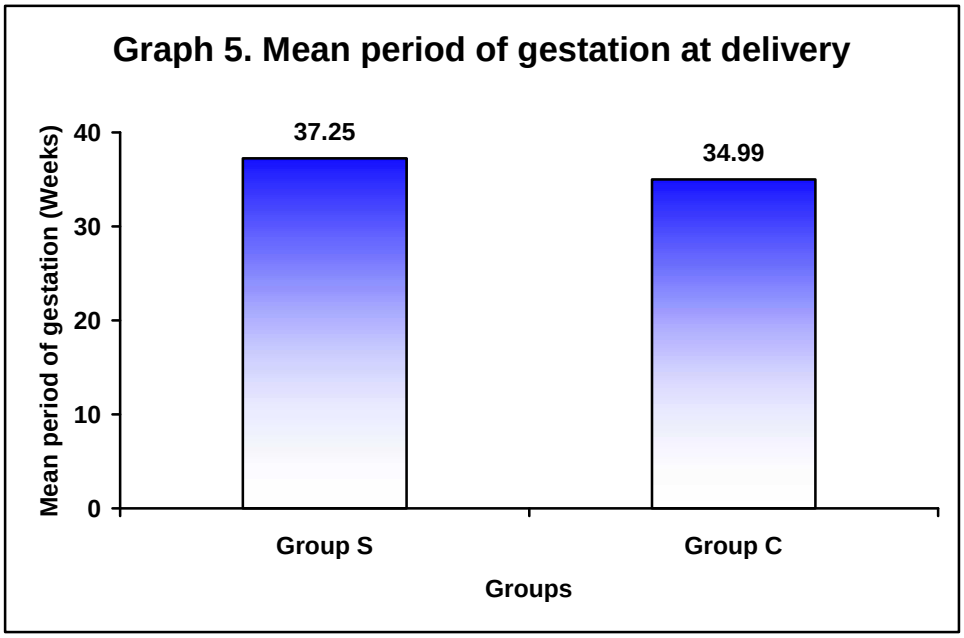


In the present study, in Group S majority of the women (35.41%) delivered between 37 to 40 weeks at the time of delivery as compared to 28.88 % in group C. Majority of the women in Group C (37.77%) delivered between 34 to 36.6 weeks (p=0.001).

Table 6. Mean period of gestation at delivery

	Group S	Group C
Mean	37.25	34.99
SD	2.51	2.62
Median	37.93	35.43
Maximum	40.71	39.43
Minimum	31.00	29.14

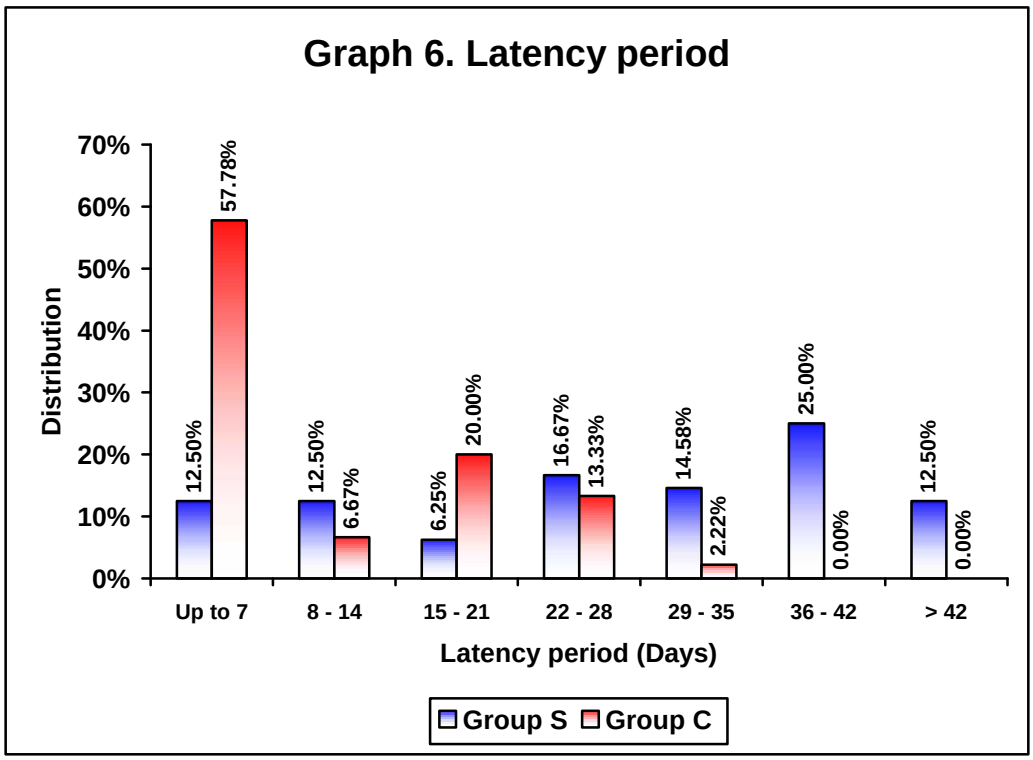
t = 4.248 **DF = 91** **p < 0.001**



In the present study the mean period of gestation at delivery was significantly high in group S (37.25 ± 2.51 weeks) compared to that in group C (34.99 ± 2.62 weeks).

Table 7. Latency period

Latency period (days)	Group S (n=48)		Group C (n=45)	
	No.	%	No.	%
Up to 7	6	12.50	26	57.78
8 - 14	6	12.50	3	6.67
15 - 21	3	6.25	9	20.00
22 - 28	8	16.67	6	13.33
29 - 35	7	14.58	1	2.22
36 - 42	12	25.00	0	0.00
> 42	6	12.50	0	0.00
Total	**48**	**100.00**	**45**	**100.00**
t = 6.768		**DF = 91**		**p < 0.001**

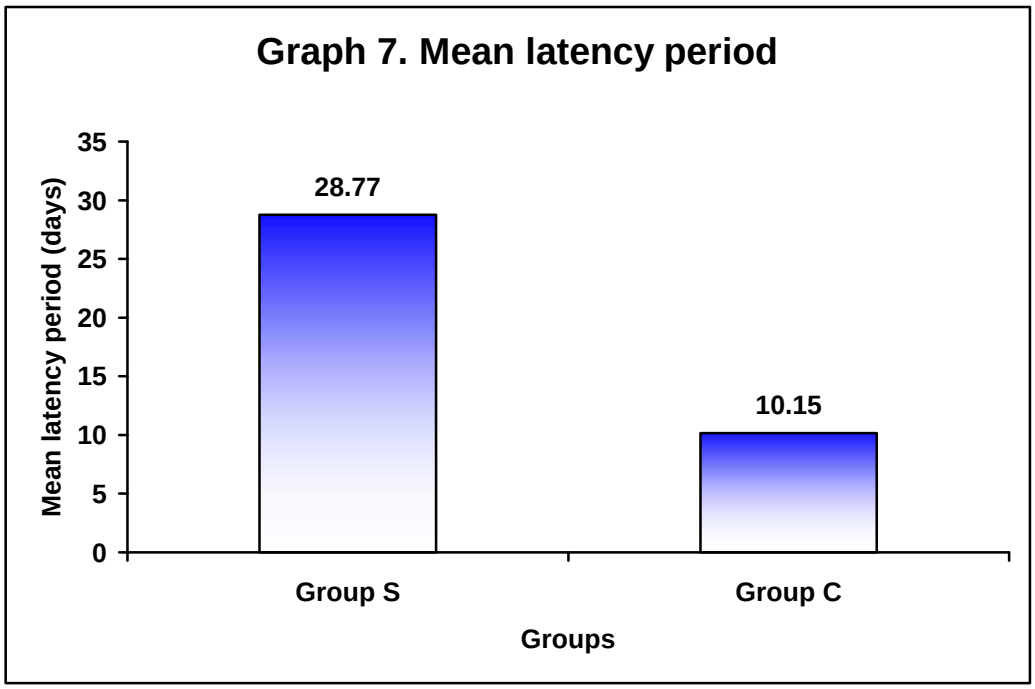


In the present study maximum latency period (beyond 42 days) was noted in Group S compared to Group C. Majority of women (25%) had a latency period between 36 to 42 days in Group S. In Group C, majority of the women (57.78%) had a latency period of less than 7 days. This difference between both the groups was statistically significant ($p < 0.001$).

Table 8. Mean latency period

Latency period	Group S (n=48)		Group C (n=45)	
	Mean	**SD**	**Mean**	**SD**
Mean	28.77	15.95	10.15	9.55

t = 6.768 **DF = 91** **p < 0.001**

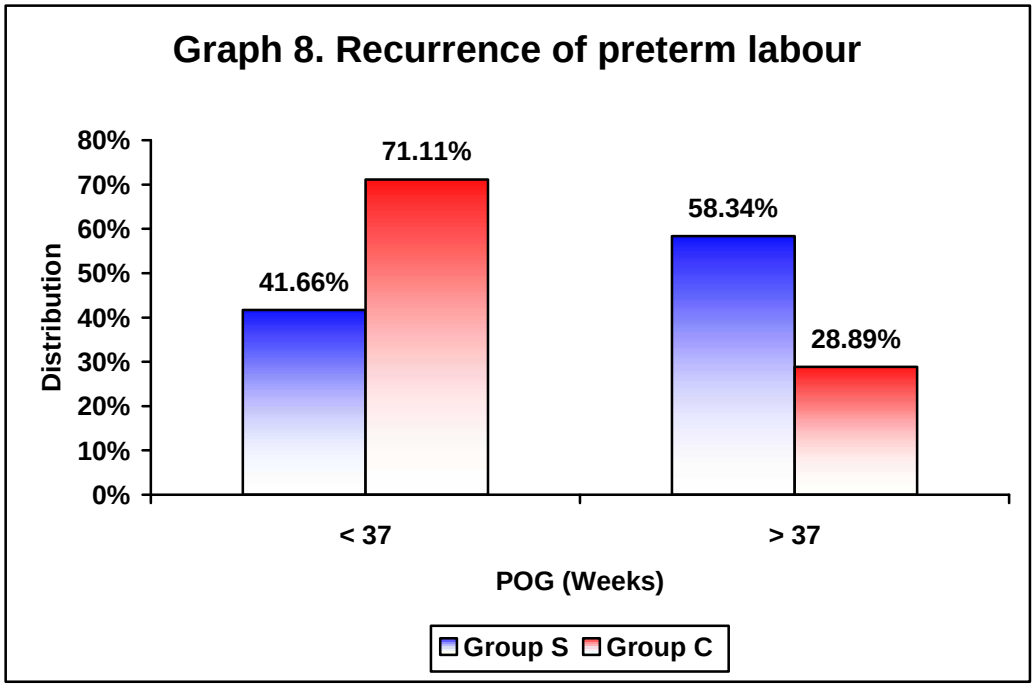


The mean latency period in group S was significantly higher than that of group C (28.77 ± 15.95 vs 10.15 ± 9.55 days; p<0.001).

Table 9. Recurrence of preterm labour

POG (weeks)	Group S (n=48)		Group C (n=45)	
	No.	**%**	**No.**	**%**
< 37	20	41.66	32	71.11
> 37	28	58.34	13	28.89
Total	**48**	**100.00**	**45**	**100.00**

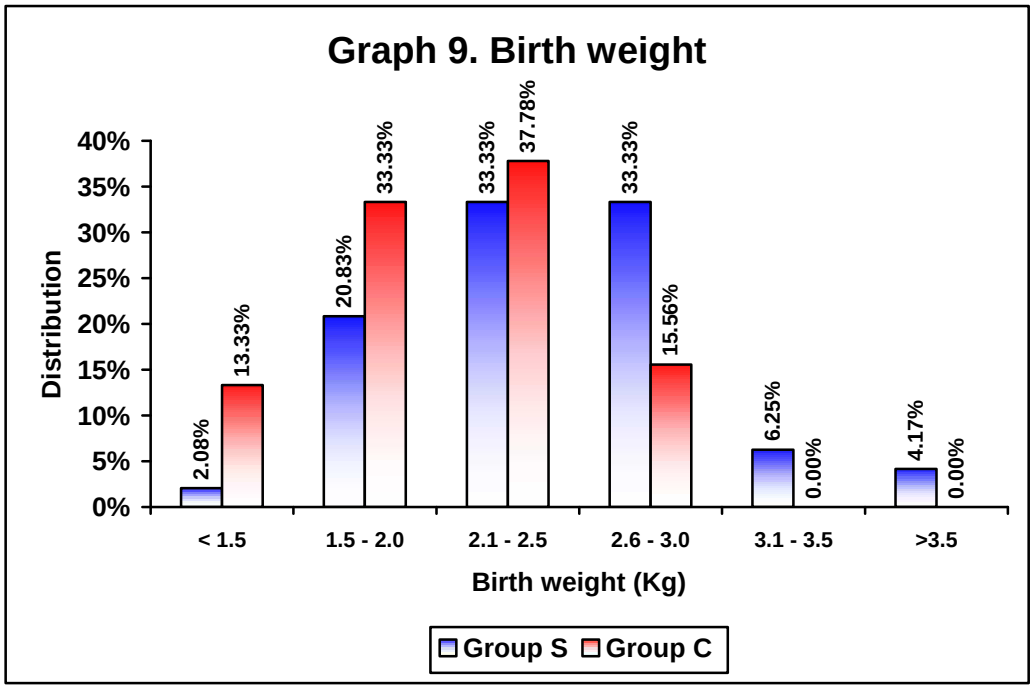
$x^2_1 = 20.193$ **$p < 0.001$**



In the present study the recurrence of preterm labour was significantly high in the control group as 71.11% of the mothers delivered before 37 weeks compared to only 41.66% mothers in the group S ($p<0.001$). This was statistically significant.

Table 10. Birth weight

Birth weight (Kg)	Group S (n=48)		Group C (n=45)	
	No.	**%**	**No.**	**%**
< 1.5	1	2.08	6	13.33
1.5 - 2.0	10	20.83	15	33.33
2.1 - 2.5	16	33.33	17	37.78
2.6 - 3.0	16	33.33	7	15.56
3.1 - 3.5	3	6.25	0	0.00
>3.5	2	4.17	0	0.00
Total	**48**	**100.00**	**45**	**100.00**

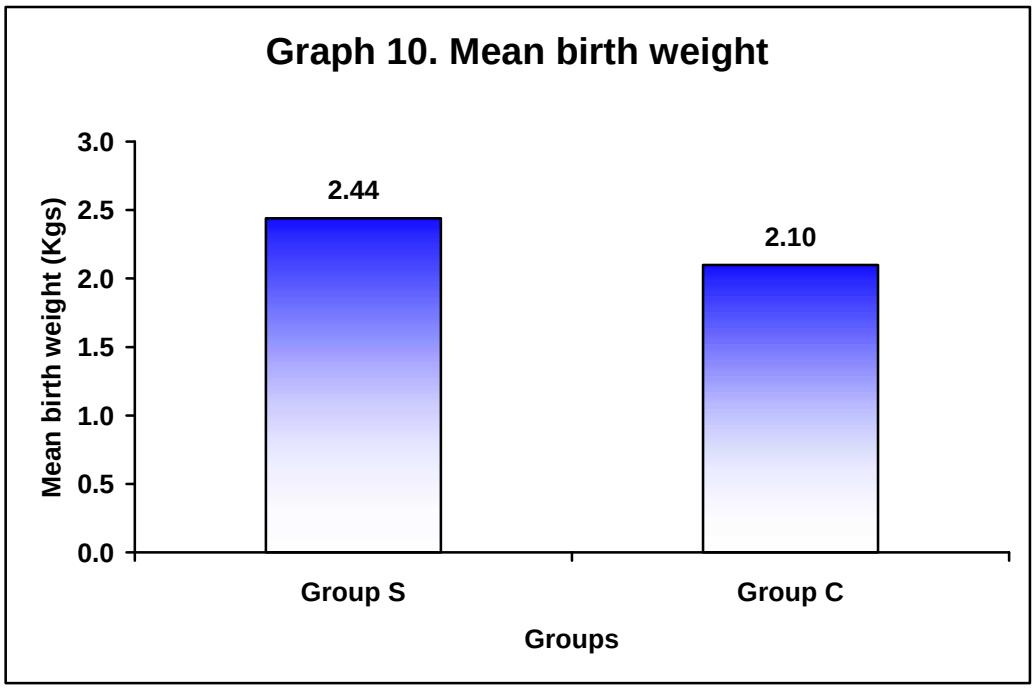


In the present study, 21 babies (43.75%) in Group S had birth weight more than 2.5 Kg which was significantly higher than that in Group C, in which only 7 babies (15.56%) had birth weight more than 2.5 kg (p=0.003).

Table 11. Mean birth weight

Birth weight	Group S (n=48)		Group C (n=45)	
	Mean	**SD**	**Mean**	**SD**
Mean	2.44	0.52	2.1	0.52

t = 3.151 **DF = 91** **p = 0.002**

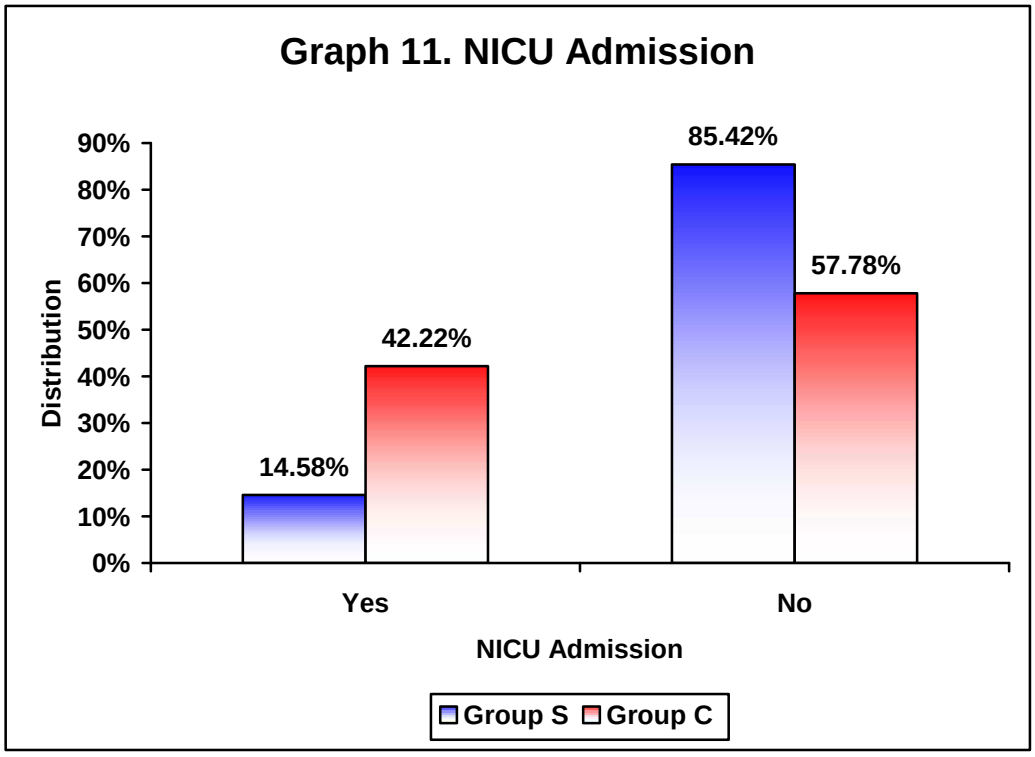


The mean birth weight of babies in group S (2.44 ± 0.52 Kg) was significantly higher than that in group C (2.10 ± 0.52 Kg)

Table 12. NICU Admission

NICU Admission	Group S (n=48)		Group C (n=45)	
	No.	**%**	**No.**	**%**
Yes	7	14.58	19	42.22
No	41	85.42	26	57.78
Total	**48**	**100.00**	**45**	**100.00**

$x^2_1 = 8.809$ **p = 0.003**



In the present study, only 7 babies (14.58%) from group S were admitted in NICU whereas in group C, 19 (42.22%) babies were admitted in NICU. This difference was statistically significant. (p = 0.003)

Chapter 6

Discussion

DISCUSSION

The present randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum. A total number of 98 pregnant women who fulfilled the inclusion criteria were included in this study. The eligible women were then randomized into two groups of 49 each based on computer generated randomization namely study group (Group S) who received 400 mg of vaginal micronized progesterone and control group (Group C) who did not receive any drug.

Of the 98 patients who were randomized, 5 patients were loss to follow up, of which 4 patients were from the control group, while 1 patient belonged to the study group. Thereby a total of 48 (97.96%) women completed follow up in group S, and 45 (91.84%) in group C.

In the present study, majority of the patients were in the age group of 21 to 25 years, but the distribution was not comparable in both the groups (48.98% vs 59.18%). The mean age in group S was 22.73 ± 3.47 years whereas, in group C it was 24.55 ± 4.14 years (p=0.020).

In this study, the number of primigravidae and muligravidae were almost equal in both the groups and thus they were both comparable.

In this study, 33.33% of the women had gestational age between 28 to 31.6 weeks, 32 to 33.6 weeks and 34 to 36 weeks each, at the time of enrollment in group S and in group C, 48.89% had gestational age between 34 to 36 weeks

followed by 31.11% with gestational age between 32 to 33.6 weeks and 20% with 28 to 31.6 weeks. The gestational age at enrollment was comparable in both the groups (p=0.243).

In the present study, in group S majority of the women (35.41%) delivered between between 37 to 40 weeks of gestation as compared to 28.88% in group C. Most of the women in group C (37.77%) delivered between 34 to 37 weeks. The mean period of gestation at delivery was significantly high in group S (37.25 ± 2.51 vs 34.99 ± 2.62 weeks; p<0.001) compared to group C.

Another study[42] in 2004, aimed to evaluate the efficacy of maintenance oral nifedipine in pregnant women initially treated with intravenous ritodrine and verapamil for threatened preterm labor. It included 73 patients with threatened preterm labor with intact membranes. Patients were randomized to receive either maintenance oral nifedipine therapy (n=37) administered 20 mg every six hours or no treatment (controls, n=36) after discontinuation of acute intravenous tocolysis. The study showed that, compared to the control group, the gestational age at delivery (37.03 +/- 2.06 vs. 35.1 +/- 3 weeks, p=0.003) were higher in the nifedipine maintenance therapy group.

In the present study the recurrence of preterm labour was significantly high in the control group, as 71.11% of the mothers delivered before 37 weeks compared to only 41.66% mothers in the group S (p<0.001). This was statistically significant, suggesting that there was a reduction in the recurrence rate of preterm labour in the study group compared to the control group.

A randomized controlled trial[15] evaluated the efficacy and safety of vaginal progesterone (400 mg) in prevention of recurrent preterm labor on 70 patients with preterm labor treated with intravenous magnesium sulfate in perinatology department of Valiasr hospital. The study reported that, recurrence of preterm labor was not significantly different between the two groups. Authors concluded that, the use of vaginal progesterone suppository after successful parenteral tocolysis failed to reduce the incidence of recurrent preterm labor.

Another randomized double blind clinical trial[40] conducted to evaluate the efficacy of 200 mg vaginal progesterone in order to prevent preterm birth in women with episodes of threatened preterm labour included 173 women with singleton pregnancies between 28-36 weeks of gestation, who were hospitalized for preterm labour. Results showed that, treatment with progesterone was not associated with a reduction in the rate of preterm labour before 34 weeks [cases: 9 (10.8%) vs. controls: 8 (10%)] and 37 weeks [cases: 45 (54.2%) vs. controls: 33 (41.2%)].

A meta-analysis[38] analyzed published randomized trials assessing the efficacy of maintenance tocolytic therapy after short-term tocolysis in patients with acute preterm labor. Of 17 studies identified, 12 met criteria for meta-analysis. These 12 trials included 1590 patients, including 855 who received maintenance tocolysis and 735 comparison patients who received placebo or no maintenance treatment. Compared with placebo or no treatment, the pooled odds ratio for preventing preterm delivery was 0.95 (95% confidence interval, 0.77-1.17), and the odds ratio for preventing recurrent preterm labor was 0.81 (95% confidence interval, 0.64-1.03). This meta-analysis concluded that, maintenance

tocolytic therapy after successful treatment of an acute episode of preterm labor does not reduce the incidence of recurrent preterm labor or preterm delivery.

In Cochrane Database of Systematic Reviews,[41] a few authors assessed the effects of oral betamimetic maintenance therapy after threatened preterm labour for preventing preterm birth. A total of 13 RCTs with a total of 1551 women were considered. The rate of preterm birth (less than 37 weeks) showed no significant difference in six RCTs, four comparing ritodrine with placebo/no treatment and two comparing terbutaline with placebo/no treatment (RR 1.11, 95% CI 0.91 to 1.35; 644 women). Thus, in this review, it was observed that the betamimetics ritodrine and terbutaline did not reduce the rate of preterm birth (eight trials).

Another study[42] aimed to evaluate the efficacy of maintenance oral nifedipine in pregnant women initially treated with intravenous ritodrine plus verapamil for threatened preterm labor. It included 73 patients with threatened preterm labor with intact membranes. Patients were randomized to receive either maintenance oral nifedipine therapy (n=37) administered 20 mg every six hours or no treatment (controls, n=36) after discontinuation of acute intravenous tocolysis. The study concluded that, maintenance therapy did not decrease the recurrence of preterm labor episodes.

Thus, other studies that were done, assessing the efficacy of various maintenance tocolytics in patients with arrested preterm labour, did not show any reduction in the rate of recurrence of preterm labour in the study group compared

to the control group.[15,16,38,40,41,42] However in our study there was a significant reduction in the rate of recurrence of preterm labour in the study group ($p<0.001$).

In the present study maximum latency period (beyond 42 days) was noted in group S with majority of women (25%) having a latency period between 36 to 42 days whereas in group C, maximum latency period was within 35 days with more than half (57.78%) of the women having a latency period of less than 7 days. The mean latency period in group S was significantly higher than that of group C (28.77 ± 15.95 vs 10.15 ± 9.55 days; $p<0.001$). This difference between both the groups was statistically significant ($p< 0.001$), suggesting that the latency period was longer in the group of pregnant women treated with progesterone maintenance therapy as compared to the control group.

Few other similar studies that were conducted, assessing the role of maintenance tocolysis echoed this result.[15,40,42]

A randomized controlled trial[15] evaluated the efficacy and safety of vaginal progesterone (400 mg) in prevention of recurrent preterm labor on 70 patients with preterm labor treated with intravenous magnesium sulfate in perinatology department of Valiasr hospital. Study concluded that, the use of vaginal progesterone suppository after successful parenteral tocolysis was associated with a longer latency preceding delivery. Latency to delivery was significantly longer in progesterone-treated women (36.1 versus 24.5 days) ($p< 0.05$).

Another study[42] aimed to evaluate the efficacy of maintenance oral nifedipine in pregnant women showed that, compared to the control group, the

mean ± SD time gained from initiation of maintenance therapy to delivery (26.65 +/- 18.89 vs. 16.14 +/- 12.91 days, p=0.007) and the gestational age at delivery (37.03 +/- 2.06 vs. 35.1 +/- 3 weeks, p=0.003) were higher in the nifedipine maintenance therapy group. The study concluded that, the gestational age and time gained from initiation of maintenance therapy to delivery were longer in women receiving oral maintenance tocolysis with nifedipine.

A randomized double blind clinical trial[40] showed that, the mean latency until delivery in the cases was longer than the control group (23.88 ± 18.01 vs 16.67 ± 12.90; p=0.040). Log rank analysis revealed a significant difference for mean time to delivery between the two groups (p=0.028). Overall, the study concluded that prophylactic administration of 200 mg vaginal progesterone suppositories after successful tocolysis in patients with threatened idiopathic preterm labour is associated with a longer latency to delivery.

The results of the various studies[15,40,42] concurred with the results of our study.

In the present study, 21 babies (43.75%) in group S had birth weight more than 2.5 Kg compared to significantly less number of babies, i.e. 7 babies (15.56%) in group C (p=0.003). The mean birth weight of babies in group S (2.44 ± 0.52 Kg) was significantly higher than that in group C (2.10 ± 0.52 Kg).

A randomized controlled trial[15] in Valiasr Hospital showed that, the birth weights were significantly higher in the group treated with progesterone (maintenance tocolysis) as compared to the control group. Thus this study

showed significant difference in the birth weights in the study and control groups ($p<0.050$).

A randomized double blind clinical trial[40] reported no significant difference between birth weights in both the groups. The mean birth weight in the control group was 3025.9 ± 494.31 compared to 2996.56 ± 578.67 in the study group.

However our study has shown a significant increase in the mean birth weight in the study group.

In the present study, 7 babies (14.58%) from group S were admitted in NICU whereas in group C, 19 (42.22%) babies were admitted in NICU. This difference was statistically significant ($p=0.003$), suggesting that significantly less number of NICU admissions were noted in group S compared to group C (14.58% vs 42.22%; $p=0.003$).

Other similar studies[15,16,38,40,41,42] that were conducted, also did not show any difference in the rate of admission to neonatal intensive care unit between the study and control groups, nor did they show any association with improved perinatal outcome in the study group.

A randomized controlled trial[15] in perinatology department of Valiasr hospital reported no significant differences were found in the NICU admission between the case and control groups. There were 13 (39.4%) NICU admissions in control group as compared to 9 (24.3%) in the study group.

A randomized double blind clinical trial[40] conducted to evaluate the efficacy of 200 mg vaginal progesterone in order to prevent preterm birth in women with episodes of threatened preterm labour in 173 women reported no significant difference between NICU admissions and perinatal outcome in the study and control groups. There were 2 NICU admissions in the control group compared to 3 in the study group.

A study[41] to evaluate the efficacy of maintenance oral nifedipine in pregnant women initially treated with intravenous ritodrine and verapamil for preterm labor showed that the perinatal outcomes were similar in both the maintenance and control groups.

Our study concluded that, there were significantly less number of NICU admissions in the study group, probably due to the increase in the mean birth weight in this group as a result of significant increase in the latency period.

Chapter 7

Conclusion

CONCLUSION

We conclude that, maintenance tocolytic therapy with micronized progesterone (400 mg) upto 37 weeks of gestation in patients with arrested preterm labour significantly prolongs the latency period (28.77 ± 15.95 days). It significantly reduces the rate of recurrence of preterm labour (71.11% vs 41.66%; $p<0.001$). It also results in better perinatal outcome by improving the birth weight (2.44 ± 0.52 vs. 2.10 ± 0.52 Kg; $p=0.002$) and reducing the need for NICU admissions (14.58% vs 42.22%; $p=0.003$).

Chapter 8

Summary

SUMMARY

Preterm labour complicates 5-10% of pregnancies and is a leading cause of neonatal morbidity and mortality worldwide. The effectiveness of tocolytics in patients with preterm labour, to stop uterine contractions (acute tocolysis) or maintain quiescence (maintenance therapy) has been reviewed in the past. Use of tocolytics in patients with threatened preterm labour, may help in prolonging pregnancy, and thereby reduce the incidence of preterm labour and perinatal morbidity. Many drugs have been used for this purpose viz. nifedepine, magnesium sulphate, beta-mimetics, indomethacin, atosiban, etc. Most of these drugs have been further tested for maintenance tocolysis. However, long term use of these drugs was observed to have adverse effects and reduced efficacy, due to which they are not recommended for maintenance tocolysis. On the other hand, progesterone has long been considered as an important agent in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of preterm delivery. Hence, the present study was undertaken to determine whether maintenance tocolytic therapy with vaginal micronized progesterone (400 mg) therapy upto 37 weeks of gestation in patients with arrested preterm labour prolongs the latency period.

This study was a randomized controlled trial conducted in the Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Belgaum. A total of 98 pregnant women fulfilling the inclusion criteria were included in this study. Based on computer generated random numbers, these women were randomized into two groups of 49 each,

namely study group (Group S) which received 400 mg of vaginal micronized progesterone and control group (Group C) which did not receive any drug.

Of the 98 patients, 5 patients were lost to follow up, of which 4 patients were from the control group, while 1 patient belonged to the study group. Thereby, 97.96% of women completed follow up in group P, compared to 91.84% in group C.

In this study most of the women were aged between 21 to 25 years with the mean age of 22.73 ± 3.47 years in group S 24.55 ± 4.14 years in group C. The number of primigravidae and muligravidae were almost equal in both the groups. In group S majority of the women (35.41%) had period of gestation between 37 to 40 weeks at the time of delivery as compared to 28.88 % in group C. Most of the women in group C (37.77%) delivered between 34 to 37 weeks. The mean period of gestation at delivery was significantly high in group S (37.25 ± 2.51 weeks) compared to that in group C (34.99 ± 2.62 weeks). The recurrence of preterm labour was significantly high in the group C as 71.11% of the women delivered before 37 weeks of gestation compared to only 41.66% in group S. In the present study maximum latency period (beyond 42 days) was noted in Group S compared to Group C. Majority of women (25%) had a latency period between 36 to 42 days in Group S. In Group C, majority of the women (57.78%) had a latency period of less than 7 days. This difference between both the groups was statistically significant ($p<0.001$). The mean latency period in group S was significantly higher than that of group C (28.77 ± 15.95 vs 10.15 ± 9.55 days; $p<0.001$). In group S, 21 babies (43.75%) had birth weight more than 2.5 Kg compared to significantly less number of babies, i.e. 7 babies (15.56%) in group

C. The mean birth weight of babies in group S (2.44 ± 0.52 Kg) was significantly higher than that in group C (2.10 ± 0.52 Kg). In the present study, significantly more number of babies (42.22%) from group C were admitted in the NICU compared to 14.58% of babies from group S.

The results of this study showed that, maintenance tocolytic therapy with vaginal micronized progesterone (400 mg) in patients with arrested preterm labour significantly prolongs the latency period and reduces the recurrence of preterm labour. The perinatal outcome was better in the study group as there was increase in the birth weight thereby reducing the number of NICU admissions.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

Study: A randomized controlled trial assessing the role of progesterone as a maintenance therapy following arrested preterm labour

Principal Investigator: Dr. **** ******

Guide **:** Dr. **** *******

We request you to be a participant in the above said research to be conducted at KLE'S Teaching Hospital by Dr. ***** ******, Postgraduate student in the Dept. of Obstetrics and Gynecology at J.N. Medical College, Belgaum. Ph. No. ***** ******.

Your participation in this study is your voluntary decision whether or not to participate will not affect your current or future relationship with the KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre.

Procedure Involved

If you agree, in this research, we would subject you to either of the two study drugs till you deliver. This study is done to see the effect of the drugs in prolonging the duration of your pregnancy, for the benefit of your baby.

Risk and benefits

There are no additional risks involved in this procedure, as they are getting the same conventional treatment that they would receive, if they were not part of the trial. If any complications arise during the procedure then the patients

will be treated with best of our knowledge. There will be no compensation or payment for such medical treatment.

If you attain any complication during the procedure you may contact Dr. **** *****, Professor, Ph. No. ****** ***** and Dr. **** *****, postgraduate in the dept of Obstetrics and Gynecology.

During the course of study you will be informed of any significant new findings such as changes in risks and benefits resulting from participation in the research.

Privacy and Confidentiality

The only people who will know that you are a research participant are members of the research team. No information about you or provided by you, during the research will be disclosed to others without your written consent. When the results of the research are published or discussed the conferences, no information will be disclosed that would reveal your identity. Any information obtained in connections with this study and that can be identified with you remain confidential and will be disclosed only with your permission.

Voluntary participation

Your participation in this study will help us identify a superior drug amongst the two that will help us treat the future patients with the same drug. You are free to discontinue the participation in the study at any time for any reasons and you will not be paid any reimbursement for participation in the research.

If you have any questions about your rights or research as research participant you may contact Principal JNMC, Belgaum. Ph. No. ****** ******. You will be given a copy of this form for your information and to keep for your records.

Statement of Consent

To voluntarily agree to take part in this study I must sign on the line below: If you chose to take part in this study I may withdraw at any time I am not giving up any of my legal rights, by signing this form. My signature below indicates that I have read or have read to me this entire consent form including the risks and benefits and had all questions answered, I will be given a copy of this consent form.

Signature of the Subject:

Name: Date:

Signature of the investigator:

Name: Date:

Annexures

Annexure II

ANNEXURE II – PROFORMA

STUDY: A randomized controlled trial assessing the role of progesterone as a maintenance therapy following arrested preterm labour.

IDENTIFICATION

Sr no:_____

Randomization no:_____ Date:_____

Name:_____ I.P.No:_____

Age:_____

Address: _____

_____

_____

Telephone No:

INFORMED CONSENT

Was the consent given	Y	N

INCLUSION CRITERIA

1) Singleton pregnancy	Y	N
2) Gestational age between 28-36 wks	Y	N
3) Confirmed gestational age (by LMP/1st or 2nd trimester USG)	Y	N
4) Threatened preterm labour arrested with depin tocolytic regimen (>12hrs)	Y	N

EXCLUSION CRITERIA

1) Cervical encerclage	Y	N
2) Chorioamnionitis	Y	N

3) Preterm premature rupture of membranes (PPROM) Y N

ELIGIBILITY

Is the woman eligible? Y N

OBH : Gravida para abortion living

LMP: / / EDD: / /

1st trimester USG: CRL - 2nd trimester USG: BPD -

EDD - AC -

HC -

FL -

EDD -

POG:

Patient put on micronized progesterone vaginal pessaries : Y N

Date of initiation of treatment :

ADVERSE EFFECTS (if any) :

MATERNAL OUTCOME:

Date and time of delivery :

Period of gestation at delivery :

Latency period:

PERINATAL OUTCOME:

Gestational age :

Birth Weight :

NICU Admission Y N

If yes, indication :

RESULT :

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

LMP	- Last menstrual period
EDD	- Expected date of delivery
POG	- Period of gestation
Kg	- Kilograms
NICU	- Neonatal intensive care unit
M	- Multi
P	- Primi
S	- Spontaneous
I	- Induction
Y	- Yes
N	- No
-	- Not applicable

ANNEXURE III - MASTER CHART - GROUP S

Serial Number	Randomization Numbe	In patient Number	Age (Years)	Date of admission	Parity	LMP	EDD	POG		Randomization date	Delivery date	Method of delivery	POG		Latency period (Days)	Birth weight (Kg)	NICU Admission
								Weeks	Days				Weeks	Days			
1	T-1	392220	20	12.11.10	M	19.3.10	26.12.10	35	6	15.11.10	26.11.10	S	37	6	11	2.1	N
2	T-2	393410	21	20.11.10	P	??	7.1.11	33	1	23.11.10	25.1.11	I	40	4	60	3.1	N
3	T-3	393796	19	23.11.10	P	21.3.11	28.12.10	35	0	25.11.10	23.12.10	I	39	0	28	2.7	N
4	T-4	397605	22	21.12.10	P	??	8.2.11	33	1	24.12.10	31.1.11	S	38	5	38	2.7	N
5	T-5	400818	26	14.1.11	M	??	9.3.11	32	2	17.1.11	7.2.11	S	35	2	21	2.1	N
6	T-6	404214	22	4.2.11	P	31.6.10	7.4.11	31	1	7.2.11	27.3.11	S	38	3	48	2.1	N
7	T-7	404500	24	11.2.11	M	7.6.10	14.3.11	35	4	14.2.11	14.3.11	S	40	0	28	3.6	N
8	T-8	406760	30	28.2.11	M	3.7.10	10.4.11	34	1	3.3.11	11.4.11	S	40	1	39	3.7	N
9	T-9	409506	18	19.3.11	M	17.7.10	24.4.11	34	6	22.3.11	27.4.11	S	40	0	36	2.7	N
10	T-10	411001	20	14.2.11	P	5.7.10	12.4.11	31	6	31.3.11	3.4.11	S	32	5	3	1.7	Y
11	T-11	413173	20	13.4.11	P	19.8.10	26.5.11	33	5	16.4.11	16.5.11	S	38	0	30	2.3	N
12	T-12	413926	20	19.4.11	M	??	29.6.11	29	6	22.4.11	22.5.11	S	34	5	33	2.5	N
13	T-13	414605	19	23.4.11	M	8.9.10	15.6.11	32	3	26.4.11	14.6.11	S	39	6	49	3.3	N
14	T-14	417613	21	14.5.11	M	16.9.10	23.6.11	34	2	17.5.11	24.6.11	I	40	1	38	2.6	N
15	T-15	419163	23	23.5.11	M	2.10.10	9.7.11	33	2	26.5.11	28.5.11	I	34	0	2	1.7	Y
16	T-16	420824	22	3.6.11	M	25.10.10	1.8.11	31	4	6.6.11	15.7.11	S	37	1	39	2.6	N
17	T-17	422049	25	12.6.11	P	14.10.10	21.7.11	34	3	15.6.11	23.7.11	S	40	2	38	2.7	N
18	T-18	422261	28	13.6.11	P	16.10.10	23.7.11	34	2	16.6.11	23.6.11	S	35	5	7	2.5	N
19	T-19	429039	22	26.7.11	P	16.12.10	23.9.11	31	4	29.7.11	15.8.11	S	34	3	20	2	N
20	T-20	430903	26	8.8.11	M	3.1.11	10.10.11	31	0	11.8.11	13.9.11	S	35	5	33	1.7	Y
21	T-21	434140	30	29.8.11	M	4.1.11	11.10.11	33	6	1.9.11	21.9.11	S	36	5	20	2.6	N
22	T-22	435572	20	9.9.11	P	5.1.11	12.10.11	35	2	11.9.11	14.9.11	S	36	0	2	2.4	N
23	T-23	435755	24	9.9.11	M	13.1.11	20.10.11	34	1	11.9.11	20.10.11	S	40	0	39	2.7	N
24	T-24	436685	23	15.9.11	P	4.2.11	11.11.11	31	6	18.9.11	14.10.11	S	35	2	26	2.7	N
25	T-25	436834	23	12.8.11	P	30.12.10	7.10.11	32	0	15.8.11	23.9.11	S	38	0	39	2	N
26	T-26	433333	21	17.8.11	P	12.12.10	19.9.11	35	2	20.8.11	19.9.11	S	40	0	30	2.3	N
27	T-27	437396	21	19.9.11	P	30.1.11	6.11.11	33	1	22.9.11	23.10.11	S	38	0	31	2.4	N
28	T-28	438134	20	23.9.11	M	4.2.11	11.11.11	33	0	25.9.11	1.11.11	S	38	4	37	2.5	N
29	T-29	444411	25	14.10.11	M	23.3.11	30.12.11	29	0	17.10.11	20.12.11	S	38	0	63	3	N
30	T-30	441672	28	18.10.11	M	??	15.12.11	31	5	21.10.11	17.12.11	S	40	2	57	3	N
31	T-31	442311	24	11.11.11	P	21.4.11	28.1.12	28	6	14.11.11	23.12.11	S	34	2	39	1.8	Y
32	T-32	445661	25	15.11.11	M	16.4.11	23.1.12	30	1	24.11.11	28.1.12	S	40	5	65	3	N
33	T-33	447295	20	25.11.11	M	15.4.11	22.1.12	31	5	28.11.11	25.12.11	S	36	0	27	2.1	N
34	T-34	451165	22	21.12.11	P	??29.3.11	22.1.12	35	3	24.12.11	-	-	-	-	-	-	-
35	T-35	451812	25	26.12.11	M	26.5.11	3.3.12	30	3	29.12.11	5.1.12	S	31	6	7	1.2	Y
36	T-36	452041	26	27.12.11	M	28.4.11	5.2.12	34	2	30.12.11	22.1.12	S	38	0	23	2.4	N
37	T-37	454315	27	11.1.12	M	6.5.11	13.2.12	35	2	14.1.12	28.1.12	S	37	4	14	2.5	N
38	T-38	456462	19	26.1.12	P	7.6.11	14.3.12	33	2	29.1.12	7.2.12	S	35	0	9	2	N
39	T-39	458577	23	13.2.12	P	3.7.11	10.4.12	32	0	16.2.12	24.2.12	S	33	4	8	1.6	Y
40	T-40	459434	34	15.2.12	M	18.6.11	25.3.12	34	4	18.2.12	17.3.12	S	38	3	27	2.4	N
41	T-41	461331	20	28.2.12	P	??20.6.11	7.5.12	30	2	3.3.12	1.4.12	S	34	6	29	2	N
42	T-42	463413	24	14.3.12	P	8.7.11	15.4.12	34	0	17.3.12	24.3.12	S	36	6	7	2.2	N
43	T-43	467624	17	11.4.12	P	28.8.11	4.6.12	32	2	14.4.12	25.4.12	S	34	3	10	2.1	N
44	T-44	472670	24	23.5.12	M	26.9.11	3.7.12	32	4	26.5.12	17.6.12	S	36	1	22	2.6	N
45	T-45	477474	18	10.6.12	P	28.10.11	4.8.12	31	1	13.6.12	21.7.12	S	38	1	38	2.7	N
46	T-46	477930	20	13.6.12	P	24.11.11	1.9.12	28	4	16.6.12	30.6.12	S	31	0	14	1.6	Y
47	T-47	481047	21	2.7.12	M	9.11.11	16.8.12	33	4	5.7.12	15.8.12	S	39	6	41	3.2	N
48	T-48	481752	22	6.7.12	P	31.10.11	7.8.12	35	3	9.7.12	7.8.12	S	40	0	29	2.7	N
49	T-49	482871	20	13.7.12	P	18.11.11	25.8.12	33	6	16.7.12	9.8.12	S	37	5	27	2.9	N

ANNEXURE III - MASTER CHART - GROUP C

Serial Number	Randomization Numbe	In patient Number	Age (Years)	Date of admission	Parity	LMP	EDD	POG		Randomization date	Delivery date	Method of delivery	POG		Latency period (Days)	Birth weight (Kg)	NICU Admission
								Weeks	Days				Weeks	Days			
1	C-1	398553	22	29.12.10	M	15.5.10	22.2.11	32	3	31.12.10	23.1.11	S	36	0	23	2.1	N
2	C-2	399719	21	6.1.11	M	3.5.10	10.2.11	34	6	9.1.11	14.1.11	S	36	0	5	2.9	N
3	C-3	406265	20	14.2.11	P	17.6.10	24.3.11	34	4	17.2.11	17.4.11	S	39	0	28	3	N
4	C-4	405030	31	15.2.11	M	5.7.10	12.4.11	32	0	18.2.11	3.3.11	S	33	6	13	2.4	N
5	C-5	406937	22	1.3.11	P	16.7.10	23.4.11	32	3	4.3.11	6.4.11	I	37	1	33	2.4	N
6	C-6	409826	24	22.3.11	P	19.7.10	26.4.11	34	6	25.3.11	17.4.11	S	38	5	27	3	N
7	C-7	411342	24	30.3.11	P	8.9 10	15.6.11	29	0	2.4.11	5.4.11	I	29	6	3	1.2	Y
8	C-8	412052	19	6.4.11	P	14.8.10	21.5.11	33	4	9.4.11	30.4.11	I	37	0	24	2.3	N
9	C-9	413213	25	14.4.11	P	7.9.10	14.6.11	31	2	18.4.11	4.5.11	S	33	4	19	1.9	Y
10	C-10	413548	35	16.4.11	M	11.8.10	18.5.11	35	6	19.4.11	28.4.11	I	37	2	9	2.2	N
11	C-11	417201	24	11.5.11	P	22.9.10	29.6.11	33	0	14.5.11	15.5.11	S	33	4	1	1.8	Y
12	C-12	417710	22	14.5.11	P	17.9.10	25.6.11	34	0	17.5.11	20.5.11	I	34	6	3	1.6	Y
13	C-13	419218	20	23.5.11	P	18.10.10	25.7.11	31	0	26.5.11	14.6.11	S	33	5	19	2	Y
14	C-14	420426	23	31.5.11	P	5.10.10	12.7.11	34	0	3.6.11	4.6.11	S	34	4	1	1.8	Y
15	C-15	421823	25	10.6.11	M	1.11.10	8.8.11	31	4	13.6.11	3.7.11	S	34	3	20	2.3	N
16	C-16	426009	22	8.7.11	P	9.12.10	16.9.11	30	0	11.7.11	-	-	-	-	-	-	-
17	C-17	426462	19	11.7.11	P	2.11.10	9.8.11	35	5	14.7.11	20.7.11	S	37	0	6	2.4	N
18	C-18	431168	25	9.8.11	M	13.12.10	20.9.11	34	0	11.8.11	12.8.11	I	34	3	1	1.8	Y
19	C-19	424242	37	9.9.11	M	??	13.10.11	35	1	12.9.11	14.9.11	I	35	6	2	1.9	Y
20	C-20	436448	30	14.9.11	M	14.1.11	21.10.11	34	2	17.9.11	7.10.11	S	37	4	20	3	N
21	C-21	438662	22	28.9.11	P	2.2.11	9.11.11	34	0	1.10.11	16.10.11	I	36	4	15	1.8	Y
22	C-22	437751	24	21.9.11	M	8.2.11	15.11.11	32	1	24.9.11	11.10.11	I	34	4	17	2.4	N
23	C-23	438274	26	24.9.11	M	1.2.11	8.11.11	33	4	27.9.11	-	-	-	-	-	-	-
24	C-24	440292	26	10.10.11	M	1.2.11	8.11.11	35	6	13.10.11	20.10.11	S	37	2	7	2.3	N
25	C-25	442311	24	21.10.11	M	9.3.11	16.12.11	32	0	24.10.11	28.10.11	I	33	0	4	1.4	Y
26	C-26	445423	27	13.11.11	M	?18.2.11	28.12.11	33	3	16.11.11	19.11.11	S	34	2	3	2.1	N
27	C-27	446063	21	17.11.11	M	20.3.11	27.12.11	34	2	20.11.11	25.11.11	I	35	3	5	1.8	Y
28	C-28	446412	25	19.11.11	P	24.3.11	31.12.11	34	0	22.11.11	13.12.11	S	37	3	21	2.5	N
29	C-29	450021	23	14.12.11	M	8.4.11	15.1.12	35	3	17.12.11	11.1.12	S	39	3	25	2.5	N
30	C-30	448843	30	6.12.11	P	24.4.11	31.1.12	32	0	9.12.11	10.12.11	S	32	4	1	2	N
31	C-31	451462	27	23.12.11	P	6.6.11	13.3.12	29	0	25.12.11	26.12.11	S	29	3	1	1.2	Y
32	C-32	451968	23	27.12.11	M	30.6.11	7.3.12	30	0	29.12.11	30.12.11	S	30	3	1	1.7	Y
33	C-33	452853	23	2.1.12	P	15.5.11	22.2.12	32	5	4.1.12	5.1.12	S	33	1	1	1.7	Y
34	C-34	453348	20	5.1.12	P	8.5.11	5.2.12	35	4	8.1.12	12.1.12	S	36	4	4	1.9	Y
35	C-35	454177	21	11.1.12	P	2.5.11	3.3.12	35	6	14.1.12	17.1.12	S	36	5	3	2.3	N
36	C-36	458565	35	9.2.12	M	15.7.11	22.4.12	33	0	23.2.12	26.2.12	S	33	3	3	1.25	Y
37	C-37	455555	23	9.2.12	M	21.6.11	28.3.12	33	0	11.2.12	12.2.12	S	33	2	1	1.6	Y
38	C-38	462117	22	5.3.12	M	4.7.11	11.4.12	34	5	7.3.12	12.3.12	S	35	5	5	2.5	N
39	C-39	463263	30	13.3.12	M	14.7.11	2.4.12	34	3	16.3.12	28.3.12	S	36	4	12	2.3	N
40	C-40	470572	22	1.5.12	P	28.9.11	5.7.12	30	5	3.5.12	5.5.12	S	31	3	2	1.9	N
41	C-41	474553	20	23.5.12	P	28.9.11	5.7.12	33	6	26.5.12	19.6.12	S	37	1	24	2.4	N
42	C-42	475284	24	28.5.12	M	?17.9.11	3.7.12	34	6	31.5.12	-	-	-	-	-	-	-
43	C-43	477327	24	9.6.12	M	5.10.11	12.7.12	35	2	12.6.12	18.6.12	S	36	4	6	2.7	N
44	C-44	474595	27	23.5.12	M	?17.11.11	2.9.12	28	6	16.6.12	18.6.12	S	29	1	2	1.2	Y
45	C-45	477980	23	13.6.12	M	21.10.11	27.7.12	33	5	16.6.12	18.6.12	S	34	3	2	2.5	N
46	C-46	473951	23	20.6.12	P	25.11.11	2.9.12	29	3	22.6.12	23.6.12	S	29	6	1	1	Y
47	C-47	481331	27	4.7.12	M	26.10.11	3.8.12	35	5	7.7.12	23.7.12	S	38	0	16	2.7	N
48	C-48	482623	21	12.7.12	P	15.11.11	22.8.12	34	1	15.7.12	-	-	-	-	-	-	-
49	C-49	484138	30	21.7.12	P	?27.11.11	27.8.12	34	5	24.7.12	11.8.12	S	37	5	18	2.7	N